SYNTHESIS AND REACTIONS OF BICYCLO[1.1.0]BUTANES

by

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B. S. (*maxima cum laude*), A. Mickiewicz University, 2003

Submitted to the Graduate Faculty of

Arts and Sciences in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2009

UNIVERSITY OF PITTSBURGH

FACULTY OF ARTS AND SCIENCES

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University of Pittsburgh, 2009

This dissertation describes methods for the synthesis of bicyclo[1.1.0]butanes and their reactions. The bicyclo[1.1.0]butyl skeleton was first assembled by intramolecular, amide directed Simmons-Smith cyclopropanation of propargyl amides and cyclopropenes. However, a more general approach applicable to the synthesis of amines, alcohol, esters, and amides was developed. This method is based on the generation of bicyclo[1.1.0]butyllithium from *gem*-dibromocyclopropanes *via* sequential transmetallation reactions with alkyllithium reagents and addition to electrophilic acceptors.

Studies on the reaction of bicyclo[1.1.0]butanes were focused on thermal and metal-catalyzed transformations. Bicyclo[1.1.0]butanes activated by an aromatic group underwent highly chemo- and diastereoselective intramolecular pericyclic reactions under mild conditions. The outcome of these processes was controlled by the selection of the allylating reagents, and *N*-allyl amides gave exclusively formal ene products. On the other hand, cinnamyl amides participated in an intramolecular cycloaddition reaction. The postulated presence of radical in the mechanism of these reactions was supported by chemical and spectroscopic (ESR) studies.

In the metal-catalyzed cycloisomerization reactions, an intramolecular cyclopropanation of allyl amides catalyzed by complexes of Rh(I) is described. These reactions proceeded *via* metal carbene intermediates, which were selectively generated by applying phosphine additives

with different steric and electronic properties. Based on the mechanistic proposal, the synthesis of pyrroles from bicyclo[1.1.0]butanes was achieved using a Rh(I)/bidentate ligand catalytic system and hindered amides. Finally, cycloisomerization reactions of propargyl amides and ethers as well as electron-deficient bicyclo[1.1.0]butanes catalyzed by Pt(II) are described. These reactions proceeded *via* a series of carbene intermediates to give polycyclic nitrogen- and oxygen-containing heterocycles, which could be of utility in research and development.

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LIST OF ABBREVIATIONS

a.u.	Atomic Unit
Ac	Acetyl
Acac	Acetylacetonate
An	Acrylonitrile
Ar	Aromatic ring
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
n-Bu	*n*-Butyl
t-Bu	*tert*-Butyl
Bz	Benzoyl
Cod	1,5-Cyclooctadiene
COE	Cyclooctene
Cp	Cyclopentadienyl
Cy	Cyclohexyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DHP	3,4-Dihydro-2*H*-pyran
DIAD	Diisopropyl azodicarboxylate

DIOP	(+)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPEA	*N*,*N*-Diisopropylethylamine
DMAD	Dimethyl Acetylenedicarboxylate
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin Periodinane
DMS	Dimethyl sulfide
dppb	1,4-Bis(diphenylphosphino)butane
dppb	1,3-Bis(diphenylphosphino)propane
dppe	1,2-Bis(diphenylphosphino)ethane
dppm	Bis(diphenylphosphino)methane
ESR	Electron Spin Resonance Spectroscopy
Et	Ethyl
EWG	Electron-withdrawing group
HMPA	Hexamethylphosphoramide
HOMO	Highest Occupied Molecular Orbital
LAH	Lithium aluminum hydride
LG	Leaving group
LUMO	Highest Occupied Molecular Orbital
MCPBA	3-Chloroperbenzoic acid
Me	Methyl
MNP	2-Methyl-2-nitrosopropane

Morph	*N*-Morpholinyl
Ms	Methanesulfonyl
MS	Mass Spectrometry
MS-TOF	Time-of-Flight Mass Spectrometry
MTAD	4-Methyl-1,2,4-triazoline-3,5-dione
μW	Microwave irradiation
ND	Not determined
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear Magnetic Resonance Spectroscopy
P.E.	Petroleum ether
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Ph	Phenyl
i-Pr	*i*-Propyl
n-Pr	*n*-Propyl
PPTS	Pyridinium 4-toluenesulfonate
RT	Room temperature
SES	2-(Trimethylsilyl)ethanesulfonyl
TBAF	Tetra-*n*-butylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl

Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFE	2,2,2-Trifluoroethanol
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
Tol	4-Methylphenyl
TPAP	Tetra-*n*-propylammonium perruthenate
Tris	2,4,6-Triisopropylbenzenesulfonyl
Ts	4-Toluenesulfonyl
TSA	4-Toluenesulfonic acid
ZPVE	Zero Point Vibrational Energy

ACKNOWLEDGEMENTS

I want to thank Prof. Peter Wipf for his guidance and the freedom to learn chemistry. Prof. S. G. Nelson, Prof. Craig S. Wilcox, and Prof. Billy W. Day are acknowledged for serving as members on my committee. Their experience and insights will have a lasting influence. I greatly appreciate Professor Paul Floreancing's input on my graduate research proposal. Over the last years, I had the privilege to participate in Wipf group meetings (Tuesday and Saturday), P50/P01 meetings, and the departmental organic group meetings. Attending these meetings was both an inspiring and an enjoyable experience.

I want to thank all Wipf group members, especially coworkers who I collaborated with on the chemistry of strained molecules, namely Dr. Laurent Ferrié, Mr. Adam T. Hoye, Dr. Robert B. Lettan, II, Mr. Byong-kyu Shin, Dr. Corey R. J. Stephenson, Dr. Masafumi Ueda, Dr. Grace Woo, and Dr. Zenglai Fang. Professor Sunil Suxena is thanked for an exciting collaboration. The CMLD personnel have always been extremely helpful and I want to thank all past and present members of the Center, particularly Mr. Pete Chambers. A stimulating and friendly atmosphere in the lab was always provided by my labmates, particularly Ms. Melissa M. Sprachman, who has been the most understanding and supportive labmate. I am indebted to Michelle L. Paul for her outstanding administrative work and support. Nancy Woodring has provided considerable hospitality, and I am deeply thankful for it. I want to express my special thanks to Dr.

Kalyani J. Patil for patience, support, and, foremost, friendship. The past three years wouldn't have been as rich and stimulating without her encouragement.

Finally, all that is described in this document wouldn't be possible without the continuous support of my parents and my brother. They have always encouraged me to pursue my dreams and inspired me with limitless love.

1.0 SYNTHESIS OF BICYCLO[1.1.0]BUTANES

The search for new synthetic methods to construct complex molecules is a fascinating area of organic chemistry and critical for the development of organic synthesis and related fields. Studies on the fundamental reactivity open the way towards general chemical methodologies and contribute to the advancement of the frontiers of organic synthesis. Small carbocyclic systems like cyclopropanes and cyclobutanes have played an important role in this quest due to their structural features that provide unique reactivity and allow for rapid increase in molecular complexity. Surprisingly, bicyclo[1.1.0]butane (**1**),[1,2] one of the smallest and most strained bicyclic systems, has not yet attracted wide interest in organic synthesis. Efficient methods for the *de novo* synthesis of bicyclo[1.1.0]butane, methodologies for the incorporation of this carbocycle into other organic molecules, and an understanding of its reactivity still remain major challenge in the chemistry of this molecule. Progress in these areas will be critical in the development of new synthetic strategies and will add significantly to the repertoire of chemical transformations.

1.1 INTRODUCTION

1.1.1 Fundamental Properties of Cyclopropanes

In many respects, the cyclopropane ring is unique among organic molecules. Unlike other cyclic alkanes, it undergoes facile addition of electrophiles across the σ-bond, but is quite resistant towards substitution reactions. It is also capable of stabilizing an electron-deficient center *via* conjugation, while the release of strain in other strained carbocycles (e.g. cyclobutane) leads to a rearrangement of the carbocation.[3] These and other chemical properties of cyclopropanes (the π-character of its C-C bonds, substituent effect on the reactivity and structure, and delocalization of electrons in the plane of the ring[4]) are explained by MO models.[5] According to the MO formalism, the bonds between carbon atoms are formed through hybrid sp^3 orbitals (the Förster-Coulson-Moffitt model[6,7]) or, alternatively, *via* union of three sp^2 hybridized fragments (the Walsh model[8]). Cyclopropane may be also considered to represent a resonance hybrid of the π-complexes of methylene-ethane.[9] This stabilization is reminiscent of the aromatic ring in benzene (σ-aromaticity[10]) and may partially compensate for the high ring strain of cyclopropane.

Due to their reactivity, cyclopropanes continue to be used extensively in organic synthesis.[11] The majority of the reactions involves opening the strained ring *via* electrophilic or nucleophilic addition,[12] or reduction, and ring expansions. Recent applications in total synthesis include spirotenuipesine A,[13] nakadomarin,[14] pleocarpenene,[15] ventricos-7(13)-ene,[16] minfiensine,[17] and mycalamide A[18] (Figure 1).

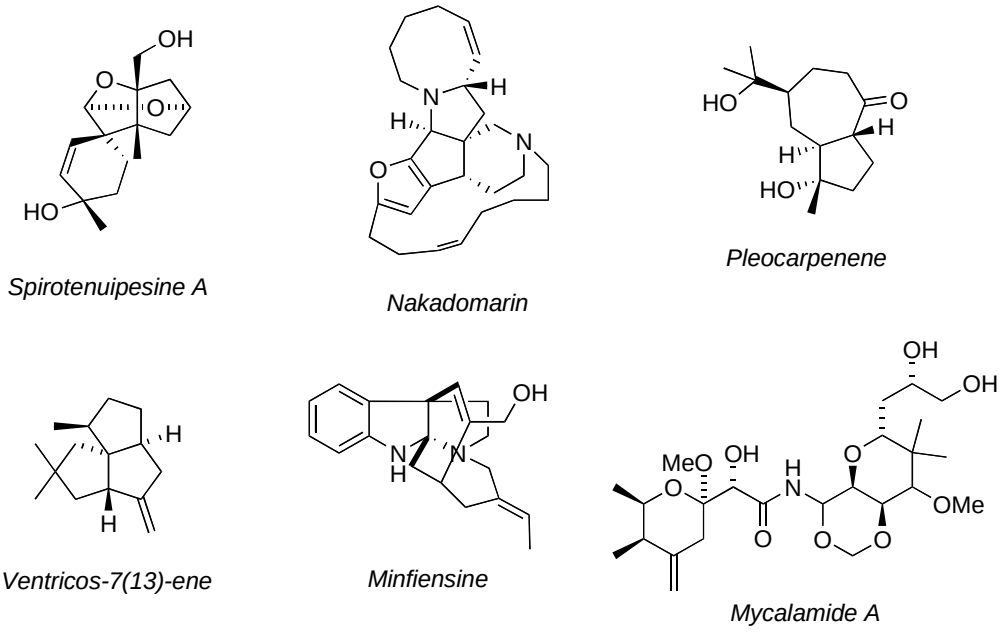


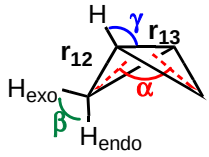
Figure 1. Selected natural products synthesized using cyclopropane building blocks.

In the context of the synthesis of bicyclo[1.1.0]butanes, *gem*-dihalocyclopropanes are of special interest.[19] These reagents, obtained from alkene additions of dihalocarbene generated under phase-transfer conditions,[20-23] were used as precursors in the synthesis of *mono*-halocyclopropanes, cyclopropenes, bicyclo[1.1.0]butanes (*vide infra*), cummulenes, and derivatives of cyclopentene. *gem*-Chlorocyclopropanes, when exposed to stoichiometric amounts of silver salts, can provide access to products difficult to obtain by other methods.[24] Also, these compounds are useful synthetic precursors for the synthesis of *gem*-dialkyl cyclopropanes, as exemplified by the total synthesis of ingenol by Winkler *et al*.[25]

1.1.2 Structure of Bicyclo[1.1.0]butane

The geometrical parameters of various bicyclo[1.1.0]butanes have been determined using all major structural methods (μW, NMR, X-ray) accompanied by extensive theoretical calculations[26-28] (Table 1). The analysis of the crystal structure of bicyclo[1.1.0]butane revealed that that all CC bonds are slightly shorter than those in cyclopropane (1.512 Å)[29] and in spite of the difference in reactivity and electronic structure, the central C_1C_3 and side C_1C_2 bonds are of similar length. Bicyclo[1.1.0]butane adopts a highly puckered structure (C_{2v} symmetry) and the interflap angle α for most of the bicyclo[1.1.0]butanes is close to 123º. It is important to note that α is correlated with the length of the C_1C_3 bond[30] – elongation of the central bond (caused by steric bulk) results in a larger α. The bridgehead carbons in bicyclo[1.1.0]butane possess an inverted geometry – all four substituents at C_1 or C_3 are restricted to one hemisphere.

Table 1. Structural parameters for bicylo[1.1.0]butane.



Method[a]	α	β	γ	C_1C_2	C_1C_3	C_1H_1	C_2H_{exo}	C_2H_{endo}
NMR[31]	120.2	110.2	128.0	1.507	1.507	1.142	1.194	1.167
Electron Diffraction[31]	122.8	111.6	125.5	1.507	1.502	1.108	~1.106	~1.106
Microwave[32]	122.4	115.3	128.2	1.498	1.497	1.071	1.093	1.093
B3LYP/6-311+G*[b]	121.9	114.3	129.3	1.492	1.500	1.078	1.087	1.091

[a] Angles are given in degrees and bond lengths in Ångstroms. [b] Unpublished data.

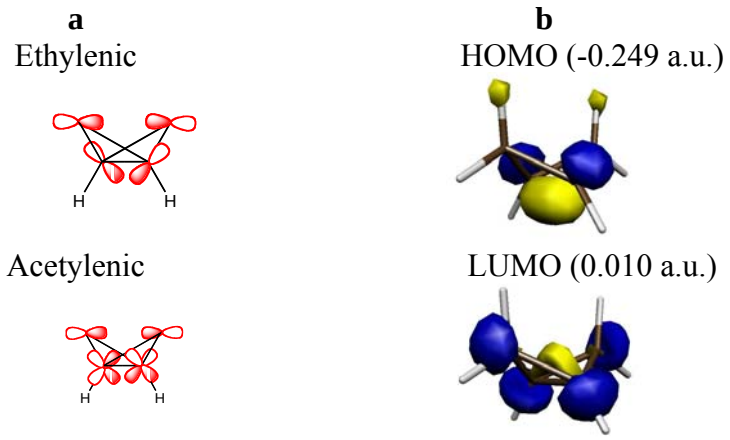
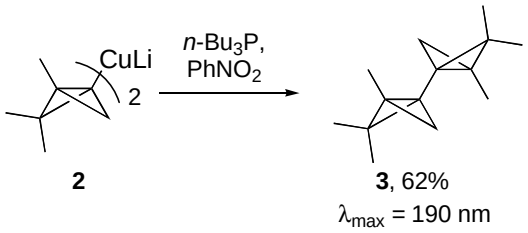
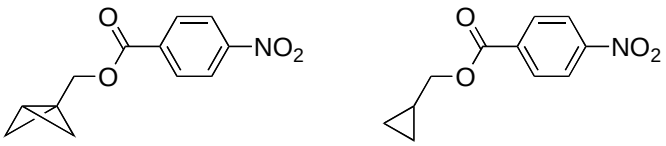


Figure 2. (a) Walsh-type orbitals for bicyclo[1.1.0]butane. (b) Representation of the frontier orbitals calculated at the B3LYP/6-31G* level.

The π-character of the C_1C_3 bond has been extensively documented both experimentally[1,2,33-35] and theoretically.[36,37] For example, Moore *et al.*[33] were able to synthesize bicyclo[1.1.0]butane dimer **3** *via* oxidative coupling of Cu-derivative **2** (Scheme 1). The UV/VIS analysis showed that its λ_{max} is located at 190 nm. This might suggest that the two bicyclo[1.1.0]butane moieties are in conjugation, resulting in a red shift in the UV spectrum. Wiberg *et al.*[1] have shown that solvolysis of the benzoate ester of bicyclo[1.1.0]butane **4** is ca. 1000 times faster than in the analogous cyclopropyl derivative **5** (Figure 3).



Scheme 1. Synthesis of bicyclo[1.1.0]butane dimer **3**.



4 **5**

Figure 3. Structures of bicyclo[1.1.0]butyl and cyclopropyl esters **4** and **5**.

To further support the hypothesis of the significant π-character of the central bond, NMR studies have been performed. The ${}^{1}J_{CH}$ coupling constant of the C_1H bond corresponds to 40 % *s*-character[38] and an exceptionally low (-5.4 to -17.5 Hz) ${}^{1}J_{CC}$ for C_1C_3 is calculated to correspond to 11% *s*-character of the orbital hybrid.[11] In spite of the substantial similarity of the central bond in bicyclo[1.1.0]butane to a π-bond, it fails to participate as a good dienophile in Diels-Alder reactions.[39] It also has been suggested that the C_1C_3 bond may possess considerable diradical character (*vide infra*).[40]

Bicyclo[1.1.0]butane is a very strained molecule. The strain energy (SE),[41] defined as the standard enthalpy of a structure relative to a strainless structure (real or hypothetical) made up from the same atoms with the same types of bonding, falls in the range between 63.9 and 66.5 kcal·mol^{-1} (with ΔH_f[43] 51.9 kcal·mol^{-1}), depending on the group increments used.[42-46] Theoretical analyses revealed that the substitution on bicyclo[1.1.0]butane may affect the strain energy. For

instance, a cyano group placed at C_1 reduces the strain by ca. 6 kcal·mol^{-1}.[47] Similar trends can be observed for substitutions by aromatic groups (Figure 4). This relationship is consistent with the notion that the conjugation of the central bond with the π-system leads to an overall stabilization.

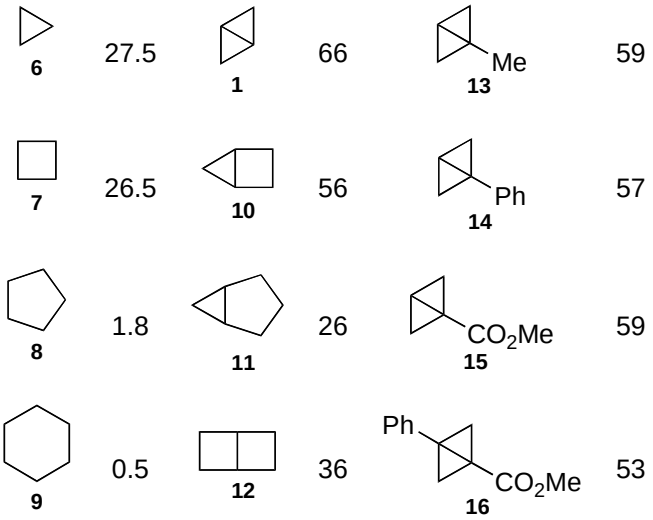


Figure 4. Experimental (**6**–**12**) and calculated (**13**–**16**) ring strain energies (kcal·mol^{-1}) for common mono- and bicyclic systems.

The strain energy in bicyclo[1.1.0]butane does not follow the additivity rule for small bicyclic systems. If the strain energy of cyclopropane is 27 kcal·mol^{-1},[3] bicyclo[1.1.0]butane possesses an extra 8.9 kcal·mol^{-1} that originates from the fusion of two cyclopropane rings. The difference between observed and estimated strain energy may be explained by considering the nonbonding 1,3-carbon/carbon interactions in cyclobutane[48] (Dunitz-Schomaker hypothesis)[49] that were calculated to account for 18 kcal·mol^{-1} of the total strain energy in *c*-C_4H_8. Steric repulsions as well as the carbon-carbon electronic interactions represent two faces of the 1,3-nonbonded

interactions. Recently, this interpretation was challenged by Baric and Maksic,[50] who suggested that the increased strain originates from angular deformations around the terminal carbon atoms (Baeyer strain). The electronic properties of bicyclo[1.1.0]butane play a critical role in determining the strain energies of the entire bicyclic system as well as its reactivity. Release of strain is a major driving force for the reactions of bicyclo[1.1.0]butane – common reactions involve isomerization to 1,3-butadiene, formation of cyclobutane by reaction with electrophiles or nucleophiles and transformation to cyclobutene.

1.1.3 Bicyclo[1.1.0]butane in Nature

No natural product containing a bicyclo[1.1.0]butane has been isolated so far. However, it is likely that bicyclo[1.1.0]butyl moiety may be present as a transient intermediate or, even if stable towards biological conditions, may undergo side reactions during isolation and purification processes. The first example of a bicyclo[1.1.0]butane-containing compound derived from a living organism was reported in 2007 by Brash *et al*.[51] The authors studied the activity of lipoxygenase (LOX) derived from *Anabaena* sp. The fusion protein was expressed in *E. coli* and the semi-purified enzyme was reacted in a biphasic system (aqueous pH 8 buffer/hexane) in the presence of 9-hydroperoxylinoleic acid **19** – a product of oxygenation of linolenic acid by the lipoxygenase domain. After full consumption of the substrate, the mixture was treated with CH_2N_2 and a reverse-phase HPLC purification afforded a 2:1 mixture of bicyclo[1.1.0]butylvinyl epoxide **17** and leukotriene-type epoxide **18** (Figure 5).

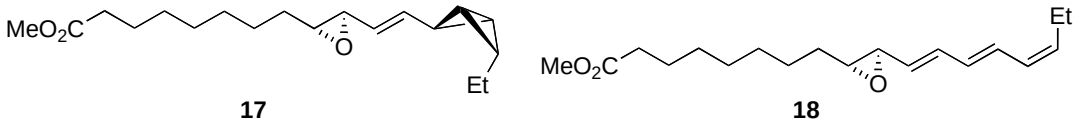
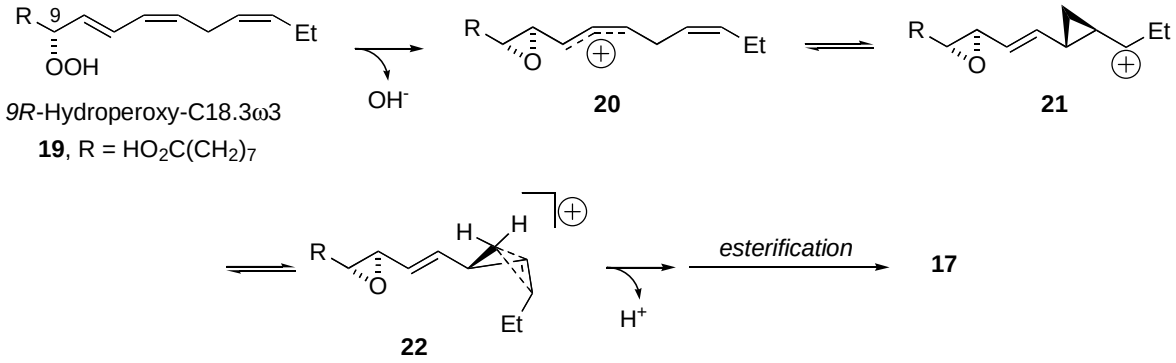


Figure 5. Structures of **17** and **18**.

Biosynthetically, these products can arise from a rearrangement of hydropeoxide **19** to an allyl carbocation **20** with a concomitant formation of the oxirane ring. This intermediate can be further rearranged into a cyclopropyl cation **21**, a pathway known for the formation of a cyclopropyl ring in natural products.[52,53] Further loss of a proton and rearrangement *via* a non-classical carbocation leads to an acid, which upon esterification gives the isolated product **17** (Scheme 2).



Scheme 2. Proposed biosynthesis of **18**.

1.1.4 Synthesis of Cyclopropanes

Due to the general synthetic utility of cyclopropanes, numerous preparative methods have been developed. According to Charette *et al.*,[54,55] cyclopropanation reactions can be classified

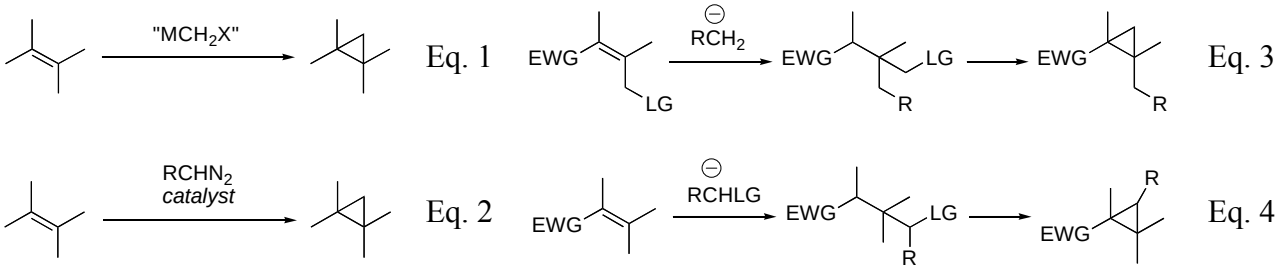
into three major categories depending on the mechanism of formation of the cyclopropyl ring (Scheme 3):

A. halomethylmetal-mediated cyclopropanations (1),

B. transition metal-catalyzed decompositions of diazo compounds (2), and

C. nucleophilic addition-ring closures (3 and 4).

Synthetic and mechanistic aspects of each of these categories will be discussed in this chapter.



Scheme 3. Methods for the synthesis of cyclopropanes.

1.1.4.1 Halomethylmetal-Mediated Cyclopropanations

The Simmons-Smith[56] cyclopropanation reaction is considered the most versatile and general method for the synthesis of the smallest carbocycle. The key features of this methodology include high stereospecificity with respect to the double bond geometry and tolerance to various functional groups. Additionally, the presence of chelating groups in the proximity to the double bond has a dramatic effect on the selectivity in these reactions.

The initial report for the synthesis of zinc carbenoids $XZnCH_2X$ involved reaction of CH_2I_2 with a zinc/copper couple. A subsequent report by Wittig[57-61] showed that diazomethane reacts with ZnI_2 to give the same type of species. However, a major development in the generation of zinc carbenoids was reported by Furukawa[62,63] who showed that Et_2Zn reacts with CH_2I_2 to give presumably $EtZnCH_2I$. Denmark[64,65] further expanded the utility of zinc carbeoinds and

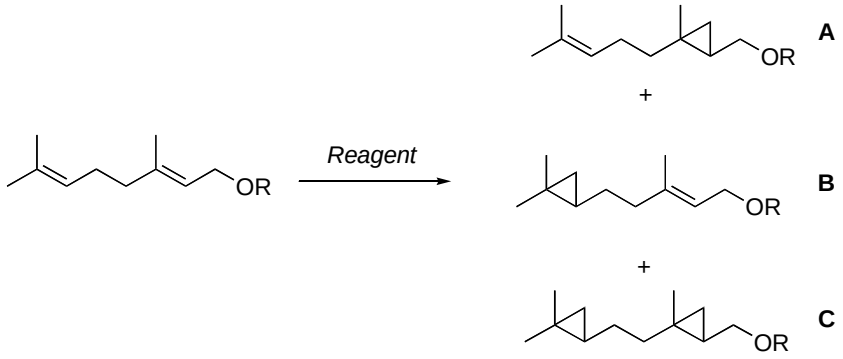
showed that $Zn(CH_2Cl)_2$ is more reactive than the analogous $EtZnCH_2Cl$ and (iodomethyl)zinc analogues. Other reagents that have been reported include samarium[66,67] and aluminum carbenoids.[68] Their reactivity and selectivity in the cyclopropanation reactions of isolated and activated double bonds is compared in

Table 2. Recently, new and more reactive reagents have been developed, and these include $CF_3CO_2ZnCH_2I$ (Shi's reagent),[69,70] or substituted iodomethylzinc alkoxides.[71,72]

The solid-state structures of the Simmons-Smith reagent stabilized by ethers[73,74] as well the Denmark reagent stabilized by quinoline[75] ligands have been solved. However, it is postulated that $IZnCH_2I$ exists in equilibrium with ZnI_2 and $Zn(CH_2I)_2$ (the Schlenk equilibrium). The solution structure of the Furukawa reagent has also been established *via* NMR studies, and this reagent is present in the equilibrium with Et_2Zn and $Zn(CH_2I)_2$, eventually undergoing rearrangement into PrZnI. [64,76]

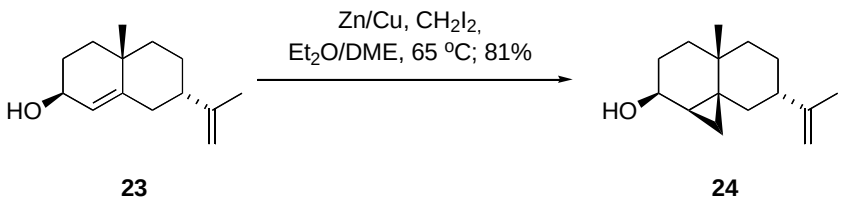
Due to the electrophilic nature of metal carbenoids, the choice of the solvent may influence the reactivity and stability of these reagents. CH_2Cl_2 and $(CH_2Cl)_2$ are the most common reagents, but the use of coordinating solvents leads to decreased reactivity. In some cases, however, this property may be used to stabilize the reactive intermediate in the reactions performed on a large scale.

Table 2. Comparison of the regioselectivity of metal carbenoids.



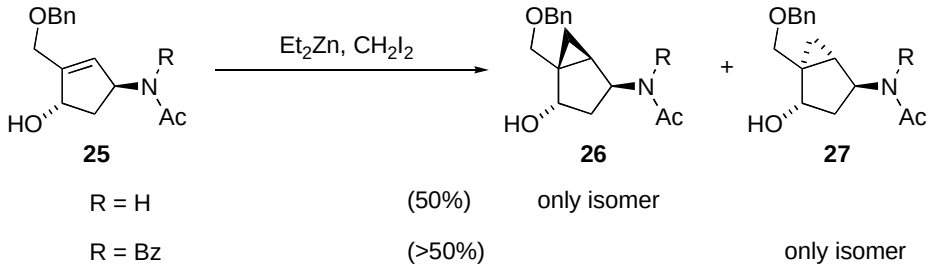
Reagent	A		B		C	
	R = H	R = Bn	R = H	R = Bn	R = H	R = Bn
Et_2Zn, CH_2I_2, Et_2O, rt	74	97	2	1	3	<1
i-Bu_3Al, CH_2I_2, CH_2Cl_2, rt	1	67	76	0	4	0
Sm/Hg, CH_2IX, THF, -78 ^oC	98	75	0	0	0	0

The Simmons-Smith reagents undergo a cyclopropanation reaction *via* "butter-fly" transition state. Recent theoretical studies have indicated that the five-centered transition state model involving the interaction of zinc carbenoid with $ZnCl_2$ (Lewis acid) is kinetically favored over the transition state with a four-membered "dimer" of $ZnCl_2$. The presence of a Lewis basic site (for example, alcohol, ether, ester, or amide) directs the delivery of the carbenoids to the double bond. The coordinating ability of oxygen is illustrated in the reaction of **23** to give **24** in high yield and excellent selectivity (Scheme 4). The ability of oxygen to direct the delivery of a metal carbene has also been used in the reaction of acyclic allylic alcohols.

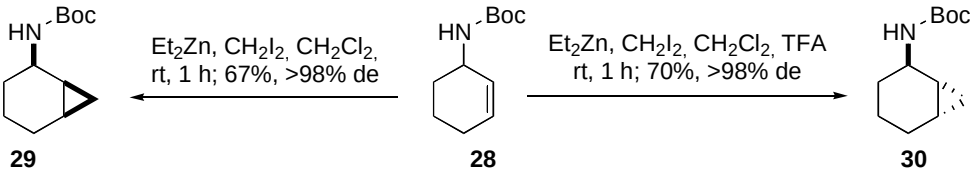


Scheme 4. Synthesis of cyclopropyl alcohol **24**.

Amides are useful directing groups, and they can effectively compete with oxygen-based directing groups as demonstrated in Scheme 5.[77] In the presence of free 2° amide, this moiety controlled the delivery of a zinc carbene to a trisubstituted bond in a modest yield. Alternatively, when this position was blocked by a benzoyl group, the same carbenoid furnished a different diastereoisomer in an excellent *dr*. The effect of the zinc carbenoid on the amide-directed cyclopropanation has been studied recently, and the choice of the cyclopropanating reagent proved to be critical in determining the selectivity in the reactions of the allylic amide **28** (Scheme 6).[78]



Scheme 5. Amide-directed cyclopropanation with the Furukawa reagent.

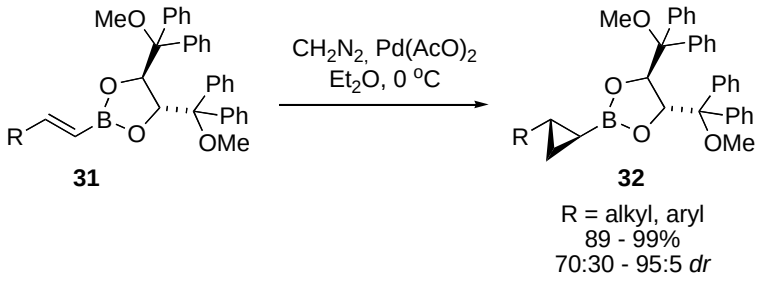


Scheme 6. Amide-directed cyclopropanation of **28**.

Amines are generally not suitable substrates in the cyclopropanation reactions as the zinc carbenoid is quenched with a basic atom to give a nitrogen ylide. This observation was applied in the development of a highly diastereoselective [2,3]-sigmatropic rearrangement reaction by Aggarwal.[79]

1.1.4.2 Transition Metal-Catalyzed Decomposition of Diazo Compounds

The decomposition reactions of diazomethane, TMS-diazomethane as well as the reactions with diazocompounds substituted with electron-withdrawing groups are versatile synthetic transformations in the synthesis of cyclopropanes.[80] The reactions with CH_2N_2 are typically performed with Pd(II) precursors,[81] although it is possible that the metal undergoes an initial reduction to Pd(0) and this species is a reactive intermediate.[82,83] Highly diastereoselective cyclopropanations using CH_2N_2 have been developed by Pietruszka (Scheme 7).[84-90]



Scheme 7. Cyclopropanation of vinylboronate esters.

Among diazocompounds with electron-deficient groups, esters have been used most, typically in the presence of Cu, Rh, Ru, Co, Fe, Os, Pd, Pt, Cr. Metals such as Rh, Cu, Os, and Ru are the optimal catalyst for reactions with electron-rich alkenes, and Pd reacts with electron-neutral systems most efficiently. The mechanism of these reactions is believed to involve the formation of a metal carbene, which reacts with the alkene to minimize the steric interactions in the transition state. This reaction usually leads to *trans*-isomer of cyclopropane, and Cu salts are particularly selective in these reactions.[91,92] Rh(II) salts are also well-known to provide high selectivities. These observations led to development of efficient enantioselective reactions. Also, iodonium or sulfonium ylides can be used as the carbene precursors.[93,94]

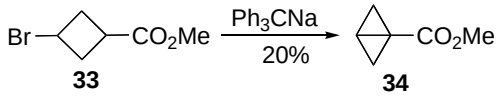
1.1.4.3 Nucleophilic Addition - Ring Closure

The third category of cyclopropanation reactions involves the intramolecular displacement reaction initiated by nucleophilic addition to Michael acceptors (referred as Michael-initiated ring closure, MIRC).[95] The leaving group can be a part of the electrophilic component, and suitable nucleophiles include alkoxides, tiolates, cyanides, Grignard reagents, and enolates.[96] If the leaving group is located on the nucleophilic component, the ylides derived from sulfur, phosphorus, arsenium and tellurium are the most convenient reagents.[97]

1.1.5 Synthesis of Bicyclo[1.1.0]butane

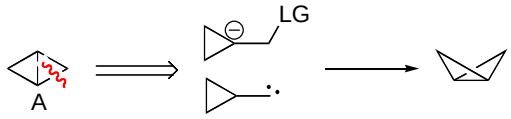
The first reproducible report on the synthesis of the bicyclo[1.1.0]butane skeleton was presented by Wiberg and Ciula[98] who used sodium triphenylmethide to furnish bicyc-

lo[1.1.0]butyl methylcarboxylate **34** in 20% yield (Scheme 8). The parent molecule was first obtained in 1963 by Lemal[99] and Wiberg.[100] After these seminal papers, a number of different approaches to the bicyclo[1.1.0]butyl skeleton have been developed. The direct syntheses of the bicyclo[1.1.0]butane ring can be divided into five major categories, depending on the type of bonds constructed.

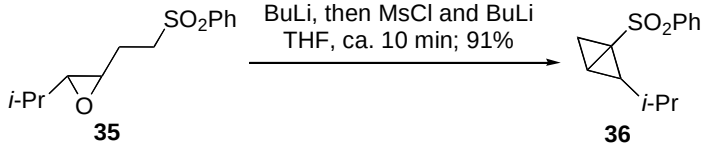


Scheme 8. Synthesis of bicyclo[1.1.0]butyl methylcarboxylate by Wiberg.[100]

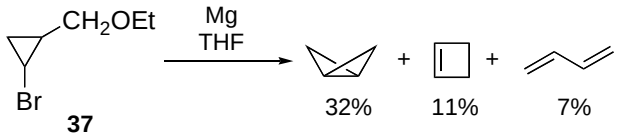
1.1.5.1 Synthesis of the Lateral Bond



Starting from properly functionalized cyclopropanes, bicyclo[1.1.0]butane can be accessed *via* intramolecular displacement of a leaving group,[101-104] including such a sluggish nucleofuge as EtO^-.[105] Some examples are given in Schemes 9 and 10.

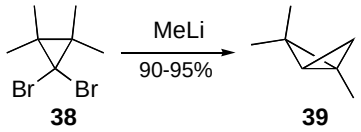


Scheme 9. Tandem synthesis of bicyclo[1.1.0]butane **36**.



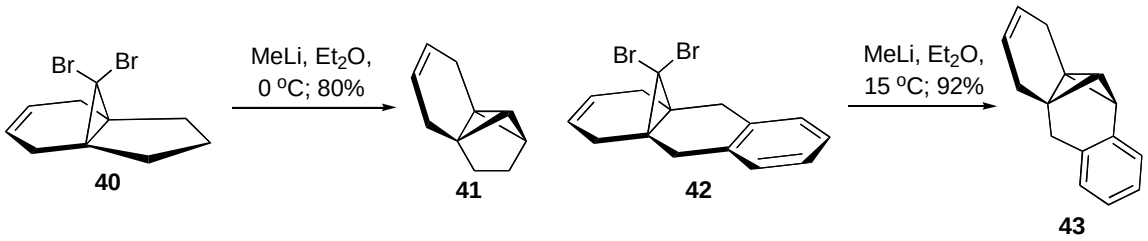
Scheme 10. Synthesis of a bicyclo[1.1.0]butane by an ionic displacement reaction.

However, the most common approach for the construction of the lateral CC linkage in bicyclo[1.1.0]butane involves insertion of cyclopropylidene, generated from *gem*-dibromocyclopropanes, into a CH bond (Scheme 11).[106-108] The carbene approach does not proceed without complications[109] – the second major pathway for these reactions is the opening of cyclopropylidene and formation of an allene.[110] The ratio of bicyclo[1.1.0]butane/allene can be controlled by the use of bulky substituents (i.e. *t*-Bu) that may direct insertion into the CH bond.[111]



Scheme 11. Synthesis of **39** by carbene insertion. [112]

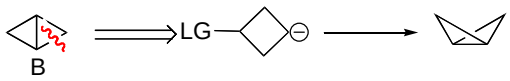
Paquette *et al.*[113] carried out systematic studies on the carbene insertion into CH bonds and found that the proximity of the cyclopropylidene to the CH bond and the nucleophilicity of the later were the factors responsible for the observed selectivity (Scheme 12).



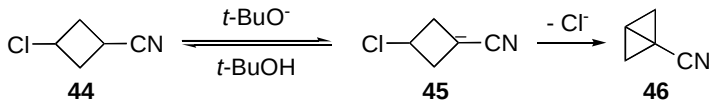
Scheme 12. Insertion reactions of cyclopropylidenes into CH bonds.

Another method for the synthesis of a bicyclo[1.1.0]butane *via* this pathway involves the decomposition of *p*-tosylhydrazone salts in protic solvents.[114-116]

1.1.5.2 Construction of the Central C_1C_3 Bond

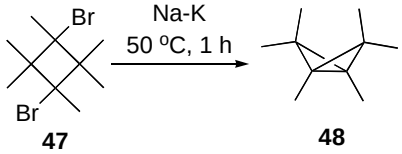


Joining the two bridgehead carbons in bicyclo[1.1.0]butane is one of the most popular methods and is commonly achieved by displacement of a halogen from the activated (CN, RO_2C) cyclobutane derivative (Scheme 13).[117-119] The reversibly formed anion **45**[119] possesses a low barrier of inversion, and it was demonstrated that the subsequent displacement step is stereospecific.[118]



Scheme 13. Synthesis of 1-cyanobicyclo[1.1.0]butane by displacement of Cl^-.

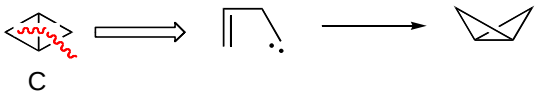
The bridging carbons can also be joined under reductive conditions using the Wurtz-type protocol, as shown in Scheme 14.[120]



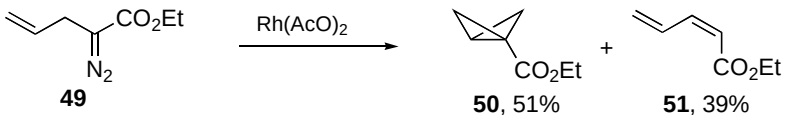
Scheme 14. Würtz coupling of 1,3-dibromocyclobutane.

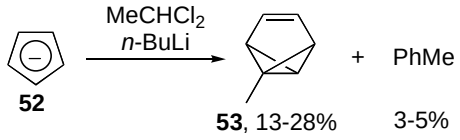
Other methods for the construction of the central bond in bicyclo[1.1.0]butane include a thermal decarboxylation, the reductive coupling of the dithioketones,[121] the pyrolysis of *p*-tosylhydrazone salts of a cyclobutane[122] or the photolysis of diazo compounds.[123,124]

1.1.5.3 Simultaneous Formation of Central and Lateral Bonds



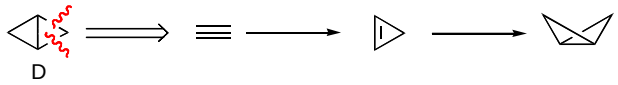
The simultaneous formation of central and lateral bonds is performed by an intramolecular insertion of a carbene into an alkene.[125] Scheme 15 demonstrates typical examples for this transformation.[126,127]



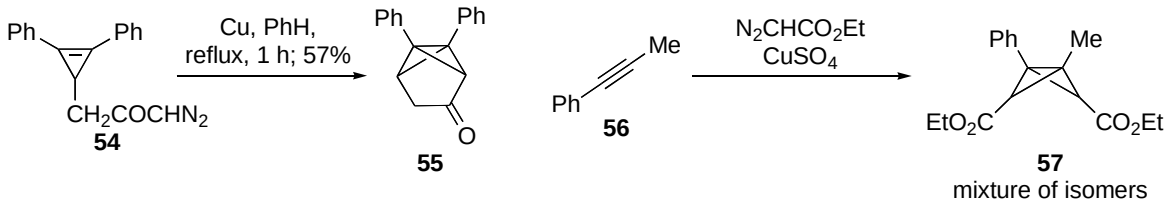


Scheme 15. Carbene additions to alkenes.

1.1.5.4 Addition of Carbene to Cyclopropene



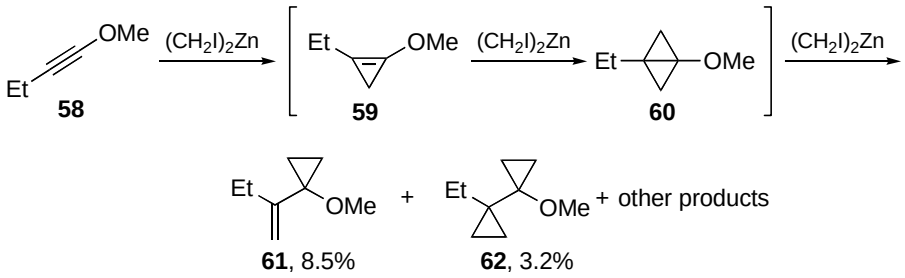
The synthesis of the bicyclo[1.1.0]butane ring *via* addition of a methylene unit offers the widest possibilities to access functionalized bicyclo[1.1.0]butanes. Typically, these transformations involve the addition of a carbene derived from a diazo compound under thermal [128] or UV conditions,[129] as exemplified in Scheme 16. Some highly strained systems have also been prepared *via* decomposition of diazo compounds,[128,130] but this type of reaction is usually not stereospecific and a mixture of *endo*- and *exo*-isomers was obtained for unsymmetrically substituted carbenes.[131]



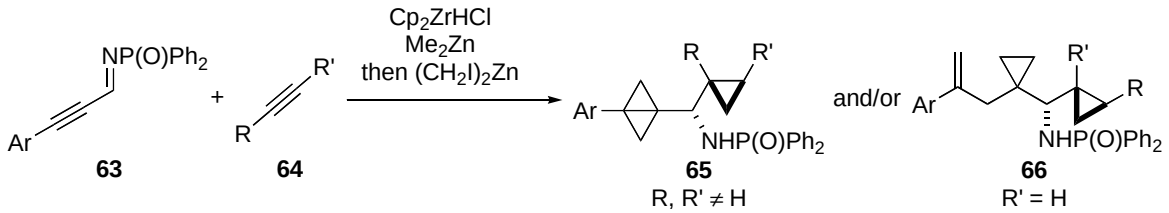
Scheme 16. Synthesis of bicyclo[1.1.0]butanes by double addition to alkynes.

In many cases, a direct addition of two CH_2 units or their synthetic equivalents has proven troublesome, suffering from low yield, and the application of nucleophilic reagents such as

Ph_2SCMe_2 showed little improvement.[132] Although the diazo compounds have been commonly used to close the strained ring, the first example of an application of zinc carbenoids in the addition reaction to a C≡C bond was reported by Schwartz[133] who exposed methyl ynol **58** to a mixture of zinc and diiodomethane and obtained a mixture of mono- and dicyclopropanated products (Scheme 17). The formation of these compounds has been explained by the intermediacy of a bicyclo[1.1.0]butane that subsequently underwent a reaction with the reactive carbenoid species. The potential of these conditions for the synthesis of bicyclo[1.1.0]butanes was explored by Wipf *et al.*[134] who in the course of their studies on imine additions discovered that the CH_2 unit can be delivered to propargyl amides to give bicyclo[1.1.0]butanes **65** or *C,C*-dicyclopropylmethylamines **66** in good yield (Scheme 18). The authors were able to show that the course of the reaction depends on the steric environment at the α-position of the propargyl amide; however, only disubstituted alkynes were able to undergo this transformation efficiently. Isotope-labeling studies using CD_2I_2 revealed that the zinc carbenoid intermediate is responsible for the formation of the bicyclo[1.1.0]butane. To further support the mechanism of the cascade reaction, **65** was resubjected to the mixture of CH_2I_2/Et_2Zn and the rearranged product **66** resulting from incorporation of two additional methylene units was obtained.

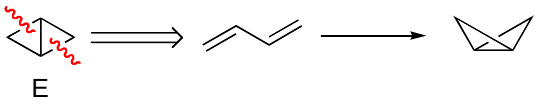


Scheme 17. Reaction of $(CH_2I)_2Zn$ with ynol **58**.

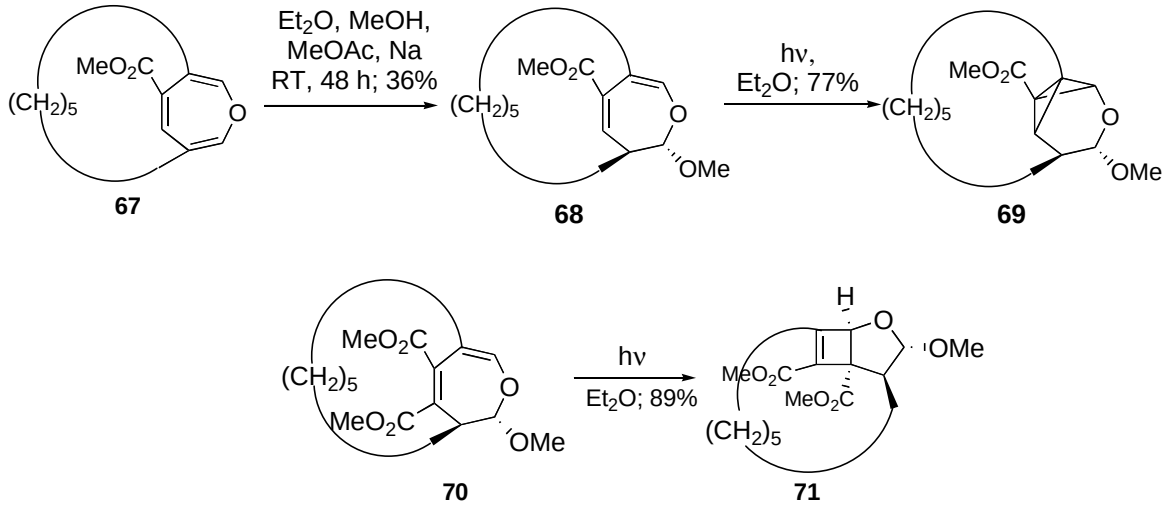


Scheme 18. Cascade synthesis of bicyclo[1.1.0]butanes and *C,C*-dicyclopropylmethylamines by Wipf.[134]

1.1.5.5 Simultaneous Formation of Two Lateral Bonds



The last category of methods for the synthesis of bicyclo[1.1.0]butane involves the simultaneous formation of two lateral bonds from 1,3-dienes *via* a photochemical activation. [135-142] The ratio of bicyclo[1.1.0]butane and the commonly observedcyclobutene in this transformation depends on the substitution of the conjugated diene, and, as confirmed theoretically,[141] the conformation of the 1,3-diene (the preferred conformation is *s-trans*, but the optimal orbital overlap is achieved when the two enes are in a perpendicular arrangement). In a recent application of this approach,[143,144] it was shown that the conjugated, cyclic triene underwent cyclization to afford bicyclo[1.1.0]butane **69**, but, curiously, the cyclic diene **70** afforded only the [2+2] product **71** (Scheme 19).[143]



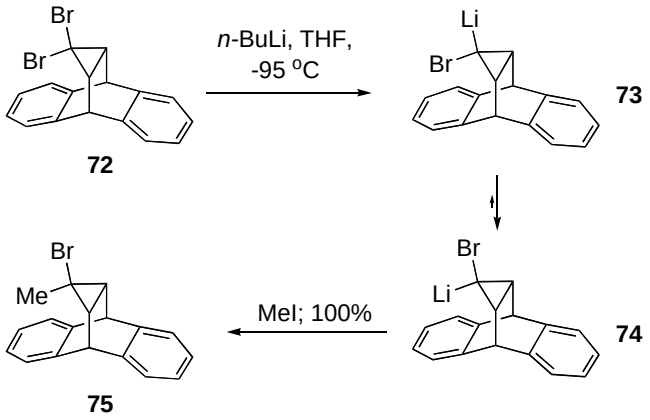
Scheme 19. Photochemical synthesis of bicyclo[1.1.0]butane **69** and cyclobutene **71**.

1.1.6 Halogen-Metal Exchange Reactions

The metal-halogen exchange reaction, discovered by Wittig[145] and Gilman,[146] is one of the most versatile method for selective generation of organometallic derivatives.[147] These reactions are usually performed on bromides and iodides, and only few examples include reactions of *gem*-dichlorocyclopropanes. Lithium is the most common metal applied in these transformations, although a few examples of bromine/sodium and bromine/potassium exchange processes are known. The exchange reactions are typically carried out in a coordinating solvent and only few minutes or seconds are required to reach completion when alkyllithium reagents are used in Et_2O or THF at -75 ^oC. The rapid formation of the organolithium derivative has been used for the formation of functionalized substrates. The mechanism of the reactions with bromide and iodides is postulated to involve an initial attack of a carbanion onto bromine, followed by a collapse of the

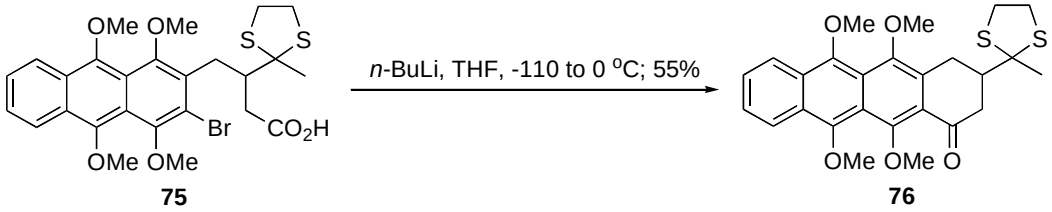
ate complex.[148,149] Other mechanistic schemes (e.g. the SET pathway) may operate in the reactions of alkyl halides.

Formation of organolithium reagents usually takes place under kinetic control as demonstrated by the displacement of a less-sterically hindered halogen in *gem*-dihaloalkenes.[150-152] This intermediate may, however, undergo equilibration to a thermodynamically more stable (*E*)-isomer and this intermediate is subsequently trapped with electrophiles. Similarly to alkenes, exchange reactions of *gem*-dibromocyclopropanes proceed under kinetic control, but these species are not configurationally stable.[153] In the model system **72**, the more-accessible bromide undergoes the exchange reaction first, followed by a fast conversion to **74** and trapping of the thermodynamic intermediate (Li stabilized by the π-ring) leads to **75** in a quantitative yield (Scheme 20). It has been also shown that the organolithium reagents prepared from *gem*-dichlorocyclopropanes[154] as well as Grignard reagents generated from *gem*-dibromocyclopropane[155] do not undergo equilibration.

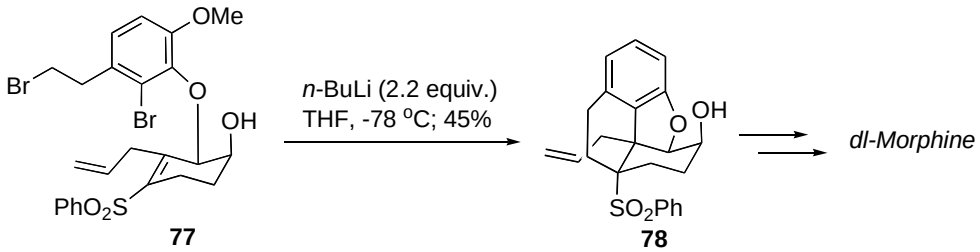


Scheme 20. Methylation of **72** *via* metal-halogen exchange reaction.

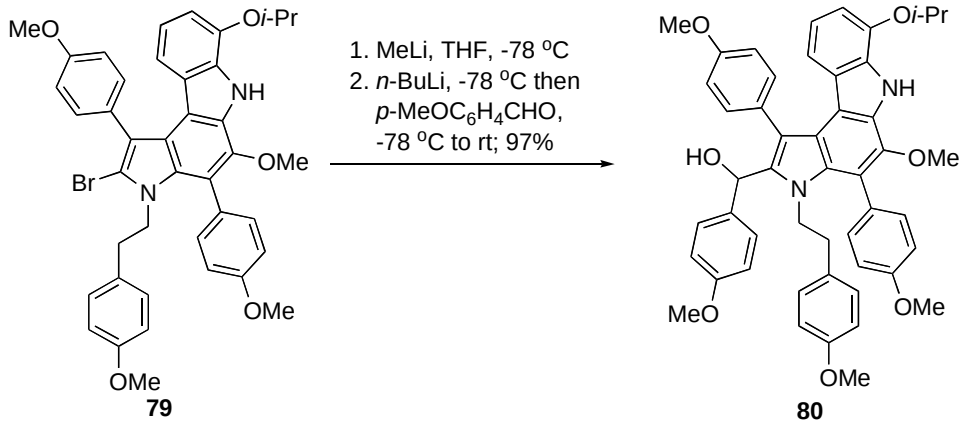
Metal-halogen exchange reactions can be performed on complex organic molecules. Three instructive examples highlighting the utility of these processes include applications in the synthesis of natural products. In the studies towards the anthracycline antibiotic dunomycin, Whithlock *et al.* developed a protocol in which lithium salt of a carboxylic acid **75** acts as an anionic equivalent of a Friedel-Cratfs acylation (Scheme 21).[156] During the total synthesis of *dl*-**(±)**-morphine, Toth and Fuchs demonstrated that a facile exchange reaction with aryl *vs.* alkyl bromide followed by a Michael addition and cyclization led to the tricyclic intermediate **78** in 45% yield (Scheme 22).[157] More recent examples include the initial treatment of **79** with MeLi to remove the acidic N-H proton followed by the treatment with *n*-BuLi and quenching with an aromatic aldehyde to afford **80** in an impressive 97% yield (Scheme 23). This intermediate was taken on further and converted into dictyodendrin B,[158,159] a potent telomerase inhibitor.



Scheme 21. Synthesis of **76**.



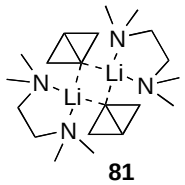
Scheme 22. Preparation of intermediate **78** for the preparation of (±)-morphine.



Scheme 23. Lithium-bromide exchange reaction in the synthesis of dictyodendrin B.

1.1.7 Acidity of Bicyclo[1.1.0]butane

Based on the molecular structure of cyclopropanes, one may suspect that the C-H bond would be characterized by increased acidity as compared to saturated alkanes.[160] The *p*Ka value of cyclopropane estimated using an exchange method by Streitwieser is 46,[161] but this value is variable depending on the substitution around the strained ring. As a consequence of the annelation, the bridged position of bicyclo[1.1.0]butane is expected to be significantly more acidic than in cyclopropanes. Given that the observed $^1J_{CH}$ is 205 Hz (41 % *s*-character), this value may correspond to a pK_a around 36. There is no experimentally determined acidity of bicyclo[1.1.0]butane, but position C1 can be deprotonated using alkyl organolithiums (e.g. *n*-PrLi in Et_2O)[162] and a stable complex of 1-lithiumbicyclo[1.1.0]butane and TMEDA has been characterized by X-ray analysis (Figure 6).[163] This complex exists in a dimeric form and the bridging lithium atoms are oriented in a tetrahedral arrangement of nitrogen and carbon ligands.



81

Figure 6. Lithiumbicyclo[1.1.0]butane-TMEDA complex **81**.

Numerous derivatives of bicyclo[1.1.0]butanes have been converted into the corresponding organolithiums and subsequently quenched with electrophiles. Representative examples include tricyclo[4.1.0.0^{2,7}]heptane,[125,164-168] tricyclo[3.1.0.0^{2,6}]hexane,[125,164,169] tricyclo[2.1.0.0^{2,5}]pentane,[125,164] and benzvalene.[170] Additionally, some ill-characterized complexes of bicyclo[1.1.0]butane with magnesium,[171] metalloids (Sn), and transition metals (for example, silver[33]) have been reported; but the stability as well as the detailed structure of these compounds are not known.

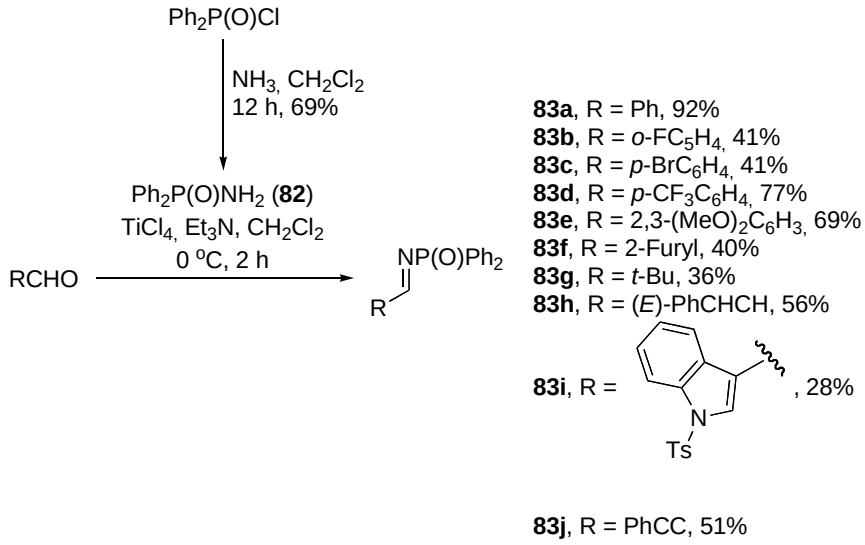
A modification of the synthesis of bicyclo[1.1.0]butyllithium was reported by Brinker who developed a simple protocol for the cyclization from *gem*-dibromocyclopropane followed by a second exchange reaction with *t*-BuLi.[104] This methodology is the most versatile method for the synthesis of bicyclo[1.1.0]butanes to date.

1.2 RESULTS AND DISCUSSION

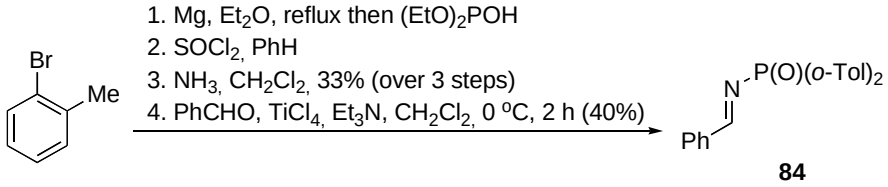
1.2.1 Synthesis of Imines

Addition of a nucleophilic reagent to an activated imine is a convenient method for the synthesis of amines.[172] We anticipated that bicyclo[1.1.0]butylmethylamines derived from the corresponding imines can be interesting synthetic building blocks and valuable substrates for further elaborations. To access this type of compounds, three different methods for the synthesis have been studied which all rely on the nucleophilic addition of the corresponding organometallic reagent to imines.

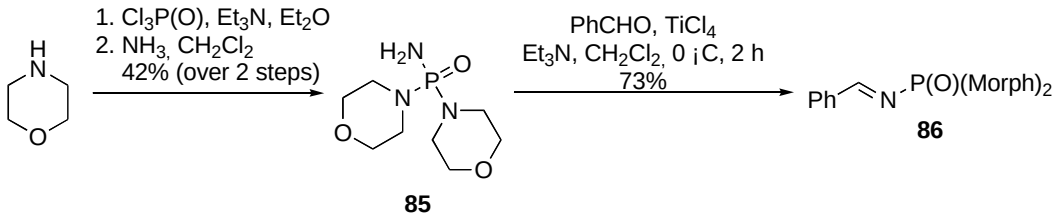
For the systematic studies of the scope of the synthesis of bicyclo[1.1.0]butanes, numerous imines with varying electronic and steric properties have been prepared. We were particularly interested in using *P*,*P*-diphenylphosphinamides[173] as practical nitrogen protecting groups, due to the mild acidic conditions used for their removal and the convenient methods for their preparation. Imines derived from non-enolizable aldehydes were prepared according to a published protocol[88] involving the condensation of the aldehyde with diphenylphosphinamide in the presence of $TiCl_4$ and Et_3N (Scheme 24). In some cases (i.e. **83c**), the low yield was attributed to the instability of the product during the isolation process.



Scheme 24. Synthesis of *P,P*-diphenylphosphinyl imines **83**.



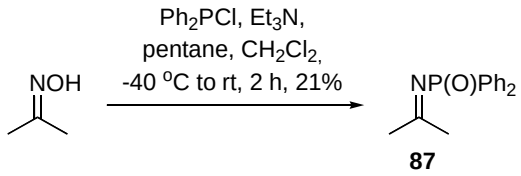
Scheme 25. Synthesis of imine **84**.



Scheme 26. Synthesis of imine **86**.

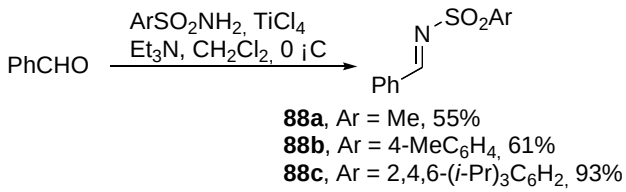
Sterically hindered imine **84**[174] was obtained from 2-bromotoluene by a sequence of reactions depicted in Scheme 25 involving addition of the Grignard reagent to diethyphosphite, chlo-

rination with $SOCl_2$ and reaction with ammonia.The desired amide was later reacted with benzaldehyde to afford **84**. The novel imine **86**[175] was prepared from PhCHO and triamide **35** was obtained from morpholine by a series of reactions shown in Scheme 26. The imine derived from acetone was prepared from the corresponding oxime that was subsequently treated with diphenylchlorophosphine at -40 ^oC in the presence of Et_3N.[176,177] The reaction mixture was slowly warmed to rt, allowing the radical rearrangement[178] to take place to give **87** (Scheme 27).

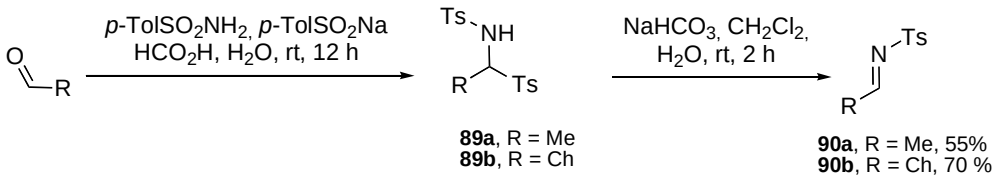


Scheme 27. Synthesis of imine **87**.

Sulfonyl based imines (**88a**,[179] **88b**,[179] **88c**[180]) were prepared by a similar method using the corresponding amides and benzaldehyde (Scheme 28). However, aldimines possessing α-protons were prepared *via* condensation of cyclohexane carboxaldehyde with *p*-$TolSO_2NH_2$ in the presence of *p*-$TolSO_2Na$. The resulting adducts **89** were stirred with a saturated solution of $NaHCO_3$ to afford **90** (Scheme 29).[181]



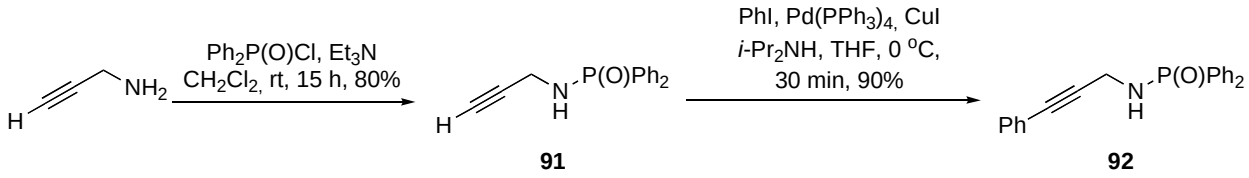
Scheme 28. Synthesis of sulfonimines **88a-c**.



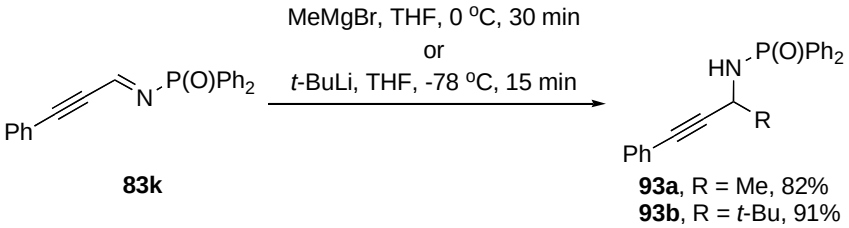
Scheme 29. Synthesis of imines **90**.

1.2.2 Synthesis of Bicyclo[1.1.0]butane via Double Carbene Addition

Previous studies[134] in the Wipf group demonstrated the potential of a reaction of propargyl amides with zinc carbenoids for the synthesis of bicyclo[1.1.0]butanes, but it was also noted that only sterically hindered amides gave rise to isolated bicyclo[1.1.0]butane derivatives. To test the scope of this methodology, propargyl amides with different groups in the α-position were prepared. Propargyl amine was reacted with *P,P*-diphenylphosphinyl chloride followed by coupling with iodobenzene to give **92**. Amides **93a** and **93b** were prepared by the addition of the corresponding Grignard or lithium reagent to **83k**. Amide **94** was prepared by addition of phenylacetylene to imine **83a** (Schemes 30-32).



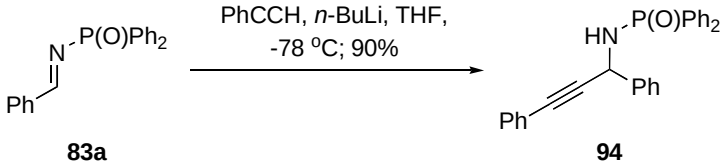
Scheme 30. Synthesis of amide **92**.



83k

93a, R = Me, 82%
93b, R = *t*-Bu, 91%

Scheme 31. Synthesis of amides **93**.



83a **94**

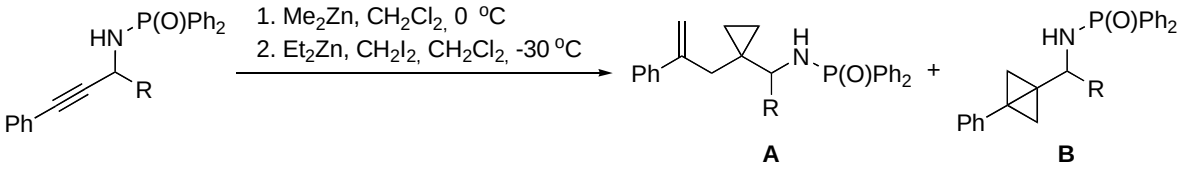
Scheme 32. Synthesis of amide **94**.

Amides **92-94** were treated with 1 eq of Me_2Zn at 0 °C, and after stirring for 1 h the solution was cooled to -30 °C and transferred *via* cannula into the cold (-30 °C) solution of $(CH_2I)_2Zn$ in CH_2Cl_2. In each case, the reaction mixture was allowed to warm to 0 °C and no reaction was observed at temperatures below -10 °C. Table 3 summarizes the results of this study. In the case of **92** and **93a**, the only detected products for this reaction were the rearranged derivatives **95** and **96**. For **94**, almost equimolar amounts of **97** and **98** were isolated. In contrast, **93b** was recovered from the reaction mixture (Table 3).

In order to test the effect of the terminal substitution at the alkyne moiety, several derivatives were studied. Reaction of imine **83a** with terminal alkynes in the presence of *n*-BuLi led to formation of amides **99a-c** (Scheme 33). These compounds were subjected to the standard cyclopropanation conditions: treatment with Me_2Zn followed by addition of an excess of $(CH_2I)_2Zn$.

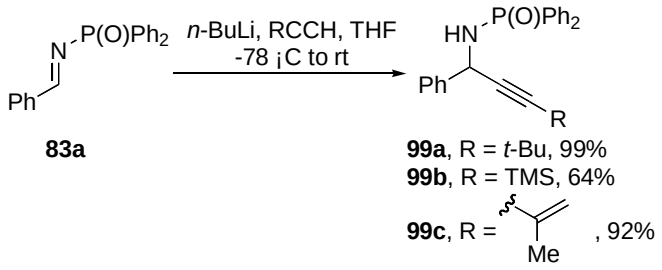
None of these cases resulted in a clean reaction. Instead, side products were observed, and in the case of the bulky *t*-Bu group only starting material was recovered.

Table 3. Reactions of α-substituted propargyl amides with $(CH_2I)_2Zn$ in CH_2Cl_2.



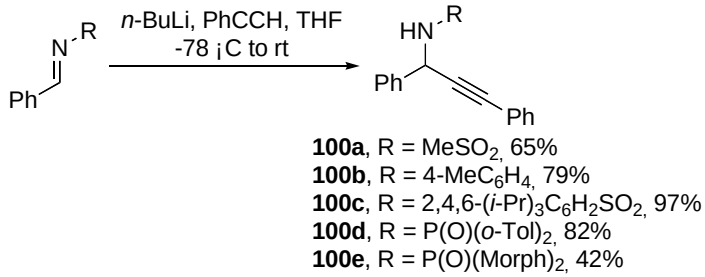
A **B**

Entry	R	A	B
1	H	64% (**95**)	-
2	Me	85% (**96**)	-
3	*t*-Bu	No Reaction	
4	Ph	29% (**97**)	30% (**98**)



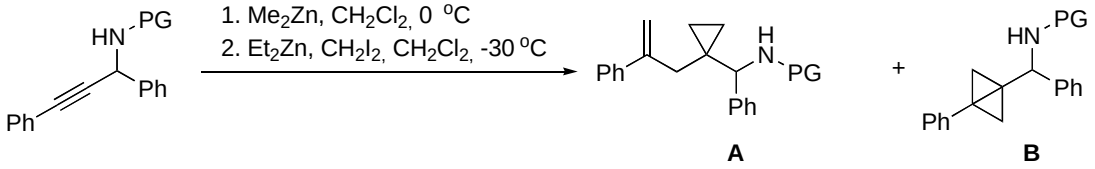
Scheme 33. Synthesis of terminally substituted propargyl amides **99**.

These initial results demonstrated the importance of the steric environment at the propargylic position and the need for conjugation of the alkyne to an aromatic group. For further studies on the synthesis of bicyclo[1.1.0]butanes, the 1,3-diphenylpropargyl amine scaffold was selected, and protecting groups with different steric and electronic properties were chosen. Scheme 34 depicts the synthesis of the substrates. Addition of phenylacetylene to imines afforded the desired amides **100a-e** in very good yields.



Scheme 34. Synthesis of amides **100**.

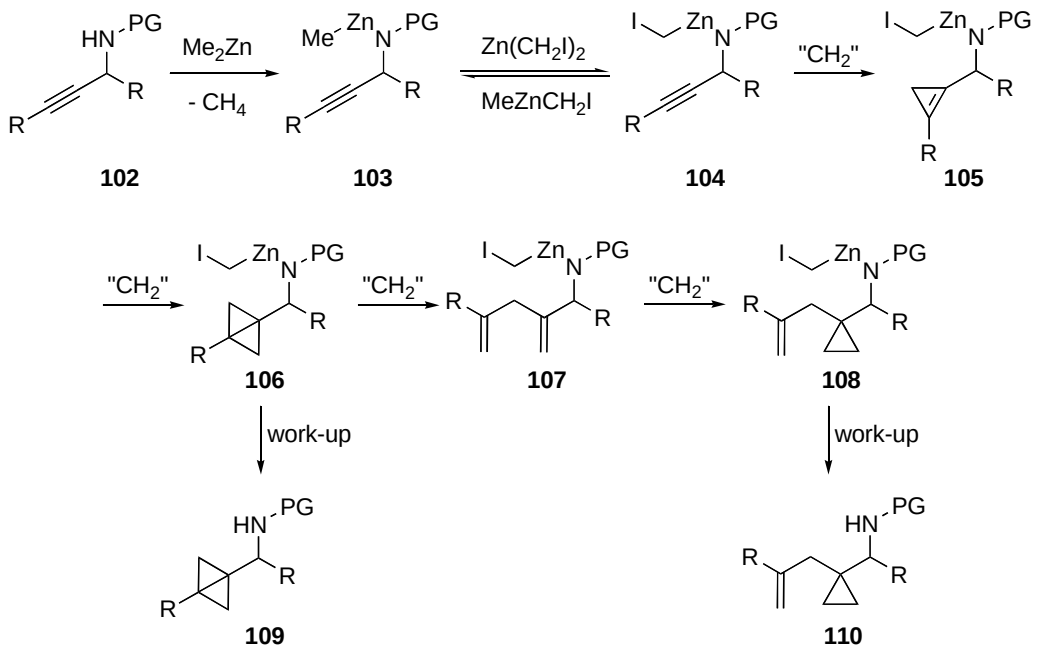
Table 4. Reactions of propargyl amides with $(CH_2I)_2Zn$.



Entry	PG	A	B
1	Ms	51% (**101a**)	-
2	Ts	26% (**101b**)	-
3	Tris	63% (**101c**)	-
4	(*o*-Tol)$_2$P(O)	-	<5%
5	(*N*-Morph)$_2$P(O)	No reaction	
6	Cbz	No reaction	

All sulfonamides (entry 1-3) gave only rearranged product (Table 4). Efforts to stop the reaction at the stage of the intermediate bicyclo[1.1.0]butane were unsuccessful: reducing the loading of zinc carbenoid or lowering the reaction temperature resulted in the recovery of the starting material together with small amounts of **101**. However, slow warming revealed that the reaction started around -5 ^{o}C. Furthermore, the more sterically demanding di(*o*-toluyl)phosphinamide **100d** was resistant to these conditions.

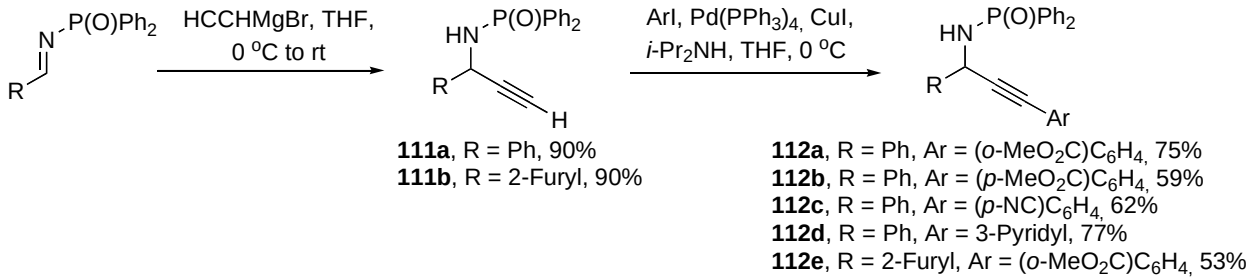
The mechanism for the formation of cyclopropylbenzylamides **110** from propargyl amides **102** is depicted in Scheme 35. Deprotonation of amide **102** results in the formation of the intermediate **103** which is possibly in an equilibrium with the bis(iodomethyl)zinc reagent to give **104**. The removal of the proton and the formation of the anionic nitrogen is an important step for this transformation: attempts to react propargyl amides with an excess of Furukawa reagent without removal of the N-H with Me_2Zn or using strong Lewis acid ($BF_3{\cdot}Et_2O$) as a promoter resulted only in recovery of the starting material. Subsequent intramolecular delivery of the carbenoid unit results in the formation of the cyclopropene derivative **105** that undergoes further addition of CH_2, and, in the case of small substituents in the α-position, bicyclo[1.1.0]butane **106** reacts with two additional carbene molecules. In the course of these studies we were not able to isolate the protonated derivative **105**. Possibly, the first addition of CH_2 is the slowest step in the overall sequence.



Scheme 35. Mechanism of the synthesis of **109** and **110** from amides **102**.

Based on these results, we decided to utilize the *P,P*-diphenylphosphinyl group as a suitable protecting moiety, and, because of their simplicity of preparation, use aryl substituents in the α-position. Propargyl amide **112b** was used as a model substrate for the further optimization of the reaction conditions (Scheme 36 and Table 5). Although the conditions in entry 2 seemed to be optimal for the synthesis of bicyclo[1.1.0]butane **113**, efforts to reproduce these results on a larger scale (1-2 mmol) were not successful. In many cases, the reaction proceeded to the rearranged product or simply gave a very low yield of bicyclo[1.1.0]butane combined with a substantial amount of the starting material. In order to alleviate this problem, we decided to reduce the loading of $(CH_2I)_2Zn$ and form the carbenoid species at a lower temperature (-50 ^oC). The aging time required for the formation of the carbenoid reagent was also shortened (no more than 10 min), possibly resulting in a higher overall concentration of $(CH_2I)_2Zn$ in solution. We no-

ticed also that in order to obtain the best yields, the reaction had to be stopped after a substantially shorter time.

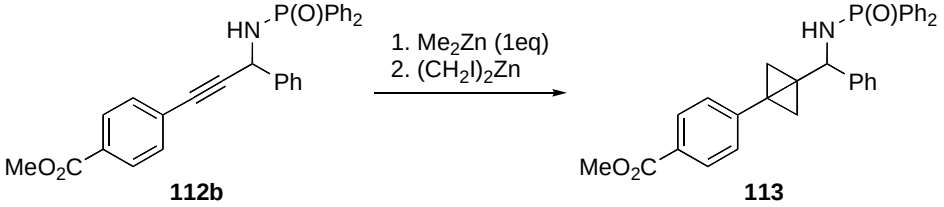


111a, R = Ph, 90%
111b, R = 2-Furyl, 90%

112a, R = Ph, Ar = (*o*-MeO_2C)C_6H_4, 75%
112b, R = Ph, Ar = (*p*-MeO_2C)C_6H_4, 59%
112c, R = Ph, Ar = (*p*-NC)C_6H_4, 62%
112d, R = Ph, Ar = 3-Pyridyl, 77%
112e, R = 2-Furyl, Ar = (*o*-MeO_2C)C_6H_4, 53%

Scheme 36. Synthesis of propargyl amides **112**.

Table 5. Optimization of reaction conditions for double addition of $(CH_2I)_2Zn$ to **112b**.



112b **113**

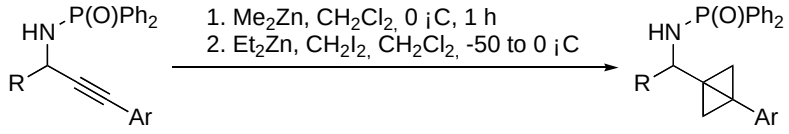
Entry	Equiv. of $(CH_2I)_2Zn$	Solvent	Temperature/Time	Yield
1	2.5	$(CH_2Cl)_2$, DME	-30 to 0 °C	30%
2	2.5	CH_2Cl_2	-30 to 0 °C	52%
3	1.13	CH_2Cl_2	-30 to 0 °C	37%
4	2	CH_2Cl_2	-50 to 0 °C	42%

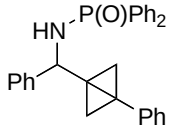
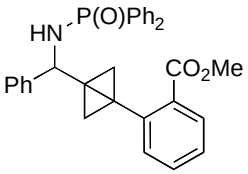
After establishing a reliable method for the construction of bicyclo[1.1.0]butane **113**, we decided to explore the scope of this transformation. Scheme 35 depicts the synthesis of the substrates. Addition of ethynylmagnesium bromide to imines gave amides **111** in very good yields. Sonogashira coupling of **111** with the corresponding aromatic iodides proceeded also smoothly to furnish amides **112**. It is worth noting that when the reaction was performed on a multigram

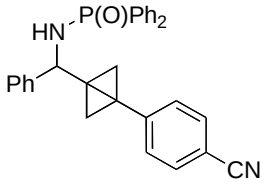
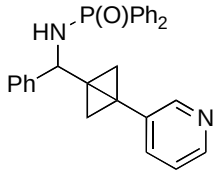
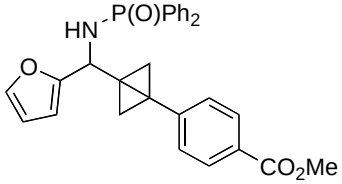
scale, mechanical stirring was required to assure efficient mixing (large amounts of precipitate were formed).

Table 6 summarizes the scope of the synthesis of bicyclo[1.1.0]butane derivatives *via* the directed double addition of zinc carbenoids under the optimized conditions. The yields of these transformations ranged from modest to good, and the remainder of the mass balance was either unreacted starting material or small amounts of rearranged cyclopropylbenzylamides of type **110**. Each reaction had to be optimized individually in order to obtain the best yields and the reaction time and control of temperature seemed to be crucial. Carrying out the reactions for an extended period of time resulted in the formation of substantial amounts of rearranged product with the sole exception of substrate **112d**, which, in order to obtain a reasonable yield, had to be treated with $(CH_2I)_2Zn$ for 14 h. The substantial slowdown of the reaction could be explained by a strong coordination of zinc to the pyridyl nitrogen that competed with the desired transformation.

Table 6. Scope of the synthesis of bicyclo[1.1.0]butanes *via* double carbene addition.



Entry	Substrate	Product	Yield
1	**43**	 **98**	21%
2	**112b**	 **114a**	56%

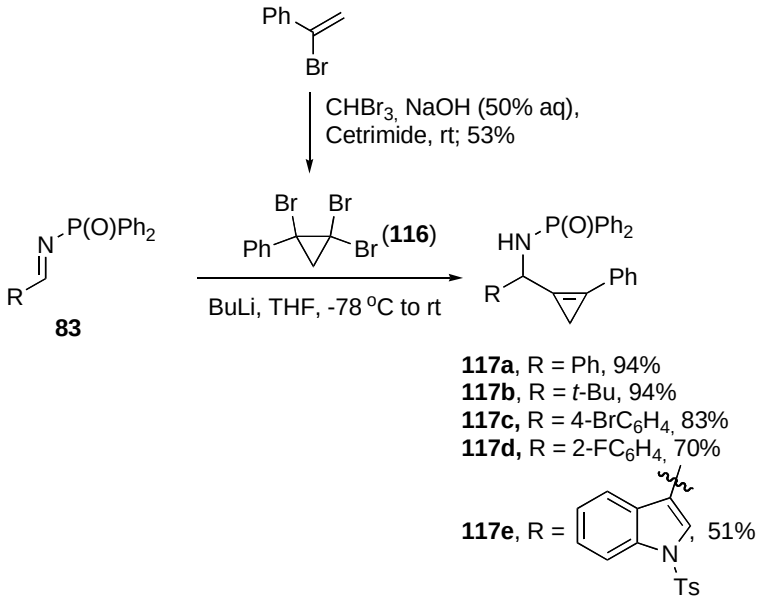
3	**112c**	 **114b**	35%
4	**112d**	 **114c**	40%
5	**112e**	 **114d**	40%

1.2.3 Synthesis of Bicyclo[1.1.0]butanes by Carbene Additions to Cyclopropenes

The direct addition of zinc carbenoid to the propargyl amides suffered from serious limitations due to the formation of the rearranged products **110**. An excess of carbene was required to initiate the reaction sequence, and careful control of the conditions was necessary in order to obtain reproducible yields. In the course of our studies, it was not possible to isolate the putative cyclopropene intermediates **105** or diene **107** (Scheme 35), possibly because the first addition step to propargyl amides was slow whereas the subsequent CC bond forming reactions were much more facile. Based on this observation, we reasoned that the amide-directed addition of carbene to cyclopropene derivative **105** may provide an efficient method for the synthesis of bicyclo[1.1.0]butanes. Earlier examples of the construction of bicyclo[1.1.0]butane by addition to

cyclopropene were carried out by decomposition of diazo compounds, but the yields of the latter transformation were notoriously low.[129]

Cyclopropenyl amides **117** can be prepared from the lithium reagent generated from 1-bromocyclopropene. Treatment of 1,2,2-tribromo-1-phenylcyclopropane (obtained from α-bromostyrene) with two equivalents of *n*-BuLi at -78 °C followed by addition of imines **83** furnished products **117** in good yields (Scheme 37).

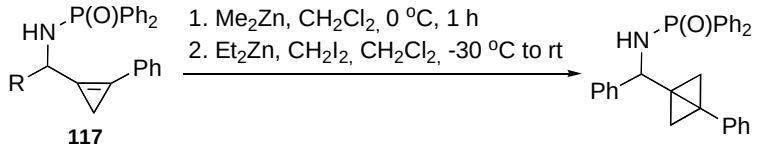


Scheme 37. Synthesis of cyclopropenyl amides **117**.

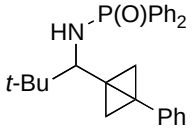
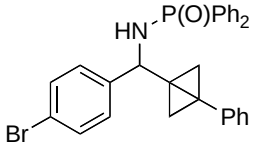
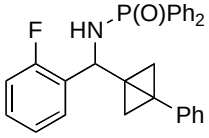
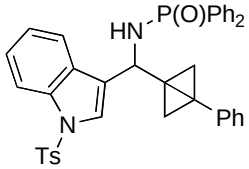
Amides **117** were subsequently treated with a solution of Me_2Zn followed by addition of a mixture of CH_2I_2/Et_2Zn. The reaction proceeded smoothly when one equivalent of $(CH_2I)_2Zn$ was employed. In case of more elaborate substrates. In order to activate the addition step, an excess (2.5 equiv.) of cyclopropanating reagent had to be used. As in the case of the double addi-

tion protocol, sterically demanding groups located in the α-position blocked the delivery of carbenoid to the cyclopropene ring (Table 7).

Table 7. Scope of the synthesis of bicyclo[1.1.0]butanes *via* addition to cyclopropenes.

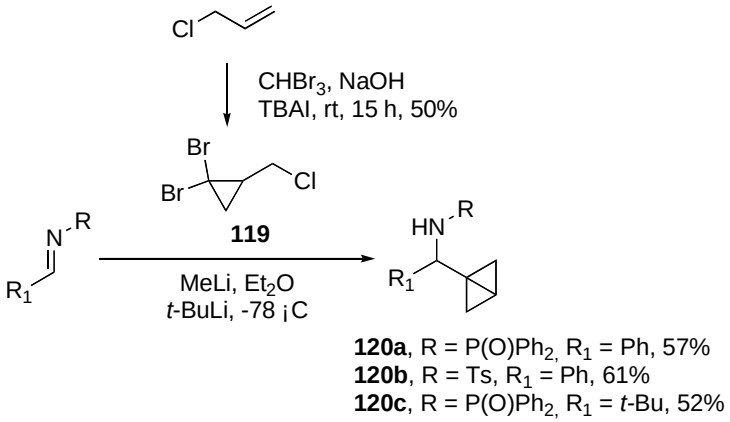


117

Entry	Substrate	Product	Yield
1	**117a**	**98**	46%
2	**117b**	 **118a**	N.R.
3	**117c**	 **118b**	19%
4	**117d**	 **118c**	31%
5	**117e**	 **118d**	40%

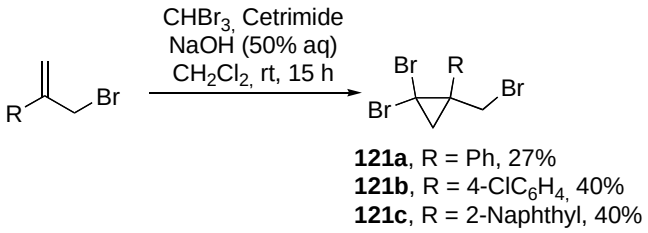
1.2.4 Synthesis of Bicyclo[1.1.0]butane by Addition of Bicyclo[1.1.0]butyllithium

The two previous methods for the synthesis of functionalized bicyclo[1.1.0]butanes are restricted to substrates that possess groups compatible with Simmons-Smith conditions. Also, sterically hindered bicyclo[1.1.0]butanes could not be accessed *via* a directed mono- or double carbenoid addition. To overcome this problem, we decidemd to explore a third route for the synthesis of bicyclo[1.1.0]butanes. The strategy in this approach was based on a well established lithium-bromide exchange phenomenon that is especially facile for bromine atoms attached to carbons having high *s*-character. This type of reaction has been documented for 1-bromobicyclo[1.1.0]butane.[104] Although a few methods for the synthesis of 1-bromobicyclo[1.1.0]butane have been reported,[182] we envisioned that its high instability and susceptibility to the acidic conditions could be problematic. In order to avoid potential stability problems, we decided to perform a one-pot 1-bromobicyclo[1.1.0]butane formation and lithium-halogen exchange process. 2,2-Dibromo-1-(chloromethyl)cyclopropane **119** was used as the model substrate for the direct synthesis. Following the literature protocol,[183] **119** was obtained as a colorless oil from allyl chloride. Treatment of **119** with one equivalent of MeLi at -78 ^{o}C followed by warming to -50 ^{o}C resulted in the synthesis of 1-bromobicyclo[1.1.0]butane. The reaction mixture was then cooled to -78 ^{o}C and treated with *t*-BuLi, followed by the addition of a solution of imine **83a** or **83b** to afford **120a** and **120b** in 57% and 61% yield, respectively (Scheme 38).



Scheme 38. Synthesis of monosubstituted bicyclo[1.1.0]butanes **120**.

After demonstrating the feasibility of this approach, we turned our attention to the synthesis of 3-substituted bicyclo[1.1.0]butylbenzylamides, since activated bicyclo[1.1.0]butanes are suitable substrates for the ene reaction (*vide infra*). In order to reduce a possible risk for carbene rearrangement that might result in the formation of an allene, bromine instead of chlorine was used as a leaving group.

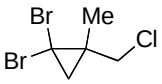
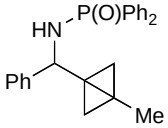
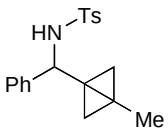


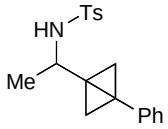
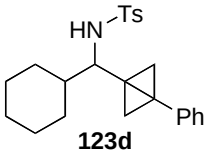
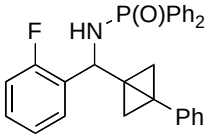
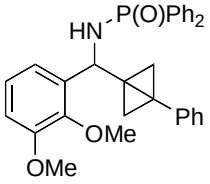
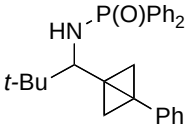
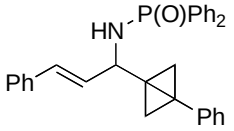
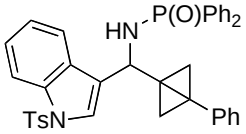
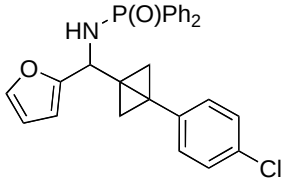
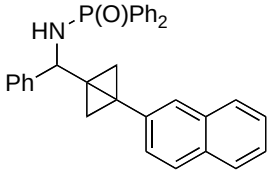
Scheme 39. Synthesis of tribromocyclopropanes **121**.

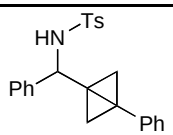
Reaction of α-bromomethylstyrene,[184] 2-(4-chlorophenyl)allyl bromide, and 2-(2-naphthyl)allyl bromide with $CHBr_3$ (Scheme 39) under the standard phase-transfer conditions afforded the desired compounds in modest yields. Due to the low polarity of these compounds,

alternative pathway developed for the synthesis of **121** involves a protection/deprotection strategy using the THP group and α-hydroxymethylstyrene. Similarly, 1,1-dibromo-2-(chloromethyl)-2-methylcyclopropane (**122**) was obtained under the same reaction conditions as a colorless oil in 78% yield. Application of the same approach as for the synthesis of **86** afforded substituted bicyclo[1.1.0]butanes in good yields (Table 8). Sterically hindered (entry 8) and unsaturated (entry 9) bicyclo[1.1.0]butanes could also be obtained *via* direct addition to imines. Addition of the anion of bicyclo[1.1.0]butane proceed smoothly also for various heterocycles. It is important to note that the purification process was simpler compared to the directed addition protocols using zinc carbenoids. Usually, a small excess (2-5 equiv.) of the *gem*-dibromocyclopropane was used to assure a full conversion of the imines into amide (less than 2 equiv. leads to incomplete consumption). For the reactions using cyclopropanes **121a-c**, a competitive addition of MeLi to imines was not observed, as may be expect based on the influence of the stabilizing group on the acidity (equilibrium) between methyl and bicyclo[1.1.0]butyl anions.

Table 8. Synthesis of bicyclo[1.1.0]butanes *via* direct addition of bicyclo[1.1.0]butyllithium to imines.

Entry	Imine	*gem*-Dibromocyclopropane	Bicyclo[1.1.0]butane	Yield
1	**83a**	 **122**	 **123a**	62%
2	**88a**	**122**	 **123b**	24%
3	**83a**	**121a**	**98**	73%

4	**90a**	**121a**	 **123c**	60%
5	**90b**	**121a**	 **123d**	75%
6	**83b**	**121a**	 **118c**	71%
7	**83e**	**121a**	 **123e**	65%
8	**83g**	**121a**	 **118a**	71%
9	**83h**	**121a**	 **123f**	95%
10	**83i**	**121a**	 **123g**	77%
11	**83f**	**121b**	 **123h**	67%
12	**83a**	**121c**	 **123i**	82%

13	**88a**	**121a**	 **123j**	59%

The synthesis of bicyclo[1.1.0]butanes was also extended to trapping reactions with carbonyl electrophiles. Some representative examples are shown in Table 9. It is important to note that the alcohols derived from addition to aldehydes were purified by high-vacuum distillation and that the major impurity observed in these reactions was the MeLi addition product. Efforts to purify these compounds on SiO_2 led to decomposition whereas the use of neutral alumina led to significantly lower yields. In contrast, esters and ketones are stable to column chromatography and they can be safely stored at -30 ^{o}C with a small amount of radical inhibitor (BHT) to prevent polymerization. Some of the bicyclo[1.1.0]butyl derivatives are crystalline solids, and the X-ray structure of **125c** and **126** are depicted in Figures 7 and 8, respectively.

In order to facilitate the synthesis of bicyclo[1.1.0]butanes, it was anticipated that other organometallic derivatives may provide a convenient alternative to lithium reagents. To this end, trapping of *in situ* generated bicyclo[1.1.0]butyllihium with $MgBr_2 \cdot Et_2O$ led only to decomposition. Efforts to transmetallate bicyclo[1.1.0]butylithium to zinc ($ZnCl_2$) or copper ($CuBr \cdot DMS$) reagents led only to isomerization to cyclobutenyl anion which subsequently was trapped with the electrophile (*P*,*P*-diphenylphosphinyl imine). However, it was found that other electrophiles such as *n*-Bu_3SnCl and esters of boronic acid are suitable reagents for the synthesis of these building blocks (Scheme 40). Organostannanes **128** can be purified by distillation under reduced pressure, but they undergo instantaneous decomposition on purification on SiO_2 or neutral alumina with hexane as an eluent. Compounds **128** are also air- and moisture stable but can be stored at ambient conditions for at least 2 weeks.

Table 9. Trapping of bicyclo[1.1.0]butyllithium with carbonyl electrophiles.

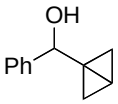
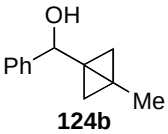
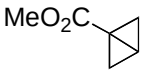
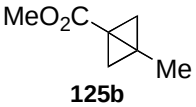
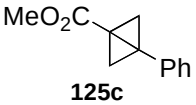
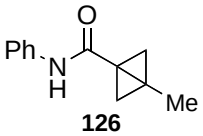
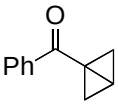
Entry	*gem*-Dibromocyclopropane	Electrophile	Product	Yield
1	**119**	PhCHO	 **124a**	68%
2	**122**	PhCHO	 **124b**	80%
3	**119**	MeO_2CCl	 **125a**	25%
4	**120**	MeO_2CCl	 **125b**	54%
5	**121a**	MeO_2CCN	 **125c**	26%
6	**119**	PhNCO	 **126**	74%
7	**119**	PhCOCl	 **127**	24%

Figure 7. X-ray structure of ester **125c**.

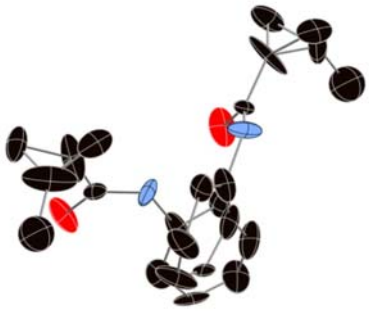
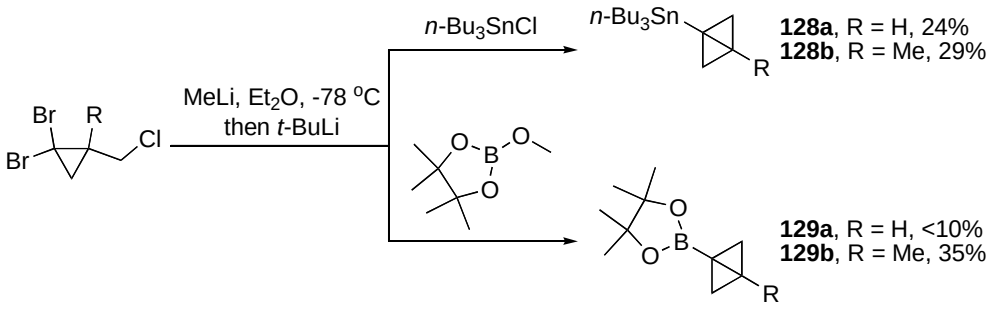


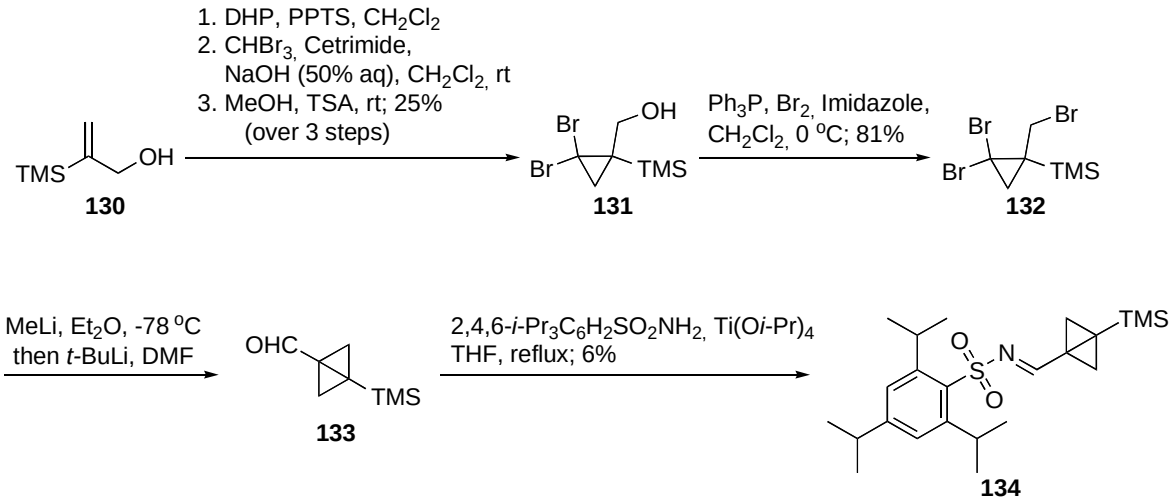
Figure 8. X-ray structure of amide **126**.



Scheme 40. Synthesis of tin and boron derivatives of bicyclo[1.1.0]butane.

Further studies were focused on development of reagents that could be used in reactions when the addition of bicyclo[1.1.0]butyllithium was not feasible. Because of the possible applications of bicyclo[1.1.0]butanes in the synthesis, the monosubstituted derivative was selected as the most useful subclass. However, the aldehyde derivative was not stable to typical synthetic manipulations and the terminal position of bicyclo[1.1.0]butane was protected by the TMS group in order to increase the stability of the aldehyde. TMS-substituted cyclopropane **132** was obtained *via* a standard protocol starting from alcohol **130** (Scheme 41) and was converted into aldehyde followed by reactions with the hindered sulfonamide to give imine **134**. This crystalline

solid is a stable example for a bicyclo[1.1.0]butyl acceptor, potentially useful in the nucleophilic addition reactions.



Scheme 41. Synthesis of imine **134**.

1.2.5 Synthesis of Enantiomerically Enriched Bicyclo[1.1.0]butanes

In the course of our studies on the synthesis of bicyclo[1.1.0]butanes, it was deemed necessary to explore routes to enantiomerically pure bicyclo[1.1.0]butyl amides. These precursors are potentially valuable building blocks in the synthesis of complex organic molecules. The double carbene addition to enantiomerically pure propargyl amides is a feasible strategy to assemble enantioenriched bicyclo[1.1.0]butanes, but this approach is limited to reactions with conjugated alkynes. Alternative methods are enantioselective additions to imines as well as diastereoselective addition to imines attached to a chiral auxiliary.

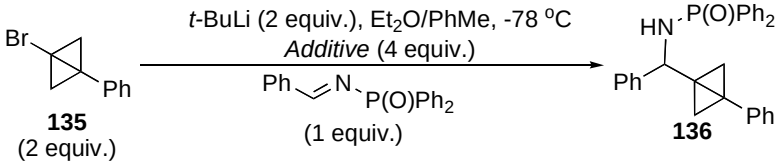
1.2.5.1 Enantioselective Addition

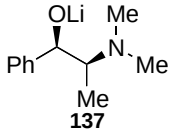
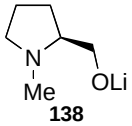
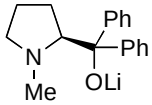
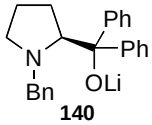
Many methodologies for the enantioselective addition of organolithium reagents rely on the use of electron-rich imines (e.g. PMP substituted) in the presence of catalytic amounts of a chiral ligand.[185] However, the steric hindrace of the bicyclo[1.1.0]butyl group in addition to the long reaction times required for the addition to deactivated imines may lead to the decomposition of the organolithium species and the low reaction yield. We further anticipated that electron-poor imines may serve as suitable precursors for the enantioselective addition of organolithium reagents. However, this approach would require the use of stoichiometric amounts of a chiral additive in order to achieve products in enantioenriched form. Tribromide **121a** was reacted with MeLi followed by *t*-BuLi, and this mixture was then treated with an appropriate chiral additive. It was found that only a minimal level of induction was observed if chiral aminoalcohols or amines were used. We speculated that the presence of the lithium salt in the reaction mixture may be responsible for the accelerated addition of the bicyclo[1.1.0]butyl anion to imine. Although 1-bromobicyclo[1.1.0]butane is a low boiling liquid, this reagent is not practical for the addition reactions, and we selected 1-bromo-3-phenylbicyclo[1.1.0]butane as a suitable substrate for the transmetallation-addition reactions. After the halogen-lithium exchange reaction with *t*-BuLi was complete, the resultant bicyclo[1.1.0]butyllithium reagent was treated with the corresponding chiral additive (2 equiv.), stirred at -78 ^{o}C for 10 min, and a solution of imine **83a** was added over 10 min at -78 ^{o}C (Table 10). The crude mixture was quenched with EtOAc, purified, and analyzed by HPLC (Chiracel AD-H, Hex:*i*-PrOH 9:1, 1 mL/min, t = 13.8 min and 18.2 min).

It was found that the proline-derived additives gave the most promising results. However, the yields of these reactions were usually low and very dependent on the ligand used as well as on the batch of bromobicyclo[1.1.0]butane. Although additive **139** gave the best results, the

yields in these reactions were inversely proportional to the level of stereoinduction. Spareteine, in contrast, was found to give low but consistent yields and *ee*. Due to the low reproducibility, these studies on the enenatioselective addition reactions were abandoned.

Table 10. Enantioselective addition of bicyclo[1.1.0]butyllithium to *P,P*-diphenylphosphinyl imine **83a**.



Entry	Additive[a]	Yield	*ee*
1	 **137**	<5 %	ND
2	 **138**	14%	25%
3	 **139**	21-59%	5-78%
4	 **140**	56%	4%
5[b]	(-)-sparteine	54%	16%
6	(-)-sparteine	60%	27%

[a]The corresponding lithium salts were generated by treatment of the ligands with MeLi or *t*-BuLi at -78 °C prior to addition to organolithium reagent. [b]4 equiv. of *t*-BuLi were used.

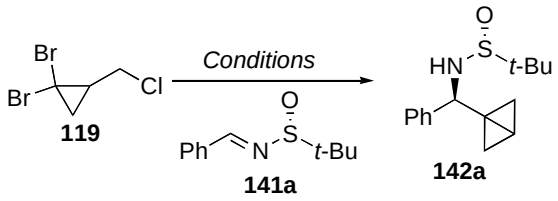
1.2.5.2 Diastereoselective Addition to Sulfinyl Imines

In order to access non-racemic bicyclo[1.1.0]butyl amines, we explored diastereoselective addition reactions. Due to practicality, chiral sulfinyl imines developed by Ellman[186] were

used. However, this type of imines were shown to provide their best *dr* for reactions with Grignard reagents or if transition metals or additives were used. Because of the difficulties in the preparation of the Grignard reagent of bicyclo[1.1.0]butane, the studies on the reactions using this type of imines were limited to organolithium reagents.

Table 11 lists the results of the optimization studies using **119** and imine **141a**. The reaction proceeded with good conversions but low *dr*, and addition of a non-polar solvent as well as efforts to remove inorganic precipitates by filtration did not result in a notable improvement. We speculated that the excess of the lithium salts present in the reaction mixture may be responsible for the low diasteroinduction. Bidentate amines which are known to strongly chelate lithium (including organolithium reagents) and based on this observation, we speculated that achiral additives may be effective additives. We found that an excess of TMEDA added prior to the addition of imine **141a** was sufficient to deliver amide **142a** in good yield and *dr*.

Table 11. Optimization studies on the addition of organolithium reagents to chiral imine **144a**.

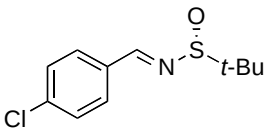
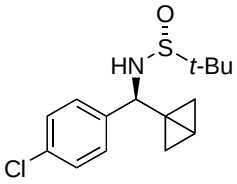
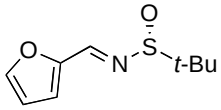
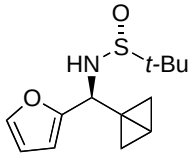
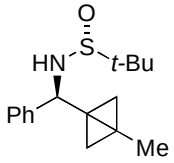
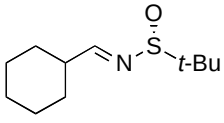
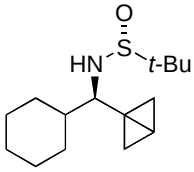
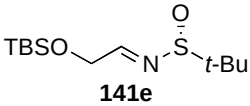
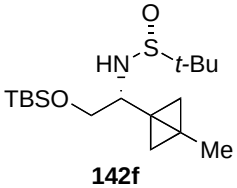


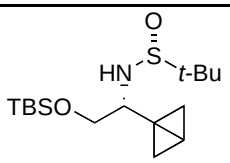
Entry	Conditions	yield	*dr*
1	MeLi, *t*-BuLi, Et_2O, -78 ^oC	ND	68:32
2	MeLi, *t*-BuLi, Et_2O then Me_3Al, -78 ^oC	ND	50:50
3	MeLi, *t*-BuLi, Et_2O then Me_3Al, TMEDA, -78 ^oC	ND	88:12
4	MeLi, *t*-BuLi, TMEDA, Et_2O, -78 ^oC	51%	>95:5

[a]Reactions performed at 0.1 mmol scale. [b]Based on ^1H NMR of a crude reaction mixture

The scope of this reaction is presented in Table 12. Aryl (entries 1-4) as well as alkyl (entries 5-7) substitution on the imine was tolerated and addition of the chelating amine had a beneficial effect on the diastereoslectivity in all tested reactions. Although in some cases the effect was only small, this general method provides a diastereoselective access to bicyclo[1.1.0]butyl amides. It is noteworthy that the amount of MeLi addition product observed in the reactions with *P*,*P*-diphenylphosphinyl or sulfonyl-based imines was low.

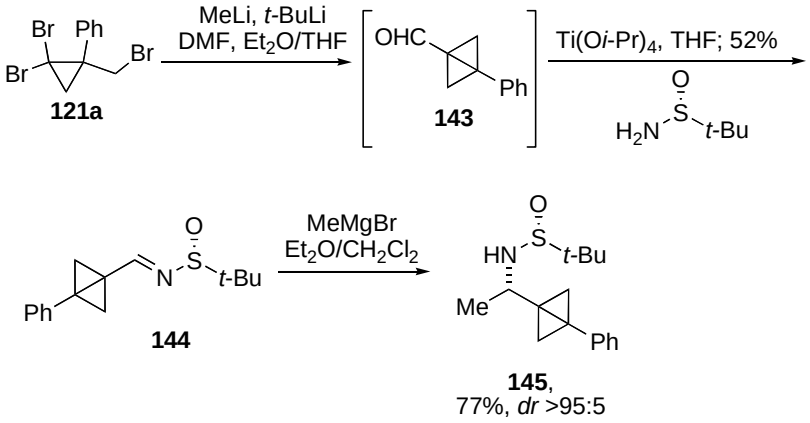
Table 12. Diastereoselctive addition of bicylo[1.1.0]butyllithium reagents to sulfinyl imines.[a]

Entry	Imine	Product	No Additive *dr*[b]	TMEDA Added Yield	TMEDA Added *dr*[b]
1	 **141b**	 **142b**	65:35	71%	96:4
2	 **141c**	 **142c**	81:19	72%	92:8
3	**141a**	 **142d**	76:24	55%	87:13
4	 **141d**	 **142e**	54:46	48%	83:17
5	 **141e**	 **142f**	90:10	50%	94:6

6	**141e**	 **142g**	79:21	61%	95:5

[a]Reactions were carried out using optimized conditions form Table 11, entry 4. [b]Determined by ^{1}H NMR of a crude reaction mixture. [c]Isolated yield of the major diastereomer.

In addition to the diastereoselective reaction using chiral sulfinyl imines, we investigated the reactions using chiral bicyclo[1.1.0]butylimines. When bicyclo[1.1.0]butylcarboxaldehyde **143**, obtained in the reaction of bicyclo[1.1.0]butyllithium with DMF, was treated with a chiral amide in the presence of Ti(*i*-PrO)$_4$, imine **144** was obtained in a good yield. It is worth noting that conditions utilizing stronger Lewis acids such as $TiCl_4$ led to decomposition of the desired product whereas other dehydrating agents like $MgSO_4$, $BF_3{\cdot}Et_2O$ or silicon based Lewis acids led to recovery of the starting material. Treatment of **144** with Grignard reagents afforded the corresponding protected bicyclo[1.1.0]butylamides in good to excellent yields. However, efforts to add bicyclo[1.1.0]butyllithium to ketimines failed, most likely due to the steric hindrance of the organolithium reagent.



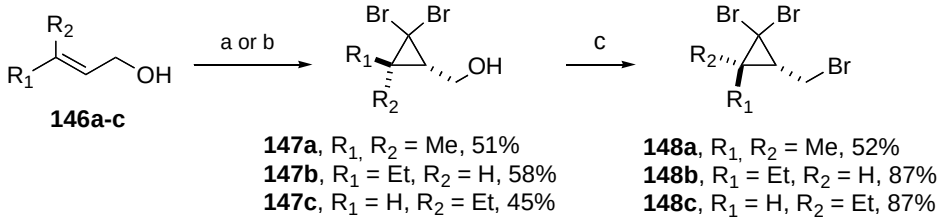
Scheme 42. Synthesis of chiral bicyclo[1.1.0]butyl imine and addition of Grignard reagents.

The relative configuration of the newly formed C-C band was assigned based on the precedence of Ellman.[187,188] These authors proposed that the reaction proceeds *via* a chelate transition state for the addition of Grignard reagents. The use of organolithium reagents lowered the observed selectivities, but the absolute configuration remained the same. In the cases where the addition of organolithiums is preformed in the presence of a chelating amine, other factors that control the absolute configuration have to be taken into account.

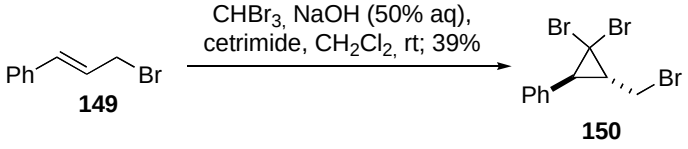
1.2.6 Synthesis of 2-Substituted Bicyclo[1.1.0]butanes

In addition to the synthesis of 1,3-disubstituted bicyclo[1.1.0]butanes, we were interested in exploring routes to 2-substituted analogs with a defined configuration at the methine position. In order to access these diastereomerically pure bicyclo[1.1.]butanes, it was envisioned that the relative stereochemistry of the alkenes used in the synthesis of the precursors could be translated into the relative stereochemistry around the strained ring (*endo* vs. *exo*). However, in order to successfully implement this approach, the incoming organolithium reagent must approach one of the bromine atoms from the side of the chloro(bromo)methyl group or, if not, the equilibration of the carbonion must proceed faster than the 3-*exo*-tet cyclization. Given that the carboanions generated from *gem*-dibromocyclopropanes are not configurationally stable at -78 ^{o}C, it is likely that the cyclization may proceed faster at this temperature than opening of the cyclopropane. This methodology would be suitable for the synthesis of well-defined bicyclo[1.1.0]butyl structures and applicable in the synthesis of **17**.

In order to test the feasibility of this approach, a series of *gem*-dibromoderivatives was prepared using methods described previously. Alcohols **146a-c** were first protected with a THP or TBS group followed by the addition of carbene, and the protective group was removed using TBAF or MeOH/TSA (Scheme 43). However, cinnamyl bromide was cleanly converted to **150** under identical conditions in 39% yield (Scheme 44). Additionally, the temporary protection of **146a-c** with a THP group ensured the stereochemical integrity of the newly formed cyclopropane and facilitated purification from non-polar by-products. Alcohols **147a-c** were then converted into bromides using a standard protocol.



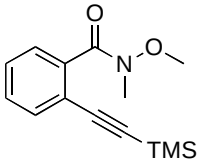
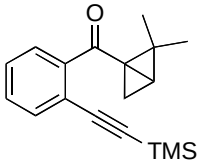
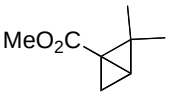
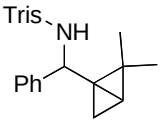
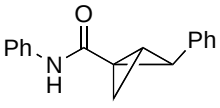
Scheme 43. Synthesis of tribromocyclopropanes **148**. Reagents and conditions: for **147a**: a) i. DHP, PPTSA, CH_2Cl_2, rt, ii. $CHBr_3$, NaOH (50% aq), cetrimide, CH_2Cl_2, rt; iii. MeOH, PTSA, rt. For **147b,c**: b) i. TBSCl, Imidazole, DMF, CH_2Cl_2, rt, ii. $CHBr_3$, KO*t*-Bu, pentane, 0 ^oC to rt; iii. TBAF, THF. c) Ph_3P, Br_2, Imidazole, CH_2Cl_2, 0 ^oC.

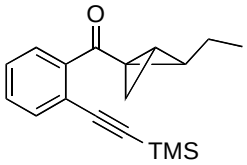
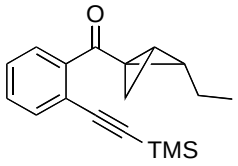


Scheme 44. Synthesis of tribromocyclopropane **150**.

Treatment of **148a-c** and **150** with MeLi in Et_2O at -78 ^oC followed by a second metallation step with *t*-BuLi gave the corresponding organolithium derivatives which were trapped with Weinreb amides (entries 1, 5, and 6), isocyanate (entry 4), and chloroformate (entry 3). For the reactions with substituted *gem*-dibromocyclopropanes, the crude reaction mixture showed the formation of diene, and it was also postulated that this reaction may proceed *via* elimination of an exocyclic halogen atom from the cyclopropyl anion. Although the bicyclo[1.1.0]butanes conjugated to a carbonyl group were stable towards purification, efforts to obtain **152c** from imine **88c** were unsuccessful due to decomposition of the product on SiO_2, and this compound isomerized readily in the presence of trace amounts of acid. We also found that trapping of the organolithium derivative generated from **148a** with *n*-Bu_3SnCl was not successful; under these conditions only the MeLi addition product was observed.

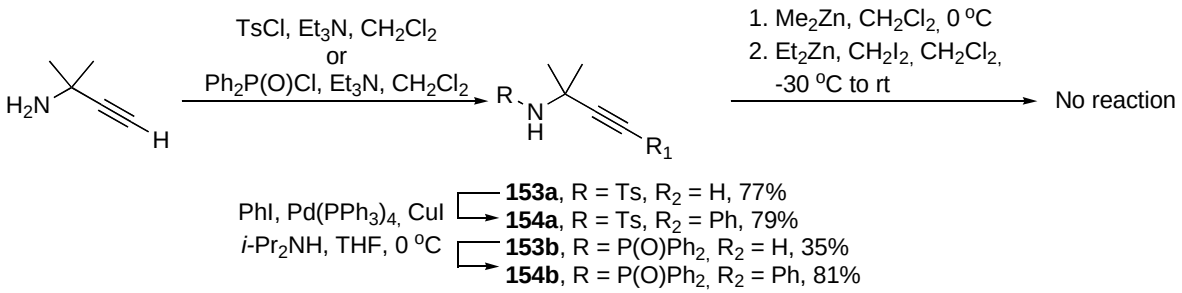
Table 13. Synthesis of 2-substituted bicyclo[1.1.0]butanes.

Entry	Dibromocyclopropane	Electrophile	Product	Yield
1	**148a**	 **151**	 **152a**	44%
2	**148a**	MeO_2CCl	 **152b**	48%
3	**148a**	**88c**	 **152c**	<5 %
4	**150**	PhNCO	 **152d**	65%

5	**148b**	**151**	 **152e**	68%
6	**148c**	**151**	 **152f**	39%

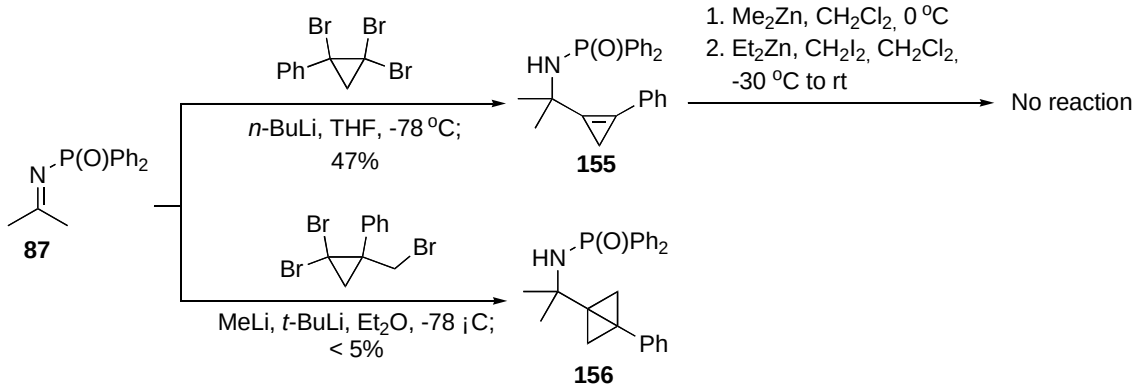
1.2.7 Synthesis of *gem*-Disubstituted Bicyclo[1.1.0]butanes

In order to access a broader range of bicyclo[1.1.0]butanes, the synthesis of *gem*-disubstituted bicyclo[1.1.0]butanes was studied briefly. Protection of the nitrogen moiety with $Ph_2P(O)Cl$ or TsCl, followed by a Sonogashira coupling with iodobenzene, furnished amides **154** in good yields. These compounds were first exposed to Me_2Zn and subsequently transferred into a solution of $(CH_2I)_2Zn$ in CH_2Cl_2. After overnight stirring at room temperature, the starting amides were recovered and no detectable amounts of bicyclo[1.1.0]butanes were observed.



Scheme 45. Synthesis of dimethylpropargyl amides **154** and attempted synthesis of bicyclo[1.1.0]butanes.

A cyclopropene derivative was prepared *via* addition to imine **87**. Exposure of **155** to another batch of $(CH_2I)_2Zn$ resulted in the recovery of the starting material (Scheme 46). Finally, using the direct addition protocol, exposure of imine **87** to an excess of phenyl- bicyclo[1.1.0]butyllithium did not result in the formation of dimethylbenzylbicyclo[1.1.0]butane **156**.



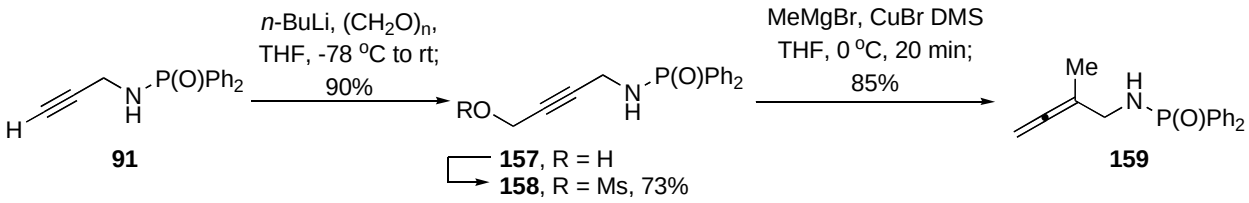
Scheme 46. Attempted synthesis of *gem*-dimethyl amide **156**.

1.2.8 Cross-Coupling Reactions of Bicyclo[1.1.0]butylstannane

In the course of our studies on the synthesis of functionalized bicyclo[1.1.0]butanes, we became interested in a direct cross-coupling methodology to access bicyclo[1.1.0]butanes conjugated with an aromatic group. To this end organostannanes **128a,b**, boronate **129b** and bicyclo[1.1.0]butyllithium reagents were used to couple with 4-iodoanisole or methyl 4-iodobenzoate using typical Pd-based coupling conditions. However, these reagents did not provide the desired products under a variety of conditions – either no reaction was observed by ^{1}H NMR or, after extensive heating, the organometallic reagents rearranged into alkenes.

1.2.9 Reaction of Zinc Carbenoids with Allenyl Amides

Reactions of zinc carbenoids with propargyl amides have proven to be a source of interesting chemical transformations. We were intrigued by the possibility of applying the amide-directed cyclopropanation conditions to reactions with allenyl amides. Previous studies on alcohol directed addition reactions have shown that methylenecyclopropanes or spiropentanes are the major products from these reactions.[189]

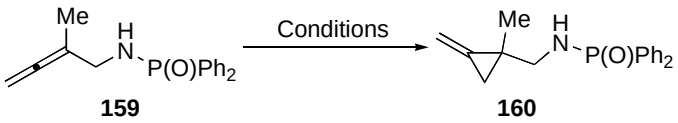


Scheme 47. Synthesis of amide **159**.

Scheme 47 depicts the synthesis of allenyl amide **159** which was used to optimize the reaction conditions for cyclopropanation. The reaction of diphenylphosphinamide **91** with formaldehyde followed by conversion of alcohol into mesylate led to **158** that was subsequently reacted with a cuprate to afford the allenyl amide in a very good yield. Exposure of **159** to Me_2Zn followed by addition of the zinc carbenoid resulted in the formation of methylenecyclopropane derivative **160**. Table 14 presents the optimization studies. A large excess of the cyclopropanating reagent was needed in order to obtain a good yield, but, interestingly, methylenecyclopropanes did not undergo further addition reactions and we were not able to detect any spiro-

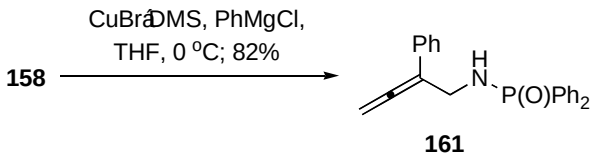
cyclopentane in the reaction mixture. The combination of CH_2ICl and Et_2Zn which is known to produce more reactive carbenes[190] gave results similar to the reaction with CH_2I_2 and Et_2Zn, whereas a reaction with samarium carbenoid[67] was very slow and a large amount of starting material was recovered. Exposure of **161** (Scheme 48) to an excess of zinc carbenoid species resulted only in recovery of the starting material, and even after prolonged time no reaction was observed. Literature searching revealed that successful reactions of allenyl alcohol are restricted to relatively unhindered substrates lacking the substitution in the α-position.[191] The limited scope of this transformation prevented further studies.

Table 14. Reaction of allenyl amide **159** with $(CH_2I)_2Zn$.



159 **160**

Entry	Conditions	Yield
1	a. Me_2Zn, CH_2Cl_2, 1 h b. Et_2Zn (2.5 eq), CH_2I_2 (5 eq), CH_2Cl_2, reflux, 6 h	58%
2	a. Me_2Zn, CH_2Cl_2, 1 h b. Et_2Zn (2.5 eq), CH_2ICl (5 eq), CH_2Cl_2, -30 to 0 °C, 4.5 h	68%
3	a. Me_2Zn, CH_2Cl_2, 1 h b. Et_2Zn (5 eq), CH_2I_2 (10 eq), CH_2Cl_2, -30 to 0 °C, 4 h	72%
4	a. Me_2Zn, CH_2Cl_2, 1 h b. Sm (5 eq), CH_2I_2 (5 eq), -78 °C to rt, overnight	46%

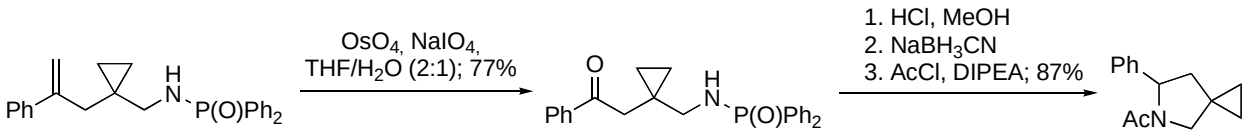


161

Scheme 48. Synthesis of amine **161**.

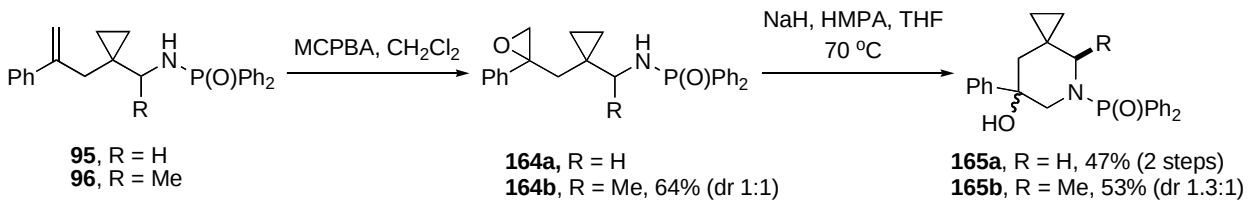
1.2.10 Diversity-Oriented Synthesis of Azaspirocycles

Diversity Oriented Synthesis (DOS) has became a powerful strategy for the targeting of a variety of biological systems using small molecules.[192,193] The power of this approach lies in the combination of the combinatorial methods for the synthesis of diverse molecules with efficient screening techniques. From the chemical perspective, access to a diverse library of molecules can be accelerated by special synthetic methods, particularly multicomponent and cascade reaction techniques. We felt that the products of the cascade reaction of propargyl diphenylphosphinamides with zinc carbenoids may provide an interesting molecular scaffold for the synthesis of azaspirocycles based on pyrrolidines and piperidines. Thus, the alkene portion of **95** was cleaved using Lemieux-Johnson conditions to afford ketone **162** which was then subjected to reductive amination conditions. Removal of the protecting group, treatment with $NaBH_3CN$ and acylation of the resulting secondary amine with AcCl furnished **163** in 87% overall yield. In order to access the piperidine derivatives, the styrenes **95** and **96** were treated with MCPBA and the resulting diastereomeric mixtures of epoxides was cyclized by treatment with NaH to afford **165a,b**.



95 **162** **163**

Scheme 49. Synthesis of pyrrolidine **163**.



95, R = H
96, R = Me

164a, R = H
164b, R = Me, 64% (dr 1:1)

165a, R = H, 47% (2 steps)
165b, R = Me, 53% (dr 1.3:1)

Scheme 50. Synthesis of piperidines **165a-b**.

1.3 CONCLUSIONS

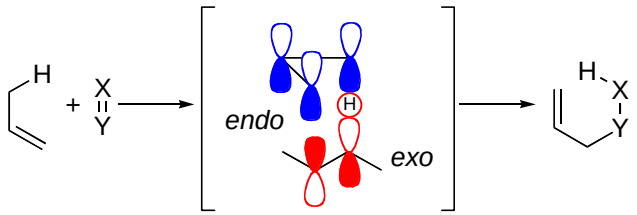
This chapter describes our methodologies for the synthesis of bicyclo[1.1.0]butanes. We developed two methods utilizing the addition of zinc carbenoids generated under Furukawa's conditions. Theses reactions proceeded well for conjugated propargyl amides but the steric requirements at the branching position as well as the protective groups controlled the outcome of the cycloaddition reactions. The most general method is the addition of the lithium anion of bicyclo[1.1.0]butane, generated from its bromo derivative. This method was successfully applied to the synthesis of amides, alcohols, aldehydes, imines, and esters. Using chiral imines, we have also shown that the corresponding amides can be obtained in high yield and *dr*. Finally, methodologies for the stereocontrolled introduction of substituents at positions 1-, 2-, and 3- of bicyclo[1.1.0]butanes were developed.

2.0 PERICYCLIC REACTIONS OF BICYCLO[1.1.0]BUTANES

2.1 INTRODUCTION

2.1.1 Ene Reaction

In the course of our studies on bicyclo[1.1.0]butanes, it was discovered that this strained system undergoes an ene reaction with allyl and propargyl counterparts. The ene reaction, originally defined by Alder,[194] is the reaction of an olefin containing an allylic hydrogen with compounds possessing a multiple bond (Scheme 51).[195-199] The reaction resembles other 6*e* pericyclic processes such as the Diels-Alder reaction or the 1,5-hydrogen shift. Oppolzer and Snieckus[196] classified intramolecular ene reactions into three main categories, according to whether X in the enophile is bonded to the ene portion at the a (Type I), b (Type II) or c (Type III) position (Figure 9).



Scheme 51. HOMO-LUMO interaction in the ene reaction.

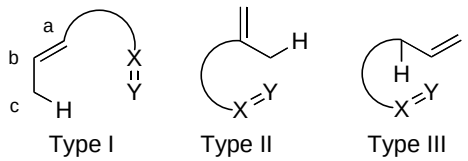
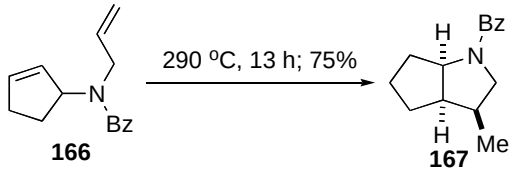


Figure 9. Classification of intramolecular ene reactions.

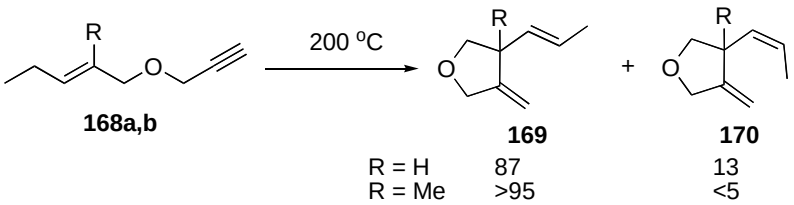
From a mechanistic standpoint, the mode of reaction can be predicted by the analysis of the HOMO of the ene, the LUMO of the allylic CH bond, and the LUMO of the enophile (Scheme 51). Based on this analysis, the ene reaction can be classified as a $[_{\sigma}2_s+_{\pi}2_s+_{\pi}2_s]$ process[200] in the Woodward-Hoffman notation[201] and obeys the *endo* rule. The concerted nature of this process has been demonstrated both experimentally[202,203] and theoretically.[204] However, in some cases the intermediacy of radical[205]or ionic[206] intermediates has been postulated. Some ene reactions (C^2-C^6 (Schmittel)/ene cyclization) may also proceed *via* a highly asynchronous transition state which cannot be described by a single minimum-energy path, suggesting that borderline (concerted/radical) mechanisms controlled by dynamic effects are operating.[207]

The enophile components of the reaction consist of π-bonded molecules characterized by low-lying LUMO. Typical examples include multiple CC bonds (alkenes, allenes, alkynes, benzyne[208]), carbon-heteroatom multiple bonds (C=O,[209-213] C=N,[214] C=S,[215,216] C=P[217]), heteroatom-heteroatom multiple bonds (N=N,[218-228] ^{1}O=O,[229-231] N=O,[232] S=O[233]) and charged π-species ($C=N^+$, $C=S^+$, $C\equiv N^+$, $C\equiv O^+$).[234-238] The variety of enophiles that can be used in this transformation makes the ene reaction a versatile tool in organic synthesis. However, an uncatalyzed ene reaction usually requires harsh thermal conditions – experimentally estimated activation parameters for the ene reaction of propene and ethylene[239] show highly unfavorable enthalpic and en-

tropic terms, which correlated well with the computational data.[240] The thermal ene reaction with unactivated components can be performed only in an intramolecular fashion. These reactions usually are carried out at high temperatures (e.g. 400 – 500 °C) or under milder conditions with prolonged reaction times. Oppolzer[241] found that a variety of pyrrolidines can be obtained by the intramolecular ene reaction of *N*-allyl and *N*-homoallyl amides in good yields despite harsh reactions conditions – the *cis*-substituted pyrrolidines were obtained in 55-90% yield irrespectively of the geometry of the reacting alkene. A representative reaction is depicted in Scheme 52. However, substitution of the olefinic part in the intramolecular ene reactions often translates into greater (*E*)-/(*Z*)-selectivity as demonstrated by the reaction of substituted propargyl ethers **168** (Scheme 53).[242] The outcome of these reactions can be rationalized by considering $A^{1,3}$-strain which is maximized in the transition state leading to **169**. Another application of the unactivated olefins in the tandem Claisen-ene reaction was disclosed by Ziegler and Mencel.[243]



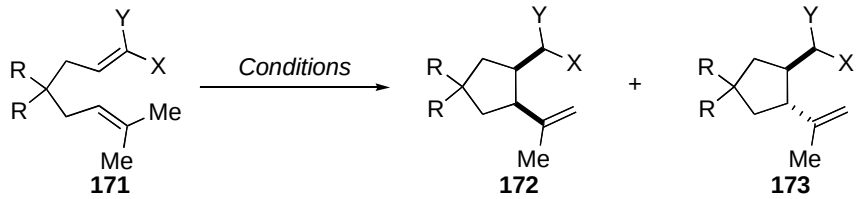
Scheme 52. Thermal ene reaction of allyl amide **166**.



Scheme 53. Intramolecular ene reaction of unactivated propargyl ethers **168a,b**.

Intramolecular ene reactions can be carried out under much milder conditions if the enophile is substituted with an electron-withdrawing group such as ester, amide, or ketone. These reactions can be conducted under even milder conditions if a Lewis acid is used to promote the intramolecular proton transfer. A systematic variation of the geometry and substitution in the enophile part conducted by Ghosh and Sarkar[244] showed that the relative stereochemistry of the alkene part is directly responsible for the diastereoselection in these reactions in addition to a dramatic influence on the reaction rate. Doubly activated alkenes (Table 15, entries 3 and 6) gave the products in highest *dr* as well as in the shortest reaction times.

Table 15. Effect of alkene and geminal ene substitution on rates and stereoselectivities in thermal ene reactions.[244]

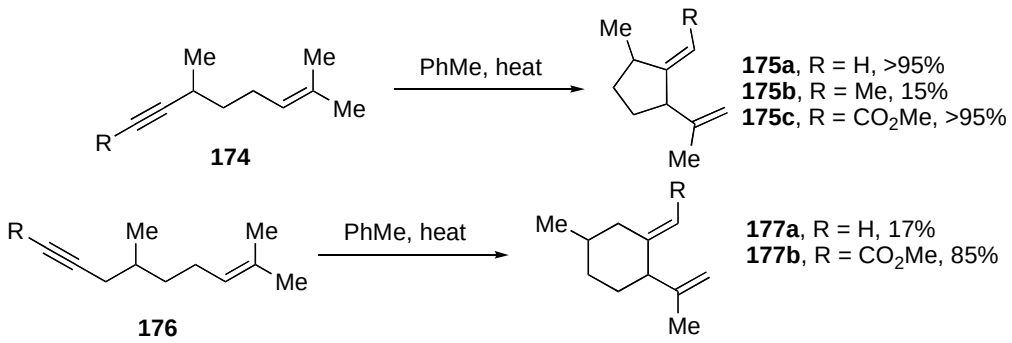


171 **172** **173**

Entry	R	172	173	Conditions	Yield	172/173
1	H	CO_2Me	H	253 ^oC/40 h	80%	76:24
2	H	H	CO_2Me	253 ^oC/40 h	75%	43:57
3	H	CO_2Et	CO_2Et	255 ^oC/5 h	70%	13:87
4	Me	CO_2Me	H	222 ^oC/35 h	85%	72:28
5	Me	H	CO_2Me	222 ^oC/35 h	80%	40:60
6	Me	CO_2Et	CO_2Et	117 ^oC/65 h	80%	20:80

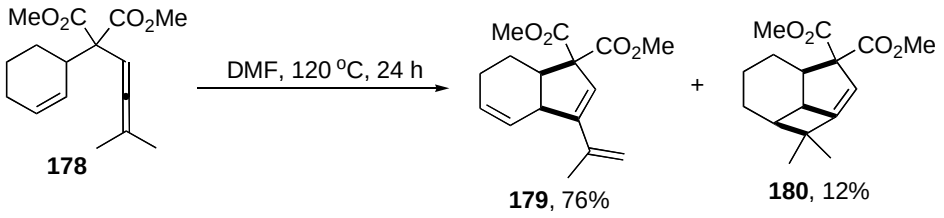
Alkenes are usually more active than alkenes in the ene reactions. Numerous examples of the intramolecular cyclization reactions of 1,6- and 1,7-ynynes are known, although the later require harsher conditions. A systematic study by Snider and Killinger[245] showed that the alkyl substitution at the terminal alkyne position retards the reactions (alkyne acts as an enophile) whe-

reas methyl esters have a significant accelerating effect. The effect on the reaction yield is even more pronounced in the cyclization reactions of 1,7-ynynes, as shown in Scheme 54.



Scheme 54. Rate acceleration of the electron-withdrawing group on the ene reaction.

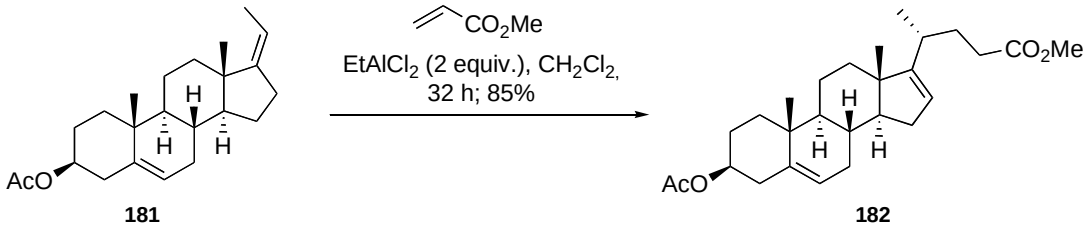
In some cases, other pericyclic reaction can compete with the ene reaction.[199] During studies on the palladium-catalyzed carbocyclizations of enallenes, Nahri *et al.*[246] observed that unactivated olefins underwent a thermal ene reaction in DMF at an unusually low temperature (Scheme 55). The product was contaminated with the [2+2] cycloaddition product **180** and the ratio of the two was dependent on the solvent used. The cycloisomerization was particularly facile for cyclic substrates although the acyclic precursor yielded a mixture of ene and [2+2] cycloadduct in 35% combined yield. Another common reaction competing with the ene cyclization is the [4+2] cycloaddition.[247]



Scheme 55. Intramolecular ene cyclization of allenes.

Intermolecular ene reactions are usually performed with very reactive alkenes such as maleic anhydride or acrylates, although monoactivated enophiles have found little use in organic synthesis due to low regioselectivity and reaction yield. In some cases when a reactive double bond (acryloyl chloride) is used in combination with a reactive ene component (β-pinene), the yield of this reaction can be significantly improved (85%).[248] By varying the ene component in the reactions with maleic anhydride, Nahm and Cheng[249] showed that the enophile reacts at the less-substituted position of the alkene. *cis*-Alkenes gave >6:1 *endo*-selectivity in the *threo*-product, whereas *trans*-alkenes resulted in the formation of a 4.2:1 ratio of the *erythro*-product in a 1.5:1 *endo*-selectivity.

Inukai and Snider were the first to demonstrate the accelerating effect of Lewis acid on the intermolecular ene reaction.[250,251] These reactions are characterized by high regioslectivity and can be performed with more functionalized substrates (Scheme 56). The Lewis acid promoted olefin ene reactions proceed efficiently, however, only for the unsubstituted or α-substituted α,β-unsaturated carbonyl compounds. Substituents at the β-position sterically prevent access to alkene but also stabilize the positive charge developed upon complexation with the Lewis acid. Crotonaldehyde in the presence of an excess of $EtAlCl_2$ reacts reversibly with the alkene, and this complex rearranges *via* an alkyl/hydride shift or reversibly forms cyclobutane.[252]

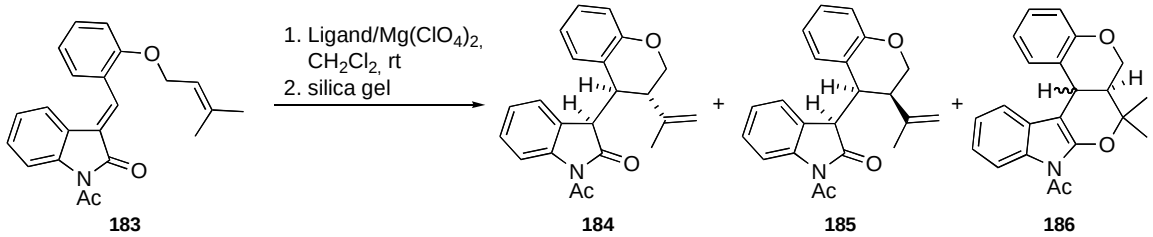


181 182

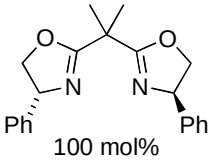
Scheme 56. Intermolecular Lewis acid promoted ene reaction.

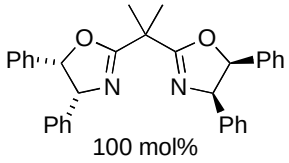
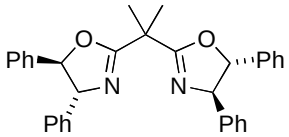
Unlike the carbonyl ene reactions,[253] an asymmetric version the olefin-ene cyclization is still at its infancy. In the first report by Narasaka *et al.*,[254] the authors used stoichiometric amounts of a TADDOL-based titanium complex to provide a mixture of ene and Diels-Alder products in very good yields. A catalytic version of the olefin-ene reaction appeared in 1996,[255] and, although the *ee* and the diastereoselectivities were only modest, it provided an improvement with respect to amount of the [4+2]-cycloaddition product (Table 16). Xia and Ganem utilized the Mg-based system in their synthesis of (-)-α-kainic acid, but the levels of chiral induction using stoichiometric amounts of the commercial bis-oxazolines were low.[256]

Table 16. Enantioselective Alder-ene reaction.[255]

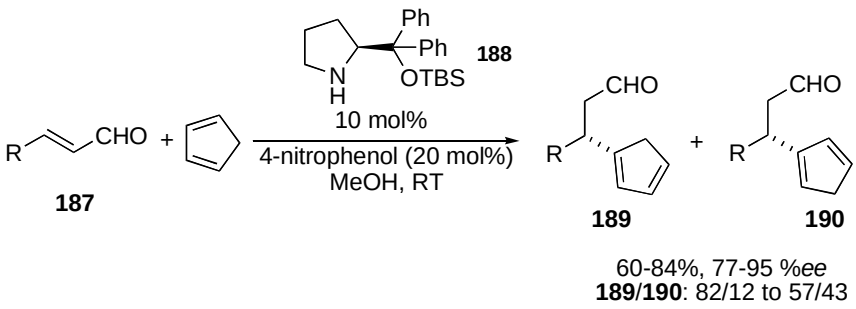


183 184 185 186

Ligand	Yield	184	185	186
 100 mol%	quant.	65% (30% ee)	16	19

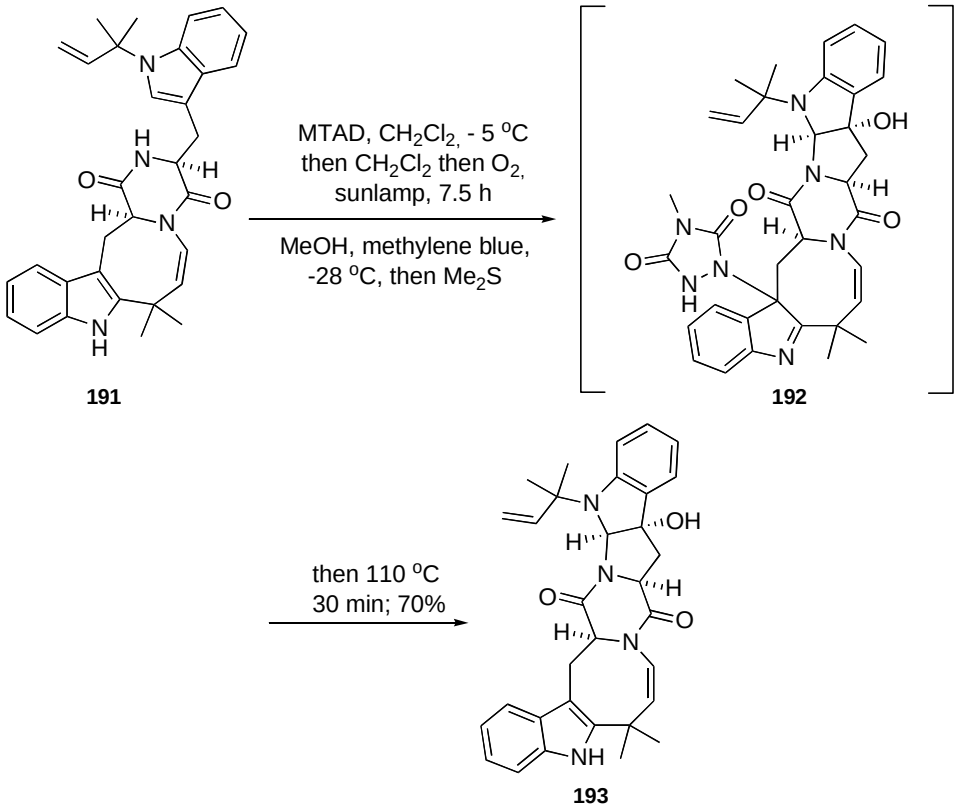
 100 mol%	quant.	53% (51% ee)	19	28
 100 mol%	quant.	75% (88% ee)	15	10
33 mol%	85%	73 (81% ee)	15	12

A mechanistically different enantioselective ene reaction with cyclopentadiene was reported by Hayashi *et al.*[257] (Scheme 57). The proline-derived catalyst was used in the reactions with cinnamyl and other aldehydes conjugated with the aromatic ring to furnish a mixture of dienes **189** and **190** in good yields and *ee*'s. This organocatalytic transformation could be effected only if the hydroxyl moiety in **188** was blocked by a silicon-based protective group. It is also noteworthy that catalyst **188** promoted only formation of **189** and **190** in a highly chemoselective fashion, whereas other organocatalysts have been shown to catalyze highly-enantioselective Diels-Alder reactions on structurally and electronically similar systems.[258]

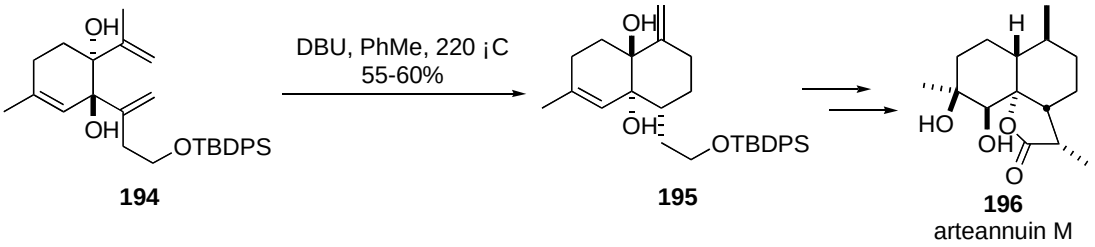


Scheme 57. Enantioselective ene reaction of cyclopentadiene and conjugated aldehydes.

The utility of the ene reaction in the synthesis of complex organic molecules has been well documented. For example, in an enantioselective synthesis of okaramine N, Corey *et al*.[259] used *N*-methyltriazolinedione (MTAD) as a protecting group of the indole moiety that was later unmasked *via* a retro-ene reaction (Scheme 58). An interesting example of the tandem oxy-Cope/ene reaction was demonstrated by Barriault[260] in the synthesis of (+)-arteannuin M (Scheme 59).

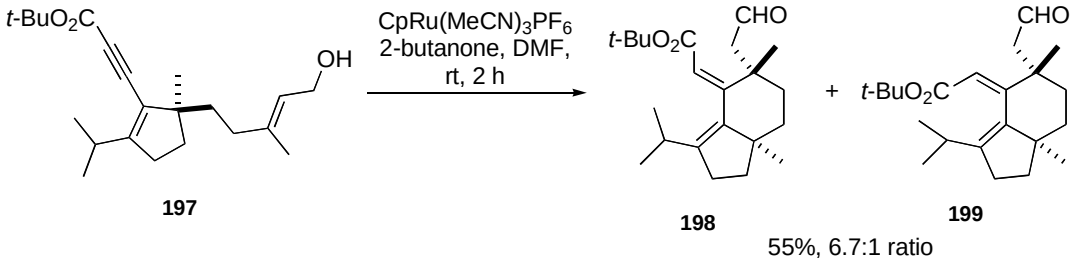


Scheme 58. Ene reaction in the synthesis of okaramine N.



Scheme 59. Application of a tandem oxy-Cope/ene reaction in the synthesis of arteannuin M.

Ene type reactions are not only restricted to proton transfer reactions, but can be carried out on allylmetal derivatives (metallo-ene reaction).[261] Common metals used to perform this transformation catalytically include Rh,[262] Ru,[263,264] Pd,[265] Ni,[266-268] Pt,[269] and Fe.[270] Scheme 60 depicts a strategic cycloisomerization step in the recent synthesis of (+)-allocyathin B_2 by Trost[271] using $CpRu(MeCN)_3PF_6$.



Scheme 60. Cycloisomerization reaction in the synthesis of (+)-allocyathin B_2.

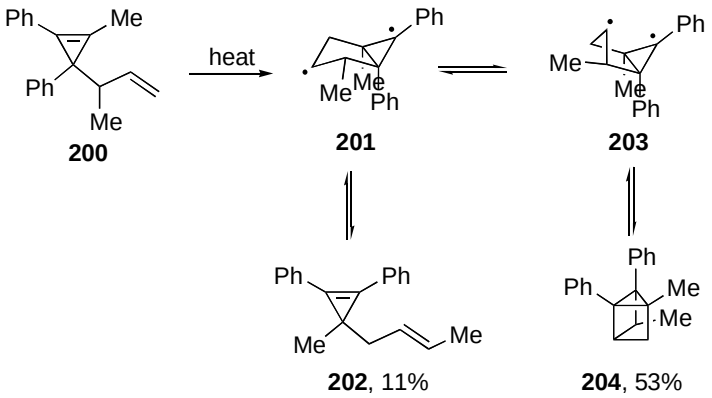
A special class of ene reaction involves transfer of a proton from a carbonyl group, and this intramolecular transformation is commonly referred to as Conia reaction.[272] The initial step is a reversible enol formation followed by a cyclization, and the *cis*-product under the thermal conditions equilibrates to the more stable *trans*-form. Tandem[273] as well as metal catalyzed variants are known.[268,274]

2.1.2 [2+2] Cycloaddition Reactions

In the context of the reactions of bicyclo[1.1.0]butanes, the [2+2]-cycloaddition reactions of alkenes and alkynes are interesting because of the similarity between the central bond in bicyclo[1.1.0]butane and a carbon-carbon π-bond. Only thermal [2+2] cycloaddition reactions are discussed here, and the reactions proceeding *via* ketene[275] or photochemical cycloaddition processes[276] have been reviewed elsewhere.

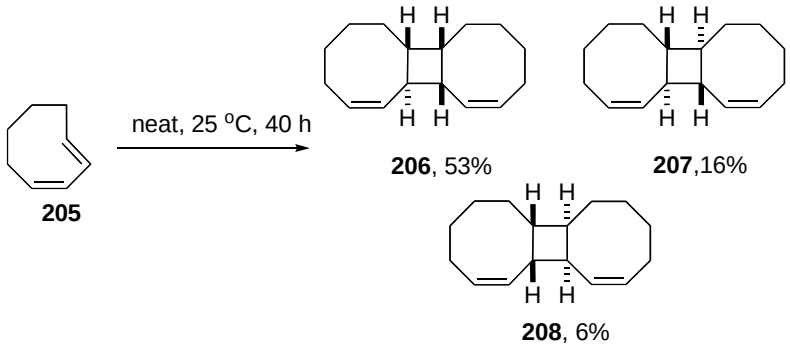
In general, the formal [2+2] cycloaddition reactions are observed in highly activated olefins. This involves alkenes as a part of a strained ring, alkenes at the bridgehead position, and *trans*-cycloolefins. Additionally, the formal [2+2] cycloaddition reactions are observed in electron-deficient olefins in the reactions with partners matching electronically the deactivated alkenes. The cycloaddition reactions are particularly facile for the strained alkenes embodied into a 4- or 3-memberred ring. Cyclopropenes readily undergo dimerization to tricyclo[3.1.0.$0^{2,4}$]hexanes.[277,278] Similarly, methylenecyclopropanes dimerize in a highly selective fashion (98:2) to give head-to-head dimers in 35% yield.[279] Bicyclo[2.2.0]hex-1(4)-ene was converted into the cycloadduct at 0 ^{o}C, and this intermediate subsequently underwent a [2+2]-retroaddition affording two different, highly strained olefins.[280] Padwa has described fascinating cycloaddition reactions involving cyclopropenes (Scheme 61).[281] The formation of the cycloaddition product **204** and the formal Cope rearrangement product **202** proceeds *via* the common diradical intermediate **201** which fragments into **202**. Alternatively, ring inversion followed by a

radical recombination leads to product **204**. Other examples of thermal as well as photochemical [2+2] reactions have also been described.[282]



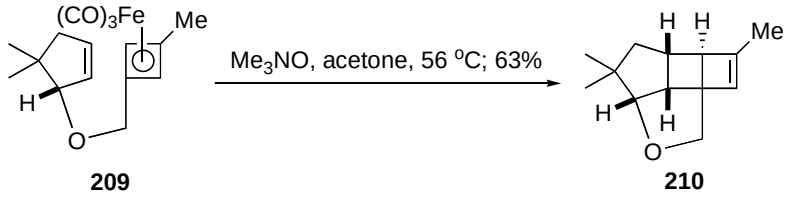
Scheme 61. Thermal isomerization of cyclopropenes by Padwa.

Strained *trans*-alkenes are particularly good reagents in thermal [2+2] cycloaddition reactions. One interesting reaction of this class of molecules was studied by Padwa (Scheme 62). (*E*,*Z*)-1,3-Cyclooctadiene **205** spontaneously underwent dimerization at room temperature to a mixture of three head-to-head dimers **206**-**208**, in addition to bicyclo[4.2.0]-oct-7-ene.[283,284] The presence of 1,4-diradicals has been detected using spin-trapping agents.[285] Alkenes located at the bridgehead positions are also considered as very reactive species and they readily participate in the cycloaddition reactions.[286]



Scheme 62. Dimerization of (*E*,*Z*)-cycloocta-1,3-diene.

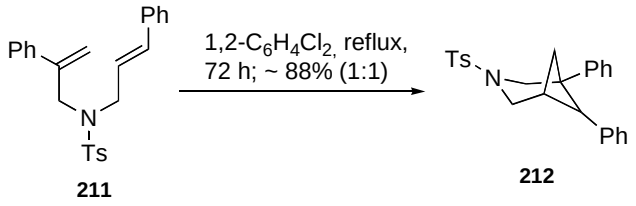
As many of the strained alkenes are unstable, methods for generation of viable precursors from readily available starting materials have been developed. Snapper and coworkers have developed an efficient approach to numerous polycyclic natural products using iron-complexed cyclobutadienes.[15,287-289] The stabilizing metal is liberated from the diene under oxidative conditions and the reactive organic fragment undergoes an intramolecular [4+2] cycloaddition (Scheme 63). These reactions are very efficient for the ether and carbocyclic linkers, but the [4+2] cycloaddition product (in which cyclobutadiene acts as a diene) observed for the reactions with the tethered 1,3-dienes is the thermodynamic product. The systems described by the authors are in many respects unique as the strained fragment can act as a diene or dienephile, depending on the nature of the reacting partner.



Scheme 63. Intramolecular cycloaddition of cyclobutadiene by Snapper.

Interesting observations were reported regarding the reaction of cyclic alkynes, which react with alkenes with a remarkable stereospecificity.[290,291] The authors reasoned that the initial step is a [2+1] cycloaddition to generate a carbene which, depending on the substrate, can further rearrange *via* [1,2] shift to furnish the formal [2+2] cycloadduct or forms a polycyclic product *via* a C-H insertion.[292-294]

The regiochemistry of the isomerization reaction is usually controlled by the relative stabilities of the diradicals. Oppolzer[295] showed that the cycloaddition reaction can proceed *via* two complementary pathways if the stabilizing group is placed at the terminal or internal position of the alkene. Thermal isomerization of amides **211** gave exclusively a 1:1 diasteromeric mixture of **212** (Scheme 64). A similar reaction with bis-cinnamyl amides afforded only a mixture of [2+2]-cycloaddition products.

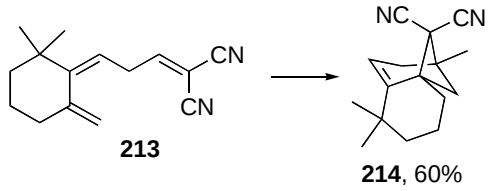


211 **212**

Scheme 64. Thermal [2+2] cycloaddition reaction by Oppolzer.

The earliest example of the thermal [2+2] cycloaddition reaction is the dimerization of acrylonitrile and in this reaction a mixture of *cis*- and *trans*-cyclobutenes is observed, similarly to the dimerization of styrenes, 1,2-butadiene, and vinylacetylene.[296] A typical thermal isomerization reaction is depicted in Scheme 65.[297] The reactions of electron-deficient alkenes are me-

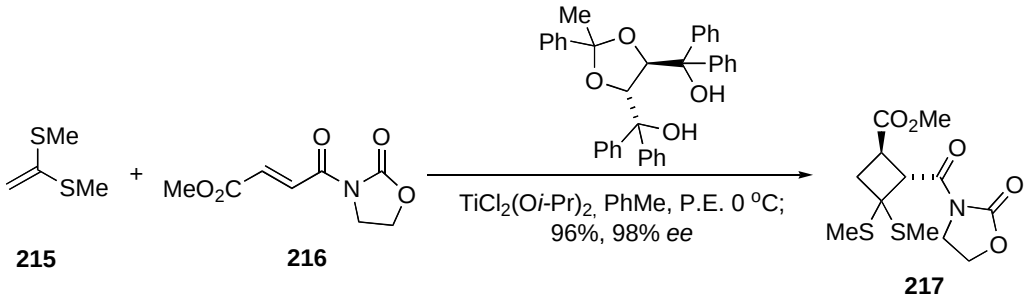
chanistically interesting phenomena as radical and/or ionic mechanism can operate for these substrates. Hall[298]designed a general protocol to determine the extend of the diradical character in these reactions. This analysis was based on the notion that the diradical/zwitterionic intermediates may promote radical/ionic copolymerization prior to rotation into the gauche conformation, leading to the cyclized product. The authors found that the diradical mechanism operates for a broad range of substrates and, as expected, the zwitterionic mechanism can operate for the enamines as well as vinyl ethers reacting with very electron-poor olefins.[299]



213 **214**, 60%

Scheme 65. Thermal [2+2] cycloaddition reaction of electron-deficient alkenes.

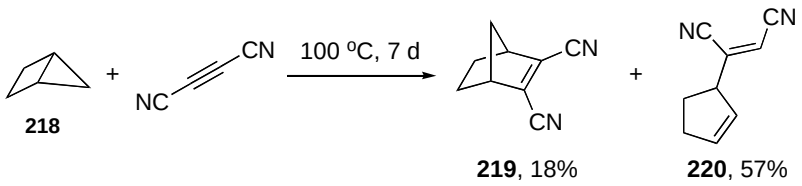
The first general enantioselective [2+2]-cycloaddition reactions were described by Takeda[300] and Narasaka.[301,302] Alkenyl disulfides and monosulfides as well as allenyl sulfides are suitable substrates for the titanium-based catalyst, and a representative example is shown in Scheme 66. Other alternatives for the synthesis of enantiomerically pure cyclobutanes via [2+2] cycloaddition involve the diastereoselective cycloaddition in the presence of Et_2AlCl[303] or $ZnCl_2$.[304]



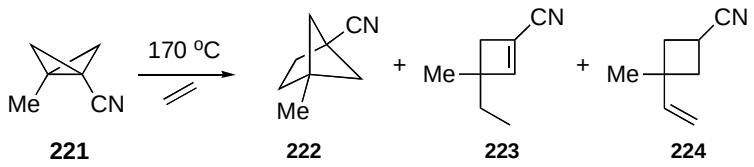
Scheme 66. Enantioselective [2+2] cycloaddition.

2.1.3 Ene Reactions of Strained σ-Bonds

Of particular interest in the context of the ene and [2+2] cycloaddition reactions are the reactions of small carbocyclic molecules with alkenes and alkynes. The first example of this type of reactions in strained bicyclic systems was reported by Gassmann and Mansfield,[305-307] who described a spontaneous reaction of bicyclo[2.1.0]pentane with dicyanoacetylene (Scheme 67). The authors observed two major products arising from the formal ene reaction of the acetylene moiety and the σ-bond of the bicycle as well as [2+2] cycloaddition product. In a related case, Blanchard and Cairncross[308,309] described the first example of the reaction of bicyclo[1.1.0]butane **221** with ethylene (Scheme 68).



Scheme 67. Reaction of bicyclo[2.1.0]pentane with dicyanoethylene.



Scheme 68. Reaction of 1-cyano-3-methylbicyclo[1.1.0]butane with alkenes.

Early studies on the mechanism of the ene reaction revealed the following facts:

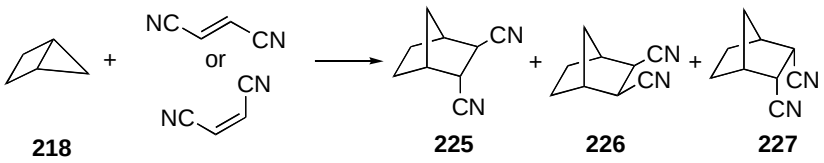
a) the success of the ene reaction with small bicyclic molecules depends on the strain energy – bicyclo[1.1.0]butane and bicyclo[2.1.0]pentane reacted with DMAD almost spontaneously, whereas the less strained bicyclo[3.1.0]hexane showed no detectable reactivity. The reactivity trends were correlated with the strain energy.

b) alkynes and alkenes with electron-withdrawing substituents were effective in reactions with strained bicyclic systems. For example, dicyanoacetylene reacted with bicyclo[2.1.0]propane at room temperature, but diphenylacetylene was inert at 160 °C for a few days.[117,118]

c) formation of the ene product competes with the [2+2] pathway. The preference for either pathway was rationalized by the steric hindrance at the bridgehead position and the electronic nature of the alkene/alkyne.

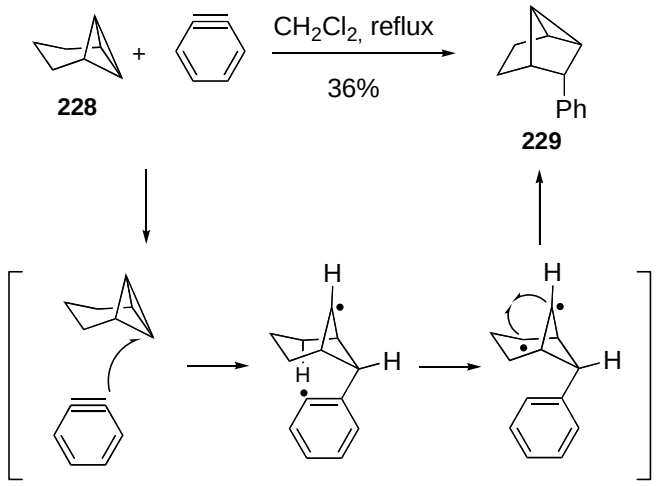
Gassmann and others[310,311] have carried out some studies in order to determine the nature of the intermediates involved in the ene and [2+2] reactions. Since the ene and [2+2] cycloaddition reactions showed second order kinetics (first order in the bicyclic systems), three major mechanistic pathways have been considered: 1) formation of the zwitterionic intermediates that collapse to form the products, 2) both pathways proceed *via* diradical intermediates that recombine to give the products, and 3) the ene pathway was a concerted process. To rule out the intermedia-

cy of ionic intermediates, bicyclo[2.1.0]pentane was reacted with DMAD in solvents varying in polarity from benzene to MeCN. The authors observed only a rate change of 1.27 that was interpreted as a disagreement with the ionic mechanism. If the ene and [2+2] reactions proceeded *via* the concerted pathway, two different transition states would govern the product distribution and the relative population of these products should change when temperature or solvents were varied. The studies showed that this was not the case and no significant temperature dependence of the product ratio was observed. A definitive proof for the non-concerted mechanism for the [2+2] reaction was given by the reaction of bicyclo[2.1.0]pentane with fumaronitrile and maleonitrile (Scheme 69).[312] Seven products were obtained, but the major three (**225**, **226**, **227**) were formed in varying ratios (22:1:1.3 and 1:2:3) if the *trans*- or *cis*-nitrile was used, respectively. Based on this data, the authors proposed a mechanism that involved the formation of a diradical intermediate followed by recombination of the spins *via* either the ene or [2+2] pathway. To further support the radical pathway mechanism, bicyclo[1.1.0]butane **228** was reacted with benzyne to afford compound **229** (Scheme 70).[313-315]



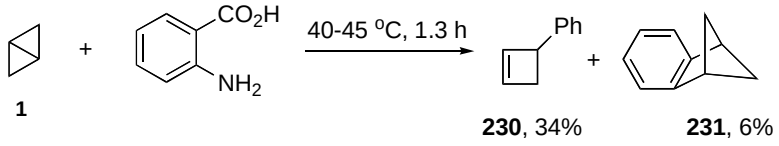
Scheme 69. Reaction of bicyclo[2.1.0]pentane with fumaronitrile or maleonitrile.

However, an ionic mechanism is a viable pathway for the reaction of bicyclo[1.1.0]butane with diazocompounds.[316] It should be mentioned that activated ketones may also participate in the ene reaction with bicyclo[1.1.0]butane.[317]

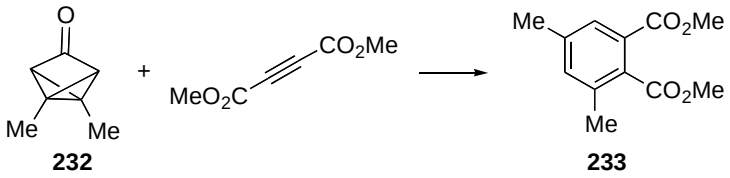


Scheme 70. Reaction of bicyclo[1.1.0]butane **228** with benzyne.

Ene reactions of strained carbocyclic systems have not found many synthetic applications. Pomerantz *et al.*[318] used benzyne for the reaction with bicyclo[1.1.0]butane to obtain **230** and **231** (Scheme 71). Deuterium labeling studies demonstrated also that benzyne approached bicyclo[1.1.0]butane from inside of the ring for ene and cycloaddition reactions. In another example, **232** was reacted with DMAD to afford the polysubstituted benzene derivative **233**, but it is worth mentioning that **232** failed to react with benzyne (Scheme 72).[317]



Scheme 71. Reaction of bicyclo[1.1.0]butane with benzyne.



Scheme 72. Synthesis of polysubstituted benzene **233**.

2.2 RESULTS AND DISCUSSION

2.2.1 Tandem Allylation-Ene Ractions of Bicyclo[1.1.0]butanes

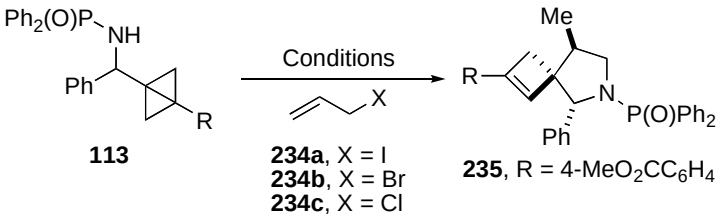
The development of practical methodologies for the synthesis of a wide range of bicyclo[1.1.0]butanes allowed us to study the reactivity of these very unique systems. We were particularly interested in exploring intramolecular reactions and since bicyclo[1.1.0]butane can participate in a variety of thermal or transition-metal promoted reactions with alkenes, we elected to study these reactions with our substrates. Initially, we applied the typical conditions used to introduce an allyl group on the amide nitrogen, and **113** was chosen as the model system (Table 17). To our temporary disappointment, strong bases (entries 1-3) used for alkylations of the amide nitrogen did not provide the desired product due to decomposition of the material. The presence of NaH in THF was sufficient to cause decomposition of **113** (entry 3). The sensitivity of bicyclo[1.1.0]butanes to base may be a result of an intramolecular opening of the strained system, and further studies revealed that bicyclo[1.1.0]butanes substituted with an aromatic ring at the terminal position are not generally compatible with strongly basic reagents. Further screening

of reaction parameters revealed that phase transfer conditions previously used for *N*-alkylations are applicable for the installation of the allyl moiety on the *P,P*-diphenylphosphinamide.[319-321] When the reaction was performed at room temperature over 14 h, a tricyclic pyrrolidine **235** that arose from a formal intramolecular Alder-ene reaction of the allyl group and the bicyclo[1.1.0]butane was isolated in modest yield (entry 5). This unique transformation has been previously observed in the intermolecular manifold (Chapter 2.1.3), but no studies on the intramolecular variant of this transformation had been reported. Further optimization revealed that the tandem alkylation-ene reaction could be performed using an excess of the allylating reagent at room temperature in the presence of a catalytic amount of Bu_4NHSO_4 to afford the rearranged product in 83% yield as a single diastereomer (entry 6). Not unexpectedly, a less reactive allyl chloride afforded **235** in diminished yield (entry 7) and the solvent exchange of PhMe to CH_2Cl_2 (entry 8) had only detrimental effects on the overall reaction yield. Depending on the stirring efficiency, the allylation step was typically complete within 30 min followed by the subsequent ene reaction that reached completion within 36 h at room temperature.

Having identified conditions for the intermolecular Alder-ene reaction, we set out to explore the scope of this unique transformation. To this end, various bicyclo[1.1.0]butanes were reacted with allyl bromide to afford the expected pyrrolidine product in good yields and excellent selectivities (Table 18, entries 1-3). However, when the reaction was performed using substituted allyl bromides (either at 2- or 3-positions), formation of the unrearranged alkyl product **236** was observed exclusively (Scheme 73). When the sample was kept neat at room temperature, the ene reaction took place over ca. one week. To accelerate this process, we decided to carry out the pericyclic transformation at an elevated temperature in PhMe, and the reaction could be completed at 110 ^{o}C over 6.5 h to afford a 67:23 mixture of diastereomers of **237**. However, because of a

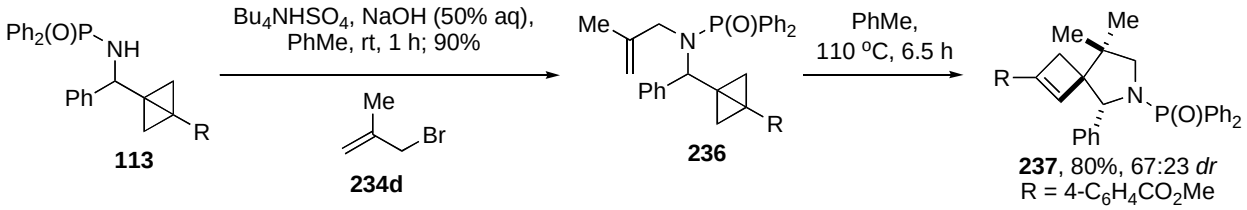
harsh nature of warm 50% aq NaOH and a possible incompatibility with the organic material, we decided to use powdered NaOH and K_2CO_3 in PhMe at 60 or 110 °C.

Table 17. Optimization of the alkylation reactions of *P,P*-diphenylphosphinamides.



Entry	Conditions[a]	Yield
1	**234a**, NaH, HMPA, THF, rt → 60 ˚C	decomp.
2	**234a**, NaHMDS, THF, -78 ˚C → rt	decomp.
3	**234a**, BuLi, THF, -78 ˚C	decomp.
4	NaH, THF, HMPA, 60 ˚C	decomp.
5	**234b**, Bu_4NHSO_4, NaOH, PhMe, rt, 14 h	44%
6	**234b**, Bu_4NHSO_4, NaOH, PhMe, rt, 36 h	83%
7	**234b**, Bu_4NHSO_4, NaOH , CH_2Cl_2, rt, 40 h	<10% + **113**
8	**234c**, Bu_4NHSO_4, NaOH, PhMe, rt, 48 h	12%

[a]NaOH was used as a 50% aq solution.

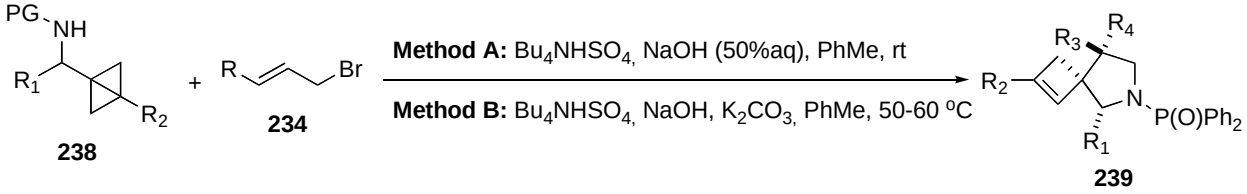


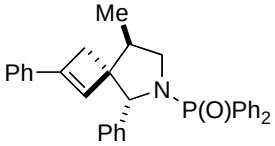
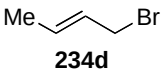
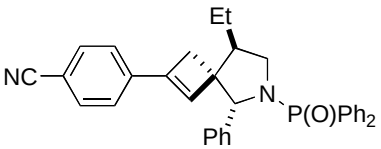
Scheme 73. Synthesis of **236** and its conversion to **237**.

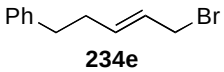
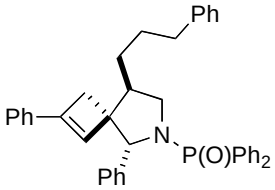
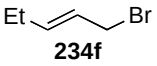
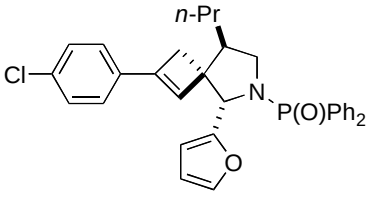
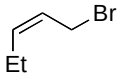
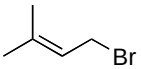
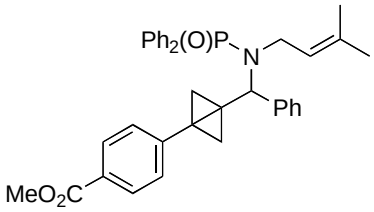
Under the optimized conditions, we were able to perform a tandem allylation-ene reaction of substituted allyl bromides with activated bicyclo[1.1.0]butanes in mainly good yields and excellent selectivities (Table 18, Method B, entries 4-6). The ene-reaction is suppressed if the

terminal position of the allyl group is disubstituted; thus, prenyl bromide (entry 6) afforded only the alkylated derivative a very good yield (entry 9). We were also interested if the geometry of the alkene counterpart influenced the selectivity and the yield of the ene reaction. To this end, (*E*)- and (*Z*)-1-bromo-2-butenes **234f** and **234g** were prepared from the corresponding alcohols (>95% diastereomeric purity by ^{1}H NMR) and reacted with bicyclo[1.1.0]butane **123h** under thermal conditions (entries 7 and 8). Analysis of the crude reaction mixture revealed that a similar selectivity (72:23:3:2 vs. 67:24:5:4) of the ene product was observed for both bromides, and the yield of this transformation was also not dependent on the relative stereochemistry of the alkene chain. However, we were able to observe the formation of all diastereoisomers in the crude reaction mixture and the selectivity of this transformation is lower when compared to other allyl bromides.

Table 18. Scope of the intramolecular ene reaction of allyl amides.



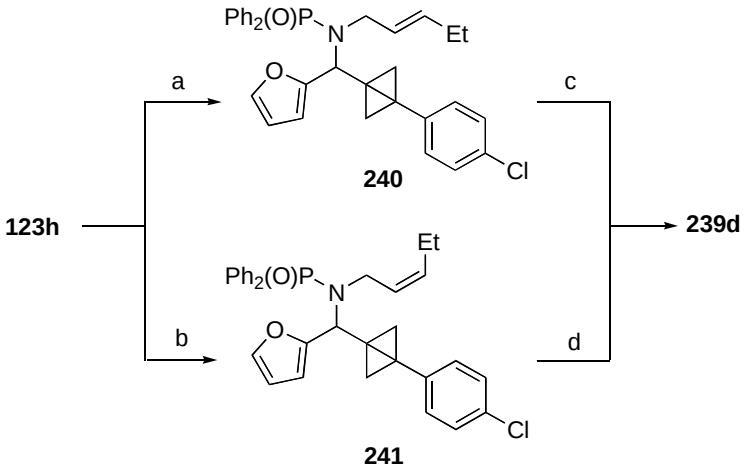
Entry	Amide	Allyl bromide	Product	Method	Yield
1	**98**	**234b**	 **239a**	A	63%
2	**114b**	 **234d**	 **239b**	B	51%

3	**98**	 **234e**	 **239c**	B	57%
4[a]	**113**	**234d**	**237**	B	66%
5[b]	**123h**	 **234f**	 **239d**	B	62%
6[c]	**123h**	 **234g**	**239d**	B	69%
7	**119**	 **234h**	 **239e**	A	99%

[a]Isolated as 70:30 mixture of diastereomers. [b]Formed as 72:23:3:2 mixture of diastereomers (determined by ^{1}H NMR of a crude reaction mixture). [c]Formed as 67:24:5:4 mixture of diastereomers (determined by ^{1}H NMR of a crude reaction mixture).

In order to exclude a possible isomerization of the double bond under the reaction conditions prior to the ene reaction, amides **240** and **241** were prepared in >95:5 diastereomeric purity. When we attempted their conversion into the corresponding ene products, we observed that the reactions proceeded in similar yields and comparable diastereoselectivities for both isomers, favoring formation of the same major diastereomer **239d** (Scheme 74). A direct conversion of the *(E)*- and (*Z)*-isomers to the rearranged pyrrolidines could be thus performed in a one pot sequence, and, depending on the availability of the geometrical isomers of the allyl bromide, both diastereomers are well tolerated in this transformation. Formation of the same major diastereomer **239d** from two geometrical isomers could be explained by a model in which the orientation

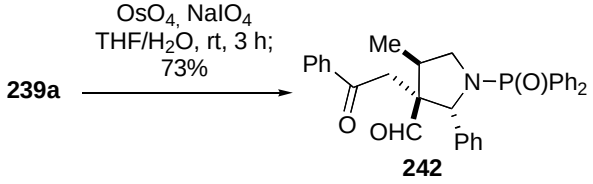
of the allyl chain is independent of the substitution at the methylene position, since it is located away from the bicyclic system (*vide infra*).



Scheme 74. Synthesis and ene reactions of **240** and **241**.

Reagents and Conditions: (a) **234f**, *n*-Bu_4NHSO_4, NaOH (aq), PhMe, 97%; (b) **234g**, *n*-Bu_4NHSO_4, NaOH (aq), PhMe, 95%; (c) PhMe, 60 ^oC, 21 h, 73%, dr 68:28:3; (d) PhMe, 60 ^oC, 21 h, 71%, dr 75:23:1.

Finally, the relative configuration of 6-azaspiro[3.4]-oct-1-enes **239a** was established by conversion to the corresponding ketoaldehyde **242** (Scheme 75, Figure 10). The stereochemistry of **239** was assigned by analogy to **239a**.



Scheme 75. Oxidative cleavage of cyclobutene **239a**.

Figure 10. X-ray structure of **242**.

2.2.2 Ene Reactions of Propargyl Amides

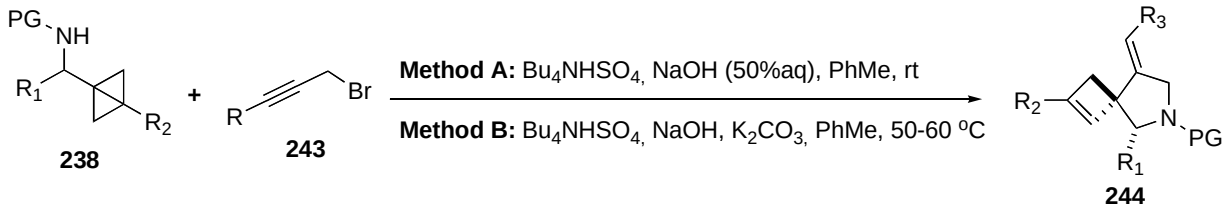
Encouraged by the successful reactions of allyl amides in the ene reactions, we tested if this transformation could be extended towards propargyl bromides. Using phase-transfer conditions, propargyl bromide was reacted with α-phenyl (Table 19, entry 1 and 3) as well as very hindered amide **118** (entry 2) to afford vinyl cyclobutenes **244** in good yields and excellent selectivities (Table 19). Interestingly, when toluenesulfonamide **98** was reacted with propargyl bromide, the desired product was isolated only in 42% yield. However, additional optimization of the reaction conditions (*n*-BuLi, -78 ^{o}C) provided the expected pyrrolidine **244d** in an improved yield (entry 3).

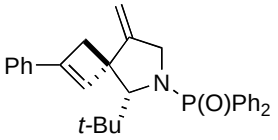
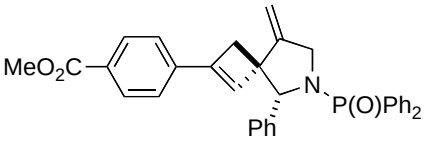
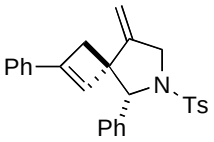
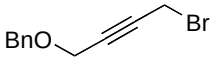
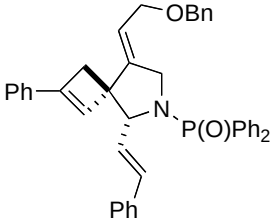
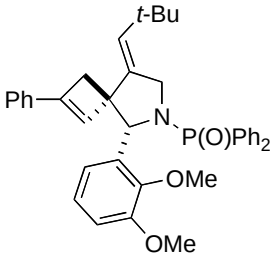
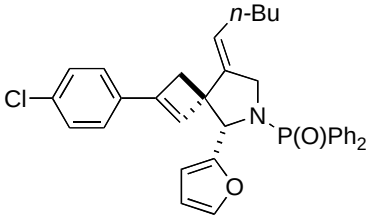
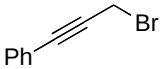
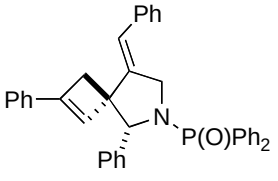
The ene reaction of alkynes and bicyclo[1.1.0]butanes can be also extended towards substituted propargyl bromides. Introduction of a bulky substituent at the terminal position of the alkyne requires elevated temperatures for the ene reaction to proceed at synthetically useful rates, otherwise only *N*-alkylated products could be isolated from the reaction mixture. Thus, propargyl bromides substituted with alkyl (entries 5-7), aryl (entries 8-10) and silicon (entry 11) groups reacted readily with bicyclo[1.1.0]butanes. Excellent selectivities (including *E*- and *Z*-selectivity

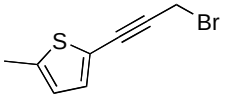
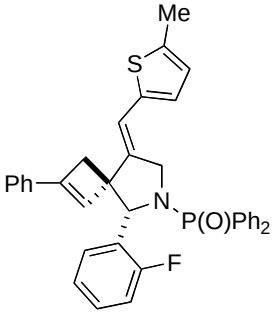
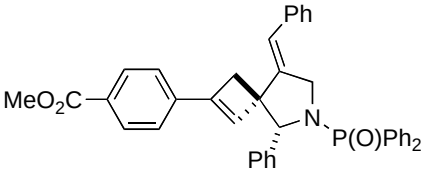
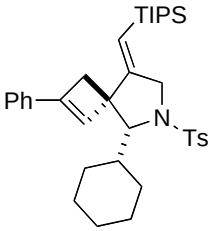
of the exocylic methylene group) were routinely observed in these reactions even if the tandem alkylation-ene reaction was performed at higher temperatures. Notably, the pericyclic reaction with propargyl amides is faster than in the case of allyl amides – alkylation and rearrangement reactions are complete within 12 h at room temperature for the unsubstitued propargyl bromide, whereas the same reaction for the allyl bromide is 2-3 times slower.

In order to determine the relative configuration of the newly formed stereocenters, 2D NMR studies were performed, but due to inconclusive results the original assignment was based on the analogy to the allyl derivatives. However, further studies showed that **244g** could be converted into HCl salt **245** (Scheme 76) and X-ray analysis of the single crystal showed that the exocyclic double bond has *(E)*-configuration, but the newly formed quaternary stereocenter possesses the configuration opposite to the allyl series (Figure 11). Additionally, the X-ray structure of **244a** was also obtained, thus providing an unambiguous assignment of the relative configuration of the unsubstituted pyrrolidines (Figure 12). The configuration of the products of the ene reactions with propargyl bromides (**244**) was assigned by analogy to **244a** and **245**. Interestingly, deprotection of the amine by treatment with HCl in MeOH demonstrated that the *P,P*-diphenylphosphinyl group can be easily removed under mild conditions in the presence of the cyclobutene and the conjugated exocyclic double bond.[173,322,323]

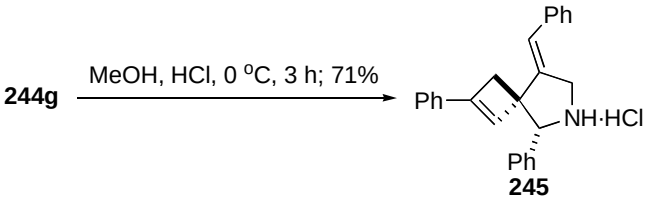
Table 19. Alkylation–Alder ene reaction of propargyl bromides.



Entry	Amide	Propargyl bromide	Product	Method	Yield
1	**118a**	**243a**	 **244a**	A	67%
2	**113**	**243a**	 **244b**	A	87%
3[a]	**123k**	**243a**	 **244c**	A	42%
4	**123f**	 **243b**	 **244d**	B	70%
5	**123e**	 **243c**	 **244e**	B	51%
6	**123h**	 **243d**	 **244f**	B	79%
7	**98**	 **243e**	 **244g**	A	51%

8	**118c**	 **243f**	 **244h**	A	23%
9	**113**	**243e**	 **244i**	A	49%
10	**123d**	 **243g**	 **244j**	A	62%

[a]Reaction performed using *n*-BuLi, THF, -78 °C to rt afforded **244d** in 71% yield.



Scheme 76. Removal of the *P*,*P*-diphenylphosphinyl group under acidic conditions.

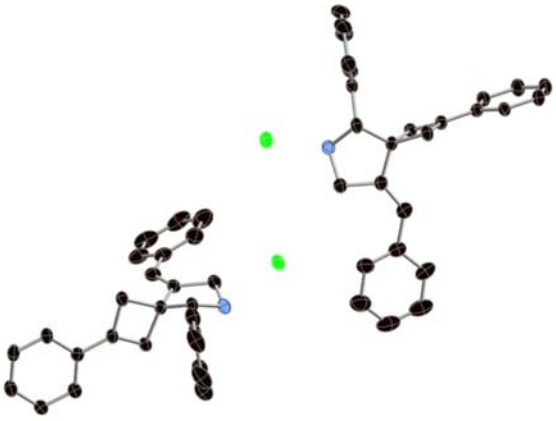


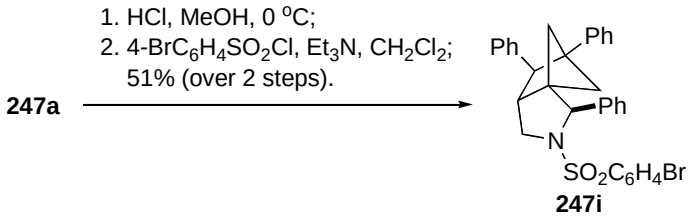
Figure 11. X-ray structure of **245**.

Figure 12. X-ray structure of **244a**.

2.2.3 [2+2] Reactions of Bicyclo[1.1.0]butane and Cinnamyl Bromides

While exploring the scope of the intramolecular ene reactions of bicyclo[1.1.0]butanes, we also studied the reactions with conjugated allyl bromides. When **98** was reacted with cinnamyl bromide, instead of the ene product we observed formation of tricyclic pyrrolidine **247a** that arose from the formal [2+2] reaction (Table 20, entry 1). Although this type of reactions has been described previously (see Section 2.1.3), both ene and [2+2] reactions were competing pathways and lack of the selectivity was a commonly encountered problem. The structure of

247a was confirmed by 1D and 2D NMR analyses including NOESY correlations. Additionally, **247a** was converted into sulfonamide **247i** (Scheme 77) and its structure was solved using X-ray crystallography (Figure 13).



Scheme 77. Synthesis of sulfonamide **247i**.

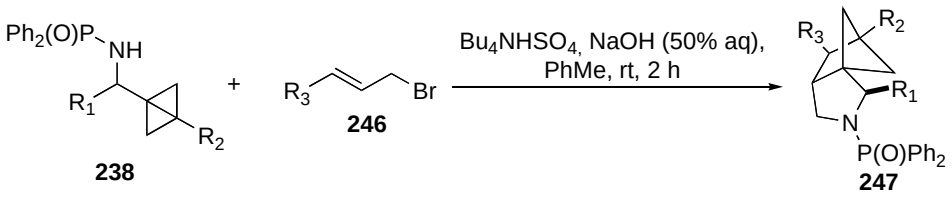
Figure 13. X-ray structure of **247i**.

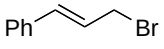
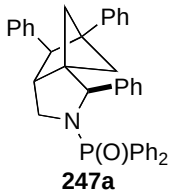
Table 20 sumarizes the scope of the [2+2] reaction using conjugated allyl bromides. Cinnamyl bromides containing electron-donating (entry 5) as well as electron-withdrawing groups (entry 6) were smoothly converted into the 3-azatricyclo[5.1.1.$0^{1,5}$]nonanes **247**. Similarly to the ene reaction, incorporation of the alkyl substitution at the vinyl position of the allyl chain that

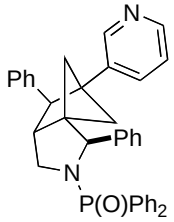
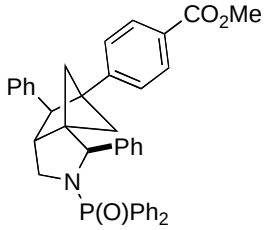
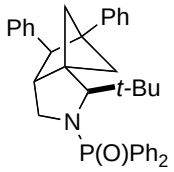
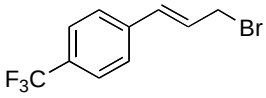
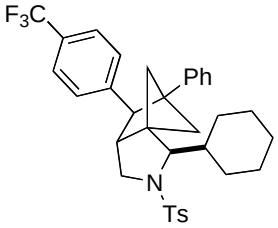
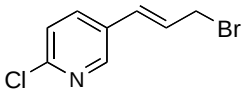
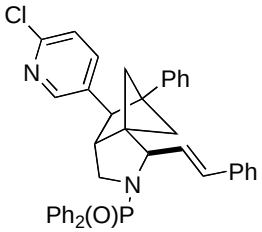
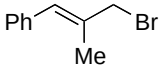
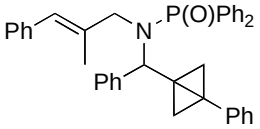
can interfere with the bicyclo[1.1.0]butyl ring afforded only the alkylated product (entry 8). The [2+2] cycloaddition reaction with conjugated allyl bromides is typically complete within two hours at room temperature, ca. 12 times faster than the ene reactions with non-conjugated alkenes, and the tricyclic pyrrolidines **247** were obtained as a single diastereoisomer. We were unable to isolate the putative cinnamyl amide intermediate, and characterization of the crude mixture after a full consumption of the starting material showed only the presence of the cycloadduct **247**.

Although the conjugated allyl bromides reacted specifically with the strained system in a [2+2] fashion, activated propargyl bromides underwent the ene reaction (Table 19). Finally, in none of the examples described in Table 20, formation of the ene product was observed, thus this reagent-controlled chemical divergence can be used in the diversity oriented synthesis of substituted heterocycles.

Table 20. Tandem alkylation – cycloaddition reaction of bicyclo[1.1.0]butanes.

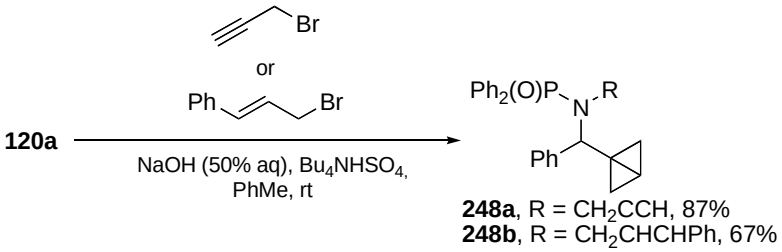


Entry	Amide	Cinnamyl bromide	Product	Yield
1	**98**	 **246a**	 **247a**	59%

2	**114c**	**246a**	 **247b**	32%
3	**113**	**246a**	 **247c**	93%
4	**118a**	**246a**	 **247d**	54%
5	**123d**	 **246b**	 **247e**	68%
6	**123f**	 **246c**	 **247f**	78%
7	**98**	 **246d**	 **247g**	71%

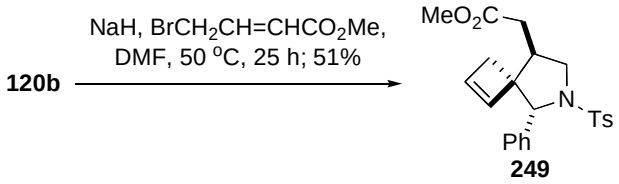
2.2.4 Reactions of Unactivated Bicyclo[1.1.0]butanes

Our studies on intramolecular ene and [2+2] reactions of bicyclo[1.1.0]butanes with alkenes and alkynes revealed that a spontaneous thermal conversion is facile only if the terminal position of the bicyclo[1.1.0]butane ring is substituted with an aromatic group. When **120a** was reacted with propargyl or cinnamyl bromide under phase-transfer conditions, formation of the alkylated products **248a,b** was observed (Scheme 78). After prolonged heating of **248a** in PhMe, no expected cyclobutene or tricyclic pyrrolidine was detected and the substrates eventually underwent decomposition. These results indicate the importance of conjugation of the strained system with an unsaturated counterpart that acts as an activator of the central bond of bicyclo[1.1.0]butanes (*vide infra*).[171,324] However, this requirement limits the scope of the ene and [2+2] methodology to compounds with aromatic rings at the terminal position of bicyclo[1.1.0]butanes. We envisioned that that incorporation of an electron deficient alkene that is capable of undergoing a formal ene reaction might be a viable strategy to overcome these limitations. This reasoning was supported by earlier studies on the pericyclic reaction of strained systems – reactions were facile with alkenes or alkynes activated by ester or nitrile groups. Additionally, electron-withdrawing groups are known to accelerate the Alder-ene reactions of regular allyl hydrocarbons, and, if the enone failed to undergo the ene reaction under the thermal conditions, Lewis acids are known to accelerate the pericyclic reactions with unactivated alkenes. However, it was unclear whether this type of system would undergo ene or [2+2] reactions.



Scheme 78. Synthesis of bicyclo[1.1.0]butanes **248a,b**.

First, we decided to explore direct alkylation methods using activated alkenes. Treatment of **120b** with NaH in DMF followed by methyl 4-bromocrotonate led to the formation of alkylated amide that subsequently could be converted into the ene product **249**. When allylation and subsequent ene reaction were performed using the combined conditions, **249** was obtained in good yield and selectivity (Scheme 79). Notably, phase transfer conditions proved to be inefficient in this reaction due to decomposition of bromocrotonate.

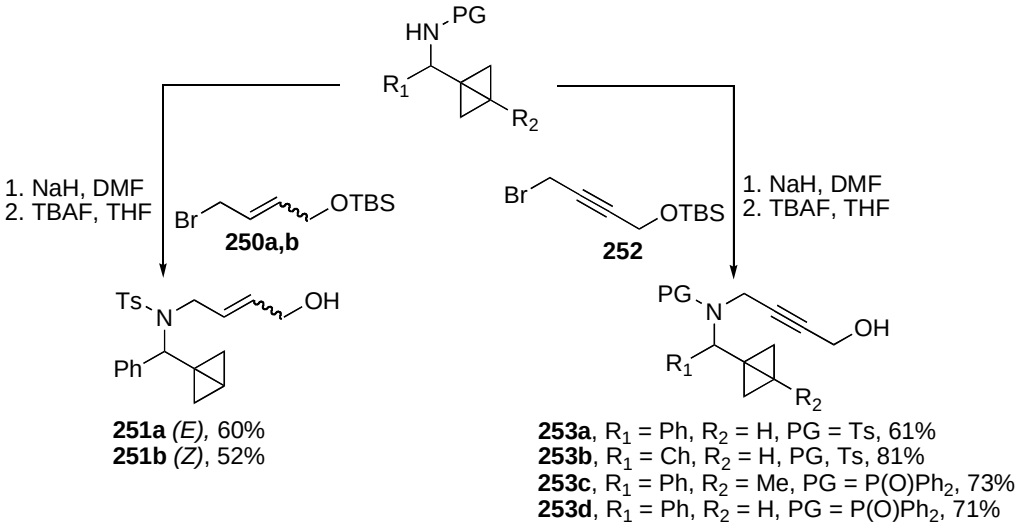


Scheme 79. Alkylation-ene reaction of methyl crotonate.

When we attempted to carry out the alkylation/ene reaction sequence on bicyclo[1.1.0]butane **120b** with methyl 4-bromobut-2-ynoate, we observed under a variety of conditions only decomposition of the alkylating reagent. Therefore, we tested methods for the introduction of the electron-withdrawing group at the terminal position of bicyclo[1.1.0]butane, and our efforts were directed towards the installation of an ester functionality at the terminal position

of the alkyne. To this end, treatment of **248a** with *n*-BuLi at -78 ˚C resulted in immediate formation of a deep-red solution followed by disappearance of the starting material. Presumably, a charge-transfer complex was formed under these conditions, followed by the ionic polymerization of either the alkyne or the bicyclo[1.1.0]butane ring.[325] Screening of different organolithium or Grignard reagents showed that decomposition of the substrate was the major obstacle.

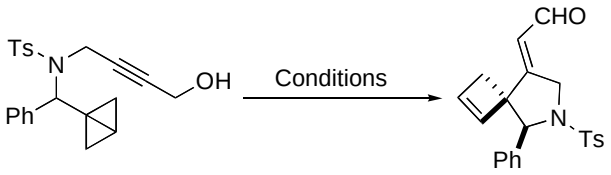
With these results, we were encouraged to look at the indirect methods to introduce an activated propargyl functionality hoping that the ene reaction was a feasible pathway for unactivated bicyclo[1.1.0]butanes and alkynes. We elected to use alcohols as masked activated alkynes that can be easily converted into propargyl aldehydes under oxidative conditions. Thus, alkylation of bicyclo[1.1.0]butylamides using NaH and TBS-protected propargyl or allyl bromide followed by liberation of the alcohol functionality using TBAF afforded alcohols **251** and **253** in good yields (Scheme 80). Due to incompatibility of bicyclo[1.1.0]butane to acidic conditions, the selection of the oxidants was restricted to reagents that operate under mildly basic or neutral conditions.



Scheme 80. Synthesis of allyl and propargyl alcohols **251** and **253**.

Table 21 lists the reaction conditions screened during the optimization studies on the tandem oxidation-ene reaction methodology and propargyl alcohol **253a** was used as the model system. Neutral conditions such as MnO_2 or TPAP[325] that have been used for allylic oxidation gave the desired product in very low yield (entries 1,2). Similarly, reactions with a weakly acidic reagent in the presence of a base resulted in a full consumption of the starting material and formation of many side products (entries 3).[326,327] Fortunately, Dess-Martin periodinane oxidation[328,329] performed at 0 ^{o}C in the presence of a bulky base afforded the desired ene product in modest yield but excellent diasteroselectivity (entry 6). Further optimization revealed that additional amounts of the base lead to an improvement of the reaction yield without deterioration of diastereoselectivity (97:3).

Table 21. Optimization of oxidation-ene reaction conditions.



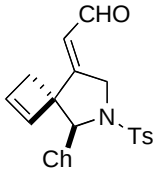
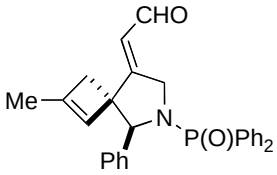
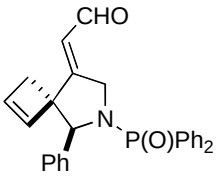
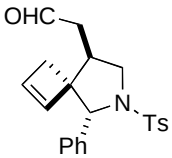
253a **254a**

Entry	Conditions	*dr*[b]	Yield[a]
1	TPAP, NMO, MS 4Å, CH_2Cl_2, rt	ND	<10%
2	MnO_2, CH_2Cl_2, rt	ND	<10%
3	PDC, CH_2Cl_2, rt	ND	<10%
4	Swern Oxidation, -78 ^oC	80:20	15%
5	DMP (1 equiv.), 2,6-Lutidine (2.5 equiv.), CH_2Cl_2, 0 ^oC	92:8	34%
6	DMP (2 equiv.), 2,6-Lutidine (5 equiv.), CH_2Cl_2, 0 ^oC	97:3	64%

[a]Based on ^1H NMR of a crude reaction mixture. [b]Isolated yield

The scope of the tandem oxidation-ene reaction methodology was explored by conversion of allyl and propargyl alcohols into pyrrolidine aldehydes (Table 22). These reactions proceeded smoothly with propargyl amides at 0 ^oC or rt and the full conversion of alcohols **253** was observed within 3-4 hours. Analysis of a crude reaction mixture after a full consumption of the substrates did not reveal the presence of the unrearranged propargyl aldehyde and under the oxidative conditions did not show detectable amounts of the [2+2] cycloadduct. Finally, it is noteworthy that oxidation of the alcohol functionality is necessary for the ene reaction to occur – prolonged heating of alcohol **253a** in PhMe resulted only in recovery of the staring material. The conjugated aldehydes are not stable and they undergo decomposition upon storage. Finally, alkylation of **118c** with homoallyl bromide under standard conditions afforded the homopropargyl amide **259** in modest yield, but efforts to access the substituted piperidine under thermal conditions failed.

Table 22. The scope of a tandem oxidation-ene reaction of propargyl and allyl alcohols.

Entry	Substrate	Product	*dr*	Yield
1	**253b**	 **255**	91:9	53%
2	**253c**	 **256**	94:6	51%
3	**253d**	 **257**	ND	59%
4	**251a**		ND	<5%
5	**251b**	**258**	ND	<5%

2.2.5 Mechanistic Analysis of Ene and [2+2] Reactions

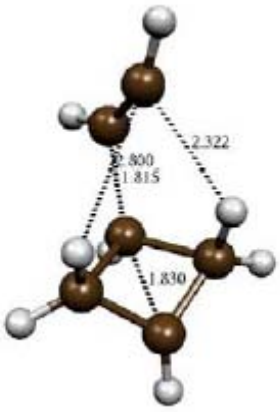
The studies on the thermal ene and [2+2] reactions of bicyclo[1.1.0]butanes provided an access to novel molecular architectures, but raising at the same time questions regarding the mechanism of these fundamental transformations. The high chemo- and diastereoselectivity was very intriguing, and a detailed mechanistic analysis may provide a basis for further advancement in the chemistry of strained molecules. Based on earlier and current studies, a mechanistic analysis of the ene and [2+2] reactions is presented below.

Our original design of the reaction of these strained systems was based on the notion that release of the strain energy would be a major driving force. Simple thermodynamic calculations indicated that all the reactions that are described in the proceeding sections are exothermic and conversion of bicyclo[1.1.0]butane into 3-ethylcyclobutene *via* reaction with ethylene releases ca. 39 kcal·mol^{-1} whereas the [2+2] reaction leading to bicyclo[2.1.1]hexane is exothermic by 47 kcal·mol^{-1}. Analogous reactions with acetylene is exothermic by ca. 55 and 51 kcal·mol^{-1}, respectively. Interestingly, the products of the pericyclic reactions with bicyclo[1.1.0]butane still retain a large portion of strain energy that may be applied in subsequent transformations (Figure 14).

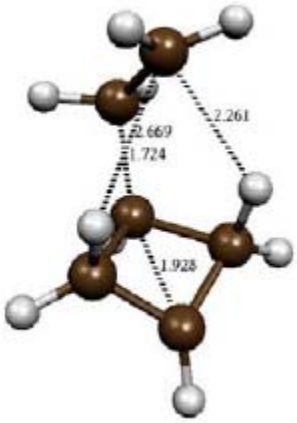
Figure 14. Energies of the reactions of bicyclo[1.1.0]butane with ethylene and acetylene calculated at the B3LYP/6-31G* level (+ZPVE).

In order to estimate the activation energies for the ene reactions, the QST3 algorithm[330] was applied in the search for the transition states (Figure 15). All located structures were reoptimized at the same level of theory and the saddle point was confirmed by the vibrational analyses – all negative frequencies are responsible for the formation of the ene product. The computed activation energies are 33 and 35 kcal·mol^{-1} for the reaction with acetylene and ethylene, respectively, and they are in close proximity to the estimated activation energy for the ene reaction of ethylene and propene (35 and 21 kcal·mol^{-1}).[239] The carbon atoms in the alkene and alkyne have

very pyramidalized geometries, but the carbons in the bicyclo[1.1.0]butane underwent a deformation to a smaller extent. The central bond of the bicyclo[1.1.10]butane experienceed significant elongation in the transition state and the distance of the newly formed CH bond is around 2.3 Å. However, attempts to locate a transition state for the [2+2] reaction of bicyclo[1.1.0]butane with ethylene resulted in a symmetrical local minimum structure that was not a transition state. A striking feature for this species is the presence of an almost planar carbon. These findings may be in accord with a radical mechanism for the cycloaddition reaction. However, the transition states for an alternatively possible two step process have not been located.



259a



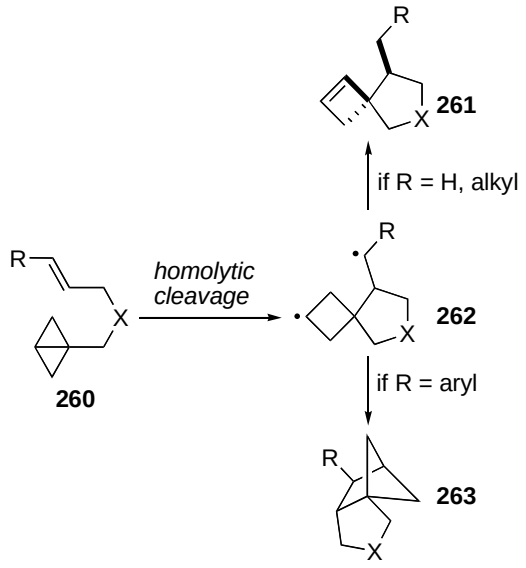
259b

Figure 15. Transition state structures for reactions of bicyclo[1.1.0]butane with acetylene and ethylene.

Concerted *vs.* Radical Mechanism. Identification of the plausible intermediates present in the ene reaction is crucial in understanding the chemical nature of the pericyclic transformation of the strained systems with alkenes and alkynes. Initially, it was proposed that both ene and

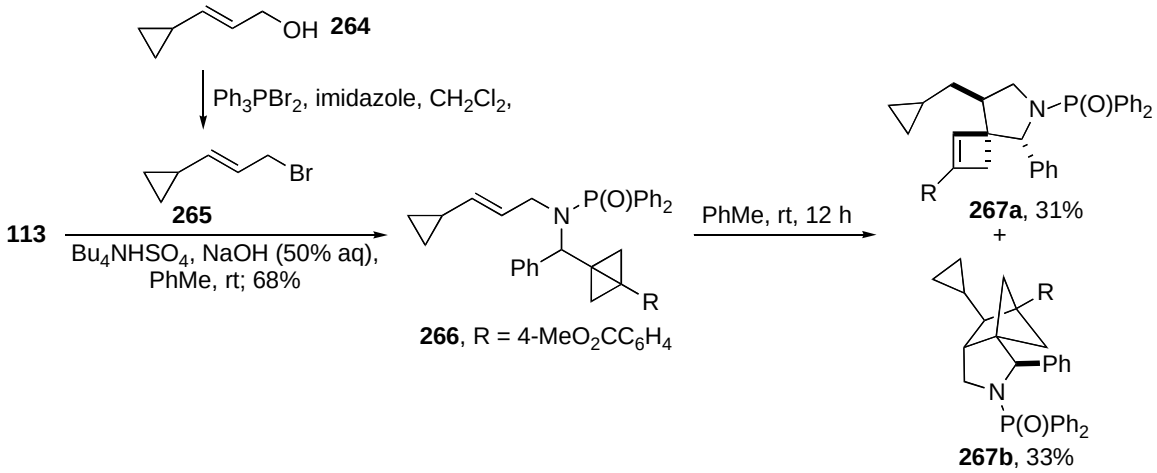
[2+2] reactions proceed *via* radical mechanism and the products of these transformations originate from a common diradical intermediate **262** (Scheme 81). This hypothesis was based on the earlier studies on the pericyclic reactions of strained systems carried out mostly using electron-deficient alkenes/alkynes or very reactive transient intermediates such as benzyne. A use of dicyanoacetylene in the pericyclic reactions with bicyclo[2.1.0]pentane led to conclusion that a negligible solvent effect is indicative of a radical or concerted mechanism. Based on these observations, the ene reactions of conjugated alkenes/alkynes (Table 22) may also proceed *via* a radical mechanism although the ionic pathway cannot be completely excluded. A convincing evidence of the radical intermediate in the reactions of bicyclo[1.1.0]butane with benzyne was given by Gassmann who observed the formation of a rearranged product that arises from the rearrangement of the diradical intermediate followed by a hydrogen transfer.

The notion that the pericyclic reaction can be initiated by a homolytic cleavage of the C_1C_3 bond in bicyclo[1.1.0]butane is supported by the theoretical calculation indicating the diradical character of this bond.[331,332] Additionally, it is believed that the ease of the interconversion of *endo*- and *exo*-isomers of 3-phenylbicyclo[1.1.0]butanes is caused by a facile formation of a stabilized diradical.[333] Although the pericyclic reactions of bicyclo[1.1.0]butanes proceed *via* two distinct pathways, a diradical intermediate may account for the formation of both products. However, the thermal cycloaddition reactions are restricted to a stepwise mechanism due to the symmetry of the alkene and the central bond in bicyclo[1.1.0]butane.[201]



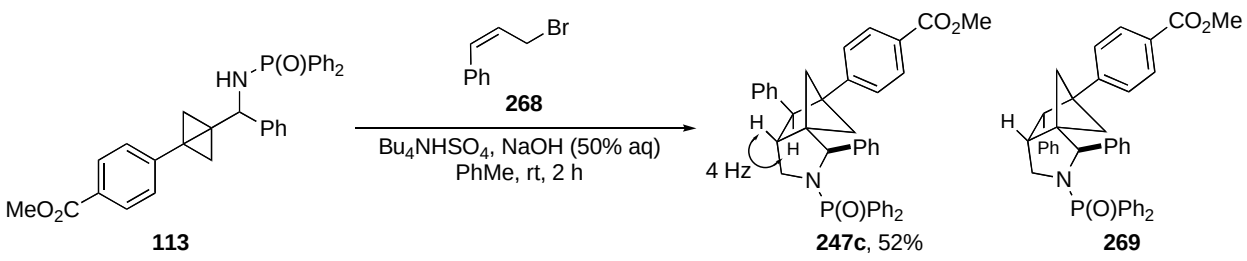
Scheme 81. Radical mechanism of ene and [2+2] reactions.

Based on earlier observations, we wondered if the diradical intermediate can be observed indirectly, and the putative radical can be detected chemically. It has been shown that opening of cyclopropyl ring is an indication of a radical intermediate[334,335] and the reverse cyclization process is 10^3 slower than the opening reaction,[336] thus the absence of the acyclic product is an indication of a very fast radical reaction. When we attempted to introduce the allylcyclopropyl probe at the amide nitrogen using in situ generated bromide **265a**, we found that quasi-stable intermediate **266** could be isolated in 68% yield (Scheme 82). Additionally, when **266** was allowed to react at room temperature in PhMe, **267a** and **267b** that retained cyclopropyl ring were isolated as the major reaction products. However, our attempts to introduce a faster radical probe such as the diphenylcyclopropyl group[337-339] using **264b** resulted only in decomposition of the material, thus preventing further studies on the reaction mechanism using fast radical probes.

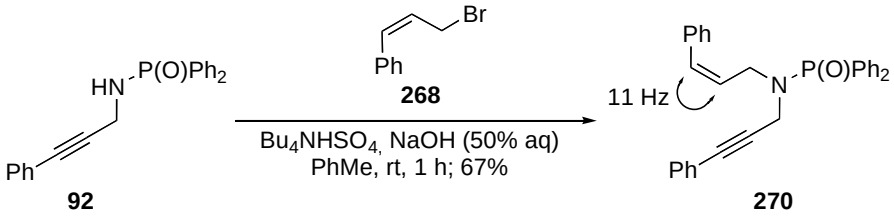


Scheme 82. Radical probe studies with **113**.

Interestingly, the presence of the radical intermediate can be inferred from the reaction using *(Z)*-cinnamyl bromide (Scheme 83). Bromide **268** was reacted with bicyclo[1.1.0]butane **113** and after 2 h at rt the tricyclic intermediate **247c** was obtained in 52% yield. No **269** that would be expected for the concerted, diastereoselective reaction was formed. The ^{1}H NMR analysis confirmed that the diagnostic vicinal coupling constant was 4 Hz (136.6^{o}) rather than the anticipated 8 Hz[114] that would correspond to two protons placed in a synclinal (3.6^{o}) arrangement. Optimization of the geometries (PM3) of the anticipated (**269**) and observed (**247c**) product revealed that the *anti*-isomer is ca. 4 kcal mol^{-1} more stable. In order to exclude possible isomerization of *Z*-cinnamyl bromide under the reaction conditions, diphenylphosphinamide **92** was reacted with bromide **268**, and the amide **270** with the conserved double bond configuration was obtained in 67% yield (Scheme 84).



Scheme 83. Reaction of **113** with (*Z*)-cinnamyl bromide.



Scheme 84. Reaction of **92** with (*Z*)-cinnamyl bromide.

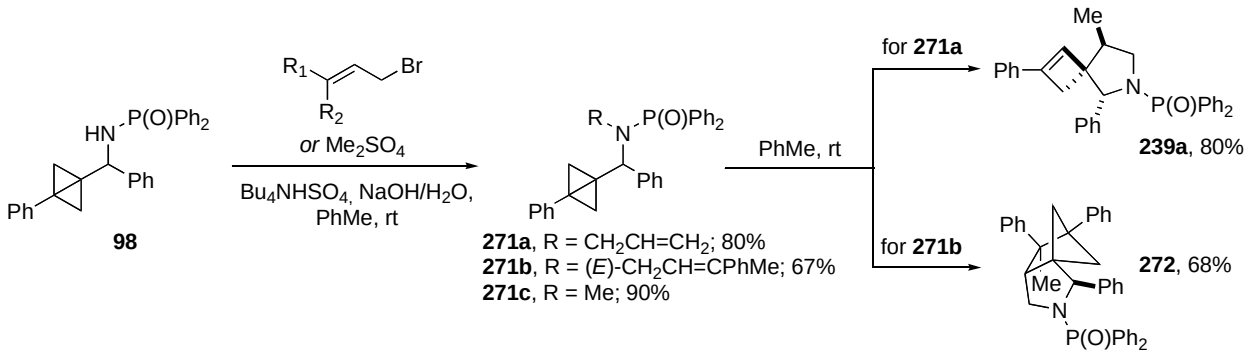
The observation that **247c** is a thermodynamic product derived from the *trans*-isomer suggests that the equilibration of the stabilized radical precedes the cyclization step and the formation of **267a** and **267b** may be due to special conformational effects that either prevent opening of the cyclopropane or facilitate the cyclization reaction. These observations can be supported by earlier studies on radical opening reactions that did not result in opening of cyclopropane ring.[340] Curiously, the combination of these results with the ene reactions (Scheme 74) leads to the notion that the relative configuration of the products of the pericyclic reactions of bicyclo[1.1.0]butane is not dependent on the geometry of the double bond. Finally, provided that the pericyclic reactions of bicyclo[1.1.0]butane proceed *via* a radical mechanism, proton transfer and recombination of the stabilized radicals are faster than the homolytic opening of the bicyc-

lo[1.1.0]butane. However, the rate determining step is the formation of a high energy diradical intermediate, thus diastereoselectivity in these reactions is governed by the first step and chemoselectivity is a result of second, faster step.

2.2.6 ESR Studies

In addition to the chemical studies, extensive Electron Spin Resonance (ESR)[341] spectroscopy studies were performed to unequivocally establish the presence of radical intermediates. The analytical measurements were performed in collaboration with Prof. Sunil Saxena and the spectral simulations and Figures 17-20 were generated by Mr. Byong-kyu Shin.

Our initial attempts to detect a radical intermediate during the ene and cycloaddition reactions were concentrated on a direct detection of radical intermediates. The unstable substrates **271a** and **271b** were prepared *via* the standard protocol (Scheme 85) and when the reaction was performed in an ESR tube for both of these reactants, weak signals were observed (Figure 16). The intensity of signal changed over time and eventually decreased to zero after ca. 24 h. In a control experiment, *N*-methyl derivative **271c** was subjected to the same measurements and the observed signal suggested that ESR-active species were generated during the rearrangement/cycloaddition reaction with bicyclo[1.1.0]butane. However, due to the low intensity and transient nature of the radical species generated in these reactions, a conclusive interpretation of the hyperfine couplings was not possible.



Scheme 85. Synthesis of the model substrates for the ESR studies.

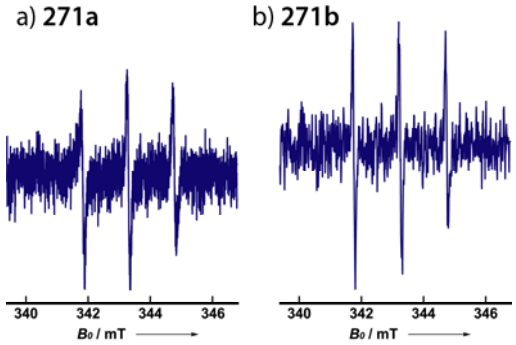


Figure 16. ESR signals generated during the rearrangement reactions of **271a** and **271b** in $CDCl_3$ at 1.5 M.

In order to generate more stable radical species suitable for the ESR analyses, spin-trapping experiments were performed.[342-346] The initial efforts were focused on the use of TEMPO as a trapping agent. However, the high intensity of the parent TEMPO signal obscured possible signals from the trapped radical intermediates. When MNP dimer (5-6 molar equivalents) was used, stable radical species were detected. We found that the signal underwent amplification over time and reached a plateau after 18 and 4 h for the rearrangement of **271a** and **271b**, respectively (initial and final spectra are depicted in Figure 17).

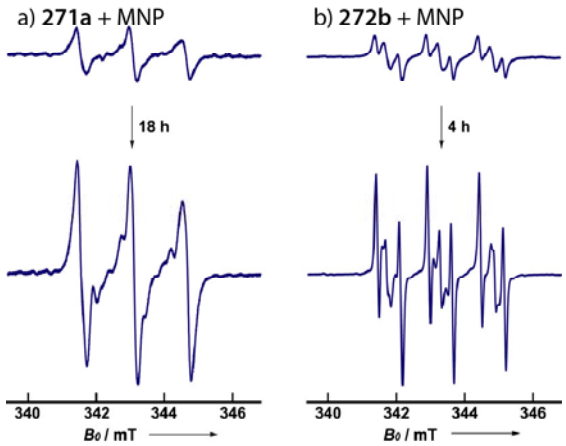
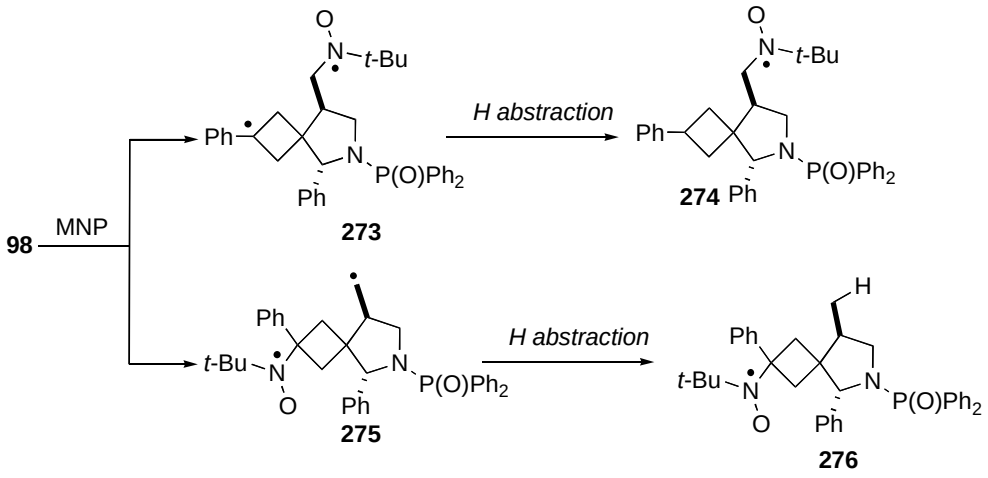


Figure 17. ESR spectra recorded during rearrangement of **271a** and **271b** in the presence of MNP.

We propose that the rearrangement reaction in the presence of the spin trapping agent results in the formation of two stable radicals **274** and/or **276** (Scheme 86). These intermediates are formed upon reaction of biradicals **273** and **275** which originally are the product of trapping of **262**[347] with MNP. Although the efficiency of radical trapping was low and we were unable to identify the trapping product *via* NMR, MS-TOF showed the presence of the monoadducts: for **274** or **276** ($C_{36}H_{40}N_2O_2P$, M^+ *m/z calc* 563.28 and $[2M+K]^+$ *calc* 1166.53), we observed *m/z* 563.54 and 1166.48. The major hyperfine coupling for **274** and **276** is a^N = 1.54 mT, which is consistent with the literature values for *N*-centered radicals.[348-350] Simulations of the ESR spectra of the two major components are presented in Figure 18, and the optimal fit between experimental spectrum is achieved assuming a 1:1 ratio of **274** and **276**.



Scheme 86. Proposed formation of spin adducts **274** and **276**.

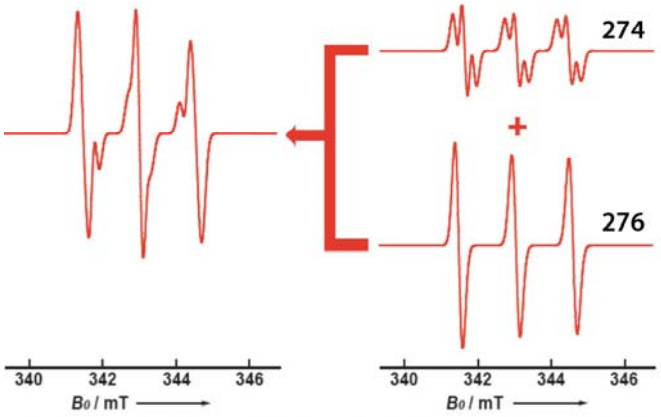


Figure 18. Simulated ESR spectrum for the mixture of adducts **274** and **276**.

In order to exclude the possibility for the interaction of solvents with the putative radical intermediates, the rearrangement reaction was performed in the presence of MNP in $CDCl_3$ and C_6D_6. No significant changes in the hyperfine coupling constants were observed and the overall structure of the signal remained the same (Figure 19).

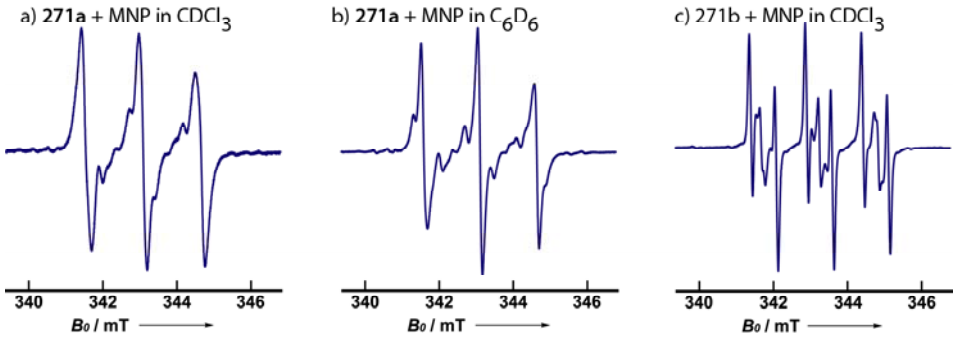


Figure 19. Solvent-derived spin adducts for the reactions of **271a** and **271b**.

Intrigued by the change in the intensity of the ESR signal, we were also interested in measuring the rate of the isomerization reaction. We found that the isomerization of **271a** showed first-order kinetics with $k = 0.056\ h^{-1}$ at 25 ^{o}C, $CDCl_3$. Similarly, NMR kinetic studies revealed that the cycloaddition of the substituted cinnamyl derivative **271b** is ca. four times faster with $k = 0.24\ h^{-1}$, 20 ^{o}C, $CDCl_3$. It is noteworthy that the reactions with the parent cinnamyl bromide are even faster (estimated ca. 18 times), whereas the incorporation of the methyl group at position 2 shut the reaction completely down. The corresponding graphs showing the dependence of concentration *vs.* time measured in 30 min and 15 min intervals for **271a** and **271b**, respectively are depicted in Figure 20 and Figure 21.

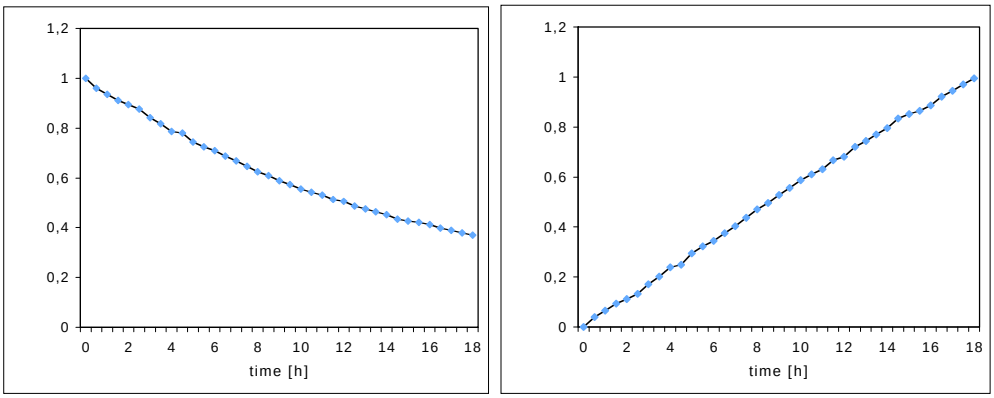


Figure 20. The graph of concentration *vs.* time for the rearrangement of **271a**.

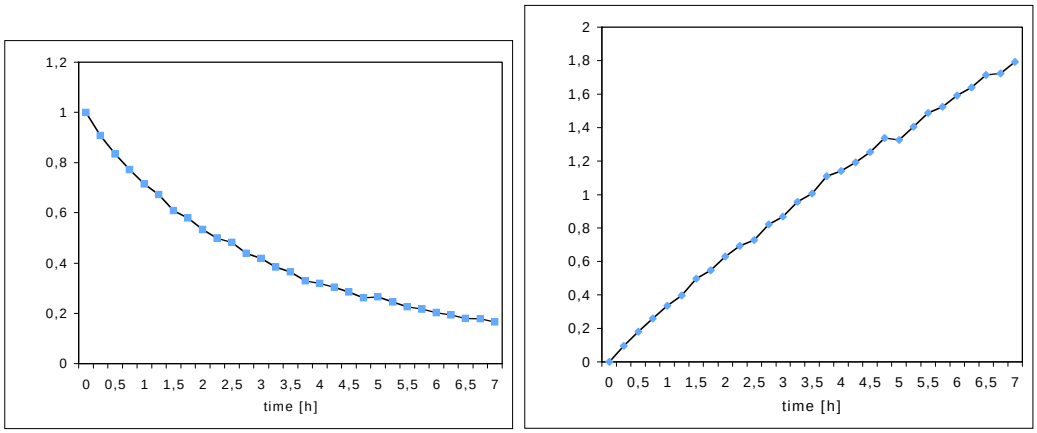


Figure 21. The graph of concentration *vs.* time for the rearrangement of **271b**.

2.2.7 The Effect of Conjugation on the Reactivity and Selectivity

The present study demonstrates that bicyclo[1.1.0]butanes activated with an aromatic ring are much more reactive than their corresponding unsubstituted analogs, or bicyclo[1.1.0]butanes with an alkyl group or hydrogen at the terminal position. Keeping in mind the radical mechanism of the ene and [2+2] reactions, the resonance stabilization of the high-energy diradical interme-

diate by aromatic groups in conjugated the bicyclo[1.1.0]butanes may contribute to the lowering of the energy of the diradical intermediate. In addition to transition state stabilization, the aromatic group is responsible for the increased reactivity of the bicyclo[1.1.0]butane due to conjugation of the central bond with the aromatic system. The effect of the conjugation on the electronic structure of bicyclo[1.1.0]butane can be studied by an analysis of the parent molecule and its substituted analogues. The structures of the model systems were optimized at the AM1 level, and selected geometrical parameters and energies of the frontier orbitals are represented in Figure 22.

Figure 22. Frontier orbitals of bicyclo[1.1.0]butanes and selected geometrical parameters. Structures were optimized at the AM1 level of theory and the energies are given at the same level in eV.

Figure 23. X-ray structures of **120b** and **123c**.
Selected Geometrical Parameters for **120a**: C_1C_2 – 1.333 Å, C_1C_3 – 1.456 Å; **123c**: C_1C_2 1.494 Å, C_1C_3 – 1.517 Å, C_1C_4 – 1.500 Å.

Substitution of the terminal position with an aromatic ring is responsible for raising the energy of the HOMO and shortening the energetic gap between the frontier orbitals as compared to the parent bicyclo[1.1.0]butane. The LUMO of 1-phenylbicyclo[1.1.0]butane is mainly located on the aromatic ring and is lower in energy compared to the unsubstituted analog. Additional information about the influence of conjugation on the reactivity of the strained system can be gained by the analysis of the geometrical parameters of bicyclo[1.1.0]butanes. The parent molecule or the 1-methylbicyclo[1.1.0]butane substituted with a simple alkyl group are characterized by similar bond lengths of the central bond whereas introduction of the phenyl group increased the bond length in 1-phenylbicyclo[1.1.0]butane to 1.51 Å. If the pericyclic reactions of bicyclo[1.1.0]butanes proceed *via* radical intermediates, the HOMO-LUMO gap would correspond the ease of electron fransfer in the intermolecular reactions. In order to relate these observations to our systems, **120b** and **123b** were crystallized from Et_2O and their single-crystal structures were obtained using X-ray crystallography. Figure 23 depicts their molecular structures, including selected geometrical parameters.

The length of the central bond in **120b** is 1.456 Å, whereas the same bond **123b** is significantly longer – 1.517 Å.[30,35,351-353] Due to the symmetry of the orbitals forming the central bond, the aromatic ring must adopt a perpendicular orientation relative to the bicyclo[1.1.0]butane ring. The dihedral angle between aromatic ring and bicyclo[1.1.0]butane is 88.3^o (98^o) and a small deviation from the optimal 90^o is caused most likely by the crystal packing forces. Furthermore, the interflap angles α defined as the angles between two cyclopropane rings for **120b** and **123b** are 117.8^o and 122.4^o, respectively. Since the reacting alkene approaches the bicyclo[1.1.0]butane from the inside of the ring, **123b** characterized by a larger α is also more accessible for the incoming alkene due to reduced steric interactions. A correlation between the length

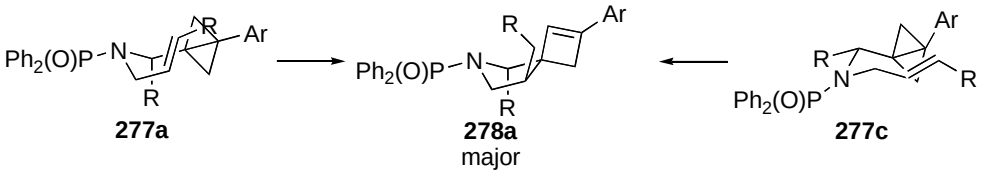
of the central bond and α in bicyclo[1.1.0]butane has also been noted by Gassmann[30] – elongation of C_1C_3 bond, as a consequence of steric or electronic bias, results in larger α. Analysis of the factors responsible for different reactivity of conjugated and non-conjugated systems indicates that the lower kinetic stability may be the major contributor to the observed reactivity of conjugated bicyclo[1.1.0]butanes.

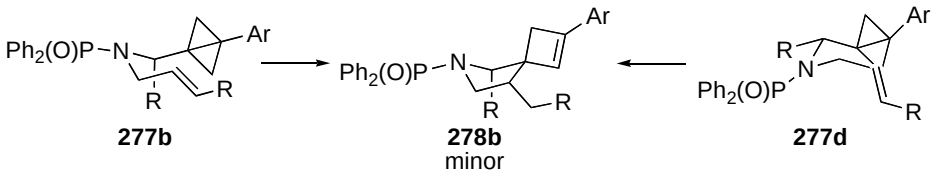
Previous results show that a significant difference in the reaction pathway is observed if the allyl group is substituted with an aromatic ring. Conversion of the bicyclo[1.1.0]butane into the azatricyclo[$5.1.1^{1,5}$]nonane is faster, as might be expected for the systems that display a lower kinetic barrier due to a low-laying LUMO. The second step in these reaction is a recombination of stabilized radicals that is a consequence of the conformational preference of the allyl chain.

Diastereoselectivity in Ene and [2+2] Reactions. In addition to high chemoselectivity, intramolecular pericyclic reactions of bicyclo[1.1.0]butanes show very high diastereoselectivity. Because only electronic factors control the ene *vs.* [2+2] selectivity, the discussion of the diastereoselectivity of the pericyclic reactions of allyl amides is only presented for the ene reaction. A parallel stereochemical analysis can be carried out for the [2+2] reactions as the products of both pericyclic reactions possess analogous stereochemistry around the pyrrolidine ring.

Based on the observed stereochemistry, we considered four possible transition states where the allyl chain is oriented in boat (**277a**,**c**) or chair (**277b**,**d**) conformations (Scheme 87). Since the stereochemistry of the endocyclic double bond in cyclobutene is coupled with the orientation of the allyl chain (intramolecular transfer of the *endo* proton of bicyclo[1.1.0]butane), formation of only two diastereoisomer **278a** and **278b** was considered. Additionally, the nitrogen atom of the *P,P*-diphenylphosphinamide is known to adopt a tetrahedral geometry as can be de-

duced from the analysis of crystal structures (e.g. **242**) as well as from NMR spectra of the amides that do not show the presence of rotamers at room temperature. Given that the bulky amide group occupies a pseudo-equatorial position, the α-substituent R is forced to accept an axial orientation so that the ene reaction must proceed *via* the boat-type conformer **277a** where the reacting alkene approaches the strained system from the inside of the bicyclo[1.1.0]butane. The preference of the allyl chain to adopt the axial conformation is a consequence of the steric interaction between R and the methylene group of the allyl chain that become more severe in the transition state. However, if R is predominantly in an equatorial form (**277a** or **277d**), this type of interaction is diminished and the allyl chain would exist in a more stable *s*-trans form leading to formation of the observed product **278a**. The presented model accounts also for a lack of difference in the selectivity of the reaction of *(E)*- and (*Z)*-alkenes since the terminal substituents are located away from the methylene groups and the vinyl carbon undergoes a pyramidalization in the transition state orienting the alkyl groups away from the reacting bicycle. However, the high selectivity (>95:5) was significantly reduced in the reaction with 2-methylallyl amide (Scheme 73). Not only the methyl group experiences severe steric interactions with the methylene groups of the bicyclo[1.1.0]butane, but a similar size of the Me and CH_2 groups leads to a low discrimination of the two possible conformers **277a** and **277b**.



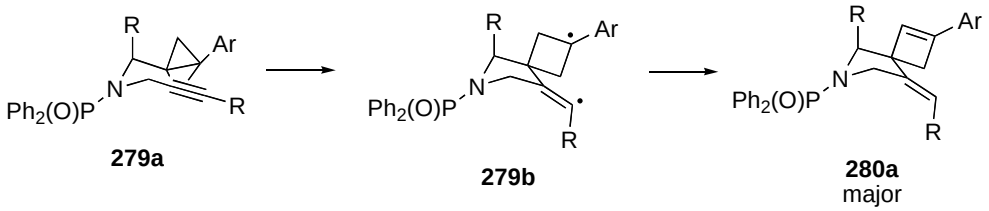


Scheme 87. Mechanistic rationale for the diastereoselctivity in the ene reaction of allyl amides.

Finally, the reversal of the diastereoseselctivity in the intramolecular reactions of propargyl amides is at first somewhat surprising. Also, the high level of transfer of the stereochemical information across the pyrrolidine ring is very interesting since the alkyne *sp* hybridized carbon orients the propargyl chain into a conformation where the triple bond parallels the central bond in bicyclo[1.1.0]butane. The bicyclo[1.1.0]butyl ring can, however, be tilted by the α-substituents, thus preexposing one of the methylene groups towards the reaction with the propargyl group. Although the crystal structures of **120b** and **123b** did not provide a conclusive support for a well-defined conformer (at least in the solid state), the conformational bias of the bicyclo[1.1.0]butane may play an important role in determining the stereochemistry of the newly formed bonds.

Two conformers of the *N*-propargyl bicyclo[1.1.0]butane are depicted in Scheme 88. Like in the case of allyl group, the axial orientation of R substituent in **279a** caused by the amide moiety led to formation of a stabilized radical that subsequently underwent a fast proton transfer reaction with a more accessible methylene group. The crystal structure of **244a** shows that the *t*-Bu group is oriented in axial position whereas the *P,P*-diphenylphosphinyl group is in an equatorial orientation, thus supporting the hypothesis that even a bulky group can be accommodated into an axial orientation. Based on this analysis, the configuration of the cyclobutene ring is determined by the axial substituent which forces one of the methylene groups in **273b** into the

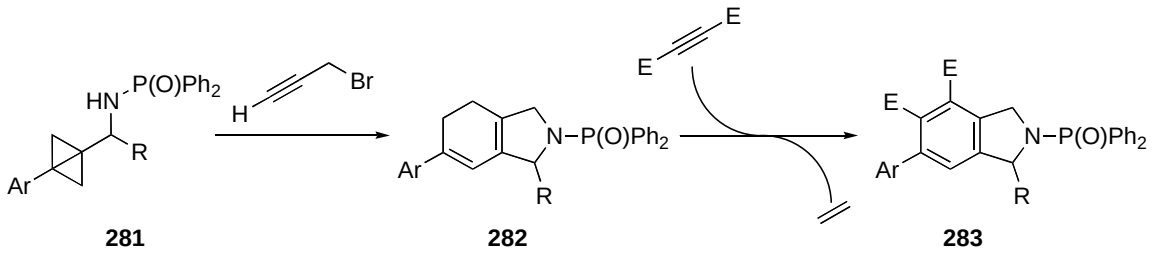
proximity of the vinyl radical. The stereochemistry of the exocyclic double bond is a consequence of the intramolecular proton transfer.



Scheme 88. Mechanistic rationale for the diastereoselctivity in the ene reaction of propargyl amides.

2.2.8 Studies towards Novel Benzannulation Methodology

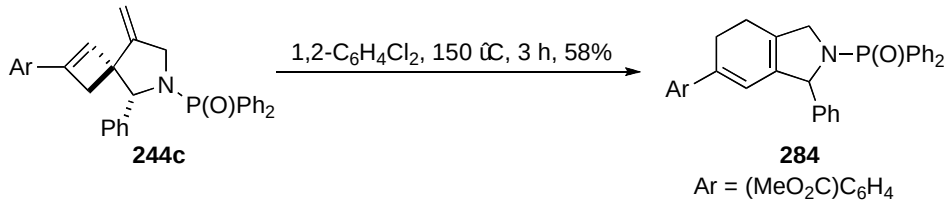
The reactive cyclobutene ring obtained by the diastereoselective ene reaction of the bicyclo[1.1.0]butane with an alkyne represents an attractive synthetic intermediate. We were especially interested in developing a benzannulation methodology based on the ene reaction of the bicyclo[1.1.0]butane with propargyl amides (Scheme 89). We envisioned that bicyclo[1.1.0]butane **281** would react with propargyl bromide to afford the ene product that subsequently undergoes a *4e*-electrocyclic opening followed by *6e*-closure. The unsaturated tetrahydroisoindole **282** would be then treated under thermal conditions with an activated alkyne that should induce a Diels-Alder/retro-Diels-Alder reaction sequence to afford the desired polysubstituted benzene derivative **283**. However, because the cyclobutene ring is substituted with groups of similar electronic and steric properties,[354] a low torquoselectivity may be envisioned resulting in the formation of a mixture of (*E*)- and (*Z*)-isomers during the initial opening step. In order to test the feasibility of this reaction sequence, conditions for the conversion of bicyclo[1.1.0]butane **282** into the tetrahydroisoindole derivative had to be established.



281 **282** **283**

Scheme 89. Approach towards polysubstituted isoindoles.

Stirring a mixture of **244c** in PhCl for 3 h at 150 °C afforded the expected tetrahydroisoindole derivative **284** in 58% yield (Scheme 90). This product was unstable upon storage and possibly underwent decomposition during purification. In order to convert **113** into **284**, a number of conditions were screened and summarized in Table 23. Unfortunately, the best yield that could be obtained in a direct reaction sequence did not exceed 38%. We felt that perhaps the strongly basic conditions led to the decomposition of the material during the extensive heating in the presence of inorganic bases.

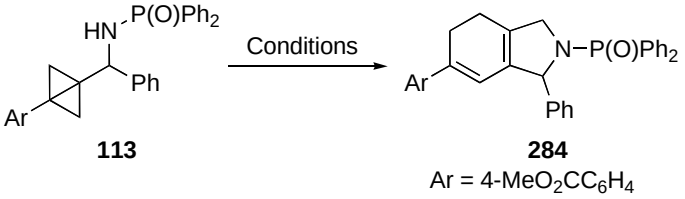


244c **284**

Ar = $(MeO_2C)C_6H_4$

Scheme 90. Synthesis of tetrahydroisoindole **284**.

Table 23. Optimization of the reaction conditions for the synthesis of **284**.

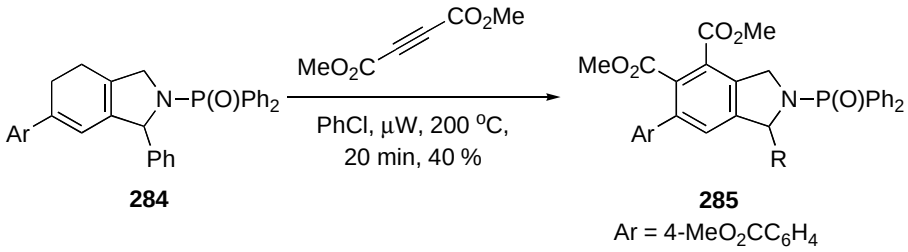


113 **284**

Ar = 4-$MeO_2CC_6H_4$

Entry	Conditions	Yield
1	Propargyl bromide, NaOH, K_2CO_3, Bu_4NHSO_4, 1,2-$Cl_2C_6H_4$, 178 ^oC, 6 h	23%
2	Propargyl bromide, NaOH, K_2CO_3, Bu_4NHSO_4, PhCl, 200 ^oC (μW), 1 h	38%
3	Propargyl bromide, NaOH, K_2CO_3, Bu_4NHSO_4, xylene, 140 ^oC, 6.5 h	32%

We also were interested in testing if the Diels-Alder/retro-Diels-Alder reaction sequence was a feasible approach towards polysubstituted benzenes. Heating **284** with an excess of DMAD afforded the expected product **285** in only 40% yield. Due to the low efficiency of the desired process, this approach towards the synthesis of polysubstituted isoindoles was not further pursued (Scheme 91).



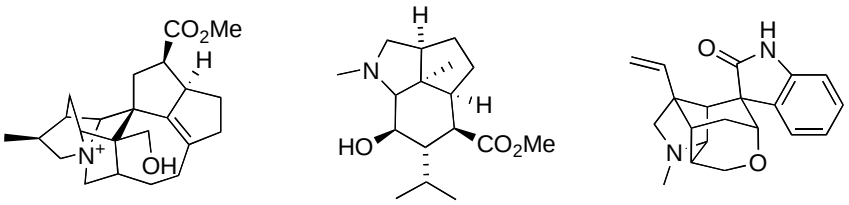
284 **285**

Ar = 4-$MeO_2CC_6H_4$

Scheme 91. Synthesis of **285**.

2.3 CONCLUSIONS

The notion that the frontier orbitals in bicyclo[1.1.0]butane possess similar symmetry as alkenes and are located around the central bond is crucial in understanding the reactivity of this strained system. However, its distinctive topological properties allow for an access to novel chemical reactivity, making bicyclo[1.1.0]butanes unique synthetic building blocks. These properties combined with the ease of this molecule to undergo a cleavage of the central bond resulted in the development of a number of highly selective transformations. We were able to demonstrate that alkenes or alkynes can initiate a pericyclic conversion of bicyclo[1.1.0]butane and, depending on the electronic nature of the double bond, two distinctive reaction pathways were observed. If the alkene is substituted with an aromatic ring, the bicyclo[1.1.0]butane is spontaneously converted into a tricyclic pyrrolidines; otherwise, a formal ene reaction is the prevailing reaction pathway. The high selectivity in these reactions is particularly noteworthy since the reactions can be performed either at room temperature or, if bulky reagents are used, at elevated temperatures using mild conditions and inexpensive reagents. Our studies showed also that the strain could be advantageously applied in a diastereoselective formation of the quaternary stereocenters. Finally, the judicious selection of the reaction conditions allowed us to perform well-orchestrated cascade reactions encompassing a palette of pericyclic transformations. This demonstrates that bicyclo[1.1.0]butanes can be successfully applied in the synthesis of polyfunctional organic molecules with the ultimate goal directed towards the synthesis of complex natural products such as the *Daphniphyllum* alkaloids (daphniglaucin A[355]), Manzamine-type natural products (nakadomarin, Figure 1), Dendrobine-type sesquiterpenoids (mubironine C[356]), or gelsemine (Figure 24).



Daphniglaucin A *Mubironine C* *Gelsemine*

Figure 24. Natural products suitable for the synthesis using pericyclic reactions of bicyclo[1.1.0]butanes.

3.0 METAL-CATALYZED REACTIONS OF BICYCLO[1.1.0]BUTANES

3.1 INTRODUCTION

Transition metals have played a central role in the development of general chemical methodologies based on the reactions of strained molecules.[357] The utility of these technologies is typically characterized by the mild reaction conditions, the predictable outcome of the reactions and the ability to tune the metal centers with an appropriate ligand. Cyclopropane, cyclobutanes, and their corresponding analogs undergo facile ring opening and these reactions follow oxidative addition and reductive elimination pathways. The fundamental aspects of the reactivity of the transition metal used, typical cyclopropane derivatives as well as selected applications will be discussed in this chapter.

3.1.1 Transition Metals and Strained Molecules

The fundamental picture of the interaction of strained carbocycles with (late) transition metals parallels a classical description of the interaction of transition metals with alkenes (Dewar-Chatt-Duncanson model[358,359]). In this model, the transition metal accepts electrons from a π C-C bond of the alkene with a simultaneous donation of *d*-electrons into the empty π*-orbitals (Figure 25). The former interaction can be viewed as a σ-bonding interaction, whereas the later resembles the π-bonding type due to their symmetry properties. The proportion of bonding and back-bonding is controlled by the nature of the metal, the electronic structure of the unsaturated counterpart and the nature of the remaining ligands. The ability of the metal to form a σ-bond is correlated with its electron affinity, and the promotion energy is responsible for the electron-donating capabilities of the metal centers. In general, ligands which increase electron density also lower the promotion energy and the electron affinity of the metal (e.g. amines). Alternatively, the ligands which reduce the overall electron density (e.g. CO) increase both of these parameters. Phosphines combine these two types of interactions as they can donate their σ-electron density acting at the same time as acceptors of π-density form the metal.

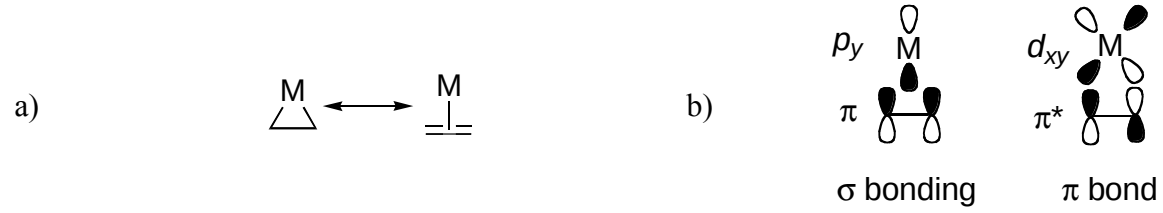


Figure 25. Resonance forms of metallacyclopropane and MO description of the Dewar-Chatt-Duncanson model.

For the interactions of the transition metals with cyclopropanes, where the strained C-C bond is regarded as having significant *p*-type character (Walsh model), the bonding σ-orbital of cyclopropane interacts with a *d*-orbital and the σ*-bond interacts with a *d*-orbital of a proper symmetry (Figure 26). The resultant four-membered intermediate (stable or intermediate) generally suffers from a poor stabilization *via d*-σ* donation, as the antibonding orbitals in cyclopropanes are located higher in energy than the π*-orbitals in olefins. In other words, the σ-bonding capability will play a more important role and the back-bonding will be of a lesser significance. The experimental support of this model was disclosed during the studies of $[PtCl_2(CH_2CH_2)]_2$ with cyclopropanes substituted with electron-withdrawing and electron-donating groups.[360] The rate of formation of metallacyclobutane was correlated with the character of the substituent and groups such as CN, MeCO, and MeO_2C completely retarded the formation of the organometallic complex. The parent cyclopropanes could be, however, regenerated by treatment with KCN.

The subsequent sections discuss the isomerization reactions of strained carbocycles catalyzed by Rh(I) complexes followed by reactions of bicyclo[1.1.0]butanes. Extensive reports on the reactions of other metals can be found elsewhere.[357,361]

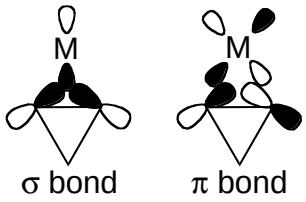


Figure 26. Bonding model in a metal-cyclopropane complex.

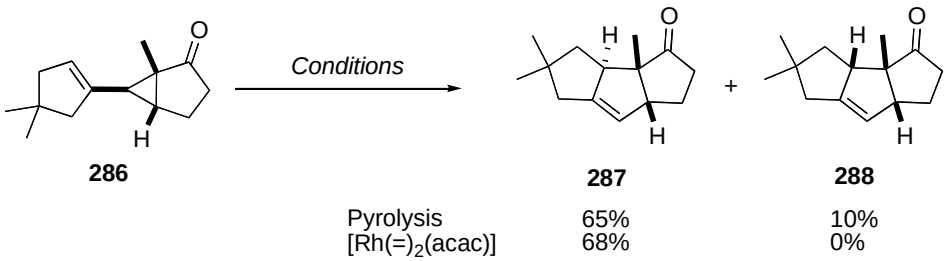
3.1.2 Rh-Catalyzed Isomerization of Cyclopropanes

The catalytic reactions of unfunctionalized cyclopropanes with rhodium are typically restricted to the cleavage of the C-C bond *via* the direct insertion of the metal into the σ-bond. Typical examples include isomerization of quadricyclane to norbornadiene,[362] but in some other related examples (isomerization of tricyclo[3.2.1.$0^{2,4}$]oct-6-ene)[363] a more complex mechanistic picture was proposed by the authors in order to explain the product distribution. In a stoichiometric manifold, an alternative mechanism is also possible – insertion into the C-H bond with a coordinatively-unsaturated Rh complex and rearrangement into the metallacycle generated.[364,365] From a synthetic perspective, silyl-protected cyclopropyl alcohols can be opened to vinyl ethers in the presence of Rh(I) catalyst with modest selectivity.[366]

The reactivity of the cyclopropyl ring is significantly higher if the strained ring is activated by an unsaturated C-C bond. Alkylidenecyclopropanes udergo a facile opening to butadiene catalyzed by rhodium hydrides ([$RhH(CO)(PPh_3)_3$]).[367] These reactions are initiated by hydrometallation of the exocyclic double bond and isomerization to a σ-allyl complex followed by a β-hydride elimination to give butadiene. The isomerization reactions have also been combined with a hydrosilylation protocol in which the metal hydride acts as a catalyst for the cyclopropane opening and the addition of silane to butadiene.[368] In cases of cyclopentenones, the reaction with Wilkinson's catalyst resulted in decarbonylation of the substrate and generation of acetylenes.[369]

Cyclopropanes are particularly useful reagents in the catalytic isomerization reactions with metal complexes if they are in conjugation with a vinyl group. One of the earlier examples of the vinylcyclopropane rearrangement reaction catalyzed by Rh(I) was described by Hudlicky (Scheme 92).[370] In addition to much lower reaction temperatures, the metal-catalyzed reaction

showed improved selectivity. The vinylcyclopropane-cyclopentene reaction, however, is usually facile for systems in which the cyclopropyl group is activated by a carbonyl or vinyl group.[371] Isomerization of vinylcyclopropanes in which the unsaturated carbon-carbon moiety is a part of the cyclic systems has been also reported.[372]

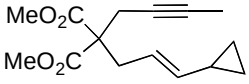
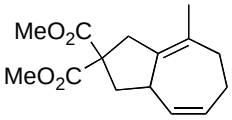
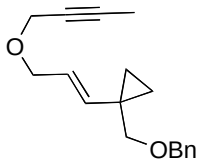
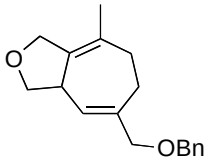
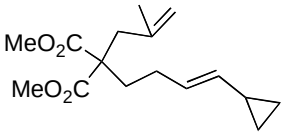
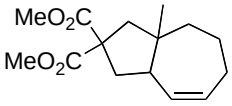
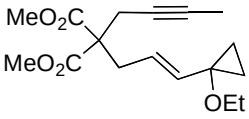
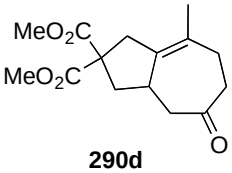
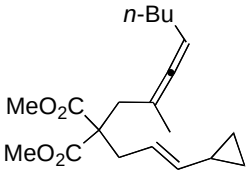
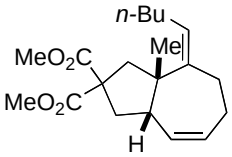


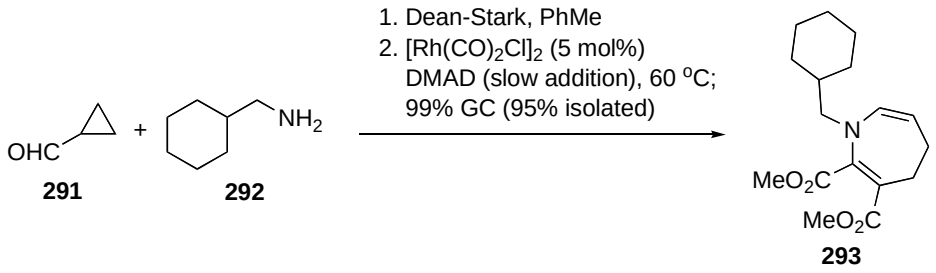
Scheme 92. Thermal and Rh-catalyzed vinylcyclopropane rearrangement.

The notion that the vinyl group facilitates the opening of the cyclopropyl ring *via* formation of a metallacyclopentate has been used extensively by Wender in the development of an intra- and intermolecular formal [5+2] cycloaddition reaction.[373] In the initial report, the researchers found that Wilkinson's catalyst was an efficient pre-catalyst for the isomerization reaction of tethered alkynes and vinylcyclopropanes.[374,375] The observation that a change from a non-polar (PhMe) to a polar solvent (TFE) had a beneficial effect on the rate of the reactions led the authors to propose that the dissociation of a chloride ligand and opening of a vacant coordination site was responsible for the rate acceleration. Addition of AgOTf in a 1:1 ratio to Wilkinson's catalyst had a dramatic effect on the reaction – the cycloisomerization was complete within 45 min, compared with days for the original catalytic system. Additionally, tethered alkenes were also effectively converted into the corresponding product with the new protocol. Table 24 lists representative examples of intramolecular [5+2] cycloaddition reactions.

The first example of an intermolecular [5+2] cycloaddition was disclosed by Wender using $[Rh(CO)_2Cl]_2$.[376] Although the unsubstituted cyclopropanes failed to give the expected products with Wilkinson's catalyst, the siloxy and alkoxy-substituted vinylcyclopropanes were effective in the generation of cyclopentenones[377] and cyclopentadienes.[378,379] An interesting extension of this methodology involves a three-component synthesis of azepines starting from an aldehyde, amine and DMAD to furnish **293** in 95% yield (Scheme 93).[380]

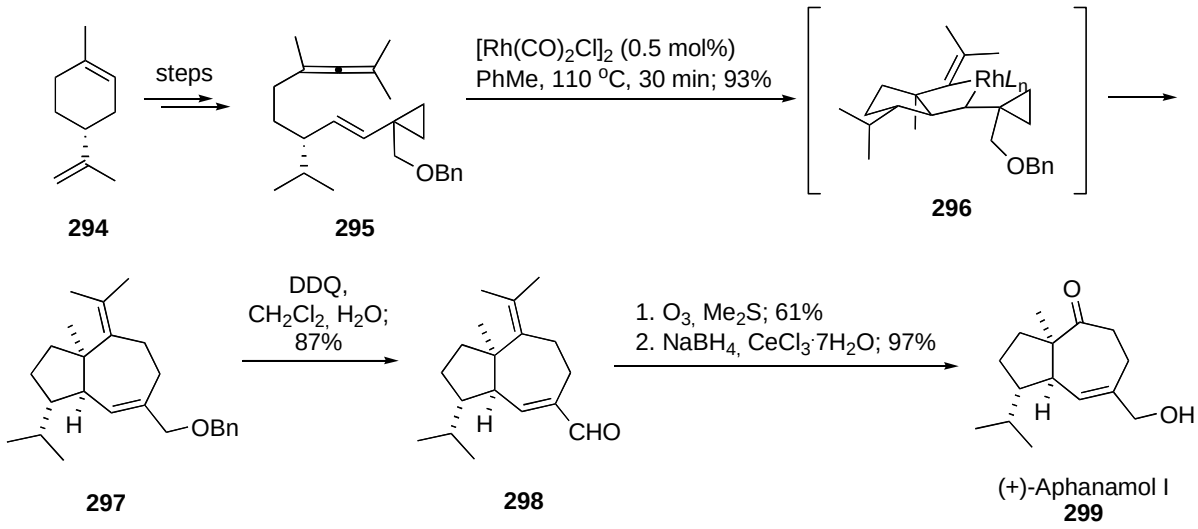
Table 24. Representative examples of Rh-catalyzed intramolecular [5+2] cycloadditions.[373]

Entry	Substrate	Catalyst	Conditions	Cycloadduct	Yield
1	 **289a**	$[Rh(PPh_3)_3Cl]$ 10 mol%	110 °C, 48 h	 **290a**	84%
2	**289a**	$[Rh(PPh_3)_3Cl]$ 0.5 mol% + AgOTf	0.23 M, 110 °C, 20 min	**290a**	83%
3	 **289b**	$[Rh(PPh_3)_3Cl]$ 5 mol% + AgOTf	110 °C, 60 min	 **290b**	90%
4	 **289c**	$[Rh(PPh_3)_3Cl]$ 0.5 mol% + AgOTf	PhMe (0.01 M), 110 °C,1 h	 **290c**	94%
5	 **289d**	$[Rh(CO)_2Cl]_2$ 5 mol%	CH_2Cl_2 (0.05 M), rt, 30 h	 **290d**	75%
6	 **289e**	$[Rh(PPh_3)_3Cl]$ 0.5 mol% + AgOTf	PhMe (0.01 M), 100 °C, 16 h	 **290e**	70%



Scheme 93. A three-component synthesis of 4,5-dihydro-1*H*-azepine **293**.

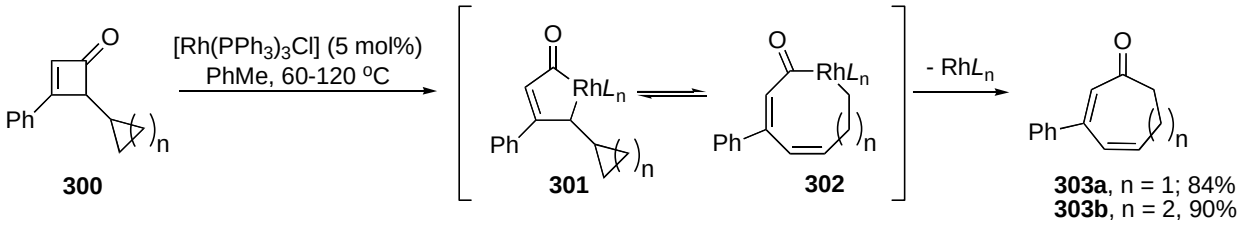
The power of this new chemical strategy was demonstrated by Wender in the synthesis of carbocyclic naturals products. For example, in the synthesis of (+)-aphanamol I, (*R*)-(+)-limonene was converted into the allenyl precursor *via* standard manipulations and the corresponding precursor was transformed into the bicyclic core using a Rh(I) catalyst in a remarkable 93% yield and in complete diastereoselectivity (Scheme 94). After additional red-ox manipulations, the natural product was obtained in 13 steps.[377]



Scheme 94. Synthesis of aphanamol I by Wender.

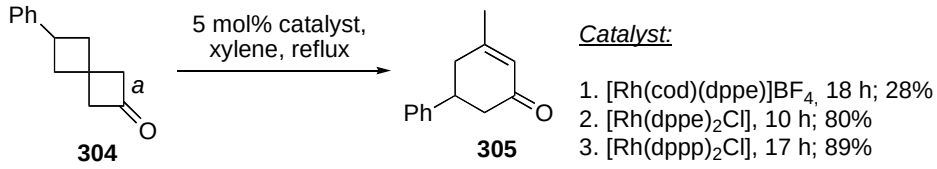
3.1.3 Rhodium-Catalyzed Isomerization Reactions of Cyclobutanes

Cleavage of the cyclobutyl ring under metal catalysis has been well documented for substrates such as cubane,[381] and bicyclo[2.1.0]pentane. Due to unique electronic properties, formation of a σ-complex with rhodium occurs readily with cyclobutenones. In the context of the synthesis of medium-sized rings, Liebskind[382] has shown that the Rh(I) catalyst undergoes preferential insertion into the σ-bond of cyclobutanone next to the acyl functionality. This intermediate rearranged into the 8-membered ring **302** and eventually regenerated the catalyst and the conjugated ketone in good yields (Scheme 95).



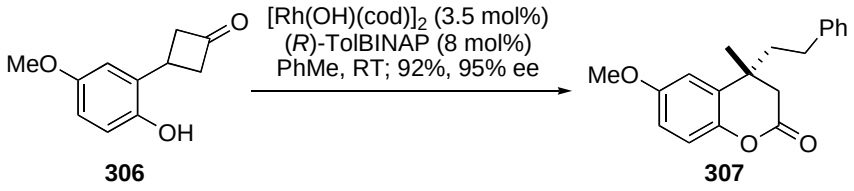
Scheme 95. Rh-catalyzed rearrangement of cyclobutenones by Liebskind.

A similar observation regarding the selectivity for C-C bond activation was reported by Murakami *et al.*[383] who investigated the isomerization reactions of spirocyclic cyclobutanones (Scheme 96). This reaction is initiated by the cleavage of the activated bond *a* next to a carbonyl group in **304** followed by β-carbon elimination and reductive regeneration of Rh(I) to give **305**. The ring strain in the spirocycle is critical to the success of these reactions – *gem*-dialkyl cyclobutenone or spiro[3.6]decan-2-one failed to react under the reported conditions.



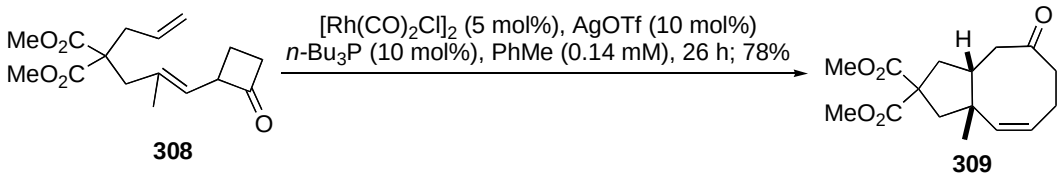
Scheme 96. Rearrangement of spirocyclic cyclobutanones.

Further studies on the isomerization reactions of cyclobutanones revealed that the strained ring can be opened asymmetrically in the presence of a chiral bidentate phosphine ligand to afford dihydrocoumarins in high yields and *ee*'s (Scheme 97).[384]



Scheme 97. Asymmetric synthesis of dihydrocoumarins.

In the context of intramolecular [6+2] cycloadditions, Wender developed a method using an electrophilic rhodium catalyst.[385] In some cases, however, decarbonylation of the metallacycle occurred and the truncated intermediate was converted into a cyclopentene in modest chemoselectivity. A representative example of the isomerization reaction of cyclobutenes is depicted in Scheme 98.

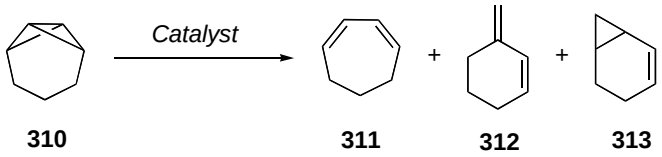


Scheme 98. An intramolecular [6+2] cycloaddition by Wender.

3.1.4 Metal-Catalyzed Isomerization Reactions of Bicyclo[1.1.0]butanes

The isomerization reactions of bicyclo[1.1.0]butanes have been studied extensively in the 1970's and early 1980's.[357] A systematic variation of the metal catalyst was reported by Gassman[386] and Table 25 lists the conditions used to test the selectivity of the isomerization reactions of Moore's hydrocarbon **310**.

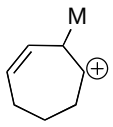
Table 25. Metal-catalyzed isomerization of Moore's hydrocarbon.



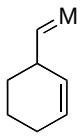
Entry	Catalyst	311	312	313
1	$AgBF_4$	100%		
2	ZnI_2	88%	11%	
3	$HgBr_2$	85%	8%	
4	$[Rh(CO)_2Cl]_2$		98%	
5	$[Ir(CO)_3Cl]_2$		91%	
6	$[(\pi\text{-}CH_2CHCH_2)_2PdCl]_2$		94%	
7	$PdCl_2(PhCN)_2$		69%	
8	$[C_6F_5Cu]_4$		74%	
9	$[(Ph_3P)_2Rh(CO)Cl]$		92%	5%
10	$[Ru(CO)_3Cl_2]_2$		44%	12%
11	PtO_2		62%	24%
12	$SnCl_2{\cdot}2H_2O$	40%		

The outcome of the isomerization reactions can be summarized as follows:

1. Bicyclo[1.1.0]butanes usually undergo opening to butadiene, but in the presence of protic solvents (MeOH), formation of ethers is a competitive pathway.[387,388]
2. Regioselectivity is controlled by the nature of the transition metal. For example, rhodium and iridium provided isomer **312** in highest selectivity, whereas late transition metals such as Zn(II) and Ag(I) gave predominantly diene **311**. The selectivity in these reactions was rationalized based on the stabilities of the two intermediates **314** and **315**. For metals with low electron affinity (Group 10), the resonance form would favor the ionic form of carbene **315** where the bonding occurs primarily *via* σ-donation to the metal. In metals such as Zn(II) or Hg(II) where the electron affinity and promotion energies are high, the only feasible stabilization can be achieved through metallocarbonium ion **314** which binds *via* σ-bonds. In metals which have high electron affinity but low promotion energy (e.g. Rh(I)), the synergistic effect of bonding and back-bonding leads to the overall highly-stable carbene intermediate **315**.



314



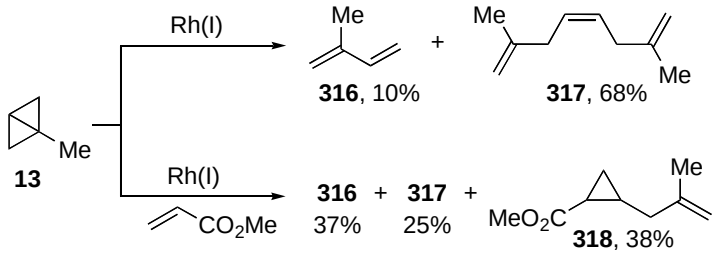
315

3. Regioselectivity of the opening reactions is dependent on the nature of the ligands and the relative ratios of the metal and ligand as well as the catalyst loading. For example, changing the loading of $PdCl_2(Ph_3As)_2$ in the isomerization reaction of 1,2,2-trimethylbicyclo[1.1.0]butane from 0.3 mol% to 3.0 mol% shifted the ratio of linear to branched dienes from 3:1 to 1:0. A similar effect has been noted for the isomerization

reactions with $PdCl_2(PhCN)_2$, as well as $PdCl_2(Ph_3P)_2$, but to a lesser extend. These observations were rationalized based on the exchange mechanism of the weakly-chelating ligands with the butadiene products.[389]

3.1.4.1 Rhodium

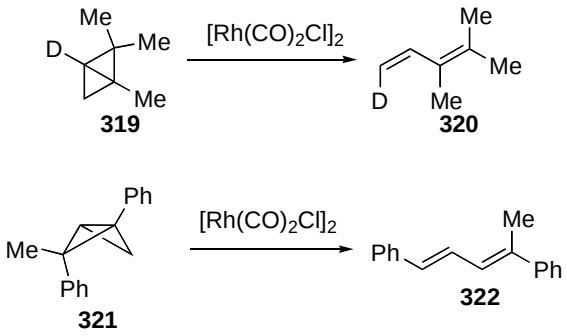
The first report describing an isomerization reaction of bicyclo[1.1.0]butane with Rh(I) was published by Gassman,[386,388-396] who demonstrated that simple bicyclo[1.1.0]butanes underwent rearrangement to 1,3-butadiene. Isolation of (*Z*)-2,7-dimethylocta-1,4,7-triene **317** in the reactions of **13** was initially interpreted as an indication of a carbene intermediate (Scheme 99). This hypothesis was later confirmed by reacting **13** in the presence of methyl acrylate, which afforded cyclopropane **318**; other studies supported the hypothesis that rhodium promotes the isomerization of bicyclo[1.1.0]butanes *via* cleavage of two geminal σ-bonds and formation of a carbene. The selectivity of these reactions is complementary to a thermal opening of bicyclo[1.1.0]butanes that proceeds by cleavage of two vicinal σ-bonds.



Scheme 99. Isomerization reactions of bicyclo[1.1.0]butane **13**.

The mode of ring-opening in these reactions was studied using bicyclo[1.1.0]butanes substituted at the terminal positions. For example, substitution at C1 with a methyl group directs

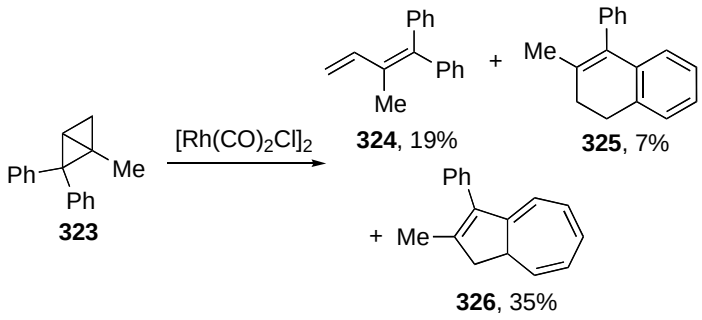
formation of a terminal carbene followed by a hydride migration (Scheme 99). On the other hand, incorporation of a stabilizing group at this position leads to preferential formation of a more substituted carbene that subsequently underwent isomerization to (*E,E)*-diene **322** (Scheme 100). The (*E)*-selectivity for the carbene isomerization was also observed in the reactions of diazocompounds catalyzed by Rh(II). 2,2-Disubstituted bicyclo[1.1.0]butanes (for example, **321**) stereospecifically rearranged into the terminal positions in diene **322**. For the reactions of 2-substituted bicyclo[1.1.0]butanes, the stereospecificity is lower than in the reactions catalyzed by Ag(I). However, extensive studies on the isomerization of substituted bicyclo[1.1.0]butanes have not been reported.



Scheme 100. Stereospecific rearrangement of substituted bicyclo[1.1.0]butanes **319** and **321**.

Isomerization reactions, in spite of providing a plethora of mechanistic information and shaping the fundamental understanding of the reactivity of these molecules, showed limited synthetic utility. One interesting example is the isomerization reaction of 2,2-diphenyl substituted bicyclo[1.1.0]butane **323** (Scheme 101).[397] In the addition to diene **324**, azulene **326** was obtained as the main reaction product. The authors proposed that this rearrangement proceeded *via* intramolecular cyclopropanation of one of the benzene rings followed by a collapse of the

strained intermediate to **326**. This isomerization methodology was later extended towards a kinetic resolution with [Rh(DIOP)Cl], and the best result was achieved at 78% conversion with a 35% *ee* for recovered bicyclo[1.1.0]butane **323**.[398]



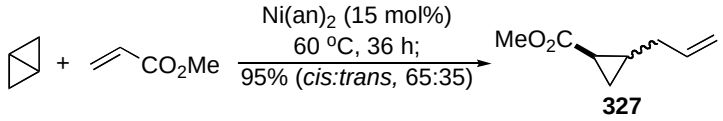
Scheme 101. Synthesis of azulene **326** *via* carbene rearrangement of **323**.

In principle, the carbenoid character of a bicyclo[1.1.0]butane can be utilized in other intramolecular processes, and formation of metal carbenes resembles the decomposition reactions of diazo compounds. However, the synthesis of these substrates or the corresponding hydrazones flanked by two substituents with α-protons is a challenging task. Moreover, the selectivity in the earlier isomerization reactions was usually substrate-controlled and the metal-carbene complex was formed only at the less substituted position of the bicyclo[1.1.0]butane. These limitations open possibilities for a selective formation of the carbenoid controlled by the selection of the reaction conditions (i.e., metals, additives, temperature, etc.).

3.1.4.2 Nickel and Palladium

A potential application of nickel in valence isomerizations was recognized by Noyori and coworkers, who studied the utility of Ni(0) complexes in reactions of bicyclo[1.1.0]butanes[399-

[401] and bicyclo[2.1.0]pentanes.[402,403] $Ni(cod)_2$ and $Ni(an)_2$ (an = acrylonitrile) were efficient catalysts for the intermolecular coupling of bicyclo[1.1.0]butanes with methyl acrylate (Scheme 102), and these reactions proceeded *via* cleavage of two terminal σ-bonds at the less substituted site. A nearly quantitative yield of a mixture of *cis*- and *trans*-isomers **327** was obtained after heating bicyclo[1.1.0]butane with an excess of an electron-deficient alkene. Reactions of dimethyl fumarate and maleate were also sluggish and afforded the corresponding cyclopropanes in low yields (35% and 31%, respectively).



Scheme 102. Ni-catalyzed cycloaddition of bicyclo[1.1.0]butane and methyl acrylate.

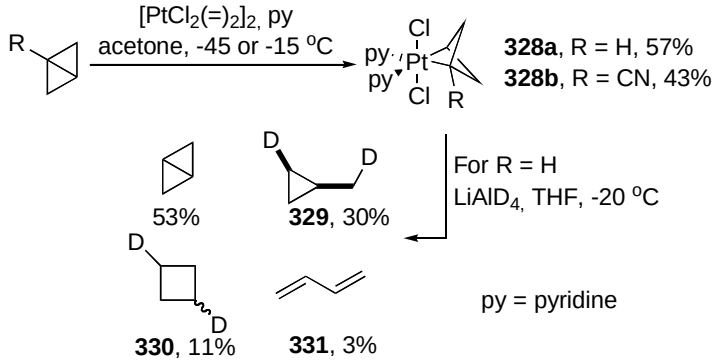
Similarly to reactions of bicyclo[1.1.1]pentane, formal ene reactions with very reactive conjugated esters and bicyclo[1.1.0]butane were observed under the catalysis of Ni(0). This competing radical reaction of bicyclo[1.1.0]butanes can be explained by a metal catalysis or can proceed spontaneously. Given the nucleophilic character of the nickel-carbene complex,[400] only electron-deficient alkenes were shown to be successful coupling partners. This requirement, however, limits the utility of this methodology, particularly in the intramolecular variant where the cyclization is fast under thermal conditions.

Palladium has only been used in the isomerization reactions and the selectivity in the catalytic opening of tricyclo[4.1.0.$0^{2,7}$]heptane **310** was dependent on the metal source, additivites, and catalyst loadings. A lack of comparative studies under identical conditions prevents a meaningful discussion of the mechanism and selectivity in these reactions. Of particular note are re-

ports by Dauben and Kielbania, who provided evidence for the formation of palladium-carbene complex **315** (M = Pd).[404,405] This stable complex obtained from an equimolar mixture of **310** and Pd(II) salt was characterized by ^{1}H NMR spectroscopy, and addition of an excess of Ph_3P to **315** promoted the rearrangement to 3-methylenecyclohex-1-ene (**312**). The authors also provided further support for the carbene nature of **315**, and a cationic mechanism for this rearrangement was excluded by conducting the reaction in MeOH.

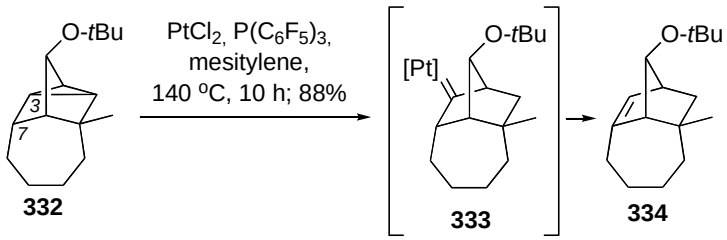
3.1.4.3 Platinum

The use of platinum in valence isomerization reactions of bicyclo[1.1.0]butanes has been limited to only three reports.[386,406,407] The selectivity in the rearrangement of **310** using heterogeneous PtO_2 was modest. On the other hand, a catalytic amount of homogenous $[PtCl_2(CH_2{=}CH_2)]_2$ (Zeise's dimer) in acetone at room temperature promoted a quantitative rearrangement of bicyclo[1.1.0]butane to 1,3-butadiene in a quantitative yield.[406] When the same reaction was performed with stoichiometric amounts of Pt(II) in the presence of pyridine, the unstable complex **328a** was isolated, demonstrating that the cleavage of the bicyclic system occurred at the central bond (Scheme 103). A more stable complex **328b** was prepared from 1-cyanobicyclo[1.1.0]butane.[407] Further NMR studies indicated that **328a** is present in a dynamic equilibrium with its valence isomers, where the metal is inserted into the lateral bonds of the bicyclo[1.1.0]butane ring. This observation was confirmed by reduction of **328a** with $LiAlD_4$, resulting in formation of **329** in 30% yield. Moreover, the thermal decomposition (above -25 ^oC) of **328a** regenerated bicyclo[1.1.0]butane, strongly supporting the notion that the bicyclo[1.1.0]butyl ring underwent a reversible formation of a quasi-stable metal complex before subsequent isomerization.



Scheme 103. Synthesis and reduction of platinacyclobutanes **328**.

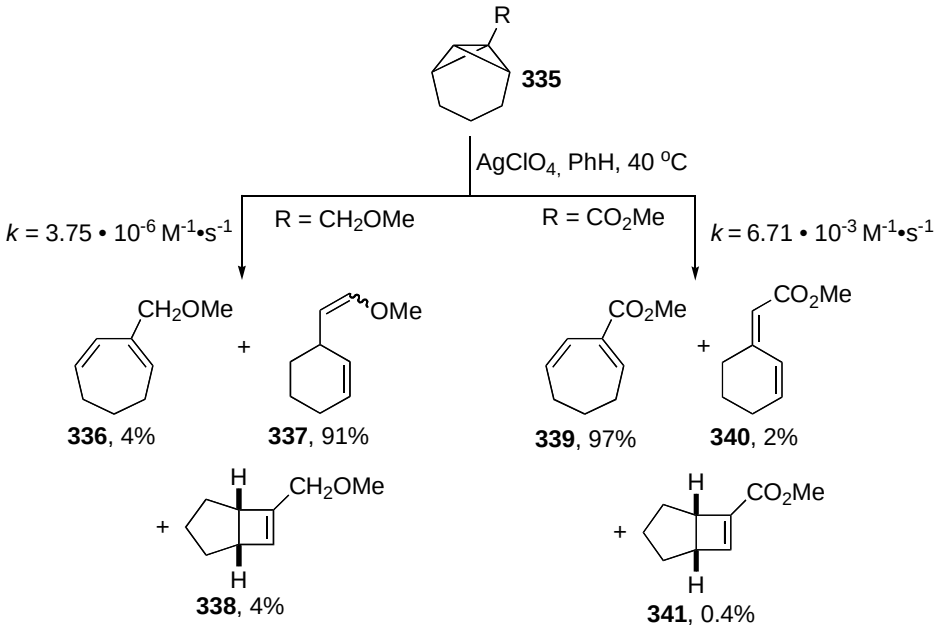
The intermediacy of platinum carbenes in valence isomerizations of homo[4+3+3] Diels-Alder cycloadducts was postulated by Snyder.[408-413] The initial mechanistic interpretation of the formation of the bridged alkene **332** involved a β-elimination pathway.[409] Subsequent labeling studies with deuterium at positions C3 and C7 in **332** showed large kinetic isotope effects (k_H/k_D = 1.54 and 5.44, respectively), supporting an α-elimination mechanism from **333** (Scheme 104).



Scheme 104. Pt(II)-catalyzed isomerization of **332**.

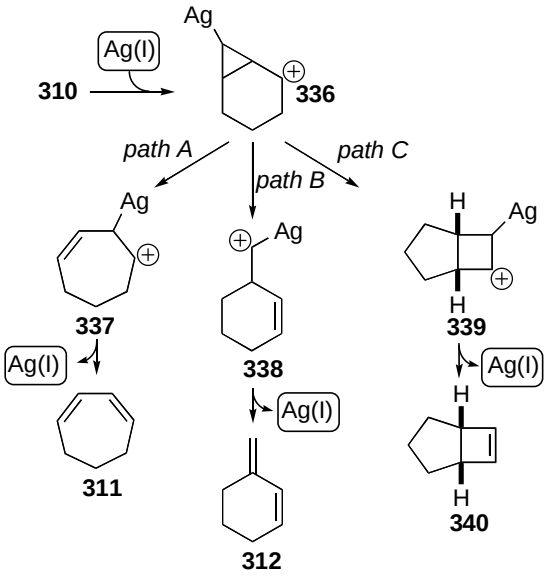
3.1.4.4 Silver

A large body of data has been accumulated on Ag(I)-catalyzed isomerization reactions during studies by Paquette[414-418] and Masamune.[419,420] These reactions proceed *via* a cationic mechanism and are generally characterized by a high stereospecificity (*endo*- and *exo*-substituents on C2 and C4 in bicyclo[1.1.0]butane are converted into (*Z)*- and (*E)*-alkenes). The electronic modifications on the bicyclo[1.1.0]butane ring play a critical role in the outcome of these reactions.[416,417] For instance, an alkyl group at position C1 in **335** favors the formation of cyclohexene **337**, whereas incorporation of an electron-withdrawing substituent changed the reaction pathway towards **339** (Scheme 105). Additionally, the isomerization reaction for the alkyl substituted bicyclo[1.1.0]butane is ca. 1800 times faster than for a methoxycarbonyl group. Similar observations were made with respect to the steric substitutions of bicyclo[1.1.0]butanes.



Scheme 105. Selective isomerizations of bicyclo[1.1.0]butanes with Ag(I).

These observations can be combined into the unified mechanistic picture depicted in Scheme 106. Initial cleavage of the lateral bond in **310** results in formation of carbocation intermediate **336**. At this stage, three mechanistically similar scenarios can occur: ring enlargement (path A) leading to 1,3-cycloheptatriene, cleavage of the lateral bond in the cyclopropyl skeleton and isomerization to cyclohexene (path B), and ring contraction followed by a loss of the metal (path C). All of these pathways operate in the presence of Ag(I), but the selectivities are correlated with the structure of the substrates.

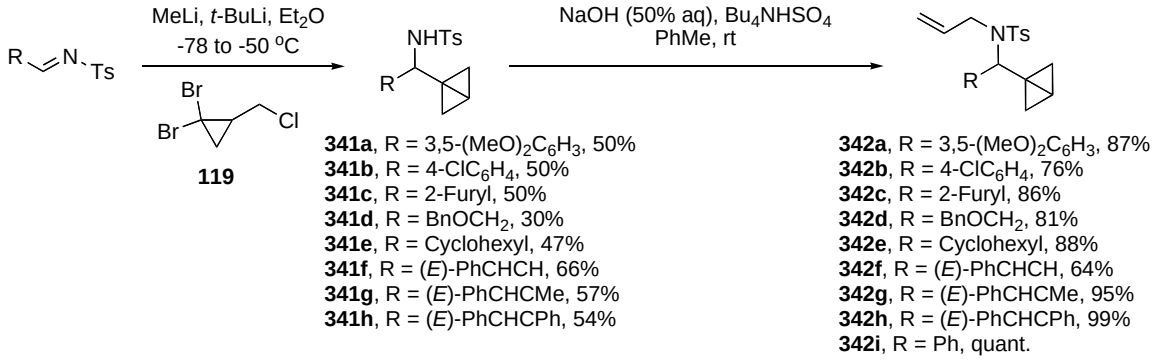


Scheme 106. A unified mechanism for the isomerization of tricyclo[4.1.0.$0^{2,7}$]heptanes by Ag(I).

3.2 RESULTS AND DISCUSSION

3.2.1 Rhodium-Catalyzed Cycloisomerization Reactions of Bicyclo[1.1.0]butanes

Based on the precedence on the isomerization reaction of strained carbocycles as well as the observations that very reactive aryl-substituted bicyclo[1.1.0]butanes participate in the intramolecular ene reaction, we postulated that in the presence of a transition metal these strained molecules would rearrange to afford the carbene intermediate. The selection of the metal was based on the observation that the highest selectivity in the isomerization reactions was achieved with rhodium. As a model system used to test the intramolecular cycloisomerization reactions, allyl amide **342i** was used and Tables 26-28 list the conditions tested to identify the optimal reaction conditions. Scheme 107 depicts the synthesis of the model system and the preparation of other substrates for the studies of the scope of the cycloisomerization process.

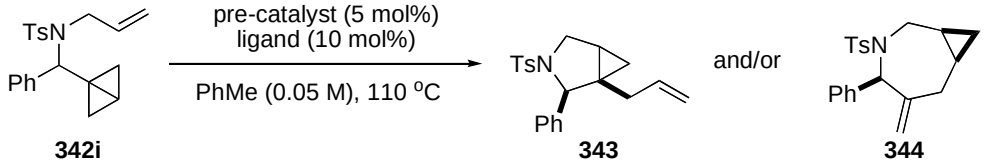


Scheme 107. Synthesis of *N*-allyl amides **342a-i**.

From the optimization studies, the following general trends can be extracted:

- a rhodium pre-catalyst with a weakly chelating group gives the best yield of pyrrolidines. Addition of a phosphine ligand is necessary to obtain synthetically useful yields.
- aromatic phosphines are the optimal additives for the overall yield and the additives with electron-neutral ligands give the best results.
- aliphatic phosphines afford pyrrolidine as the major product, but the yield of this transformation is low.
- the optimal yield is achieved using a diluted (0.05 M) solution of the substrate at a high temperature (110 ^{o}C). Lowering the temperature decreases the yield and the formation of side products (most likely polymerization) is observed by ^{1}H NMR. Similarly, decreasing the loading of catalyst has a detrimental effect on the yield.
- non-polar solvent is optimal for this reaction (PhMe) although the yield of the reactions carried out in THF is acceptable.
- the ratio of pyrrolidine/azepine is dependent on the ratio of rhodium pre-catalyst and phosphine – increasing the amount of the ligand favors formation of azepine but also decreases the overall yield.
- bidentate phosphine ligands favor formation of azepine whereas monodentate phosphines give predominantly pyrrolidine.
- the yield and diastereoselctivity of the formation of azepine are correlated with the bite angle of phosphines – the additives which give the best yield are characterized by a bite angle of about 85^{o}.[421]

Table 26. Optimization reaction of the cycloisomerization reaction of **342i** with monodentate phosphine ligands.



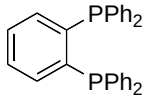
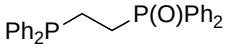
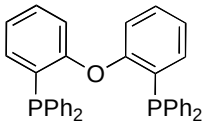
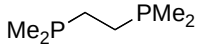
342i **343** **344**

Entry	Pre-catalyst	Ligand	Yield	
			343	**344**
1	$[Rh(CH_2=CH_2)_2Cl]_2$	Ph_3P	87% (77%)	8%
2	"	Ph_3P (20%)	70%	2%
3	"	Ph_3P (30%)	43%	11%
4	"	$(4\text{-}MeOC_6H_4)_3P$	43%	4%
5	"	$(4\text{-}FC_6H_4)_3P$	61%	1%
6	"	$(4\text{-}MeC_6H_4)_3P$	8%	4%
7	"	$(2\text{-Furyl})_3P$	31%	5%
8	"	$(C_6F_5)_3P$	7%	8%
9	$[Rh(COE)_2Cl]_2$	Ph_3P	38%	9%
10	$[Rh(COD)Cl]_2$	Ph_3P	57%	20%
11	$[Rh(CH_2=CH_2)_2Cl]_2$	Ph_2MeP	81%	9%
12	"	$n\text{-}Bu_3P$	78%	12%
13	"	$t\text{-}Bu_3P$	22%	5%
14	$[Rh(CH_2=CH_2)_2Cl]_2$ (1 mol%)	Ph_3P	71%	3%
15	Wilkinson's cat.	-	24%	49%
16	$[Rh(CH_2=CH_2)_2Cl]_2$	-	11%	10%

[a]^{1}H NMR yields were determined using an internal standard ($CHBr_3$). Isolated yields are given in parentheses.

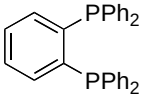
Table 27. Optimization of the cycloisomerization reaction of **342i** with bidentate phosphine ligands.

Entry	Pre-catalyst	Ligand	β[b]	343		344	
				Yield	***dr***	**Yield**	***dr***
1[c]	$[Rh(CO)_2Cl]_2$	dppm	72°	<1%	-	ND	
2	"	dppe	85°	<1%	-	83% (77%)	95:5
3	"	dppe	85°	<1%	-	63%	≥95:5

		(c = 0.1M)					
4	"	dppp	91°	<1%	-	29%	85:15
5[d]	"	dppb	95°	<1%	-	7%	78:22
6	"	 1,2-dpp-benzene	83°	<1%	-	78%	ND
7	"			23%	ND	1%	ND
8[e]	"	 DPEphos	102 °	<1%	ND	<1%	ND
9[f]	"			<1%	ND	9%	ND

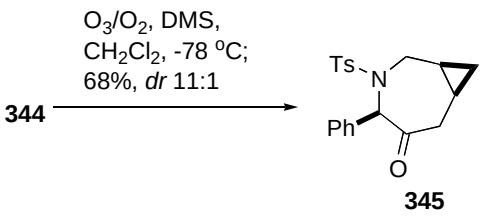
[a]Optimization reactions were performed with 5 mol% of Rh pre-catalyst, 10 mol% ligand in PhMe (0.05 M) at 110 °C. ^{1}H NMR yields were determined using an internal standard. [b]Ligand bite angle. [c]Only 2% conversion was observed. [d]Only 18% conversion was observed. [e]Only 20% conversion was observed. [f]23% of diene was observed.

Table 28. Solvent optimization for the isomerization of **342i**.

Entry	Solvent	Catalytic System	*T*	*t*	343	344
1	$(CH_2Cl)_2$	$[Rh(CH_2{=}CH_2)_2Cl]_2$, PPh_3	78 °C	15 min	52%	
2	EtOAc	"	78 °C	15 min	73%	
3	*t*-BuOMe	"	55 °C	15 min	68%	
4	THF	"	70 °C	30 min	85%	
5	$(CH_2Cl)_2$	 $[Rh(CO)_2Cl]_2$,	78 °C	15 min		4%
6[b]	EtOAc	"	78 °C	15 min		ND
7	*t*-BuOMe	"	55 °C	15 min		51%
8	THF	"	70 °C	30 min		30%

[a]Optimization reactions were performed with 5 mol% of Rh pre-catalyst, 10 mol% ligand in PhMe (0.05 M) at 110 °C. ^{1}H NMR yields were determined using internal standard. [b]Only 30% conversion was observed.

In order to establish the relative stereochemistry of the newly formed pyrrolidine **343** and azepine **344**, NOESY analyses were performed. The observed stereochemistry of **344** was further secured by converting **344** into the corresponding ketone **345** (Scheme 108) and the major diasteroisomer was crystallized from ether. The x-ray structure of **345** is depicted in Figure 27.



Scheme 108. Synthesis of ketone **345**.

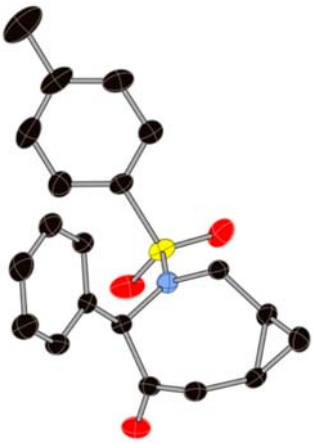
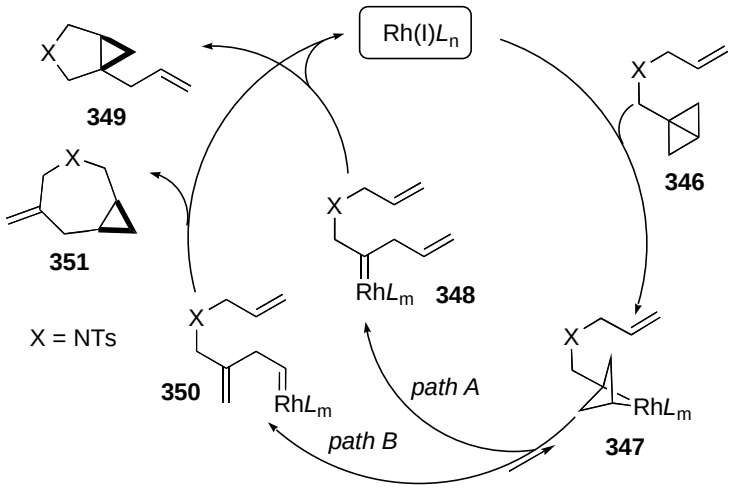


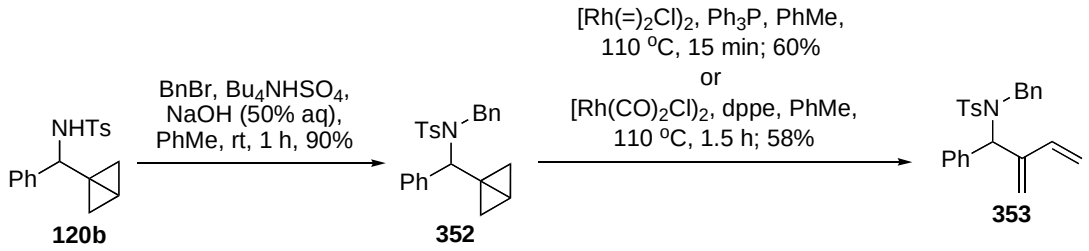
Figure 27. X-ray structure of **345**.

In order to rationalize the outcome of the isomerization reactions, we propose a mechanism depicted in Scheme 109. After dissociation of the ligands, the Rh(I) complex undergoes an oxidative insertion across the central bond in bicyclo[1.1.0]butane **346** to form the bicyclic intermediate **347**. Although this insertion is sterically very demanding, given the location of the frontier orbitals and the susceptibility of the central bond toward addition reactions, this may be the primary interaction site. At this moment, two different pathways can operate: the bicyclic intermediate **347** can rearrange into the internal carbene **348** (path A) or carbene **350** (path B). Carbene **348** is sterically more hindered and the rearrangement reaction is most likely assisted by the allyl group which participates in the delivery of the rhodium complex into the proximal bond

in bicyclo[1.1.0]butane as well as the stabilization of the carbene. The hypothesis of the metal stabilization by the allyl group is supported by experiments in which the potentially chelating group is removed and under conditions which favor formation of internal and terminal carbenes the sole product was diene **353** (Scheme 110). This compound is derived from a rearrangement of carbene **350** *via* a H-shift; no alternative diene product was observed in the ^{1}H NMR of a crude reaction mixture. Path B would be operational for the systems where the bulky ligands prevent the formation of the internal carbene **348** (steric argument) and the rearrangement of **347** would lead only to the less-hindered intermediate **350**. The resulting carbenes then undergo a reaction with the allyl group to afford the observed products **349** and **351**. Azepine **351** can be assigned as a kinetic product, whereas pyrrolidine **349** would be considered as a thermodynamic product.

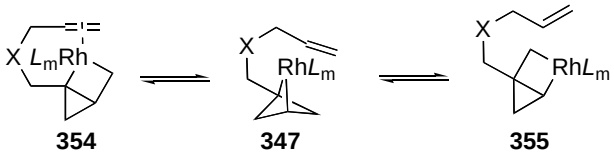


Scheme 109. Proposed mechanism for rearrangement of bicyclo[1.1.0]butanes catalyzed by Rh(I) complexes.



Scheme 110. Isomerization reaction of *N*-benzyl amide **352**.

Although the above discussion is based primarily on the kinetic arguments, the selectivity of the isomerization reactions can be also explained based on the thermodynamic stabilities of the two intermediates **348** and **350**. The equilibrium between these two intermediates may be also controlled by the ratio of **354** and **355** (Scheme 111), which can be present as intermediates in the rearrangement from **346** to **347**/**350**. Mono- and bidentate ligands may, however, impact the equilibrium at the stage of the carbene and/or bicyclic intermediates. The notion that the strained ring can be opened reversibly is supported by the reactions of allyldiazocompounds with can be transformed into bicyclo[1.1.0]butanes in the presence of $Rh_2(OAc)_4$.[126] An alternative interpretation of the observed selectivity in these reactions would involve a mechanism in which the metal complex inserts selectively into the side bonds of bicyclo[1.1.0]butanes. However, it is difficult to rationalize the high selectivity of the insertion reaction based only on the selectivity in the oxidative step.



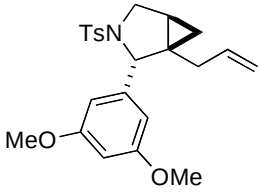
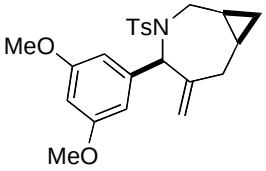
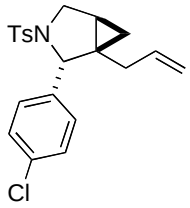
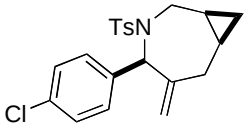
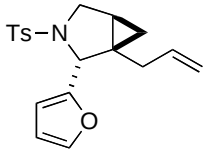
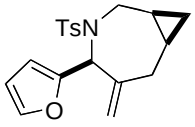
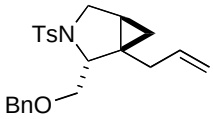
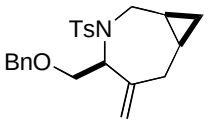
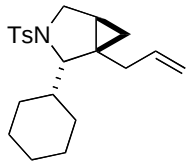
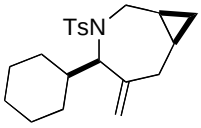
Scheme 111. Equilibrium between two alternative metallacyclobutane intermediates.

The scope of the isomerization reaction was tested by exposing the allylated amides to the optimized conditions (Table 29). It was found that the aromatic (entry 1 and 2), heteroaromatic (entry 3), and aliphatic (entries 4 and 5) groups were tolerated in the isomerization reactions. These substrates afforded both azepines **356** and pyrrolidines **357** in good to excellent yield with a complete diastereoselectivity. Notably, these isomerization reactions are also characterized by excellent chemoselectivity, as formation of only one regioisomer was observed for all testes substrates. The relative stereochemistry of the products was assigned based on analogy to the model systems **343** and **344**.

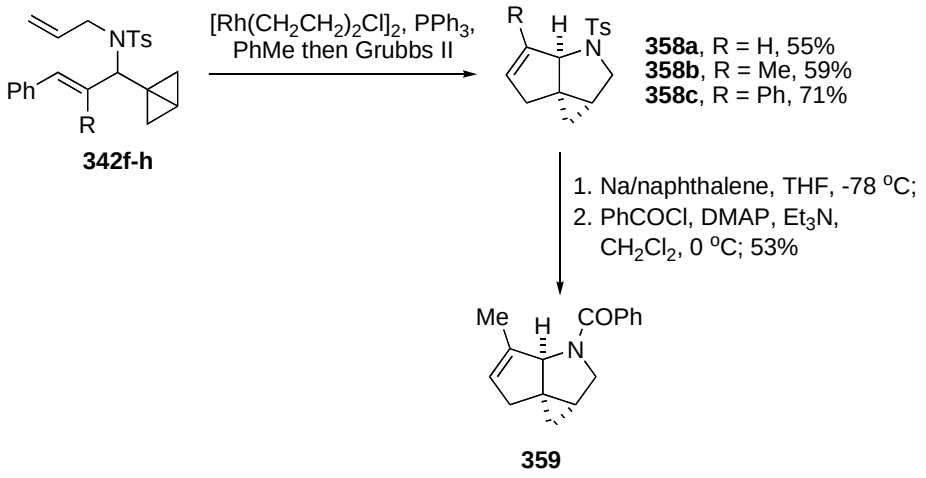
Having established an access to allylated pyrrolidines, we were interested in extending the isomerization methodology towards a tandem synthesis of polycyclic heterocycles. To this end, allyl amides **342f-h** derived from α,β-unsaturated imines were treated with a catalyst promoting the formation of pyrrolidines, and, once the cycloisomerization step was complete, a metathesis catalyst (Grubbs II)[422] was added, the mixture was stirred at 60 ^{o}C and the tricyclic products **358** were formed in good yields as single regio- and diastereomers (Scheme 112). Although the isomerization reactions were only successful with *N*-tosylamides, we were able to remove the nitrogen protective group from **358b** under reductive conditions (Na, naphthalene), and the free amine was protected as benzamide **359**. In order to assess the efficiency of the isomerization reactions with $[Rh(CH_2=CH_2)_2Cl]_2/PPh_3$, the tandem sequence was stopped at the first isomerization stage and the corresponding amide **360** was isolated in good yield (Scheme 113).

Table 29. Scope of Rh(I)-catalyzed cycloisomerization reactions.

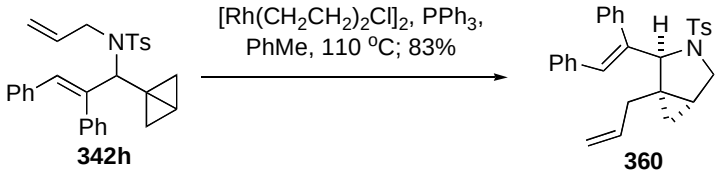
Entry	Substrate	Method A	Method B

		Product	Yield	Product	Yield
1	**342a**	 **356a**	67%	 **357a**	87%
2	**342b**	 **356b**	53%	 **357b**	80%
3	**342c**	 **356c**	75%	 **357c**	57%
4	**342d**	 **356d**	63%	 **357d**	67%
5	**342e**	 **356e**	65%	 **357e**	75%

[a]Method A: $[Rh(CH_2{=}CH_2)_2Cl]_2$ (5 mol%), Ph_3P (10 mol%), PhMe (0.05 M), 110 ^oC. [b]Method B: $[Rh(CO)_2Cl]_2$ (5 mol%), dppe (10 mol%), PhMe (0.05 M), 110 ^oC.



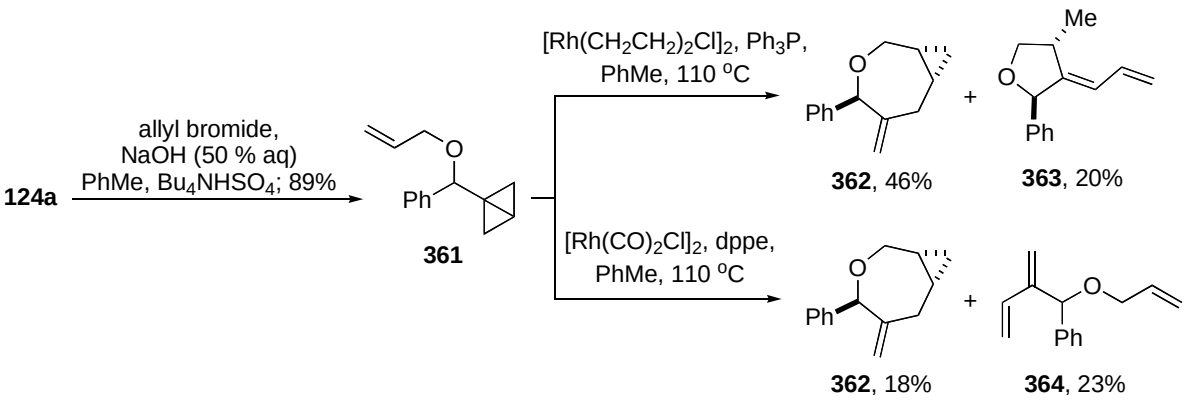
Scheme 112. Tandem isomerization-RCM synthesis of pyrrolidines **358** and **359**.



Scheme 113. Rh(I)-catalyzed isomerization of **358c**.

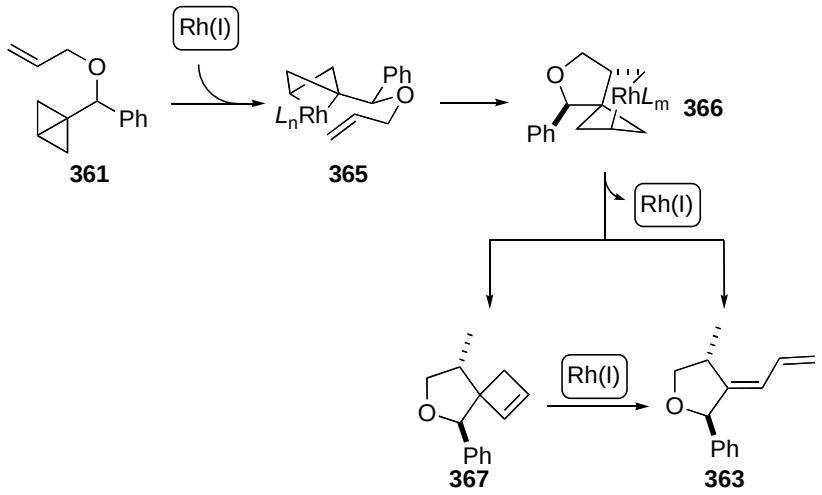
During our studies on the scope of the cycloisomerizations of bicyclo[1.1.0]butanes, interesting observations were made regarding the reactions of bicyclo[1.1.0]butyl allyl ether **361** catalyzed by Rh(I) complexes (Scheme 114). It was found that under a variety of conditions formation of three major products was observed: oxepane **362** which is formed *via* the reaction of the terminal carbene, tetrahydrofuran **363**, and butadiene **364** which is a product of a hydride migration from the terminal carbene. Interestingly, under none of these conditions we were able to find the desired tetrahydrofuran that would be expected in the reactions of the internal carbene with the allyl tether. Due to the difficulty in separation of the products, the yields in Scheme 114

were determined using an internal standard ($CHBr_3$) and the analytical samples were characterized by 1D and 2D NMR after purification using Supercritical Fluid Chromatography.



Scheme 114. Synthesis and cycloisomerization of ether **361**.

A possible mechanism for the formation of **363** is depicted in Scheme 115. After oxidative addition of Rh(I) to bicyclo[1.1.0]butane, the allyl group undergoes insertion into the metallacycle to give intermediate **366**, which can rearrange into the butadiene product **363** or, alternative, to cyclobutene **367**, which can be isomerized into product **363**. The diastereoselectivity in these reactions can be explained by considering an equatorial orientation of the aromatic substituent and a pseudo-chair transition state.



Scheme 115. Proposed mechanism for isomerization of **361**.

Finally, Figure 28 depicts substrates which upon exposure to the standard conditions led to decomposition or formation of butadiene.

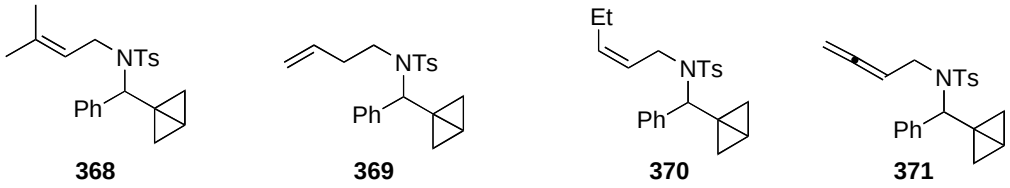


Figure 28. Difficult substrates for the Rh-catalyzed isomerization reactions.

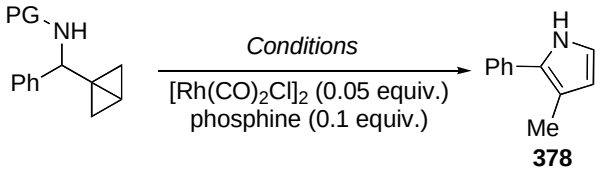
3.2.2 Synthesis of Pyrroles *via* Carbene Insertion into NH Bonds

Intrigued by the selectivity in the reactions of *N*-allyl amides, we also wondered if the corresponding metal-promoted isomerization reactions are feasible for the trapping reaction with nitrogen or oxygen nucleophiles. The insertion reaction of the metal carbenes using Cu and di-

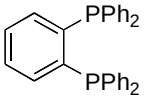
azocompounds has been described in the synthesis of enantiomerically pure aminoacids[423] and ethers.[424] It was anticipated that the sulfonamides are suitable substrates for this transformation as they may participate in the insertion reaction to give the corresponding pyrrolidines. Given that the sulfonyl group can be removed from sulfonamides *via* the isomerization of diazocompounds using catalytic $Rh_2(acac)_4$,[425,426] these substrates were postulated as viable precursors for the synthesis of pyrroles. If successful, this approach would add to the methodologies for a *de novo* construction of pyrroles[427-429] which often rely on the use of transition metals[430-446] or involve the coupling of multiple components in a highly chemoselective fashion.[447,448]

In order to test this hypothesis, simple sulfonamides were selected as model systems (Table 30) and exposed to conditions that favor the formation of a less substituted, terminal carbene. Simple alkyl (entries 1 and 2) and aryl (entry 3) sulfonamides underwent isomerization to pyrroles **378** in modest to good yields in the presence of 10 mol% dppe and 5 mol% $[Rh(CO)_2Cl]_2$ in THF (0.05 M). Increasing the steric bulk on the nitrogen atom by incorporation of Tris amide (Tris = 2,4,6-triisopropylbenzenesulfonyl) improved the reaction yield (entry 6) most likely due to inhibition of an unproductive internal carbene pathway. The conditions that were optimal for the isomerization reactions of *N*-allyl amides resulted in a lower yield of **378** (entry 4), similarly to a more rigid phosphine ligand (entry 5) which gave **378** in only 52 % yield.

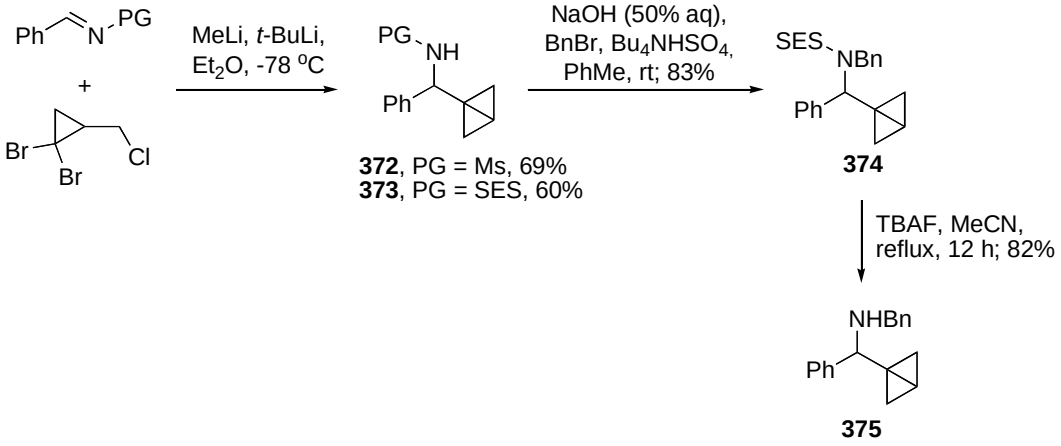
Table 30. Optimization studies in the synthesis of pyrrole **378**.



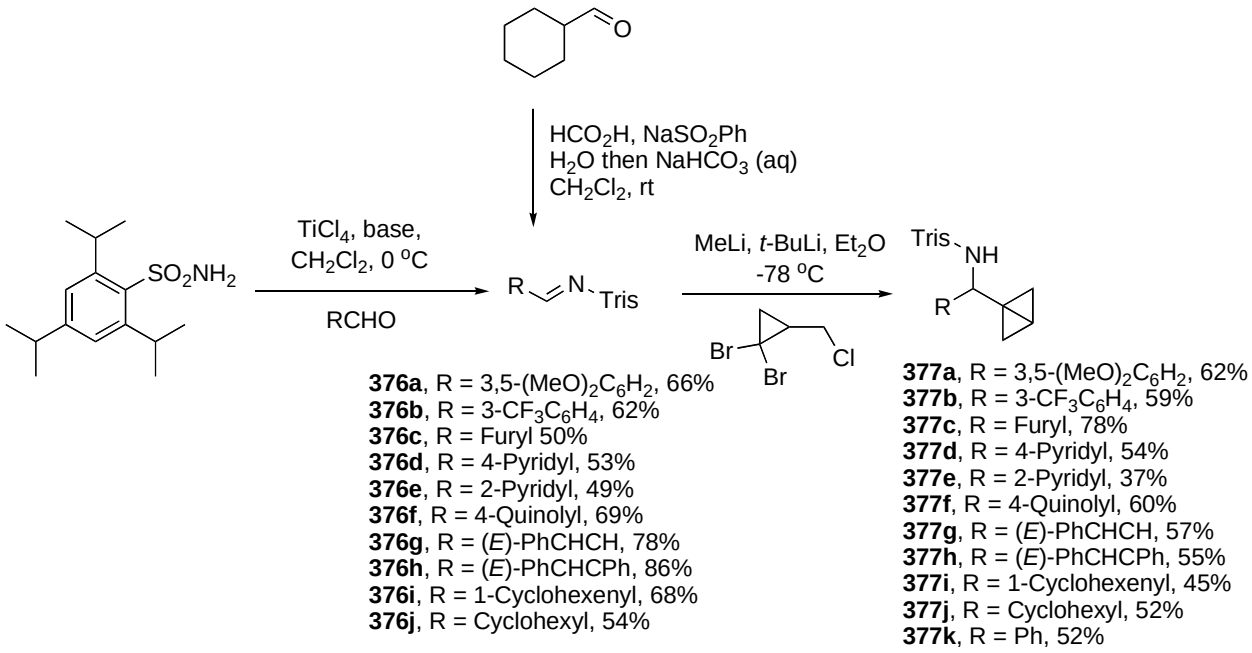
378

Entry	PG	Conditions	Yield
1	Ms (**372**)	dppe, THF, reflux	49%
2	SES (**373**)	"	56%
3	Ts (**120b**)	"	57%
4	**120b**	dppe, PhMe, reflux	52%
5	**120b**	 , THF, reflux	52%
6	Tris (**377k**)	dppe, THF, reflux	90%

The substrates for the optimization and the reaction scope studies have been prepared *via* the standard protocols outlined in Scheme 116 and Scheme 117.



Scheme 116. Synthesis of amides **373**-**375**.



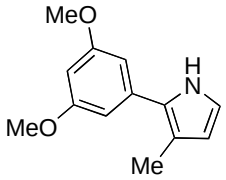
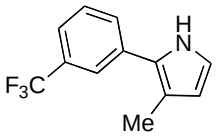
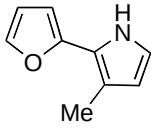
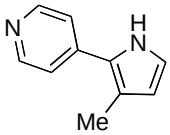
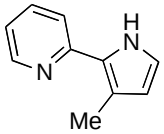
Scheme 117. Synthesis of imines **376** and amides **377**.

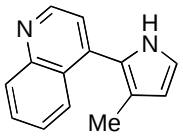
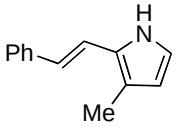
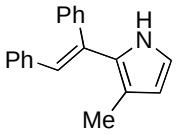
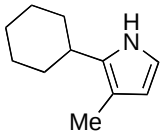
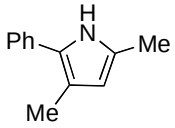
With these substrates in hand, we were able to convert aromatic (entries 1 and 2), and heteroaromatic (entries 3, 4, and 6) amides into pyrroles in good to excellent yields (

Table 31). In the presence of a chelating group (e.g. 2-pyridyl, entry 5) formation of a diene was observed. Interestingly, the styryl derivatives have proven to give the aromatic products in good yields (entries 7-9). However, aliphatic substitution gave the product in a modest yield and no reaction was observed for the 1,3-disubstituted bicyclo[1.1.0]butane **123b**. The isomerization reactions conducted using the *N*-toluenesulfonyl group instead of a bulky Tris group gave consistently lower yields although in a comparable range. It is noteworthy that the free pyrroles are prone to decomposition upon standing (particularly **379c**) and the quality of the material deteriorates over time with a concomitant formation of purple or orange solids.

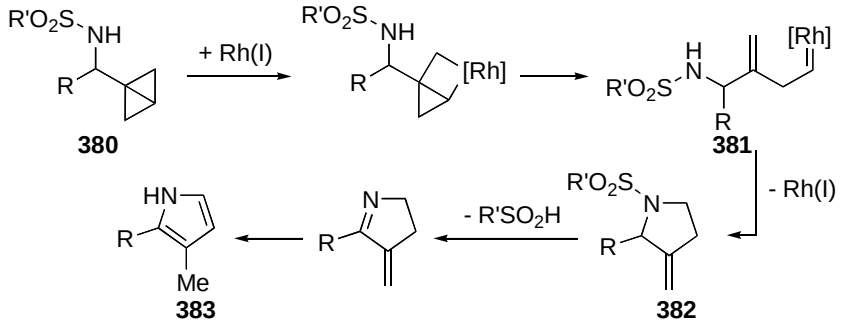
A mechanism for conversion of amides into pyrroles is postulated in Scheme 118. Insertion of Rh(I) into a bicyclo[1.1.0]butane followed by a rearrangement leads to a terminal carbene **382**. This intermediate undergoes N-H insertion reactions to give the corresponding pyrrolidine **382**. Under the thermal conditions, the protective group is eliminated and the diene undergoes a series of H-shift reactions to afford a fully aromatic ring **383**. The observations that *N*-alkyl substituted amides resulted only in formation of butadiene is consistent with a proposed catalytic cycle initiated by an NH insertion reaction (Scheme 110).

Table 31. Scope of the synthesis of pyrroles from bicyclo[1.1.0]butylamides.[a]

Entry	Substrate	Product	Yield[b]
1	**377a**	 **379a**	77% (74%)
2	**377b**	 **379b**	59%
3	**377c**	 **379c**	61% (41%)
4	**377d**	 **379d**	77%
5[c]	**377e**	 **379e**	<5%

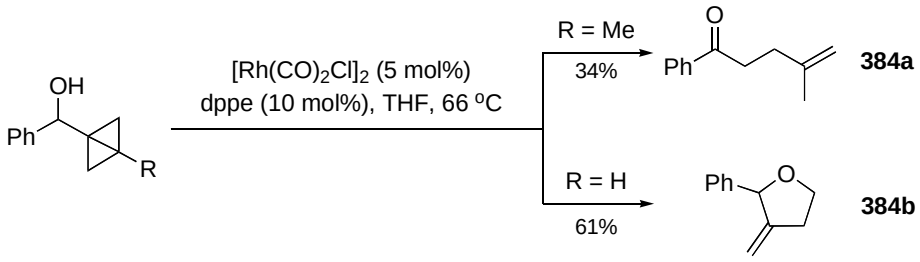
6	**377f**	 **379f**	79%
7	**377g**	 **379g**	77%
8	**377h**	 **379h**	84% (77%)
9	**377j**	 **379i**	42%
10[d]	**123b**	 **379j**	<5 %

[a]The isomerization reactions were performed under the optimized conditions from Table 30 (entry 6). [b]Yields in parentheses refer to the reaction carried out with *N*-tosyl amides. [c]Only the formation of diene was observed. [d]Reaction performed with 10 mol% AgOTf.



Scheme 118. Postulated mechanism for isomerization of bicyclo[1.1.0]butanes into pyrroles.

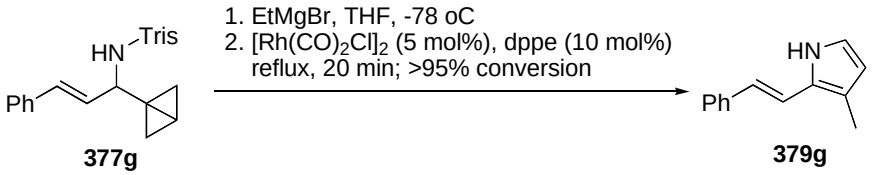
The isomerization of the alcohols was also performed under optimized conditions and afforded the ether **387** in 61% yield if the terminal position was unsubstituted (Scheme 119). It is notable that the reaction pathway changed if the methyl substitution was added and the isomerization to ketone **386** was only observed with disubstitued bicylo[1.1.0]butylalcohol **124b**. The yield of the later transformation was improved if the Wilkinson catalyst (10 mol%) was used in combination with $AgBF_4$ (10 mol%, 80% yield) or $PtCl_2$ (87% yield). We were unable to find the products derived from the insertion reaction and the isomerization to ketone suggests that the metal undergoes a preferential insertion into a more-hindered position or, alternatively, the equilibrium of the carbenes shifted by the irreversible rearrangement of ketone in substrate **124b**. We also found that amine **375** participated in the isomerization reaction to give pyrrolidine, but this compound was not stable to the standard chromatographic purification.



Scheme 119. Isomerization reactions of bicyclo[1.1.0]butyl alcohols.

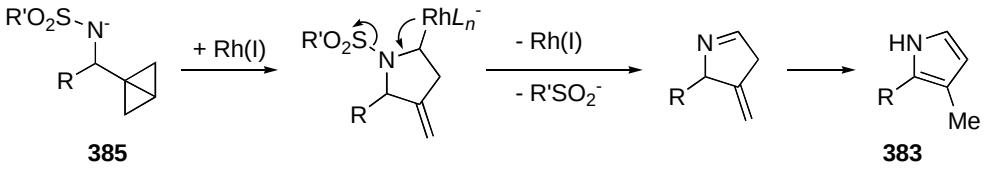
Having established a reliable protocol for the synthesis of pyrroles, it was further envisioned that the corresponding imines could be converted directly into pyrroles using a one-pot, two-step protocol initiated by the addition of bicyclo[1.1.0]butyl anion. In order to test whether the metallated amide undergoes isomerization to the aromatic heterocycle, amide **377g** was treated with Grignard reagent in THF and the crude mixture was subjected to the isomerization

conditions to furnish the desired pyrrole (Scheme 120). Although no further mechanistic studies were conducted, it is possible that the formation of pyrroles proceeded *via* a different mechanistic pathway in which the nucleophilic amide moiety undergoes addition to carbene followed by a collapse of rhodium intermediate *via* elimination of the protective group and the Rh(I) species (Scheme 121) and subsequent isomerization.[449]



377g **379g**

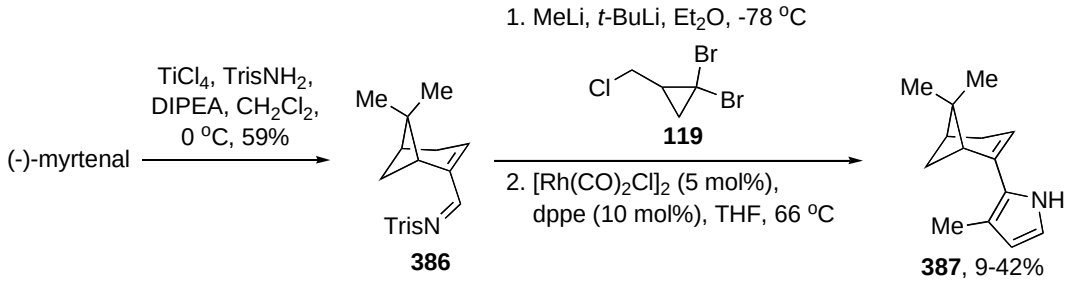
Scheme 120. Isomerization reactions of metallated amide into pyrrole.



385 **383**

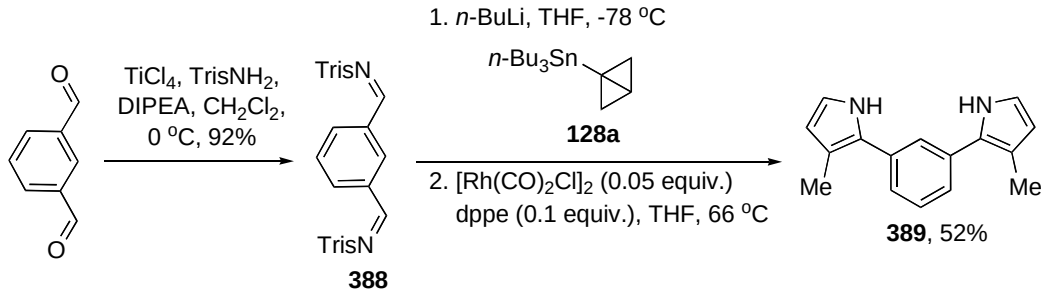
Scheme 121. Alternative mechanism for the isomerization of amides into pyrroles.

From a practical standpoint, the most efficient method for the construction of pyrroles would involve the addition of bicyclo[1.1.0]butyllithium generated from dibromocyclopropanes. After treatment of imine **386** with a solution of organolithium generated from **119**, the corresponding adduct was quenched with sat. NH_4Cl and a crude reaction mixture was exposed to the isomerization conditions affording pyrrole **387** in 42% (Scheme 122).



Scheme 122. Synthesis of pyrroles **387** *via* addition to imine **386** and isomerization.

It was reasoned that the competing methyllithium addition as well as instability of of **387** may resulted in a low reaction yield. Stannane **128a** is a stable precursor of the bicyclo[1.1.0]butyl anion, and after transmetallation with *n*-BuLi at -78 °C, it was added to imine **388** (Scheme 122). The crude mixture was then filtered through a pad of silica and exposed to the isomerization conditions to afford pyrrole **389** in 52% yield (Scheme 123). It was found that addition of Rh catalyst to the crude mixture (lithium amide) led to the formation of unidentified product which originates most likely from a transfer of carbon monoxide from the pre-catalyst. Similar observations were made if the reaction was quenched and the mixture (containing stannane) was subjected to the isomerization conditions. It was found that as the reaction progressed, formation of the mono-pyrrole derivative was observed which subsequently converted into product **389**.



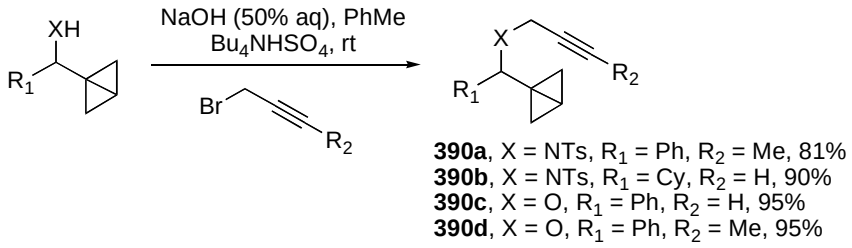
Scheme 123. Synthesis of bis-pyrroles **389**.

3.2.3 Platinum-Catalyzed Cycloisomerization Reactions of Bicyclo[1.1.0]butanes

In the course of the studies on the reactions of bicyclo[1.1.0]butanes with Rh(I), it was found that the isomerization reaction is not facile for propargyl derivatives. Addition of the substrates to pre-formed catalyst led to formation of a brown solution, which eventually led to decomposition upon heating. We speculated that late transition metals such as platinum, due to their alkynophilic character,[450] may strongly interact with alkynes, thus allowing for a more efficient coupling of bicyclo[1.1.0]butane and alkynes.[450] However, due to the presence of an alkyne group, it was anticipated that these reactions may proceed *via* a different mechanistic pathway.

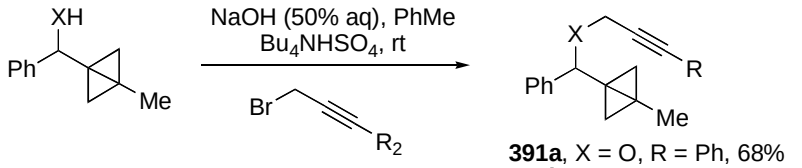
In order to test the reactivity of bicyclo[1.1.0]butanes in the presence of Pt(II) catalyst, three different classes of substrates were prepared. Mono-substituted bicyclo[1.1.0]butanes with *N*- or *O*-propargyl tethers were synthesized *via* a standard alkylation protocol (Scheme 124). 1,3-Disubstituted bicyclo[1.1.0]butanes were obtained *via* alkylation (Scheme 125) or a Mitsunobu reaction[451] (Scheme 126) with the corresponding alcohol. It is noteworthy that for these reactions the remainder of the material was a rearranged cyclobutene product, and the same protocol ap-

plied to the reaction with bicyclo[1.1.0]butylmethyl alcohol proved to give variable yields due to the instability of the product to standard purification techniques.



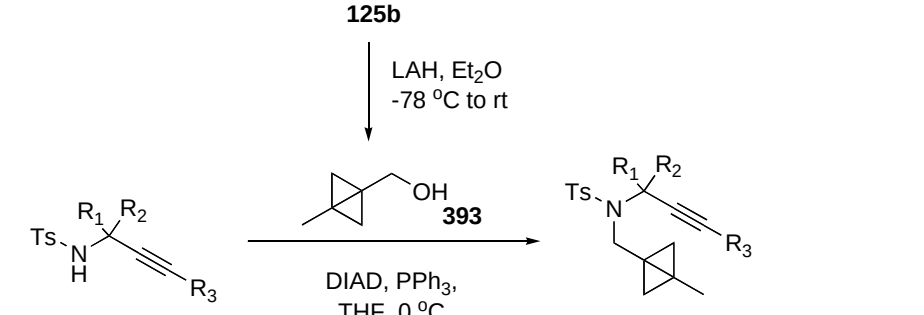
390a, X = NTs, R_1 = Ph, R_2 = Me, 81%
390b, X = NTs, R_1 = Cy, R_2 = H, 90%
390c, X = O, R_1 = Ph, R_2 = H, 95%
390d, X = O, R_1 = Ph, R_2 = Me, 95%

Scheme 124. Synthesis of propargyl amides and ethers **390**.



391a, X = O, R = Ph, 68%
391b, X = NTs, R = H, 90%

Scheme 125. Synthesis of propargyl amide and ether **391a,b**.

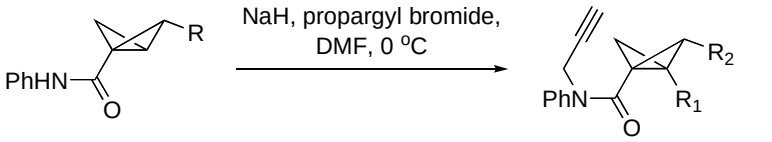


392a, R_1 = R_2 = R_3 = H
392b, R_1 = R_2 = Me, R_3 = H
392c, R_1 = Ph, R_2 = R_3 = H
392d, R_1 = R_2 = H, R_3 = Ph

394a, R_1 = R_2 = R_3 = H, 41%
394b, R_1 = R_2 = Me, R_3 = H, 43%
394c, R_1 = Ph, R_2 = R_3 = H, 27%
394d, R_1 = R_2 = H, R_3 = Ph, 35%

Scheme 126. Synthesis of propargyl amides *via* a Mitsunobu reaction.

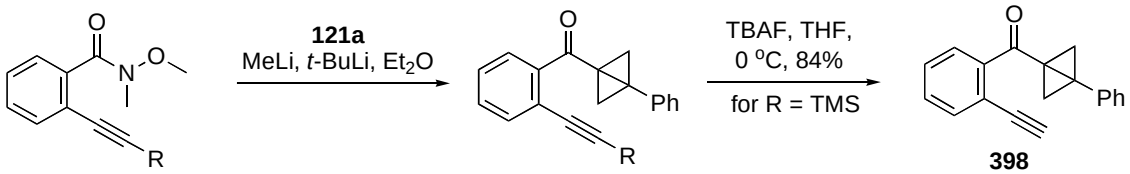
The third class of molecules synthesized involved electron-deficient bicyclo[1.1.0]butanes. These substrates were prepared *via* alkylation (Scheme 127) or addition to Weinreb amides, and the terminal alkyne group was liberated by treatment with TBAF (Schemes 128-130). Due to their highly reactive nature, efforts to remove the protective group under basic conditions from mono-substituted bicyclo[1.1.0]butane **401a** only led to decomposition.



126, R_1 = Me, R_2 = H
152d, R_1 = H, R_2 = Ph

395a, R_1 = Me, R_2 = H, 91%
395b, R_1 = H, R = Ph, 94%

Scheme 127. Synthesis of amides **395a,b**.

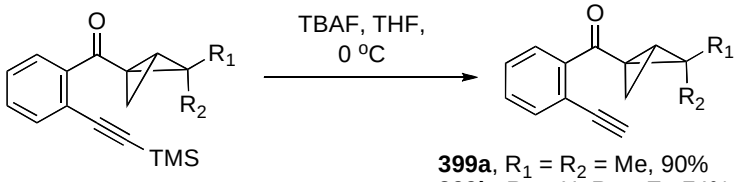


396

397a, R = TMS, 82%
397b, R = Ph, 83%

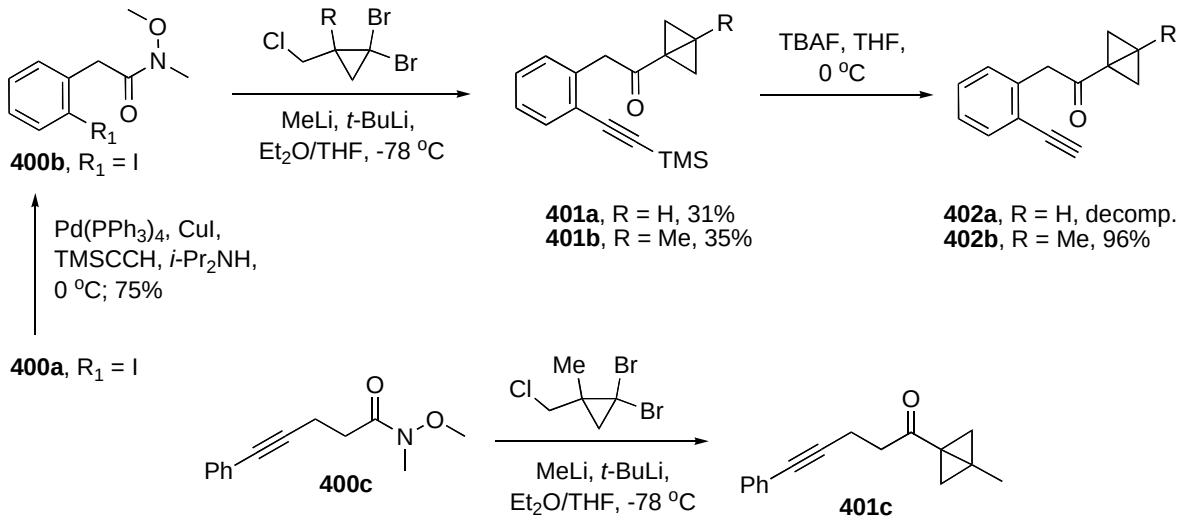
398

Scheme 128. Synthesis of **397** and **398** *via* addition and deprotection reactions.



399a, $R_1 = R_2$ = Me, 90%
399b, R_1 = H, R_2 = Et, 74%

Scheme 129. Deprotection reactions of 2-substituted bicyclo[1.1.0]butanes.



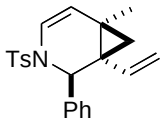
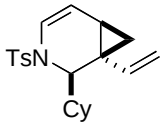
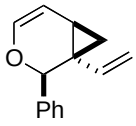
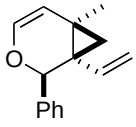
Scheme 130. Synthesis of **401** and **402** *via* addition and deprotection reactions.

When amide **390a** was treated with 10 mol% $PtCl_2$ in PhMe, cyclopropane **403a** was isolated in modest yield (Table 32, entry 1). Also, terminal alkyne **390b** gave multiple products upon heating with $PtCl_2$. Interestingly, a rearrangement reaction of ether **390c** proceeded smoothly at 50 °C with $PtCl_2$ to give vinyl ether **403c** as the only observed product in the crude reaction mixture. Efforts to convert the substituted propargyl ether **390d** gave the desired product (^{1}H NMR), but formation of various side products was observed. Monitoring the progress of this rearrangement by ^{1}H NMR showed that after ca. 40 min a clean and complete conversion of **390d** into butadiene occurred. However, after heating for a prolonged time and at elevated temperature (110 °C) this compound rearranged into **403d** and other products. The structures of **403a** and **403c** were assigned tentatively.

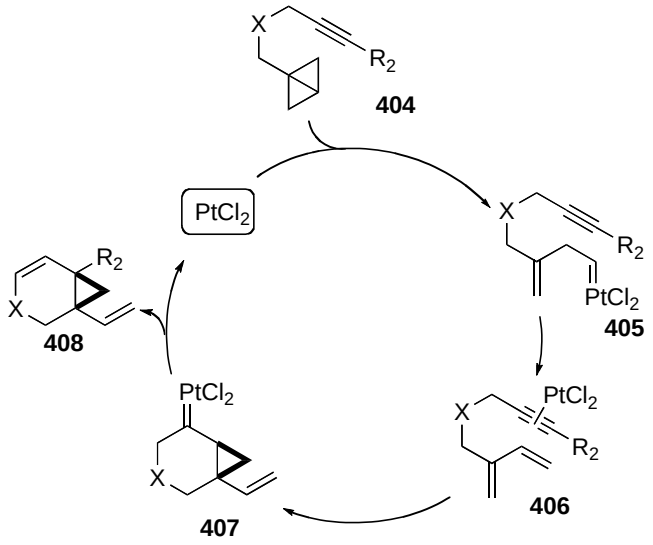
Reactions described in Table 32 can be rationalized by a mechanism depicted in Scheme 131. Because of the presence of the strained ring system, formation of the terminal Pt-carbene **405** may take place, and this intermediate undergoes rearrangement to butadiene **406**. It has been

postulated by Fürstner[452-454] that certain allyl propargyl amides or ethers may undergo an ene-yne metathesis, thus butadiene **406** may react to give another carbene intermediate **407**. This compound collapses *via* hydride shift to give the observed product **408**. The selectivity found in these pathways is controlled by a facile insertion of $PtCl_2$ into a less hindered position of the bicyclo[1.1.0]butane, which is a more reactive site as compared to the alkyne tether.

Table 32. Isomerization reactions of monosubstituted bicyclo[1.1.0]butanes catalyzed by $PtCl_2$.

Entry	Substrate	Product	Conditions[a]	Yield
1	**390a**	 **403a**	$PtCl_2$, PhMe, 110 ^oC	21%
2	**390b**	 **403b**	$PtCl_2$, PhMe, 50 ^oC	<5%
3	**390c**	 **403c**	$PtCl_2$, PhMe, 50 ^oC	61%
4	**390d**	 **403d**	$PtCl_2$, PhMe, 110 ^oC	<10%

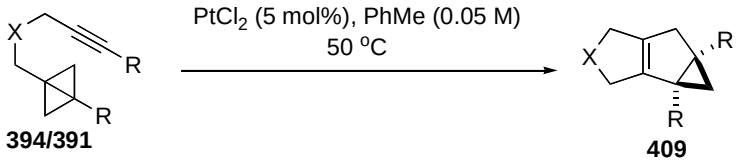
[a]Reactions were performed with 10 mol% of pre-catalyst and at concentrations 0.05 M.

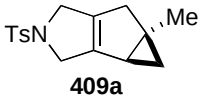
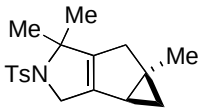
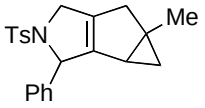
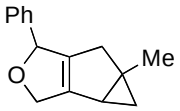
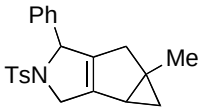
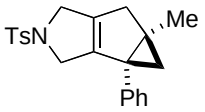


Scheme 131. Postulated mechanism for the rearrangement of terminal bicyclo[1.1.0]butanes with $PtCl_2$.

A different reaction was observed for 1,3-disubstituted bicyclo[1.1.0]butanes (Table 33). It was found that the substrates with alkyl group at the terminal position afforded tricyclic pyrrolidines **409** in good yields with 5 mol% $PtCl_2$. This observation suggests that the steric hindrance at the bicyclo[1.1.0]butane prevents addition of metal to the strained ring and the metal reacts preferentially with the alkyne tether. If the substrate possesses additional substituents, diastereoselectivity in the cycloisomerization reactions was low and changing the temperature did not perturb *dr* significantly. The diastereomeric ratio was improved, however, for a substrate in which the directing group is located in a position closer to the reacting carbene (entry 3). The substitution at the propargyl site (entry 6) was not tolerated and this substrate eventually underwent decomposition.

Table 33. Scope of the isomerization reaction of disubstituted bicyclo[1.1.0]butanes.

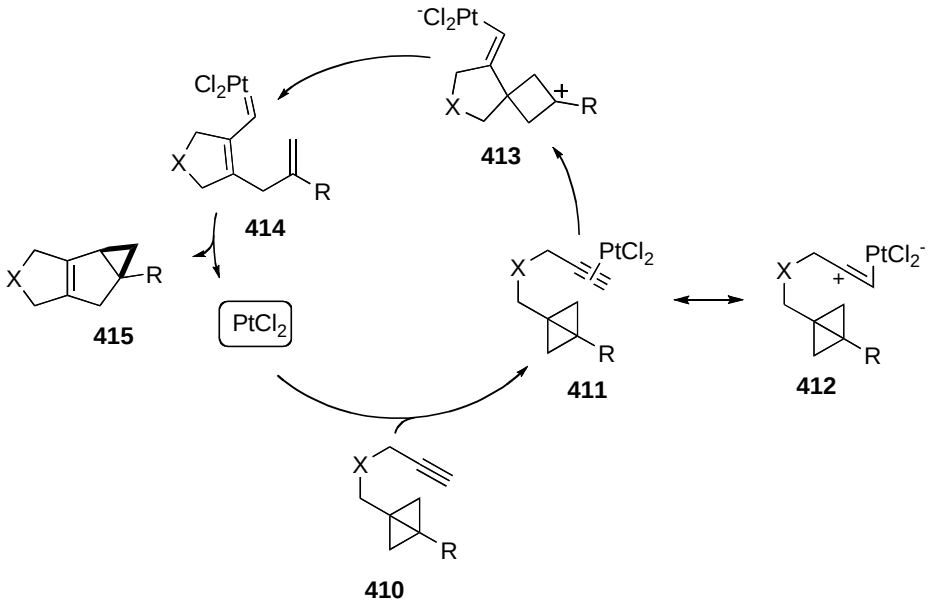


Entry	Substrate	Product	Yield
1	**394a**	 **409a**	84%
2	**394b**	 **409b**	17%[a]
3	**394c**	 **409c**	64%[b,c]
4	**391a**	 **409d**	52%[d]
5	**391b**	 **409e**	71%[e,f]
6	**394d**	 **409f**	<5%[g]

[a]Isolated by preparative TLC. Analytical sample was preparted by a SFC purification. [b]Isolated as a 72:28 mixture of diastereomers. [c]Reaction performed at 50 °C for 1 h afforded **409c** in 80% as a 78:22 mixture of diastereomers. [d]Obtained as a 53:47 ratio of diastereomers. [e]Reaction mixture was heated at 50 °C and afforded a 70:30 mixture of diastereomers. [f]Reaction performed at rt gave a 68:32 mixture of diastereomers. [g]Reaction perfomed at 120 °C for 20 h.

A postulated mechanism for the rearrangement of 1,3-disubstituted bicyclo[1.1.0]butanes is depicted in Scheme 132. Due to additional substitution on the strained ring, it is likely that the metal is initially interacting with the alkyne group (**411**) and this intermediate can be depicted as an alternative resonance form **412**. This intermediate reacts with the central bond in bicyc-

lo[1.1.0]butane and the putative carbocation **413**, stabilized by an alkyl substituent, rearranges to the metal carbene **414**. At this stage, the neighboring allyl group undergoes a cyclopropanation reaction to give the observed product **415**.

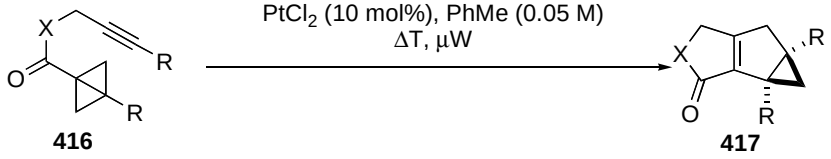


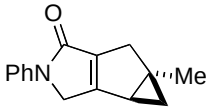
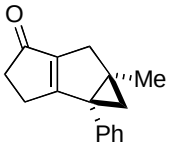
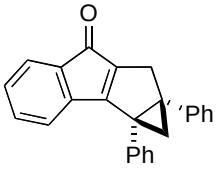
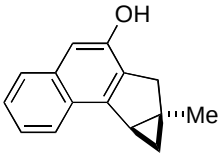
Scheme 132. Postulated mechanism for rearrangement of disubstituted bicyclo[1.1.0]butanes catalyzed by $PtCl_2$.

The scope of the isomerization reaction of electron-deficient bicyclo[1.1.0]butanes is presented in Table 34. It was found that the best yield was obtained if the reaction was performed at 150 ^oC under microwave heating with 10 mol% $PtCl_2$. Although the desired product for the reaction of **395a** was formed in PhMe at 110 ^oC using conventional heating, the yield was low. Solvent studies have also revealed that among PhMe, PhCl, or DMSO, the best yield was obtained for the aromatic systems. We found that the stability of the substrates and, presumably the propensity toward radical polymerization was a factor determining the yields of the product as the **397b** underwent instantaneous decomposition upon heating with $PtCl_2$. Attempts to rearrange

bicyclo[1.1.0]butane **402b** into the corresponding naphthalene led only to decomposition under a variety of reaction conditions. Similarly, the efforts to convert 2-substituted bicyclo[1.1.0]butanes **395**, **399a**, and **399b** resulted only in decomposition of the substrate. The structure of **417b** was assigned tentatively.

Table 34. $PtCl_2$-catalyzed isomerization of electron-deficient bicyclo[1.1.]butanes.

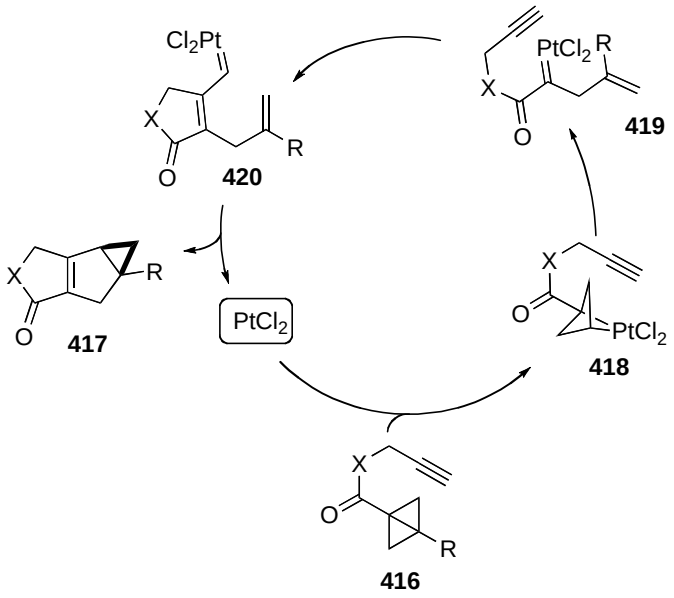


Entry	Substrate	Product	Yield
1[a]	**395a**	 **417a**	56%
2	**401c**	 **417b**	61%
3	**397b**	 **417c**	<5%
4	**402b**	 **417d**	<5%

[a]Reaction performed in PhMe at 110 °C for 45 min afforded **417a** in 42%. [b]Reaction performed in PhCl at 150 °C (μW) for 20 min afforded **417b** in 38%.

The outcome of the above reactions can be rationalized by the mechanism depicted in Scheme 133. However, due to a lower energy of the HOMO in the electron-deficient bicyc-

lo[1.1.0]butanes and their ability to form stable complexes with Pt(II), it is possible that the reactions of these substrates proceed *via* internal carbene intermediate **419** depicted in Scheme 133. After rearrangement of this intermediate *via* ene-yne metathesis reactions, carbene **420** reacts with the allyl group to give **417**. However, whatever the initial mechanism of opening of the bicyclo[1.1.0]butane is, pathways pictured on Scheme 132 and Scheme 133 converge at the same vinyl carbene **414**/**420** which eventually reacts intramolecularly with the neighboring allyl group.



Scheme 133. Alternative mechanism for ene-yne metathesis of bicyclo[1.1.0]butanes catalyzed by $PtCl_2$.

3.3 CONCLUSIONS

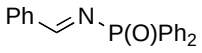
In this chapter, transition metal catalyzed reactions of bicyclo[1.1.0]butanes have been described. A common feature of these transformations is the formation of a carbene intermediate

which can be generated selectively with a proper choice of a catalyst and additives. The cycloisomerizations promoted by Rh(I) complexes are characterized by a high chemo- and diastereoselectivity, and the outcome of these reactions is correlated to the steric bulk and availability of a coordinating site at the metal center. Thus, monodentate ligands promote the formation of a more hindered, electronically stabilized, internal carbene. Alternatively, in the presence of a bidentate ligand, the terminal carbene is formed, followed by the trapping with alkenes or nitrogen nucleophiles to give azepines or pyrroles, respectively. The isomerization reactions catalyzed by $PtCl_2$ occur *via* the formation and rearrangement of Pt(IV)-carbenes. These ene-yne metathesis processes are particularly facile for bicyclo[1.1.0]butanes which are deactivated sterically (1,3-disubstituted) or electronically (electron-deficient).

4.0 EXPERIMENTAL SECTION

General Information. All moisture-sensitive reactions were performed under an atmosphere of N_2 and glassware was flame dried under vacuum prior to use. Toluene was dried by passing through a column of activated alumina and degassed prior to use either by thaw-freeze method or by bubbling N_2. CH_2Cl_2 was dried by passing through a column of activated alumina. Et_2O and THF were freshly distilled from benzophenone ketyl radical anion prior to use. TMEDA, Et_3N, *i*-Pr_2NH, *i*-Pr_2NEt, and 2,6-lutidine were distilled from CaH_2. Solutions of MeLi and *t*-BuLi purchased from Aldrich were titrated prior to use with diphenylacetic acid or a mixture of fluorene and 2,6-di-*t*-butyl-4-methylphenol. Bromides **246b** and **246c** were provided by Dr. Zhenglai Fang. Rhodium pre-catalysts, phosphine ligands, and platinum salts were purchased from Aldrich or Strem. All Rh-catalyzed reactions were performed in a base-washed and oven-dried glassware under the atmosphere of N_2. Unless otherwise stated, all reagents were used as received. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F-254 plates (particle size 0.040-0.055 mm, 230-400 mesh) and visualization was accomplished with a 254 nm UV light and/or by staining with Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}\bullet 4H_2O$ and 0.20 g of $Ce(SO_4)_2$ in 100 mL of 3.5 N H_2SO_4 solution) or a PMA solution (5.0 g of phosphomolybdic acid in 100 mL of 95% EtOH), or *p*-anisaldehyde solution (2.5 mL of *p*-anisaldehyde, 2.0 mL of AcOH, and 3.5 mL of conc. H_2SO_4 in 100 mL of 95% EtOH), or a

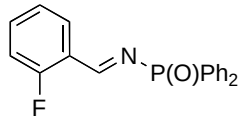
$KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1% NaOH solution). Purifications by chromatography were performed using SiO_2 (SiliaFlash® F60, Silicycle) or aluminum oxide (activated, neutral, Brockmann I, standard grade ~150 mesh, 58 Å, Aldrich). Hexanes and EtOAc used for the chromatographic separations of small- and medium-scale reaction mixtures were distilled prior to use. Supercritical Fluid Chromatography purifications were performed with MeOH and *i*-PrOH (HPLC grade) using a Mettler Toledo-MiniGram instrument. NMR spectra were recorded on Bruker AVANCE 300/500/600 instruments and were processed with TopSpin software. Chemical shifts are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants, and integration. IR spectra were obtained on a Nicolet AVATAR 360 FT-IR E.S.P. or IdentifyIR-ATR (Smiths Detection, Inc.) spectrometers. Mass spectra were obtained on a Micromass Autospec double focusing instrument. Specific optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a sodium lamp at 23 ^oC and are reported as follows: $[\alpha]_D$ (*c* g/100 mL, solvent). Microwave reactions were carried out in Biotage Initiator instrument. Melting points (uncorrected) were determined using Mel-Temp II instrument.



83a

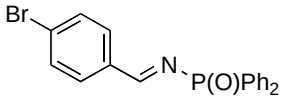
***N*-Benzylidene-*P,P*-diphenylphosphinamide (83a).**[179] **General Protocol A.** Benzaldehyde (3.2 mL, 30 mmol), diphenylphosphinamide **82** (6.4 g, 30 mmol) and *i*-Pr_2NEt (15 mL, 90 mmol) were dissolved in dry CH_2Cl_2 (100 mL), cooled to 0 ^oC and treated dropwise with a solution of $TiCl_4$ (2.0 mL, 19 mmol) in CH_2Cl_2 (30 mL). The reaction mixture was stirred at 0 ^oC for 2 h, poured into dry Et_2O (200 mL) and filtered through a pad of SiO_2 (washed with EtOAc). The

solvent was removed *in vacuo* and the residual oil was dissolved in CH_2Cl_2 followed by addition of an excess of hexanes. The precipitated product was filtered, washed with hexanes and dried to afford **83a** (8.3 g, 92%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.34 (d, J = 32.0 Hz, 1 H), 8.04-7.92 (m, 6 H), 7.61-7.42 (m, 9 H).



83b

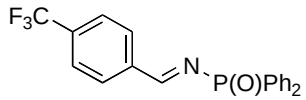
***N*-(2-Fluorobenzylidene)-*P,P*-diphenylphosphinamide (83b).**[455] According to the General Protocol A, 2-fluorobenzaldehyde (2.9 g, 23 mmol), diphenylphosphinamide **82** (5.0 g, 23 mmol) and Et_3N (9.6 mL, 69 mmol) were dissolved in dry CH_2Cl_2 (50 mL), cooled to 0 ^oC and treated dropwise with a solution of $TiCl_4$ (1.6 mL, 14 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at 0 ^oC for 2 h, poured into dry Et_2O (200 mL) and filtered through a pad of SiO_2 (washed with EtOAc). The solvent was removed *in vacuo* and the residual oil was dissolved in CH_2Cl_2 followed by addition of an excess of hexanes. The precipitated product was filtered, washed with hexanes and dried to afford **83b** (3.0 g, 41%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (d, J = 31.8 Hz, 1 H), 8.23 (td, J = 7.6, 1.8 Hz, 1 H), 7.99-7.82 (m, 4 H), 7.59-7.43 (m, 7 H), 7.30-7.25 (m, 1 H), 7.19-7.12 (m, 1 H).



83c

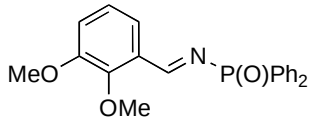
***N*-(4-Bromobenzylidene)-*P,P*-diphenylphosphinamide (83c).**[456] According to the General Protocol A, 4-bromobenzaldehyde (1.7 g, 9.2 mmol), diphenylphosphinamide **82** (2.0 g, 9.2 mmol)

and Et_3N (3.8 mL, 28 mmol) were dissolved in dry CH_2Cl_2 (50 mL), cooled to 0 ^oC and treated dropwise with a solution of $TiCl_4$ (0.63 mL, 5.8 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at 0 ^oC for 2 h, poured into dry Et_2O and filtered through a pad of SiO_2 (washed with EtOAc). The solvent was removed *in vacuo* and the residual oil was dissolved in CH_2Cl_2 followed by addition of an excess of hexanes. The precipitated product was filtered, washed with hexanes and dried to afford **83c** (1.5 g, 42%) as a colorless solid: ^1H NMR (300 MHz, $CDCl_3$) δ 9.28 (d, *J* = 31.7 Hz, 1 H), 7.97-7.86 (m, 6 H), 7.56 (d, *J* = 8.2 Hz, 2 H), 7.54-7.44 (m, 6 H).



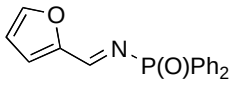
83d

***N*-(4-(Trifluoromethyl)benzylidene)-*P,P*-diphenylphosphinamide (83d).**[456] According to the General Protocol A, 4-(trifluoromethyl)benzaldehyde (2.0 g, 11 mmol), diphenylphosphinamide **82** (3.5 g, 11 mmol) and Et_3N (4.8 mL, 34 mmol) in CH_2Cl_2 (150 mL) were treated with a solution of $TiCl_4$ (0.79 mL, 7.2 mmol) in CH_2Cl_2 (20 mL) at 0 ^oC. After 2 h the reaction mixture was poured into dry ether (200 mL), filtered through pad of SiO_2, washed with EtOAc, and the solvent was removed *in vacuo*. The product was obtained by precipitation from CH_2Cl_2 with an excess of hexanes to afford **83d** (3.3 g, 77%) as a colorless solid: ^1H NMR (300 MHz, $CDCl_3$) δ 9.38 (d, *J* = 31.4 Hz, 1 H), 8.12 (d, *J* = 7.9 Hz, 2 H), 8.02-7.92 (m, 4 H), 7.76 (d, *J* = 8.0 Hz, 2 H), 7.52-7.46 (m, 6 H).



83e

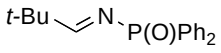
***N*-(2,3-Dimethoxybenzylidene)-*P,P*-diphenylphosphinamide (83e).** According to the General Protocol A, 2,3-dimethoxybenzaldehyde (3.9 g, 23 mmol), diphenylphosphinamide **82** (5.0 g, 23 mmol), and Et_3N (9.6 mL, 69 mmol) in CH_2Cl_2 (150 mL) were treated with a solution of $TiCl_4$ (1.6 mL, 14 mmol) in CH_2Cl_2 (20 mL) at 0 ^oC. After 2 h the reaction mixture was poured into dry ether (200 mL), filtered through a pad of SiO_2, washed with EtOAc, and the solvent was removed *in vacuo*. The product was obtained by precipitation from EtOAc with an excess of hexanes to afford **83e** (5.8 g, 69%) as a colorless solid: Mp. 128.0-129.4 ^oC (hexane/EtOAc); IR (KBr) 3061, 2958, 1689, 1615, 1581, 1480, 1268, 1206 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.55 (d, *J* = 32.2 Hz, 1 H), 7.80-7.73 (m, 4 H), 7.60 (dd, *J* = 7.8, 1.3 Hz, 1 H), 7.18-7.17 (m, 6 H), 6.87 (t, *J* = 8.0 Hz, 1 H), 6.77 (dd, *J* = 8.1, 1.2 Hz, 1 H), 3.64 (s, 3 H), 3.52 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.35, 169.26, 152.16, 151.15, 133.36, 131.68, 131.02, 130.92, 130.82, 130.70, 130.61, 130.57, 130.54, 130.51, 130.39, 128.72, 128.39, 128.11, 127.81, 127.64, 123.30, 118.46, 116.78, 61.18, 55.12; MS (EI) *m/z* (rel. intensity) 365 (M^+, 14), 334 (99), 216 (70), 201 (98), 164 (66), 77 (100); HRMS (EI) calc for $C_{21}H_{20}NO_3P$ 365.1181, found 365.1175.



83f

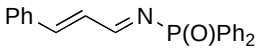
***N*-((2-Furyl)methylene)-*P,P*-diphenylphosphinamide (83f).**[457] According to the General Protocol A, 2-furaldehyde (1.9 mL, 23 mmol), diphenylphosphinamide **82** (5.0 g, 23 mmol) and Et_3N (9.6 mL, 69 mmol) in CH_2Cl_2 (100 mL) were treated with a solution of $TiCl_4$ (1.6 mL, 14 mmol) in CH_2Cl_2 (20 mL) at 0 ^oC. After 2 h the reaction mixture was poured into dry ether (200 mL), filtered through a pad of SiO_2, washed with EtOAc, and the solvent was removed *in vacuo*. The product was obtained by precipitation from CH_2Cl_2 with an excess of hexanes to afford **83f**

(2.7 g, 40%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55 (d, *J* = 32.8 Hz, 1 H), 7.96-7.89 (m, 5 H), 7.53-7.41 (m, 6 H), 7.21 (d, *J* = 3.5 Hz, 1 H), 6.61 (dd, *J* = 3.5, 1.7 Hz, 1 H).



83g

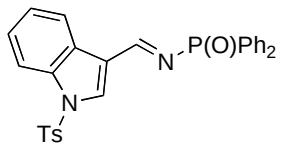
***N*-(2,2-Dimethylpropylidene)-*P,P*-diphenylphosphinamide (83g)**.[458] According to the General Protocol A, trimethylacetaldehyde (0.50 mL, 4.6 mmol), diphenylphosphinamide **82** (1.0, 4.6 mol) and Et_3N (1.9 mL, 14 mmol) in CH_2Cl_2 (10 mL) were treated with a solution of $TiCl_4$ (0.32 mL, 2.9 mmol) in CH_2Cl_2 (5 mL) at 0 ^oC. After 2 h the reaction mixture was poured into dry ether (50 mL), filtered through a pad of SiO_2, washed with EtOAc, and the solvent was removed *in vacuo*. The product was obtained by precipitation from CH_2Cl_2 with an excess of hexanes to afford **83g** (0.47 g, 36%) as a colorless solid: Mp. 139.7-140.5 ^oC (hexanes/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (d, *J* = 32.8 Hz, 1 H), 7.91-7.84 (m, 4 H) 7.49-7.42 (m, 6 H), 1.18 (s, 9 H).



83h

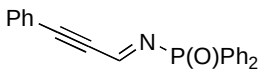
***N*-3-Phenylallylidene-*P,P*-diphenylphosphinamide (83h).**[459] According to the General Protocol A, cinnamyl aldehyde (1.2 mL, 9.2 mmol), diphenylphosphinamide **82** (2.0, 9.2 mmol) and Et_3N (3.9 mL, 28 mmol) in CH_2Cl_2 (50 mL) were treated with a solution of $TiCl_4$ (0.63 mL, 5.8 mmol) in CH_2Cl_2 (10 mL) at 0 ^oC. After 2 h the reaction mixture was poured into dry ether (100 mL), filtered through a pad of SiO_2, washed with EtOAc, and the solvent was removed *in vacuo*. The product was obtained by precipitation from CH_2Cl_2 with an excess of hexanes to afford **83h**

(1.7 g, 56%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.06 (dd, *J* = 31.7, 9.0 Hz, 1 H), 7.95-7.88 (m, 4 H), 7.59-7.54 (m, 3 H), 7.53-7.37 (bs, 9 H), 7.12 (ddd, *J* = 15.8, 9.0, 1.8 Hz, 1 H).



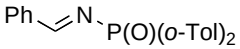
83i

***N*-((1-Tosyl-1*H*-indol-3-yl)methylene)-*P,P*-diphenylphosphinamide (83i).** According to the General Protocol A, 1-tosyl-1*H*-indole-3-carboxaldehyde (0.18 g, 0.60 mmol), diphenylphosphinamide **82** (0.13 g, 0.60 mmol) and Et_3N (0.24 mL, 1.8 mmol) in CH_2Cl_2 (5 mL) were treated with a solution of $TiCl_4$ (0.036 mL, 0.38 mmol) in CH_2Cl_2 (2 mL) at 0 ^oC. After 2 h the reaction mixture was poured into dry ether, filtered through a pad of SiO_2, washed with EtOAc, and the solvent was removed *in vacuo*. The product was obtained by precipitation from CH_2Cl_2 with an excess of hexanes to afford **83i** (0.094 g, 28%) as a colorless solid: Mp. 230 ^oC (CH_2Cl_2/hexanes, decomp.); IR (KBr) 1614, 1439, 1176, 1124 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (d, *J* = 32.7 Hz, 1 H), 8.63-8.60 (m, 1 H), 8.26 (s, 1 H), 8.12-8.02 (m, 5 H), 7.91 (d, *J* = 8.3 Hz, 2 H), 7.55-7.52 (m, 5 H), 7.34 (d, *J* = 8.5 Hz, 3 H), 2.41 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.38, 166.29, 145.92, 135.50, 135.35, 134.25, 133.92, 132.24, 1231.62, 131.49, 131.37, 130.17, 128.49, 128.33, 127.05, 126.11, 124.84, 122.88, 121.01, 120.64, 113.38, 21.52; HRMS (ES) calc for $C_{28}H_{24}N_2O_3PS$ (M+H) 499.1245, found 499.1216.



83j

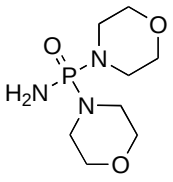
***N*-(3-Phenylprop-2-ynylidene)-*P,P*-diphenylphosphinamide (83j)**.[134] According to the General Protocol A, phenylacetylene aldehyde (0.99 g, 7.6 mmol), diphenylphosphinamide **83** (1.7 g, 7.6 mmol) and *i*-Pr_2NEt (4.0 mL, 23 mmol were dissolved in dry CH_2Cl_2 (25 mL), cooled to 0 ^oC and treated dropwise with a solution of TiCl4 (0.50 mL, 4.8 mmol) in CH_2Cl_2 (3.5 mL). The reaction mixture was stirred at 0 ^oC for 2 h, poured in to dry Et_2O, and evaporated. The residual oil was dissolved in CH_2Cl_2 and the product was obtained by precipitation with an excess of hexanes to afford **83j** (1.3 g, 51 %) as a pale yellow solid: ^1H NMR (300 MHz, $CDCl_3$) δ 9.27 (d, *J* = 32.0 Hz, 1 H), 7.97-7.85 (m, 7 H), 7.49-7.37 (m, 8 H).



84

***N*-benzylidene-*P,P*-di(2-toluyl)phosphinamide (84).**[174] To a suspension of Mg (1.4 g, 58 mmol) in dry Et_2O (100 mL) was added 2-bromotoluene (10 g, 58 mmol). The reaction was initiated by addition of dibromoethane and heated at reflux for 2 h. The reaction mixture was cooled to rt and $(EtO)_2POH$ (2.1 mL, 16 mmol) was added dropwise over 20 min. Stirring was continued at rt for 18 h. The reaction was quenched with 10% HCl and the organic layer was evaporated by heating. The remaining solid was suspended in 1.5 M NaOH (75 mL), followed by addition of bromine (2.1 mL) and the reaction mixture was heated at 70 ^oC for 2 h, cooled to rt, and treated with $Na_2S_2O_3$ followed by conc. HCl (20 mL). The mixture was extracted (3x) with $CHCl_3$, and the organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. The yellow solid was recrystallized from boiling EtOH to afford $HOP(O)(o\text{-Tol})_2$ (3.7 g, 92%) as light yellow solid. This acid was dissolved in $SOCl_2$ (15 mL) and the mixture was heated under reflux for 3 h, cooled to rt, filtered and the excess of $SOCl_2$ was removed by evaporation. The

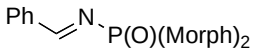
residual yellow solid was dissolved in dry CH_2Cl_2 (50 mL) and ammonia was bubbled in to the solution for 20 min. The reaction mixture was stirred at rt overnight, diluted with water and extracted (3x) with CH_2Cl_2. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. The yellow solid was recrystallized from boiling toluene to afford the di(2-toluyl)phosphinamide (1.31 g, 36%). According to the general Protocol A, benzaldehyde (0.42 mL, 4.1 mmol), di(2-toluyl)phosphinamide (1.0 g, 4.1 mmol) and Et_3N (1.7 mL, 12 mmol) in CH_2Cl_2 (20 mL) were treated with a solution of $TiCl_4$ (0.28 mL, 2.6 mmol) in CH_2Cl_2 (5 mL) at 0 ^oC. After 2 h, the reaction mixture was poured into dry ether, filtered through a pad of SiO_2, washed with EtOAc, and the solvent was removed *in vacuo*. The product was obtained by precipitation from CH_2Cl_2 with an excess of hexanes to afford **84** (0.54 g, 40%) as a colorless solid: ^1H NMR (300 MHz, $CDCl_3$) δ 9.37 (d, J = 32.2 Hz, 1 H), 8.03-7.97 (m, 4 H), 7.54-7.18 (m, 9 H), 2.45 (s, 6 H).



85

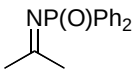
Di(*N*-morpholyl)phosphinamide (85). Freshly distilled morpholine (11 g, 0.13 mol) was dissolved in Et_2O (350 mL) and Et_3N (18 mL, 0.13 mol), cooled to 0 ^oC and treated with $POCl_3$ (6.1 mL, 65 mmol). The reaction mixture was warmed up to rt, and stirred for 5 h. The solid precipitate was filtered off and the solvent was removed *in vacuo*. The remaining oil was dissolved in CH_2Cl_2 (150 mL), cooled to -78 ^oC and ammonia was bubbled through the solution for ca. 35 min. The reaction mixture was allowed to warm up to rt, stirred overnight and filtered. The sol-

vent was evaporated and the residual solid was recrystalized from boiling THF to afford **85** (6.5 g, 42%) as a colorless solid: Mp. 148-149 ^{o}C (THF); IR (KBr) 3324, 3246, 2845, 1568, 1454, 1369, 1254, 1190 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.55 (t, *J* = 4.5 Hz, 8 H), 3.05 (dd, *J* = 9.5, 2.8 Hz, 8 H), 2.93 (bs, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 67.03, 66.95, 44.73; MS (EI) *m/z* (rel. intensity) 235 (M^+, 24), 220 (8), 204 (20), 192 (16), 178 (64), 149 (39), 86 (100); HRMS (EI) calc for $C_8H_{18}N_3O_3P$ 235.1086, found 235.1087.



86

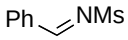
***N*-Benzylidene-*P,P*-di(*N*-morpholyl)phosphinamide (86).** According to the General Protocol A, benzaldehyde (0.65 mL, 6.4 mmol), amide **85** (1.5 g, 6.4 mmol) and *i*-Pr_2NEt (3.3 mL, 19 mmol) in CH_2Cl_2 (100 mL) were treated with a solution of $TiCl_4$ (0.44 mL, 4.0 mmol) in CH_2Cl_2 (20 mL) at 0 ^{o}C. After 3.5 h the reaction mixture was poured into dry ether (300 mL), filtered through a pad of SiO_2, washed with EtOAc, and the solvent was removed *in vacuo*. The product was obtained by precipitation from CH_2Cl_2 with an excess of hexanes to afford crude **86** (1.5 g, 73%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) representative signals δ 9.09 (d, *J* = 30.7 Hz, 1 H), 3.64-3.61 (m, 8 H), 3.19-3.18 (m, 8 H); MS (EI) *m/z* (rel. intensity) 323 (M^+, 22), 266 (15), 237 (17), 114 (100); HRMS (EI) calc for $C_{15}H_{22}N_3O_3P$ 323.1399, found 323.1388.



87

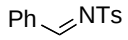
***N*-(2-Propylidene)-*P,P*-diphenylphosphinamide (87).**[176,177] Acetone oxime (3.3 g, 45 mmol) was dissolved in a mixture of pentane (70 mL) and CH_2Cl_2 (70 mL), cooled to -40 ^{o}C and treated

dropwise over 15 min with a solution of diphenylphosphinyl chloride (8.1 mL, 45 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at -40 °C for 1 h, warmed up to rt and stirred for additional 1 h. The solvent was evaporated and the residue was dissolved in CH_2Cl_2, washed (2x) with water, brine, dried (Na_2SO_4), and evaporated. The product was purified by chromatography on SiO_2 (hexanes/EtOAc, 1:9) to afford **87** (2.4 g, 21%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96-7.87 (m, 4 H), 7.52-7.40 (m, 6 H), 2.42 (d, *J* = 1.9 Hz, 6 H); MS (EI) *m/z* (rel. intensity) 257 (M^+, 35), 217 (44), 201 (100), 133 (60).



88a

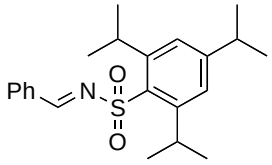
***N*-Benzylidenemethylsulfonamide (88a).**[179] According to the General Protocol A, benzaldehyde (10 g, 94 mmol), $MeSO_2NH_2$ (7.6 g, 94 mmol), and Et_3N (39 mL, 0.28 mol) in CH_2Cl_2 (150 mL) were treated with a solution of $TiCl_4$ (6.4 mL, 69 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min, poured into Et_2O (200 mL), filtered through a pad of SiO_2, and evaporated. The product was obtained by precipitation with an excess of hexanes from CH_2Cl_2 to afford **88a** (9.5 g, 55%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02 (s, 1 H), 7.95 (dd, *J* = 8.4, 1.5 Hz, 2 H), 7.68-7.63 (m, 1 H), 7.55-7.50 (m, 2 H), 3.13 (s, 3 H).



83b

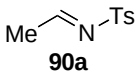
***N*-Benzylidene-(4-methylphenyl)sulfonamide (88b).**[179] According to the General Protocol A, benzaldehyde (10 g, 94 mmol), *p*-$TolSO_2NH_2$ (16 g, 94 mmol), $TiCl_4$ (6.2 mL, 59 mmol), and *i*-Pr_2NEt (48 mL, 0.28 mol) in CH_2Cl_2 (100 mL) after 1.5 h at 0 °C afforded **88b** (15 g, 61%) that

was precipitated from CH_2Cl_2 with an excess of hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (s, 1 H), 7.91 (app. t, *J* = 8.9 Hz, 4 H), 7.62 (t, *J* = 7.2 Hz, 2 H), 7.49 (t, *J* = 7.7 Hz, 2 H), 7.35 (d, *J* = 8.1 Hz, 2), 2.44 (s, 3 H).



88c

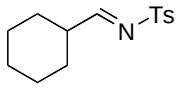
***N*-Benzylidene-tri(isopropylphenyl)sulfonamide (88c).**[180] According to the General Protocol A, benzaldehyde (0.78 mL, 7.1 mmol), 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$SO$_2$NH$_2$ (2.0 g, 7.1 mmol), and Et_3N (2.9 mL, 21 mol) in CH_2Cl_2 (20 mL) were treated with a solution of $TiCl_4$ (0.48 mL, 4.4 mmol) in CH_2Cl_2 (10 mL) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 20 min, poured into Et_2O (200 mL), filtered through a pad of SiO_2, and evaporated. The product was obtained by precipitation with an excess of hexanes from CH_2Cl_2 to afford **88c** (2.5 g, 93%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (s, 1 H), 7.95-7.92 (m, 2 H), 7.62-7.59 (m, 1 H), 7.50 (app. t, *J* = 7.5 Hz, 2 H), 7.22 (s, 2 H), 4.38 (septet, *J* = 6.7 Hz, 2 H), 2.93 (septet, *J* = 6.9 Hz, 1 H), 1.31 (d, *J* = 6.8 Hz, 12 H), 1.27 (d, *J* = 6.9 Hz, 6 H).



90a

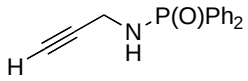
***N*-ethylidene-4-methylbenzenesulfonamide (90a).**[181] A suspension of acetaldehyde (0.44 g, 10 mmol), *p*-TolSO$_2$NH$_2$ (1.7 g, 10 mmol) and PhSO$_2$Na (1.8 g, 11 mmol) in a mixture of HCO_2H (15 mL) and water (20 mL) was stirred at rt for 12 h. The solids were filtered, washed with water (20 mL) and pentane (20 mL), and dissolved in CH_2Cl_2 (50 mL). The mixture was washed with

sat. $NaHCO_3$ (50 mL), the organic layer was dried (Na_2SO_4), and concentrated to afford **90a** (0.92 g, 47%) as a white solid.



90b

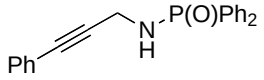
Cyclohexyl-*N*-tosylmethanimine (90b).[181] Cyclohexanecarboxaldehyde (2.1 g, 19 mmol), *p*-$TolSO_2NH_2$ (3.3 g, 19 mmol), and sodium *p*-toluenosulfinate (3.4 g, 19 mmol) were dissolved in a mixture of formic acid (30 ml) and water (30 mL). The reaction mixture was stirred at rt for 12 h, the solid was filtered off, washed with water (2x) and hexane and dissolved in CH_2Cl_2 (70 mL). A saturated solution of $NaHCO_3$ (120 mL) was added and the reaction mixture was vigorously stirred at rt for 2 h, and extracted (3x) with CH_2Cl_2. The combined organic layers were washed with water, dried (Na_2SO_4) and the solvent was evaporated to afford **90b** (3.6 g, 71%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, *J* = 4.9 Hz, 1 H), 7.81 (d, *J* = 8.4 Hz, 2 H), 7.34 (dd, *J* = 8.0, 0.6 Hz, 2 H), 2.44 (s, 4 H), 1.86-1.66 (m, 4 H), 1.38-1.23 (m, 4 H).



91

***N*-(Prop-2-ynyl)-*P,P*-diphenylphosphinamide (91).** Propargyl amine (0.50 g, 9.1 mmol) and Et_3N (1.3 mL, 18 mmol) were dissolved in CH_2Cl_2 (40 mL) and treated with $Ph_2P(O)Cl$ (2.2 g, 9.1 mmol). The reaction mixture was stirred at rt for 12 h, quenched with sat. NH_4Cl, and extracted (3x) with CH_2Cl_2. The combined organic layers were washed with water, brine, dried ($MgSO_4$) and evaporated. The product was obtained by precipitation from CH_2Cl_2 with an excess

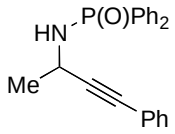
of hexanes to afford **91** (1.9 g, 80%) as a pale yellow solid: Mp. 111-113 ^{o}C (hexanes/CH_2Cl_2); IR (KBr) 2860, 1591, 1438, 1186 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93-7.86 (m, 4 H), 7.50-7.32 (m, 6 H), 4.56 (bs, 1 H), 3.72 (dd, *J* = 8.1, 2.4 Hz, 2 H), 2.25 (t, *J* = 2.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.80, 152.66, 151.67, 132.16, 132.04, 131.91, 131.17, 130.61, 128.63, 128.46, 128.16, 127.99, 81.12, 71.75, 71.75, 30.17; MS (EI) *m/z* (rel. intensity) 255 (M^+, 100), 202 (78), 186 (16), 155 (27); HRMS (EI) calc for $C_{15}H_{14}NOP$ 255.0813, found 255.0881.



92

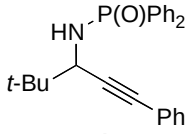
***N*-(3-Phenylprop-2-ynyl)-*P,P*-diphenylphosphinamide (92).** A suspension of $Pd(PPh_3)_4$ (0.083 g, 0.07 mmol) and CuI (0.028 g, 0.14 mmol) in freshly distilled *i*-Pr_2NH (50 mL) was cooled to 0 ^{o}C followed by addition of PhI (0.14 mL, 1.3 mmol), a solution **39** (0.55 g, 2.2 mmol) in THF (5.0 mL) and *i*-Pr_2NH (20 mL). The reaction mixture was vigorously stirred at 0 ^{o}C for 30 min, quenched with sat. NH_4Cl and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried ($MgSO_4$), and evaporated. The product was obtained by purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) followed precipitation from CH_2Cl_2 with an excess of hexanes to afford **92** (0.41 g, 90%) as a pale yellow solid: Mp. 145.5-147.0 ^{o}C (hexane/CH_2Cl_2); IR (KBr) 2891, 1489, 1438, 1194, 1115 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96-7.86 (m, 4 H), 7.51-7.35 (m, 8 H), 7.29-7.25 (m, 3 H), 3.96 (d, *J* = 8.5 Hz, 2 H), 3.54 (bs, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.58, 132.24, 132.11, 132.05, 131.63, 130.86, 128.68, 128.51, 128.32, 128.24, 122.65, 86.23, 86.49, 83.62, 31.00; MS (EI) *m/z* (rel. intensity) 331 (M^+, 92),

277 (9), 255 (23), 202 (46), 130 (100); HRMS (EI) calc for $C_{21}H_{18}NOP$ 331.1126, found 331.1117.



93a

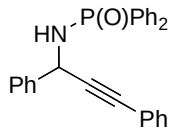
***N*-(4-Phenyl-3-butyn-2-yl)-*P,P*-diphenylphosphinamide (93a).** Imine **83k** (0.52 g, 1.6 mmol) was dissolved in THF (10 mL) cooled to 0 ^{o}C and treated with a solution of MeMgBr (1.6 mL, 4.7 mmol, c = 3.0 M in Et_2O). The reaction mixture was stirred at 0 ^{o}C for 30 min, quenched with sat. NH_4Cl and extracted (3x) with EtOAc. The combined organic layers were washed with water, brined, dried ($MgSO_4$), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **93a** (0.44 g, 82%) as a colorless oil: IR (neat) 1592, 1489, 1438, 1187 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05-7.27 (m, 15 H), 4.35-4.21 (m, 1 H), 3.34 (app. t, *J* = 8.3 Hz, 1 H), 1.60 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.99, 132.86, 132.51, 132.19, 132.16, 132.02, 131.93, 131.54, 128.88, 128.86, 128.69, 128.47, 123.21, 91.62, 91.50, 82.97, 39.96, 26.15, 26.10.



93b

***N*-(4,4-Dimethyl-1-phenyl-1-pentyn-3-yl)-*P,P*-diphenylphosphinamide (93b).** Imine **83k** (0.40 g, 1.2 mmol) was dissolved in THF (10 mL) cooled to -78 ^{o}C and treated with a solution of *t*-BuLi (1.8 mL, 3.0 mmol, c = 1.7 M in pentane). The reaction mixture was stirred at -78 ^{o}C for

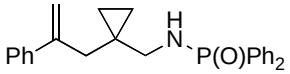
15 min, warmed up to rt, quenched with sat NH_4Cl, and extracted (3x) with EtOAc. The combined organic layers were washed with water, brined, dried ($MgSO_4$), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:1) afforded **93b** (0.43 g, 91%) as a colorless solid: Mp. 170.4-171.2 ^oC (hexane/CH_2Cl_2); IR (KBr) 1489, 1438, 1181 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08-8.01 (m, 2 H), 7.87-7.80 (m, 2 H), 7.47-7.33 (m, 8 H), 7.28-7.26 (m, 3 H), 3.85 (app. t, *J* = 10.6 Hz, 1 H), 3.28 (app. t, *J* = 10.6 Hz, 1 H), 1.09 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.17, 132.98, 132.85, 132.47, 131.91, 131.72, 131.57, 131.22, 128.57, 128.40, 128.25, 128.14, 123.10, 89.66, 84.43, 53.53, 35.95, 26.29; MS (EI) *m/z* (rel. intensity) 387 (M^+, 4), 373 (3), 330 (100), 201 (68); HRMS (EI) calc for $C_{25}H_{26}NOP$ 387.1752, found 387.1748.



94

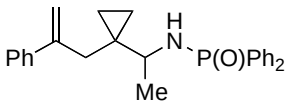
***N*-(1,3-Diphenylprop-2-ynyl)-*P,P*-diphenylphosphinamide (94). General Protocol B.** Phenylacetylene (0.63 mL, 5.7 mmol) was dissolved in dry THF (30 mL), cooled to -78 ^oC and treated with a solution of *n*-BuLi (3.6 mL, 5.7 mmol, c = 1.6 M in hexanes). The reaction mixture was stirred at -78 ^oC for 10 min and solid imine **83a** (0.70 g, 2.3 mmol) was added. The reaction mixture was allowed to warm up to rt, quenched with sat. NH_4Cl and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **94** (0.84 g, 90%) as a colorless solid: Mp. 161.6-162.6 ^oC (hexanes/CH_2Cl_2); IR (KBr) 3162, 3058, 2846, 1597, 1591, 1490, 1450, 1436, 1190, 1123 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.22-8.15 (m, 2 H), 7.98-7.92 (m, 2 H), 7.79 (d, *J* = 7.1 Hz, 2 H), 7.64-7.35 (m, 14 H), 5.50 (app. t, *J* = 9.9 Hz, 1 H), 3.70 (app.

t, J = 9.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.48, 140.42, 133.49, 132.99, 132.86, 132.15, 132.11, 132.02, 131.89, 131.80, 131.13, 128.79, 128.71, 128.54, 128.37, 128.09, 127.45, 122.81, 89.01, 88.93, 85.67, 47.24; MS (EI) *m/z* (rel. intensity) 407 (M^+, 56), 330 (10), 216 (4), 206 (100), 201 (40), 191 (19); HRMS (EI) calc for $C_{27}H_{22}NOP$ 407.1439, found 407.1421.



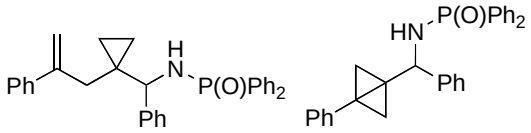
95

***N*-((1-(2-Phenylallyl)cyclopropyl)methyl)-*P*,*P*-diphenylphosphinamide (44). General Protocol C.** Amide **92** (0.30 g, 0.91 mmol) was dissolved in CH_2Cl_2 (5.0 mL), cooled to 0 ^oC and treated with a solution of Me_2Zn (0.45 mL, 0.91 mmol, c = 2.0 M in PhMe). The reaction mixture was stirred at 0 ^oC for 1 h, cooled to -30 ^oC and transferred *via* cannula into a cold (-30 ^oC) solution of $(CH_2I)_2Zn$ prepared by dropwise addition of CH_2I_2 (0.38 mL, 4.5 mmol) to a solution of Et_2Zn (0.28 g, 2.3 mmol) in CH_2Cl_2 (4.0 mL) and DME (0.27 mL, 2.3 mmol) at -30 ^oC. The reaction mixture was stirred at 0 ^oC for 4 h, quenched with sat. NH_4Cl and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried ($MgSO_4$) and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **95** (0.22 g, 64%) as a colorless oil: IR (neat) 3203, 2955, 2924, 2854, 1437, 1186, 1162, 1123, 1108 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 8.04-7.96 (m, 4 H), 7.35-7.28 (m, 2 H), 7.13-7.04 (m, 9 H), 5.21 (d, J = 1.6 Hz, 1 H), 5.06 (d, J = 1.3 Hz, 1 H), 2.88-2.74 (m, 3 H), 2.58 (s, 2 H), 0.21-0.13 (m, 4 H); ^{13}C NMR (75 MHz, C_6D_6) δ 146.61, 142.69, 135.21, 133.52, 132.69, 132.57, 131.50, 131.46, 126.72, 114.66, 47.75, 39.16, 20.44, 20.33, 10.90; MS (EI) *m/z* (rel. intensity) 387 (M^+, 4), 359 (5), 318 (5), 230 (43), 218 (93), 201 (100), 170 (63), 155 (27); HRMS (EI) calc for $C_{25}H_{26}NOP$ 387.1752, found 387.1741.



96

***N*-(1-(1-(2-Phenylallyl)cyclopropyl)ethyl)-*P,P*-diphenylphosphinamide (96).** According to the General Protocol C, amide **93a** (0.090 g, 0.26 mmol) was treated with Me_2Zn (0.13 mL, 0.26 mmol, c = 2.0 M in PhMe) at 0 ^oC. After 1 h, the reaction mixture was transferred into a solution of $(CH_2I)_2Zn$ prepared by addition of CH_2I_2 (0.11 mL, 1.3 mmol) to a solution of Et_2Zn (0.081 g, 0.65 mmol) in CH_2Cl_2 (2.0 mL) at -30 ^oC. The reaction mixture was stirred at rt for 3.5 h, quenched with sat. NH_4Cl and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried ($MgSO_4$), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **96** (0.094 g, 85%) as a colorless oil: IR (neat) 3196, 3077, 3056, 2971, 2930, 2870, 1623, 1591, 1573, 1494, 1483, 1453, 1438, 1337,1306, 1188, 1123, 1108 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.23-7.97 (m, 5 H), 7.60-7.39 (m, 10 H), 5.40 (s, 1 H), 5.23 (s, 1 H), 3.11-2.97 (m, 2 H), 2.66 (d, *J* = 14.7 Hz, 1 H), 2.38 (b, 1 H), 1.41 (d, *J* = 6.4 Hz, 3 H), 0.52-0.43 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.94, 141.93, 134.46, 133.71, 132.76, 132.55, 132.43, 132.11, 131.99, 131.79, 128.61, 128.45, 128.38, 127.53, 126.35, 115.47, 53.44, 37.44, 24.24, 24.14, 21.39, 11.20, 9.97; MS (EI) *m/z* (rel. intensity) 401 (M^+, 19), 383 (70), 283 (9), 244 (20), 218 (100), 201 (94), 184 (40); HRMS (EI) calc for $C_{26}H_{28}NOP$ 401.1909, found 401.1902.



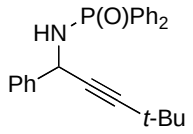
97 **98**

***N*-(phenyl(1-(2-phenylallyl)cyclopropyl)methyl)-*P,P*-diphenylphosphinamide (97) and *N*-(Phenyl-(3-phenylbicyclo[1.1.0]but-1-yl)methyl)-*P,P*-diphenylphosphinamide (98).** Amide **94** (0.30 g, 0.74 mmol) was dissolved in CH_2Cl_2 (5.0 mL), cooled to 0 ^oC and treated with Me_2Zn (0.37 mL, 0.74 mmol, c = 2.0 M in PhMe). The reaction mixture was stirred at 0 ^oC for 1 h, cooled to -30 ^oC and transferred *via* cannula into a cold (-30 ^oC) solution of Et_2Zn (0.23 g, 1.8 mmol) and CH_2I_2 (0.31 mL, 3.7 mmol) at -30 ^oC. The reaction mixture was stirred at 0 ^oC for 5 h, quenched with sat. NH_4Cl and extracted (3x) with CH_2Cl_2. The combined organic layers were washed with water, brine, dried ($MgSO_4$), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **97** (0.10 g, 30%) and **98** (0.092 g, 29%).

97. Obtained as a colorless oil: IR (neat) 1683, 1494, 1438, 1190 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 11.2, 7.4 Hz, 2 H), 7.72 (dd, *J* = 11.4, 7.6 Hz, 2 H), 7.67-7.35 (m, 6 H), 7.28-7.18 (m, 8 H), 5.26 (s, 1 H), 5.17 (s, 1 H), 4.23 (app. t, *J* = 10.6 Hz, 1 H), 3.56 (dd, *J* = 9.7 Hz, 7.0 Hz, 1 H), 3.02 (d, *J* = 15.0 Hz, 1 H), 2.39 (d, *J* = 15.0 Hz, 1 H), 0.69-0.67 (m, 1 H), 0.40-0.35 (m, 3 H) MS (EI) *m/z* (rel. intensity) 463 (M^+, 43), 345 (40), 306 (98), 246 (100), 218 (98), 201 (100); HRMS (EI) calc for $C_{31}H_{30}NOP$ 463.2065, found 463.2091.

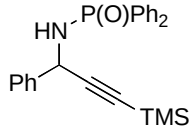
98. Obtained as a colorless oil: IR (neat) 3059, 1680, 1597, 1438, 1191 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (ddd, *J* = 10.5, 6.8, 1.5 Hz, 2 H), 7.70 (ddd, *J* = 12.1, 5.1, 1.4 Hz, 2 H), 7.56-7.38 (m, 4 H), 7.31-7.27 (m, 4 H), 7.18-7.10 (m, 4 H), 6.93 (dd, *J* = 7.8, 1.6 Hz, 2 H), 6.81 (dd, *J* = 7.7, 1.4 Hz, 2 H), 4.68 (app t, *J* = 8.5 Hz, 1 H), 4.45 (dd, *J* = 7.8, 5.3 Hz, 1 H), 2.13 (d, *J* = 6.7 Hz, 1 H), 1.99 (d, *J* = 6.7 Hz, 1 H), 0.94 (s, 1 H), 0.89 (s, 1 H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 140.44, 140.36, 135.76, 132.16, 132.04, 131.99, 131.86, 131.59, 131.44, 128.38, 128.26, 128.22, 128.11, 128.02, 127.96, 127.16, 127.01, 125.56, 125.03, 55.02, 33.18, 30.91, 28.33, 28.26, 20.15; MS (EI) *m/z* (rel. intensity) 435 (M^+, 14), 306 (50), 218 (43), 201 (100); HRMS (EI) calc for $C_{29}H_{26}NOP$ 435.1752, found 435.1749.



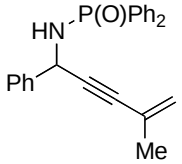
99a

***N*-(4,4-Dimethyl-1-phenylpent-2-ynyl)-*P,P*-diphenylphosphinamide (99a).** According to the General Protocol B, 3,3-dimethylbutyne (0.64 mL, 3.9 mmol) was dissolved in THF (20 mL), cooled to -78 ^oC and treated with a solution of *t*-BuLi (2.3 mL, 3.9 mmol, c = 1.7 M in pentane). The reaction mixture was stirred at this temperature for 15 min and a solution of imine **83a** (0.40 g, 1.3 mmol) in THF (10 mL) was added. The reaction mixture was allowed to warm up to rt, quenched with sat. NH_4Cl and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. The product was precipitated from CH_2Cl_2 with excess of hexanes to afford **99a** (0.50 g, 99%) as a colorless solid: Mp. 136.6-138.1 ^oC (hexane/CH_2Cl_2); IR (KBr) 2965, 1591, 1492, 1454, 1436, 1258 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.14-8.08 (m, 2 H), 7.88-7.81 (m, 2 H), 7.69 (d, *J* = 7.4 Hz, 2 H), 7.61-7.27 (m, 9 H), 5.21 (app. t, *J* = 10.1 Hz, 1 H), 3.44 (app. t, *J* = 9.6 Hz, 1 H), 1.28 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.98, 133.81, 132.93, 132.80, 131.3, 131.71, 131.59, 131.23, 128.41, 128.29, 127.61, 127.31, 94.30, 78.16, 46.53, 30.87, 27.43; MS (EI) *m/z* (rel. intensity) 487 (M^+, 43), 372 (16), 331 (46), 218 (12), 201 (96), 186 (100); HRMS (EI) calc for $C_{25}H_{26}NOP$ 387.1752, found 387.1752.



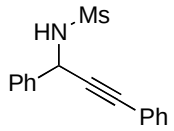
99

***N*-(3-(Trimethylsilyl)-1-phenylprop-2-ynyl)-*P,P*-diphenylphosphinamide (99b).** Trimethylsilylacetylene (0.54 mL, 6.6 mmol) was dissolved in THF (25 mL), cooled to -78 ^{o}C and treated with a solution of *t*-BuLi (3.9 mL, 6.6 mmol, c = 1.7 M in pentane). The reaction mixture was stirred at -78 ^{o}C for 15 min and solid amine 8**3a** (0.80 g, 2.6 mmol) was added. The reaction mixture was warmed up to rt, quenched with sat. NH_4Cl and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried ($MgSO_4$), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **99** (0.63 g, 64%) as a colorless solid: Mp. 142.8-144.2 ^{o}C (CH_2Cl_2/hexanes); IR (KBr) 1438, 1250, 1183, 1126 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32-8.25 (m, 2 H), 7.96-7.89 (m, 4 H), 7.23-6.97 (m, 9 H), 5.45 (app. t, *J* = 10.5 Hz, 1 H), 3.34 (app. t, *J* = 9.3 Hz, 1 H), 0.26 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.07, 140.02, 133.54, 132.89, 132.76, 132.66, 132.01, 131.98, 131.92, 131.89, 131.75, 131.62, 131.16, 131.03, 130.94, 130.35, 129.97, 128.51, 128.33, 128.02, 127.83, 127.31, 105.09, 105.01, 90.16, 59.53, 47.10, -0.16; MS (EI) *m/z* (rel. intensity) 403 (M^+, 44), 274 (46), 259 (48), 202 (76), 77 (100); HRMS (EI) calc for $C_{24}H_{26}NOPSi$ 403.1521, found 403.1217.



99c

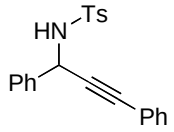
***N*-(4-Methyl-1-phenylpent-4-en-2-ynyl)-*P,P*-diphenylphosphinamide (99c).** According to the General Protocol B, 2-methylbut-1-en-3-yl (0.47 mL, 4.9 mmol) was dissolved in THF (20 mL), cooled to -78 ^{o}C and treated with a solution of *n*-BuLi (3.1 mL, 4.9 mmol, c = 1.6 M in hexanes). The reaction mixture was stirred at this temperature for 15 min and a solution of imine **83a** (0.50 g, 1.6 mmol) in THF (10 mL) was added. The reaction mixture was allowed to warm up to rt, quenched with sat. NH_4Cl and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 1:4) to afford **99c** (0.56 g, 92%) as a colorless solid: Mp. 150.2-152.1 ^{o}C (CH_2Cl_2/hexane); IR (KBr) 1598, 1489, 1438, 1348, 1244, 1115 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10-8.02 (m, 2 H), 7.87-7.80 (m, 2 H), 7.64-7.61 (m, 2 H), 7.53-7.27 (m, 9 H), 5.33-5.24 (m, 3 H), 3.51 (app. t, *J* = 9.1 Hz, 1 H), 1.89 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.32, 140.46, 133.48, 132.82, 132.69, 132.47, 131.96, 131.86, 131.73, 131.51, 131.09, 128.85, 128.59, 128.53, 128.36, 127.88, 127.26, 126.36, 122.10, 111.19, 87.85, 87.77, 86.72, 46.99, 23.27; MS (EI) *m/z* (rel. intensity) 371 (M^+, 26), 233 (17), 201 (46), 170 (100), 155 (17); HRMS (EI) calc for $C_{24}H_{22}NOP$ 371.1439, found 371.1440.



100a

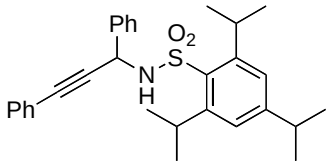
***N*-(1,3-Diphenylprop-2-ynyl)methylsulfonamide (100a).**[460] According to the General Protocol B, phenylacetylene (1.8 mL, 16 mmol) was dissolved in THF (100 mL), cooled to -78 ^{o}C and treated with a solution of *n*-BuLi (10 mL, 16 mmol, c = 1.6 in hexanes). The reaction mixture was stirred at this temperature for 10 min and solid imine **88a** (1.0 g, 5.5 mmol) was added. The

reaction mixture was allowed to warm up to rt, quenched with sat. NH_4Cl and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried ($MgSO_4$), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **100a** (1.0, 65%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75-7.72 (m, 2 H), 7.47-7.36 (m, 3 H), 7.31-7.20 (m, 3 H), 7.16-7.12 (m, 2 H), 6.33 (s, 1 H), 3.89 (s, 1 H), 2.69 (s, 3 H).



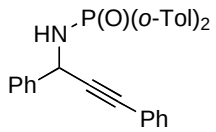
100b

1,3-Diphenyl-*N*-tosylprop-2-yn-1-amine (100b).[460,461] According to the General Protocol B, phenylacetylene (1.3 mL, 12 mmol) was dissolved in THF (20 mL), cooled to -78 ^{o}C and treated with a solution of *n*-BuLi (7.0 mL, 11 mmol, c = 1.6 M in hexanes). The reaction mixture was stirred at this temperature for 15 min and a solution of imine **100b** (1.0 g, 3.9 mmol) in THF (20 mL) was added. The reaction mixture was allowed to warm up to rt, quenched with sat. NH_4Cl and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to afford **52** (1.1 g, 79%) as a colorless solid: IR (KBr) 3268, 1491, 1332, 1155 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, 2 H), 7.59-7.56 (m, 2 H), 7.40-7.23 (m, 8 H), 7.15-7.12 (m, 2 H), 5.58 (d, *J* = 9.1 Hz, 1 H), 4.90 (d, *J* = 9.1 Hz, 1 H), 2.33 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.57, 137.46, 131.57, 129.56, 128.73, 128.59, 128.49, 128.11, 127.55, 127.34, 86.72, 85.54, 49.82, 21.40; HRMS (ES) calc for $C_{22}H_{19}NNaO_2S$ (M+Na) 384.1034, found 384.1052.



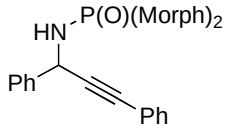
100c

***N*-(1,3-Diphenylprop-2-ynyl)-2,4,6-triisopropylbenzenesulfonamide (100c).** According to the General Protocol B, phenylacetylene (0.88 mL, 8.1 mmol) was dissolved in dry THF (20 mL), cooled to -78 ^{o}C and treated with *n*-BuLi (5.1 mL, 8.1 mmol, c = 1.6 M in hexanes). After 15 min at -78 ^{o}C, a solution of imine **88c** (1.0 g, 2.7 mmol) in THF (5.0 mL) was added. The reaction mixture was allowed to warm up to rt, quenched with sat. NH_4Cl, and extracted (3x) with Et_2O. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 6:1) to afford **100c** (1.3 g, 97%) as a colorless oil that solidified upon standing: Mp. 88.1-89.2 ^{o}C (EtOAc/hexane); IR (neat) 1599, 1490, 1462, 1329, 1192 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.3 Hz, 2 H), 7.44-7.38 (m, 3 H), 7.33-7.23 (m, 5 H), 7.07 (dd, *J* = 8.1, 1.5 Hz, 2 H), 5.75 (d, *J* = 8.7 Hz, 1 H), 5.02 (d, *J* = 8.7 Hz, 1 H), 4.22 (septet, *J* = 6.7 Hz, 2 H), 2.90 (septet, *J* = 6.9 Hz, 1 H), 1.37 (app. t, *J* = 6.8 Hz, 12 H), 1.26 (d, *J* = 6.9 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 149.9, 137.5, 133.6, 131.4, 131.3, 128.6, 128.4, 128.4, 128.0, 127.4, 123.7, 121.9, 86.7, 85.4, 49.4, 33.9, 29.8, 24.8, 24.7, 24.7, 24.6, 23.4; MS (EI) *m/z* (rel. intensity) 473 (M^+, 4), 230 (36), 410 (66), 304 (73), 282 (69), 206 (78), 191 (100); HRMS (EI) calc for $C_{27}H_{28}NO_2S$ (M-C_3H_7) 430.1841, found 430.1829.



100d

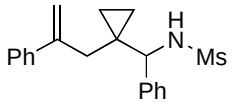
***N*-(1,3-Diphenylprop-2-ynyl)-*P,P*-di(2-methylphenyl)phosphinamide (100d).** According to the General Protocol B, phenylacetylene (0.25 mL, 2.3 mmol), and *n*-BuLi (1.4 mL, 2.3 mmol, c = 1.6 in hexanes) were stirred in THF (20 mL) at -78 ^{o}C for 15 min and a solution of imine **84** (0.17 g, 0.50 mmol) in THF (5.0 mL) was added. The reaction was continued at -78 ^{o}C for 1 h, warmed up to rt, quenched with sat. NH_4Cl, and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. The product was obtained by precipitation from CH_2Cl_2 with an excess of hexanes to afford **100d** (0.17 g, 82%) as a colorless solid: Mp. 200.4-201.4 ^{o}C (CH_2Cl_2/hexanes); IR (KBr) 2865, 1593, 1490, 1453, 1177 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 13.3, 7.7 Hz, 1 H), 7.74 (d, *J* = 7.6 Hz, 2 H), 7.56-7.16 (m, 15 H), 5.65 (app. t, *J* = 9.8 Hz, 1 H), 3.35 (app. t, *J* = 11.0 Hz, 1 H), 2.59 (s, 3 H), 2.53 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.79, 142.65, 142.41, 142.30, 140.72, 140.66, 133.54, 131.98, 131.82, 131.67, 131.63, 128.64, 128.38, 128.26, 127.93, 127.49, 125.51, 125.34, 125.30, 122.75, 89.07, 89.00, 85.49, 46.81, 21.75, 21.70, 21.48, 21.42; MS (EI) *m/z* (rel. intensity) 435 (M^+, 39), 344 (5), 229 (15), 206 (100), 191 (41); HRMS (EI) calc for $C_{29}H_{26}NOP$ 435.1752, found 435.1740.



100e

***N*-(1,3-Diphenylprop-2-ynyl)-*P,P*-di(*N*-morpholyl)phosphinamide (100e).** According to the General Protocol B, phenylacetylene (0.34 mL, 3.1 mmol) was dissolved in THF (40 mL), cooled to -78 ^{o}C and treated with a solution of *n*-BuLi (1.9 mL, 3.1 mmol, c = 1.6 M in hexanes). The reaction mixture was stirred at this temperature for 15 min and a solution of imine **86** (0.4 g,

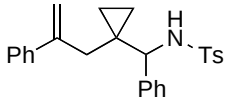
1.2 mmol) in THF (10 mL) was added. The mixture was allowed to warm up to rt, quenched with sat. NH_4Cl, and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. The product was obtained by precipitation from CH_2Cl_2 with an excess of hexanes to afford **100e** (0.19 g, 42%) as a colorless solid: Mp. 186.3-188.1 ^oC (hexane/CH_2Cl_2); IR (KBr) 1722, 1670, 1633, 1511, 1393 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.4 Hz, 2 H), 7.48-7.31 (m, 8 H), 5.50 (app. t, *J* = 9.5 Hz, 1 H), 3.80-3.50 (m, 8 H), 3.29-3.10 (m, 8 H), 2.87 (app. t, *J* = 10.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.89, 131.71, 128.86, 128.70, 128.55, 128.13, 127.13, 122.61, 89.30, 85.26, 67.36, 47.35, 45.26, 45.14; MS (EI) *m/z* (rel. intensity) 425 (M^+, 14), 339 (7), 321 (47), 191 (100); HRMS (EI) calc for $C_{23}H_{28}N_3O_3P$ 425.1868, found 425.1857.



101a

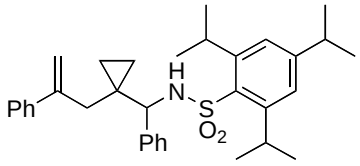
***N*-(Phenyl(1-(2-phenylallyl)cyclopropyl)methyl)-4-methylsulfonamide (101a).** According to the General Protocol C, amide **100a** (0.05 g, 0.18 mmol), and Me_2Zn (0.088 mL, 0.18 mmol, c = 2.0 M in PhMe) were stirred at 0 ^oC for 1 h, and transferred into a cold (-30 ^oC) solution of CH_2I_2 (0.071 mL, 0.88 mmol) and Et_2Zn (0.054 g, 0.44 mmol) in CH_2Cl_2 (3.0 mL). The reaction mixture was stirred at 0 ^oC for 6 h, warmed up to rt, quenched with sat. NH_4Cl, and extracted (3x) with CH_2Cl_2. The combined organic layers were washed with water, brine, dried (Na_2SO_4) and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **101a** (0.030 g, 51%) as a colorless oil: IR (neat) 1599, 1318, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53-7.41 (m, 10 H), 5.97 (s, 2 H), 5.20 (d, *J* = 7.8 Hz, 1 H), 4.20 (d, *J* = 7.7 Hz, 1 H), 2.76 (s, 3 H),

2.01-2.00 (m 2 H); 1.22-1.11 (m, 2 H), 1.04-1.00 (m, 1 H), 0.88-0.82 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 142.4, 139.6, 128.5, 128.3, 127.9, 127.4, 127.1, 125.7, 125.1, 65.2, 41.9, 25.7, 16.9, 14.2, 13.3; MS (EI) *m/z* (rel. intensity) 341 (M^+, 1), 326 (53), 246 (58), 231 (59), 184 (100); HRMS (EI) calc for $C_{19}H_{20}NO_2S$ (M-CH_3) 326.1215, found 326.1201.



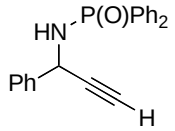
101b

***N*-(Phenyl(1-(2-phenylallyl)cyclopropyl)methyl)-4-methylbenzenesulfonamide (101b).** According to the General Protocol C, amide **100b** (0.05 g, 0.14 mmol), and Me_2Zn (0.069 mL, 0.14 mmol, c = 2.0 M in PhMe) were stirred in CH_2Cl_2 (2.0 mL) at 0 ^oC for 1 h and transferred into a cold (-30 ^oC) solution of CH_2I_2 (0.056 mL, 0.069 mmol) and Et_2Zn (0.043 g, 0.35 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was warmed up to 0 ^oC, stirred for 5.5 h, quenched with sat. NH_4Cl, and extracted (3x) with CH_2Cl_2. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded crude **101b** (0.015 g, 26%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) representative signals: δ 5.26 (d, *J* = 7.4 Hz, 1 H), 4.13 (d, *J* = 7.5 Hz, 1 H), 1.09-0.79 (m, 4 H).



101c

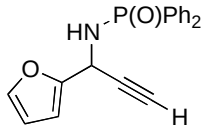
***N*-(Phenyl(1-(2-phenylallyl)cyclopropyl)methyl)-2,4,6-triisopropylbenzenesulfonamide (101c).** According to the General Protocol C, amide **100c** (0.073 g, 0.15 mmol), and Me_2Zn (0.075 mL, 0.15 mmol) in CH_2Cl_2 (2.0 mL) were treated with a solution of Et_2Zn (0.047 g, 0.38 mmol) and CH_2I_2 (0.062 g, 0.77 mmol) in CH_2Cl_2 (2.0 mL) at 0 ^oC for 5 h. The reaction mixture was quenched with sat. NH_4Cl, extracted (3x) with CH_2Cl_2 and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 9:1) afforded **101c** (0.05 g, 63%) as a colorless oil: IR (neat) 2959, 1601, 1494, 1426, 1319, 1152 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44-7.14 (m, 10 H), 7.00 (d, *J* = 6.7 Hz, 2 H), 5.39 (s, 1 H), 5.18 (s, 1 H), 4.77 (d, *J* = 6.6 Hz, 1 H), 4.57 (d, *J* = 6.6 Hz, 1 H), 4.03 (septet, *J* = 6.7 Hz, 2 H), 3.03 (septet, *J* = 6.9 Hz, 1 H), 2.62 (d, *J* = 15.3 Hz, 1 H), 2.44 (d, *J* = 15.3 Hz, 1 H), 1.33 (d, *J* = 6.9 Hz, 6 H), 1.24 (d, *J* = 6.6 Hz, 6 H), 1.18 (d, *J* = 6.7 Hz, 6 H), 0.90 (d, *J* = 9.4 Hz, 1 H), 0.48 (br s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 149.6, 149.6, 145.3, 141.9, 139.5, 133.7, 128.3, 128.2, 128.1, 128.1, 128.0, 127.4, 127.3, 127.1, 126.2, 123.5, 115.3, 60.5, 38.9, 34.1, 29.9, 24.8, 24.6, 23.7, 23.6, 23.0, 9.1, 8.3; HRMS (ES) calculated for $C_{34}H_{43}NNaO_2S$ (M+Na) 552.2912, found 552.2915.



111a

***N*-(1-Phenylprop-2-ynyl)-*P,P*-diphenylphosphinamide (111a).** A solution of *N*-benzylidene-*P,P*-diphenylphosphinamide **83a** (12 g, 39 mmol) in dry THF (100 mL) was cooled to 0 ^oC and treated with HCCMgBr (160 mL, 77 mmol, 0.5 M in THF). The reaction mixture was stirred at 0 ^oC for 30 min, slowly quenched with sat. NH_4Cl, and extracted (3x) with EtOAc. The combined

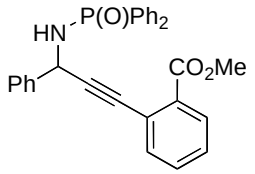
organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated. The resulting solid was purified by chromatography on SiO_2 (hexanes/EtOAc, 1:4) to afford **111a** (12 g, 90%) as a colorless solid: Mp. 152.0-153.1 ^oC (hexanes/CH_2Cl_2); IR (KBr) 3292, 3159, 3056, 2858, 1625, 1491, 1452, 1436, 1186, 1125, 1109 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.15-8.09 (m, 2 H), 7.99-7.92 (m, 2 H), 7.72-7.72 (m, 2 H), 7.66-7.35 (m, 9 H), 5.22 (td *J* = 10.1, 2.2 Hz, 1 H), 3.61 (app t, *J* = 8.9 Hz, 1 H), 2.64 (d, *J* = 2.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.84, 139.78, 133.10, 132.80, 132.72, 132.67, 132.30, 132.22, 132.18, 132.05, 131.40, 131.00, 128.80, 128.76, 128.56, 128.19, 127.26, 83.57, 83.49, 73.85, 46.58; MS (EI) *m/z* (rel. intensity) 331 (M^+, 93), 305 (50), 277 (8), 254 (12), 201 (100), 183 (19), 155 (21), 130 (67); HRMS (EI) calc for $C_{21}H_{18}NOP$ 331.1126, found 331.1129.



111b

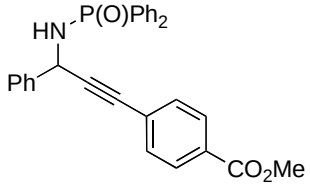
***N*-(1-(2-Furyl)prop-2-ynyl)-*P,P*-diphenylphosphinamide (111b).** Imine **83f** (3.0 g, 10 mmol) was dissolved in dry THF (50.0 mL), cooled to 0 ^oC and treated with HCCMgBr (51 mL, 25 mmol, c = 0.5 M in THF). The mixture was stirred at 0 ^oC for 40 min, quenched with sat. NH_4Cl, and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. Purification on SiO_2 (hexanes/EtOAc, 1:4) afforded **111a** (2.9 g, 90%) as a colorless solid: IR (KBr) 3293, 3138, 2853, 1636, 1438, 1191, 1126 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97-7.87 (m, 4 H), 7.51-7.36 (m, 6 H), 6.43 (dd, *J* = 3.2, 1.0 Hz, 1 H), 6.27 (dd, *J* = 3.2, 1.8 Hz, 1 H), 5.13 (dt, *J* = 8.5, 2.2 Hz, 1 H), 3.74 (t, *J* = 8.7 Hz, 1 H), 2.48 (d, *J* = 2.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.57, 142.71, 132.62, 132.35, 132.24, 132.11,

131.99, 130.91, 130.63, 128.49, 128.32, 110.31, 107.53, 81.18, 81.11, 72.56, 40.57; MS (EI) *m/z* (rel. intensity) 321 (M^+, 100), 292 (28), 244 (12), 216 (9), 201 (83), 182 (32), 120 (86), 105 (34); HRMS (EI) calculated for $C_{19}H_{16}NO_2P$ 321.0919, found 321.0912.



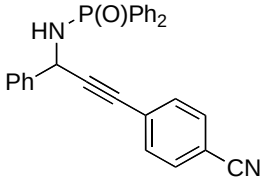
112a

***N*-(3-(2-Methoxycarbonylphenyl)-1-phenylprop-2-ynyl)-*P,P*-diphenylphosphinamide (112a). General Protocol D.** A suspension of CuI (0.057 g, 0.30 mmol) and $Pd(PPh_3)_4$ (0.17 g, 0.15 mmol) in *i*-Pr_2NH (50 mL) and THF (10 mL) was cooled to 0 °C, treated with methyl 2-iodobenzoate (0.44 mL, 3.0 mmol) and amide **111a** (1.0 g, 3.0 mmol) and stirred at 0 °C for 1 h. The reaction mixture was quenched with sat. NH_4Cl, and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **112a** (1.1 g, 75%) as a colorless solid: Mp. 172.4-174.0 ºC (hexanes/CH_2Cl_2); IR (KBr) 3167, 1721, 1591, 1566, 1486, 1436, 1254, 1189 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (ddd, *J* = 12.2, 8.0, 1.8 Hz, 3 H), 8.05-7.95 (m, 4 H), 7.84 (d, *J* = 7.3 Hz, 2 H), 7.62-7.31 (m, 9 H), 7.36-7.31 (m, 1 H), 5.51 (app. t, *J* = 10.0 Hz, 1 H), 4.01 (dd, *J* = 8.9, 1.4 Hz, 1 H), 3.91 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.50, 140.30, 140.25, 134.18, 132.84, 132.71, 131.93, 131.79, 131.67, 131.59, 131.00, 130.31, 128.57, 128.50, 128.39, 128.33, 128.04, 127.87, 127.41, 123.11, 93.92, 93.84, 84.22, 52.09, 47.45; MS (EI) *m/z* (rel. intensity) 465 (M^+, 15), 450 (12), 433 (10), 331 (100), 330 (17), 305 (8), 277 (9), 264 (4), 254 (10), 201 (67); HRMS (EI) calc for $C_{29}H_{24}NO_3P$ 465.1494, found 465.1516.



112b

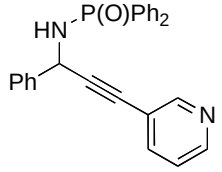
***N*-(3-(4-Methoxycarbonylphenyl)-1-phenylprop-2-ynyl)-*P,P*-diphenylphosphinamide (112b).** According to the General Protocol D, alkyne **111a** (3.0 g, 9.1 mmol), methyl 4-iodobenzoate (2.4 g, 9.1 mmol), CuI (0.17 g, 0.91 mmol) and $Pd(PPh_3)_4$ (0.52 g, 0.45 mmol) in *i*-Pr_2NH (100 mL) and THF (25 mL) afforded **112b** (2.5 g, 59%) as a colorless solid: Mp. 188.2-191.0 ^oC (hexanes/CH_2Cl_2); IR (KBr) 2951, 2847, 1721, 1604, 1493, 1451, 1437, 1404, 1308, 1276, 1186, 1126, 1109 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.11-8.04 (m, 2 H), 7.98 (d, *J* = 8.3 Hz, 2 H), 7.90-7.83 (m, 2 H), 7.68 (d, *J* = 7.2 Hz, 2 H), 7.57-7.30 (m, 11 H), 5.44 (app t, *J* = 9.7 Hz, 1 H), 3.94 (s, 3 H), 3.54 (b t, *J* = 7.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.40, 139.90, 133.21, 132.67, 132.54, 131.97, 131.84, 131.71, 131.53, 131.09, 129.61, 129.30, 128.67, 128.52, 128.35, 128.04, 127.31, 127.19, 91.93, 91.86, 52.14, 47.00; MS (EI) *m/z* (rel. intensity) 465 (M^+, 72), 388 (15), 330 (8), 264 (84), 201 (100); HRMS (EI) calc for $C_{29}H_{24}NO_3P$ 465.1494, found 465.1480.



112c

***N*-(3-(4-Cyanophenyl)-1-phenylprop-2-ynyl)-*P,P*-diphenylphosphinamide (71).** According to the General Protocol D, alkyne **111a** (0.50 g, 1.5 mmol), 4-iodobenzonitrile (0.33 g, 1.5 mmol),

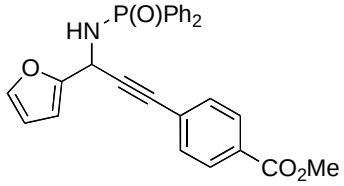
CuI (0.028 g, 0.15 mmol) and $Pd(PPh_3)_4$ (0.087 g, 0.075 mmol) in *i*-Pr_2NH (25 mL) and THF (10 mL) afforded **112c** (0.40 g, 62%) as a colorless solid: Mp. 213.3-214.8 ^oC (hexanes/EtOAc); IR (KBr) 3434, 3148, 2227, 1603, 1438, 1187, 1126, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 12.1, 7.9 Hz, 2 H), 7.91 (dd, *J* = 12.0, 8.0 Hz, 2 H), 7.71 (d, *J* = 7.3 Hz, 2 H), 7.62-7.35 (m, 13 H), 5.48 (app t, *J* = 9.6 Hz, 1 H), 4.07 (app t, *J* = 9.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.64, 139.57, 132.95, 132.49, 132.35, 132.04, 131.91, 131.81, 131.74, 131.68, 131.25, 131.12, 128.65, 128.45, 128.28, 128.06, 127.45, 127.08, 118.27, 111.49, 93.50, 93.43, 83.74, 46.82; MS (EI) *m/z* (rel. intensity) 432 (M^+, 67), 355 (4), 328 (14), 307 (3), 277 (7), 231 (92), 201 (100), 185 (17); HRMS (EI) calc for $C_{28}H_{21}N_2OP$ 432.1389, found 432.1392.



112d

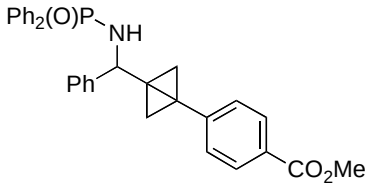
***N*-(1-Phenyl-3-(pyridin-3-yl)prop-2-ynyl)-*P,P*-diphenylphosphinamide (112d).** According to the General Protocol D, alkyne **111a** (2.0 g, 6.0 mmol), 3-iodopyridine (1.2 g, 6.0 mmol), CuI (0.11 g, 0.60 mmol) and $Pd(PPh_3)_4$ (0.35 g, 0.030 mmol) in *i*-Pr_2NH (100 mL) and THF (20 mL) were stirred at 0 ºC for 2.5 h. The reaction mixture was quenched with sat. NH_4Cl, and extracted (3x) with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4) and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:10) afforded **112d** (1.9 g, 77%) as a colorless oil that solidified upon standing: IR (neat) 3151, 3058, 1620, 1592, 1566, 1476, 1438, 1412, 1307, 1276, 1188, 1123, 1109 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.64-8.55 (m, 2 H), 8.14 (dd, *J* = 12.1, 7.7 Hz, 2 H), 7.93 (dd, *J* = 12.1, 8.0, 2 H), 7.75-

7.71 (m, 2 H), 7.61-7.36 (m, 9 H), 7.31-7.27 (m, 2 H), 5.52 (app t, *J* = 9.6 Hz, 1 H), 4.01 (app t, *J* = 8.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.86, 148.30, 139.86, 139.79, 138.41, 133.09, 132.79, 132.48, 132.38, 131.79, 131.73, 131.60, 131.39, 131.08, 128.49, 128.32, 128.22, 128.15, 127.84, 127.03, 122.70, 119.64, 92.51, 92.44, 81.82, 46.69; MS (EI) *m/z* (rel. intensity) 408 (M^+, 77), 331 (7), 305 (13), 283 (12), 207 (100), 201 (59), 192 (14); HRMS (EI) calc for $C_{26}H_{21}N_2OP$ 408.1392, found 408.1373.



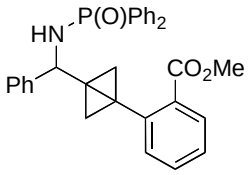
112e

***N*-(3-(4-Methoxycarbonylphenyl)-1-(2-furyl)prop-2-ynyl)-*P,P*-diphenylphosphinamide (112e).** According to the General Protocol D, propargyl amide **111b** (2.9 g, 9.1 mmol), methyl 4-iodobenzoate (2.4 g, 9.1 mmol), CuI (0.17 g, 0.91 mmol) and $Pd(PPh_3)_4$ (0.52 g, 0.45 mmol) in *i*-Pr_2NH (250 mL) and THF (20 mL) afforded **112e** (2.2 g, 53%) as a white solid: Mp. 187.1-188.8 ^oC (hexane/CH_2Cl_2); IR (KBr) 3435, 1719, 1630, 1605, 1438, 1376, 1192 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02-7.87 (m, 7 H), 7.49-7.41 (m, 8 H), 6.38 (d, *J* = 3.1 Hz, 1 H), 6.31 (dd, *J* = 2.9, 1.8 Hz, 1 H), 5.44 (t, *J* = 9.1 Hz, 1 H), 3.90 (s, 3 H), 3.79 (*t*, *J* = 8.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.39, 151.69, 151.61, 142.78, 132.78, 132.61, 132.34, 132.21, 132.15, 132.02, 131.65, 131.08, 130.91, 129.69, 129.25, 128.54, 128.37, 126.97, 110.39, 107.55, 89.51, 89.45, 83.48, 52.18, 41.28; MS *m/z* (rel. intensity) 455 (M^+, 48), 426 (8), 378 (9), 361 (8), 320 (7), 295 (12), 254 (100), 216 (25), 201 (74); HRMS (EI) calculated for $C_{27}H_{22}NO_4P$ 455.1286, found 455.1293



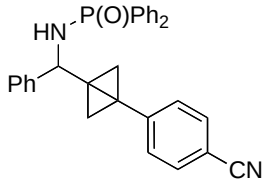
113

***N*-((3-(4-Methoxycarbonylphenyl)bicyclo[1.1.0]but-1-yl)(phenyl)methyl)-*P,P*-diphenylphosphinamide (113).** According to the General Protocol C, amide **112a** (1.0 g, 2.2 mmol) and Me_2Zn (1.1 mL, 2.2 mmol, 2.0 M in PhMe) in dry CH_2Cl_2 (80 mL) were reacted with $(CH_2I)_2Zn$ prepared by the addition of CH_2I_2 (0.69 mL, 8.6 mmol) to a solution of Et_2Zn (0.53 g, 4.3 mmol) in CH_2Cl_2 (80 mL) at -50 ^oC. The reaction mixture was warmed to 0 ^oC, stirred for 30 min, and quenched with sat. NH_4Cl. Extraction with EtOAc followed by purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4 to 1:6) afforded **113** (0.45 g, 42%) as a colorless solid: Mp. 158.3-160.1 ºC (hexanes/CH_2Cl_2); IR (KBr) 3423, 3262, 3058, 2931, 1728, 1720, 1606, 1438, 1279, 1189, 1117 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 11.9, 8.0 Hz, 2 H), 7.78 (d, *J* = 8.4 Hz, 2 H), 7.68 (dd, *J* = 11.3, 7.2 Hz, 2 H), 7.47-7.34 (m, 3 H), 7.28-7.23 (m, 3 H), 7.15-7.06 (m, 4 H), 6.90 (d, *J* = 8.3 Hz, 2 H), 6.76 (d, *J* = 7.0 Hz, 2 H), 4.60 (app t, *J* = 8.6 Hz, 1 H), 3.86 (s, 3 H), 3.68 (dd, *J* = 7.8, 5.6 Hz, 1 H), 2.23 (d, *J* = 6.6 Hz, 1 H), 1.98 (d, *J* = 6.6 Hz, 1 H), 1.00 (s, 1 H), 0.93 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.85, 142.12, 139.91, 139.83, 132.02, 131.89, 131.82, 131.70, 131.53, 131.22, 129.13, 128.28, 128.18, 128.12, 128.02, 127.94, 127.25, 126.80, 126.50, 125.24, 54.88, 51.69, 34.08, 31.61, 30.78, 30.71, 20.58; MS (ES) *m/z* (rel. intensity) 516 ($[M+Na]^+$, 100), 413 (45), 371 (10), 301 (12), 227 (17), 221 (7), 201 (5); HRMS (ES) calc for $C_{31}H_{28}NNaO_3P$ (M+Na) 516.1705, found 516.1722.



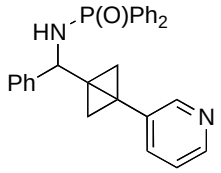
114a

***N*-((3-(2-Methoxycarbonylphenyl)bicyclo[1.1.0]but-1-yl)(phenyl)methyl)-*P*,*P*-diphenylphosphinamide (114a).** According to the General Protocol C, amide **112b** (0.46 g, 0.98 mmol) and Me_2Zn (0.49 mL, 0.98 mmol, 2.0 M in PhMe) in dry CH_2Cl_2 (40 mL) were reacted with $(CH_2I)_2Zn$ prepared by the addition of CH_2I_2 (0.31 mL, 3.9 mmol) to a solution of Et_2Zn (0.24 g, 2.0 mmol) in dry CH_2Cl_2 (40 mL) at -50 ^oC. The reaction mixture was warmed to 0 ^oC, stirred for 55 min, and quenched with sat. NH_4Cl. Extraction with EtOAc followed by purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **114a** (0.27 g, 56%) as a colorless solid: Mp. 94.1-96.0 ^oC (hexanes/CH_2Cl_2); IR (KBr) 3060, 2950, 1721, 1655, 1637, 1438, 1294, 1259, 1192, 1124, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86-7.80 (m, 2 H), 7.74-7.67 (m, 2 H), 7.53-7.38 (m, 5 H), 7.33-7.08 (m, 8 H), 6.95 (dd, *J* = 8.1, 1.1 Hz, 1 H), 6.88 (dd, *J* = 7.8, 1.5 Hz, 1 H), 4.83 (app t, *J* = 8.8 Hz, 1 H), 3.83 (dd, *J* = 8.2, 5.9 Hz, 1 H), 3.75 (s, 3 H), 1.99 (d, *J* = 6.8 Hz, 1 H), 1.79 (d, *J* = 6.8 Hz, 1 H), 0.99 (s, 1 H), 0.95 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.45, 140.78, 140.71, 136.05, 132.28, 132.15, 132.01, 131.88, 131.62, 131.57, 130.26, 129.37, 128.37, 128.28, 128.21, 128.10, 127.67, 127.23, 126.98, 125.06, 53.97, 52.21, 51.95, 34.55, 33.16, 30.69, 30.62, 19.75; MS (ES) *m/z* (rel. intensity) 747 (37), 733 (38), 603 (23), 548 (35), 516 ($[M+Na]^+$, 100), 494 ($[M+1]^+$, 58); HRMS (ES) calc for $C_{31}H_{29}NO_3P$ (M+H) 494.1885, found 494.1902.



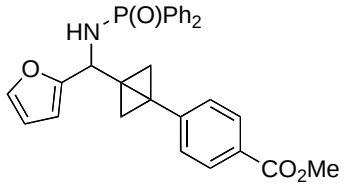
114b

***N*-((3-(4-Cyanophenyl)bicyclo[1.1.0]but-1-yl)(phenyl)methyl)-*P*,*P*-diphenylphosphinamide (114b).** According to General Protocol C, amide **112c** (1.1 g, 2.6 mmol) and Me_2Zn (1.3 mL, 2.6 mmol, 2.0 in PhMe) in CH_2Cl_2 (85 mL) were reacted with $(CH_2I)_2Zn$ prepared by the addition of CH_2I_2 (0.83 mL, 10 mmol) to the solution of Et_2Zn (0.64 g, 5.2 mmol) in CH_2Cl_2 (85 mL) at -50 ^oC. The reaction mixture was stirred at 0 ^oC for 1 h, quenched with sat. NH_4Cl, and extracted (3x) with CH_2Cl_2. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **114b** (0.41 g, 35%) as a colorless foam: IR (KBr) 3500, 3057, 2930, 2223, 1605, 1438, 1189, 1123 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (ddt, *J* = 12.0, 6.7, 1.6 Hz, 2 H), 7.61 (ddt, *J* = 12.1, 6.9, 1.4 Hz, 2 H), 7.48-7.20 (m, 7 H), 7.12-7.03 (m, 4 H), 6.80 (dd, *J* = 6.7, 1.8 Hz, 2 H), 6.65 (dd, *J* = 6.9, 1.5 Hz, 2 H), 4.50 (app. t, *J* = 8.4 Hz, 1 H), 3.46 (dd, *J* = 7.5, 5.2 Hz, 1 H), 2.17 (dd, *J* = 6.8, 1.1 Hz, 1 H), 1.88 (dd, *J* = 6.6, 0.6 Hz, 1 H), 0.96 (s, 1 H), 0.88 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.65, 139.58, 139.50, 133.77, 132.80, 132.08, 131.92, 131.80, 131.52, 131.09, 128.43, 128.37, 128.24, 128.20, 128.13, 127.56, 126.82, 125.89, 119.22, 107.91, 54.99, 34.69, 31.80, 31.61, 31.55, 20.85; MS (EI) *m/z* (rel. intensity) 460 (M^+, 44), 346 (7), 306 (17), 259 (100), 243 (38), 201 (82); HRMS (EI) calc for $C_{30}H_{25}N_2OP$ 460.1705, found 460.1703.



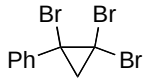
114c

***N*-((3-(Pyridin-3-yl)bicyclo[1.1.0]but-1-yl)(phenyl)methyl)-*P*,*P*-diphenylphosphinamide (114c).** According to General Protocol C, amide **112d** (0.50 g, 1.2 mmol) and Me_2Zn (0.61 mL, 1.2 mmol, 2.0 in PhMe) in CH_2Cl_2 (40 mL) were reacted with $(CH_2I)_2Zn$ prepared by the addition of CH_2I_2 (0.40 mL, 4.9 mmol) to a solution of Et_2Zn (0.30 g, 2.5 mmol) in CH_2Cl_2 (40.0 mL) at -50 ºC. The reaction mixture was stirred at 0 ºC for 14 h, quenched with sat. NH_4Cl, and extracted (3x) with CH_2Cl_2. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc/MeOH, 1:8:1) afforded **114c** (0.21 g, 40%) as a colorless foam: IR (neat) 3058, 2926, 1591, 1570, 1477, 1454, 1438, 1420, 1311, 1191, 1123, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, *J* = 3.9 Hz, 1 H), 7.97 (bs, 1 H), 7.80 (ddd, *J* = 11.9, 8.0, 1.4 Hz, 2 H), 7.66 (dd, *J* = 12.0, 7.1 Hz, 2 H), 7.42-7.20 (m, 8 H), 7.12-7.01 (m, 3 H), 6.92 (dd, *J* = 7.8, 4.7 Hz, 1 H), 6.70 (d, *J* = 6.9 Hz, 1 H), 4.52 (t, *J* = 8.3 Hz, 1 H), 3.66 (app t, *J* = 5.6 Hz, 1 H), 2.14 (d, *J* = 6.6 Hz, 1 H), 1.80 (d, *J* = 6.6 Hz, 1 H), 0.90 (s, 1 H), 0.80 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.95, 146.07, 139.87, 139.79, 133.90, 132.65, 132.19, 132.07, 131.95, 131.83, 131.61, 131.39, 128.35, 128.29, 128.25, 128.19, 128.11, 128.09, 127.47, 126.83, 122.48, 55.01, 33.65, 30.99, 28.73, 28.66, 18.07; MS (EI) *m/z* (rel. intensity) 436 (M^+, 36), 332 (16), 306 (7), 235 (15), 218 (19), 201 (60), 77 (100); HRMS (EI) calc for $C_{28}H_{25}N_2OP$ 436.1705, found 436.1692.



114d

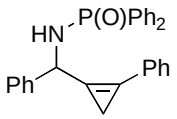
***N*-((3-(4-Methoxycarbonylphenyl)bicyclo[1.1.0]but-1-yl)(2-furyl)methyl)-*P*,*P*-diphenylphosphinamide (114d).** According to the General Protocol C, amide **112e** (0.42 g, 0.92 mmol) was treated with Me_2Zn (0.46 mL, 0.92 mmol, c = 2.0 M in PhMe) in CH_2Cl_2 (30 mL) at 0 ^oC. After 1 h, the reaction mixture was cooled and transferred *via* cannula into a solution of CH_2I_2 (0.30 mL, 3.7 mmol) and Et_2Zn (0.28 g, 1.8 mmol) in CH_2Cl_2 (30 mL). The reaction mixture was stirred at 0 ^oC for 40 min, quenched with sat. NH_4Cl, and extracted (3x) with CH_2Cl_2. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded crude **114d** (0.18 g, 40%) as a colorless foam: ^1H NMR (300 MHz, $CDCl_3$) δ 8.07-7.13 (m, 17 H), 4.80 (app. t, *J* = 9.4 Hz, 1 H), 3.97 (s, 3 H), 3.56-3.47 (m, 1 H), 2.31 (d, *J* = 6.5 Hz, 1 H), 2.27 (d, *J* = 6.8 Hz, 1 H), 1.21 (d, *J* = 7.3 Hz, 1 H), 0.99 (d, *J* = 6.8 Hz, 1 H).



116

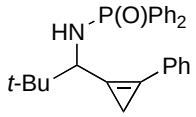
1,2,2-Tribromo-1-phenylcyclopropane (116).[462] α-Bromomethylstyrene (10 g, 55 mmol), bromoform (9.8 mL, 109 mmol) and cetrimide (1.8 g) were placed in a 250 mL flask, cooled to 0 ^oC and treated dropwise with 50% aq NaOH. The reaction mixture was allowed to warm up to rt, EtOH (1.0 mL) was added and stirring was continued for 15 h. The mixture was diluted with CH_2Cl_2, extracted, and the combined organic layers were dried (Na_2SO_4), and evaporated. The

product was purified by chromatography on SiO_2 (hexanes/Et_2O, 10:1) to afford **116** (10 g, 53%) as a pale yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.47 (m, 2 H), 7.43-7.33 (m, 3 H), 2.53 (d, *J* = 9.3 Hz, 1 H), 2.26 (d, *J* = 9.3 Hz, 1 H).



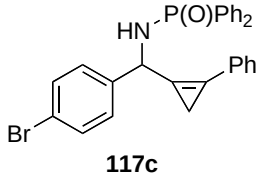
117a

***N*-(Phenyl(2-phenylcycloprop-1-enyl)methyl)-*P,P*-diphenylphosphinamide (117a). General Protocol E.** 1,2,2-Tribromo-1-phenylcyclopropane **116** (0.87 g, 2.5 mmol) was dissolved in dry THF (20 mL), cooled to -78 ^{o}C and treated dropwise with *n*-BuLi (3.7 mL, 5.5 mmol, c = 1.5 M in hexane). The reaction mixture was allowed to warm up to rt over ca. 45 min, cooled to -78 ^{o}C and a solution of *N*-benzylidenediphenylphosphinamide **83a** (0.65 g, 2.1 mmol) in THF (15.0 mL) was added. The reaction mixture was stirred at -78 ^{o}C for 15 min, warmed to rt, quenched with sat. NH_4Cl, and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. The product was purified by chromatography on SiO_2 (hexanes/EtOAc, 1:4) to afford **117a** (0.84 g, 94%) as a colorless solid: Mp. 126.4-128.7 ^{o}C (hexanes/CH_2Cl_2); IR (KBr) 3057, 1437, 1185, 1125, 1108 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94-7.84 (m, 4 H), 7.41-7.32 (m, 16 H), 5.56 (app. t, *J* = 9.6 Hz, 1 H), 4.01 (bs, 1 H), 1.43-1.41 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.83, 140.77, 133.13, 132.18, 132.04, 131.90, 131.66, 131.42, 131.30, 129.62, 128.72, 128.52, 128.32, 128.27, 128.16, 128.10, 127.48, 126.91, 114.52, 114.43, 110.97, 52.40, 8.39; MS (EI) *m/z* (rel. intensity) 421 (M^+, 19), 306 (7), 220 (100), 201 (60); HRMS (EI) calc for $C_{28}H_{24}NOP$ 421.1596, found 421.1586.



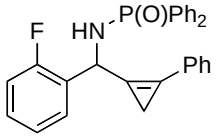
117b

***N*-(2,2-Dimethyl-1-(2-phenylcycloprop-1-enyl)propyl)-*P*,*P*-diphenylphosphinamide (117b).** According to the General Protocol E, 1,2,2-tribromo-1-phenylcyclopropane **116** (1.2 g, 3.5 mmol) was dissolved in dry THF (20 mL), cooled to -78 ^{o}C and treated dropwise with *n*-BuLi (5.4 mL, 7.0 mmol, c = 1.3 M in hexane). The reaction mixture was allowed to warm up to rt over ca. 45 min, cooled to -78 ^{o}C and a solution of imine **83g** (0.50 g, 1.8 mmol) in THF (15 mL) was added. The reaction mixture was stirred at -78 ^{o}C for 15 min, warmed to rt, quenched with sat. NH_4Cl, and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. The product was purified by chromatography on SiO_2 (hexanes/EtOAc, 1:4) to afford **117b** (0.66 g, 94%) as a colorless solid: Mp. 149.7-151.0 ^{o}C (hexanes/CH_2Cl_2); IR (KBr) 2955, 2866, 1437, 1196, 1126 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86-7.73 (m, 4 H), 7.43-7.22 (m, 11 H), 4.15 (app. t, *J* = 10.6 Hz, 1 H), 3.33 (app. t, *J* = 9.9 Hz, 1 H), 1.35 (d, *J* = 7.4 Hz, 1 H), 1.25 (d, *J* = 7.4 Hz, 1 H), 1.03 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.96, 132.79, 132.22, 132.09, 131.64, 131.58, 131.51, 131.39, 131.09, 129.09, 128.30, 128.16, 128.14, 127.93, 127.89, 114.04, 113.98, 110.16, 57.01, 36.87, 36.81, 26.56, 8.51; MS (EI) *m/z* (rel. intensity) 401 (M^+, 26), 386 (34), 344 (65), 286 (42), 201 (100), 183 (8), 169 (11), 144 (16); HRMS (EI) calc for $C_{26}H_{28}NOP$ 401.1909, found 401.1907.



117c

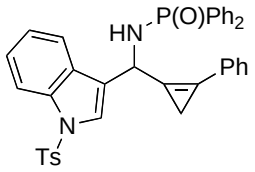
***N*-((4-Bromophenyl)(2-phenylcycloprop-1-enyl)methyl)-*P,P*-diphenylphosphinamide (117c)**. According to the General Protocol E, 1,1,2-tribromo-2-phenylcyclopropane **116** (1.0 g, 2.8 mmol), *n*-BuLi (3.5 mL, 5.6 mmol, c = 1.6 M in hexanes) and imine **83c** (0.54 g, 1.4 mmol) afforded **117c** (0.59 g, 83%) as a colorless solid: Mp. 163.3-165.1 ^{o}C (hexanes/CH_2Cl_2); IR (KBr) 1436, 1188, 1125 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89-7.75 (m, 4 H), 7.46-7.19 (m, 15 H), 5.45 (app. t, *J* = 10 Hz, 1 H), 3.57 (dd, *J* = 9.9, 6.9 Hz, 1 H), 1.33 (AB, *J* = 7.3 Hz, 1 H), 1.31 (AB, *J* = 7.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.90, 139.85, 132.73, 132.19, 132.06, 131.94, 131.81, 131.75, 131.53, 131.33, 131.03, 129.66, 128.81, 128.49, 128.40, 128.32, 128.27, 128.16, 121.39, 113.81, 113.71, 111.31, 51.93, 27.55, 8.33; MS (EI) *m/z* (rel. intensity) 499 (M^+, 49), 384 (51), 300 (17), 201 (100); HRMS (EI) calc for $C_{28}H_{23}BrNOP$ 499.0701, found 499.0689.



117d

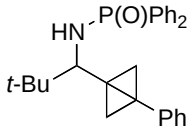
***N*-((4-Bromophenyl)(2-phenylcycloprop-1-enyl)methyl)-*P,P*-diphenylphosphinamide (117d)**. According to the General Protocol E, 1,1,2-tribromo-2-phenylcyclopropane **116** (1.0 g, 2.8 mmol), *n*-BuLi (3.5 mL, 5.6 mmol, c = 1.6 M in hexanes) and imine **83b** (0.46 g, 1.4 mmol) afforded **117d** (0.46 g, 74%) as a colorless solid: Mp. 85.3-87.0 ^{o}C (CH_2Cl_2/hexanes); IR (neat) 1687, 1614, 1490, 1439, 1191 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99-7.83 (m, 4 H), 7.51-7.27 (m, 11 H), 7.15-6.92 (m, 4 H), 5.66 (app. t, *J* = 10.2 Hz, 1 H), 4.00 (dd, *J* = 10.4, 7.5 Hz, 1 H), 1.44 (d, *J* = 7.4 Hz, 1 H), 1.39 (d, *J* = 7.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.01, 158.74, 133.12, 132.91, 132.26, 132.20, 132.13.132.07, 131.96, 131.93, 131.87, 131.84, 131.41,

141.20, 129.75, 129.42, 129.32, 128.76, 128.64, 128.58, 128.42, 128.32, 128.26, 128.23, 124.39, 124.35, 115.95, 115.67, 113.87, 113.77, 111.38, 48.58, 48.56, 8.69; (EI) *m/z* (rel. intensity) 439 (M^+, 20), 324 (28), 238 (77), 201 (100); HRMS (EI) calc for $C_{28}H_{23}NOFP$ 439.1501, found 439.1491.



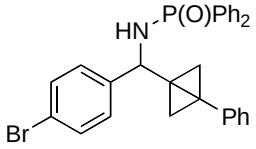
117e

***N*-((2-Phenylcycloprop-1-enyl)(1-tosyl-1*H*-indol-3-yl)methyl)-*P*,*P*-diphenylphosphinamide (117e).** According to the General Protocol E, imine **83i** (0.58 g, 1.2 mmol), 1,2,3-tribromo-1-phenylcylopropane (0.82 g, 2.3 mmol) and *n*-BuLi (3.6 mL, 4.7 mmol c = 1.3 M in hexane) in THF (15 mL) afforded **117e** (0.36 g, 51%) as a pale yellow solid: IR (KBr) 3055, 1596, 1447, 1438, 1372, 1188, 1175, 1123 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97-7.75 (m, 8 H), 7.67 (d, *J* = 7.9 Hz, 1 H), 7.54 (s, 1 H), 7.47-7.42 (m, 3 H), 7.40-7.35 (m, 5 H), 7.32-7.15 (m, 6 H), 5.83 (app. t, *J* = 9.6 Hz, 1 H), 3.64 (dd, *J* = 9.0, 7.5 Hz, 1 H), 2.32 (s, 3 H), 1.39 (AB, *J* = 7.3 Hz, 1 H), 1.38 (AB, *J* = 7.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.94, 135.50, 135.26, 132.25, 132.12, 132.02, 131.95, 131.89, 129.91, 129.83, 128.67, 128.62, 128.54, 128.37, 126.89, 124.97, 123.92, 123.41, 120.49, 113.62, 113.09, 111.39, 45.22, 21.53, 8.66; HMRS (ES) calculated for $C_{37}H_{31}N_2NaO_3PS$ (M+Na) 637.1691, found 637.1754.



118a

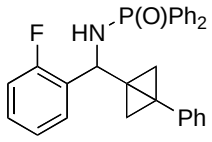
***N*-(2,2-Dimethyl-1-(3-phenylbicyclo[1.1.0]but-1-yl)propyl)-*P,P*-diphenylphosphinamide (118a).** According to the General Protocol G, 2,2-dibromo-1-bromomethyl-phenylcyclopropane **121a** (0.30 g, 0.81 mmol) in Et_2O (5.0 mL) was treated with MeLi (0.59 mL, 0.81 mmol, c = 1.4 M in Et_2O), followed by *t*-BuLi (0.56 mL, 0.81 mmol, c = 1.5 M in pentane) and a solution of imine **83g** (0.093 g, 0.32 mmol) in THF (5.0 mL). The reaction mixture was warmed up to rt, quenched with sat. NH_4Cl and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **118a** (0.094 g, 71%) as a colorless oil: IR (neat) 2957, 1438, 1188, 1123, 1109 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57-7.51 (m, 2 H), 7.45-7.21 (m, 13 H), 3.12 (dd, *J* = 11.0, 7.6 Hz, 1 H), 2.69 (dd, *J* = 11.0, 4.4 Hz, 1 H), 2.15 (d, *J* = 6.6 Hz, 1 H), 2.03 (d, *J* = 6.6, 1 H), 1.06 (s, 10 H), 0.92 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.94, 134.60, 132.84, 132.70, 132.57, 132.28, 132.16, 131.71, 131.31, 131.27, 130.00, 128.28, 128.23, 128.20, 128.07, 128.03, 127.91, 126.68, 125.51, 59.22, 37.56, 33.79, 30.23, 30.10, 27.98, 27.17, 18.23; MS (EI) *m/z* (rel. intensity) 415 (M^+, 66), 414 (46), 357 (52), 284 (11), 199 (100), 181 (26), 154 (16); HRMS (EI) calc for $C_{27}H_{30}NOP$ 415.2065, found 415.2051.



118b

***N*-((4-Bromophenyl)(3-phenylbicyclo[1.1.0]but-1-yl)methyl)-*P,P*-diphenylphosphinamide (118b).** General Protocol F. Amide **117c** (0.050 g, 0.10 mmol), Me_2Zn (0.050 mL, 0.10 mmol, c = 2.0 M in PhMe) in CH_2Cl_2 (1.0 mL) were stirred at 0 ºC for 1 h and transferred into a solution of Et_2Zn (0.025 g, 0.20 mmol) and CH_2I_2 (0.032 mL, 0.40 mmol) in CH_2Cl_2 (1.0 mL). The reac-

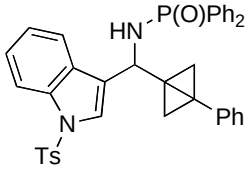
tion mixture was stirred at 0 ºC for 15min, quenched with sat. NH_4Cl and extracted (3x) with CH_2Cl_2. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded crude **118b** (0.010 g, 19%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95-7.72 (m, 5 H), 7.59-7.17 (m, 10 H), 7.05-7.02 (m, 2 H), 6.77-6.74 (m, 2 H), 4.70 (app. t, *J* = 8.7 Hz, 1 H), 3.55-3.51 (m, 1 H), 2.22 (AB, *J* = 6.6 Hz, 1 H), 2.04 (AB, *J* = 6.7 Hz, 1 H), 1.06 (s, 1 H), 1.00 (s, 1 H). The spectrum contains additional signals.



118c

***N*-((2-Fluorophenyl)(3-phenylbicyclo[1.1.0]but-1-yl)methyl)-*P,P*-diphenylphosphinamide (118c).** According to the General Protocol F, amide **117d** (0.050 g, 0.11 mmol) and Me_2Zn (0.055 mL, 0.11 mmol, c = 2.0 M in PhMe) in CH_2Cl_2 (1.0 mL) were stirred at 0 ºC for 1 h and transferred into a solution of Et_2Zn (0.028 g, 0.23 mmol) and CH_2I_2 (0.037 mL, 0.46 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred at 0 ºC for 20 min, quenched with sat. NH_4Cl and extracted (3x) with CH_2Cl_2. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **118c** (0.015 g, 31%) as a colorless solid: Mp. 128.0-129.4 ^{o}C (hexanes/CH_2Cl_2); IR (KBr) 3056, 2926, 1602, 1491, 1455, 1437, 1228, 1187, 1123, 1107 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81-7.65 (m, 4 H), 7.45-7.35 (m, 4 H), 7.29-7.26 (m, 2 H), 7.14-7.09 (m, 4 H), 6.91-6.82 (m, 4 H), 6.61 (t, *J* = 7.4 H, 1 H), 4.74 (app. t, *J* = 9.7 Hz, 1 H), 3.80 (app. t, *J* = 8.3 Hz, 1 H), 2.17 (d, *J* = 6.5 Hz, 1 H), 2.07 (d, *J* = 6.4 Hz, 1 H), 1.10 (s, 1 H), 1.05 (s, 1 H); ^{13}C NMR (75

MHz, $CDCl_3$) δ 161.49, 135.34, 132.01, 131.89, 131.81, 131.68, 131.55, 131.23, 128.76, 128.66, 128.27, 128.11, 127.95, 127.85, 127.61, 127.43, 125.26, 124.88, 123.61, 115.33, 115.04, 50.56, 32.70, 30.93, 27.33, 27.25, 19.93; MS (EI) *m/z* (rel. intensity) 453 (M^+, 11), 324 (73), 236 (41), 201 (100); HRMS (EI) calc for $C_{29}H_{25}NOFP$ 453.1659, found 453.1641.

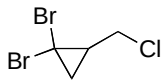


118d

***N*-((3-Phenylbicyclo[1.1.0]but-1-yl)(1-tosyl-1*H*-indol-3-yl)methyl)-*P,P*-diphenylphosphin-amide (118d).** According to the General Protocol F, amide **117e** (0.060 g, 0.098 mmol) and Me_2Zn (0.049 mL, 0.098 mmol, c = 2.0 M in PhMe) in CH_2Cl_2 (2.0 mL) were stirred at 0 ^oC for 1 h and transferred into a cold (-30 ^oC) solution of CH_2I_2 (0.039 mL, 0.049 mmol) and Et_2Zn (0.030 g, 0.024 mmol) in CH_2Cl_2 (2.0 mL). The reaction mixture was stirred at 0 ºC for 2 h, quenched with sat. NH_4Cl and extracted (3x) with CH_2Cl_2. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **118e** (0.024 g, 40%) as a colorless solid.

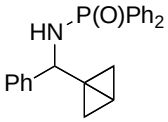
According to the General Protocol G, imine **83i**, 2,2-dibromo-1-bromomethyl-phenylcyclopropane **121a** (0.30 g, 0.81 mmol), MeLi (0.59 mL, 0.81 mmol, c = 1.6 M in Et_2O) and *t*-BuLi (0.56 mL, 0.81 mmol, c = 1.7 M in pentane) in Et_2O (5.0 mL) afforded **84** (0.15 g, 77%) as a white solid: Mp. 117.4-120.0 ^oC (CH_2Cl_2/hexanes); IR (neat) 1682, 1597, 1448, 1439, 1368, 1175 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97-7.61 (m, 8 H), 7.53-7.17 (m, 10 H), 7.09-7.02 (m, 4 H), 6.84-6.81 (m, 2 H), 4.96 (app. t, *J* = 8.5 Hz, 1 H), 3.39 (dd, *J* = 7.7, 5.1 Hz, 1 H),

2.36 (s, 3 H), 2.15, 2.11 (AB, J = 6.6 Hz, 2 H), 1.00 (s, 1 H), 0.97 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.95, 135.22, 132.02, 131.89, 131.84, 131.71, 129.80, 128.47, 128.35, 128.29, 128.25, 128.16, 128.08, 126.86, 125.41, 125.32, 124.52, 123.75, 123.04, 120.24, 113.76, 113.53, 47.84, 33.72, 31.49, 26.46, 26.39, 21.51, 20.52; MS (EI) *m/z* (rel. intensity) 628 (M^+, 2), 499 (20), 256 (35), 201 (100); HRMS (ES) calc for $C_{38}H_{33}N_2O_3NaPS$ (M+Na) 651.1847, found 651.1848.



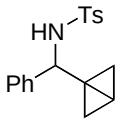
119

2,2-Dibromo-1-(chloromethyl)-cyclopropane (119).[183] Allyl chloride (9.8 mL, 0.12 mol), bromoform (7.7 mL, 0.080 mol) and Bu_4NHCl (0.032 g) were dissolved in CH_2Cl_2 (50 mL) followed by finely powdered NaOH (32 g, 0.80 mol). The reaction mixture was sonicated overnight, filtered and the solvent was removed *in vacuo*. Purification by chromatography on SiO_2 (hexane/Et_2O, 20:1) afforded **119** (9.0 g, 45%) as a light yellow oil: IR (ATR) 2957, 1443, 1433, 1370, 1265, 1101 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (dd, J = 7.1, 1.1 Hz, 1 H), 2.10-2.00 (m, 1 H), 1.93 (dd, J = 10.3, 7.4 Hz, 1 H), 1.49 (t, J = 7.4 Hz, 1 H); MS (EI) *m/z* (rel. intensity) 247 (9), 213 (10), 199 (100), 186 (45), 169 (70); HRMS (EI) calc for $C_4H_5Br_3$ [M-Cl] 210.8758, found 210.8772.



120a

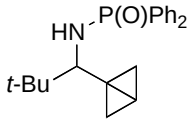
***N*-((Bicyclo[1.1.0]but-1-yl)(phenyl)methyl)-*P,P*-diphenylphosphinamide (120a). General Protocol G.** 2,2-Dibromo-1-(chloromethyl)-cyclopropane **119** (3.3 g, 13 mmol) was dissolved in dry Et_2O (50 mL), cooled to -78 ^oC and treated dropwise with a solution of MeLi (9.7 mL, 13 mmol, c = 1.6 in Et_2O). The reaction mixture was allowed to warm up to -50 ^oC over 1 h, cooled back to -78 ^oC and treated with a solution of *t*-BuLi (9.2 mL, 13 mmol). After 1 h at -78 ^oC, a solution of imine **83a** (2.0 g, 6.6 mmol) in THF (30 mL) was added and the reaction mixture was warmed up to rt, quenched with sat. NH_4Cl and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **120a** (1.3 g, 57%) as a colorless oil: IR (neat) 3058, 2925, 1615, 1453, 1438, 1193, 1123, 1109 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.94-7.72 (m, 6 H), 7.50-7.15 (m, 9 H), 4.61 (app. t, *J* = 9.3 Hz, 1 H), 3.60 (dd, *J* = 9.0, 6.6 Hz, 1 H), 1.61 (dd, *J* = 6.3, 2.8 Hz, 1 H), 1.35 (t, *J* = 2.3 Hz, 1 H), 1.22 (dd, *J* = 6.3, 2.8 Hz, 1 H), 0.54 (s, 1 H), 0.44 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.35, 142.27, 133.93, 132.21, 132.15, 132.03, 131.93, 131.81, 131.54, 131.50, 131.41, 131.34, 131.29, 128.36, 128.25, 128.18, 128.11, 127.05, 126.64, 54.92, 32.49, 31.75, 15.26, 15.20, 1.88; MS (EI) *m/z* (rel. intensity) 359 (M^+, 36), 306 (52), 290 (11), 201 (99), 158 (100); HRMS (EI) calc for $C_{23}H_{22}NOP$ 359.1439, found 359.1429.



120b

***N*-((Bicyclo[1.1.0]but-1-yl)(phenyl)methyl)-*p*-toluenosulfonamide (120b).** According to the General Protocol G, 2,2-dibromo-1-(chloromethyl)-cyclopropane **119** (5.0 g, 20 mmol) was dis-

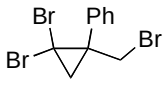
solved in dry Et_2O (30 mL), cooled to -78 ºC and treated dropwise with a solution of MeLi (15 mL, 20 mmol, c = 1.4 M in Et_2O). The reaction mixture was allowed to warm up to -50 ºC over 1 h, cooled to -78 ºC and treated with a solution of *t*-BuLi (12 mL, 20 mmol). After 20 min, a solution of imine **88a** (2.6 g, 10 mmol) in THF (20 mL) was added, the reaction mixture was allowed to warm up to rt, quenched with sat. NH_4Cl, and extracted (3x) with Et_2O. The combined organic layers were washed with water, brine, dried (Na_2SO_4) and evaporated. The oil was purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to afford **120b** (1.9 g, 61%) that was precipitated from CH_2Cl_2 with an excess of pentane: Mp. 128.0-129.9 ºC (pentane/CH_2Cl_2); IR (KBr) 3038, 2932, 1600, 1457, 1437, 1324, 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65-7.62 (m, 2 H), 7.21-7.18 (m, 5 H), 7.12-7.08 (m, 2 H), 4.96 (d, *J* = 6.6 Hz, 1 H), 4.76 (d, *J* = 6.8 Hz, 1 H), 2.40 (s, 3 H), 1.51 (t, *J* = 4.6 Hz, 1 H), 1.27 (d, *J* = 4.9 Hz, 2 H), 0.64 (d, *J* = 0.8 Hz, 1 H), 0.55 (bs, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 139.4, 137.8, 129.3, 128.2, 127.4, 127.1, 126.8, 57.8, 32.4, 31.4, 21.4, 14.1, 1.5; MS (EI) *m/z* (rel. intensity) 313 (M^+, 12), 260 (31), 158 (73), 155 (54), 91 (100); HRMS (EI) calc for $C_{18}H_{19}NO_2S$ 313.1137, found 313.1134.



120c

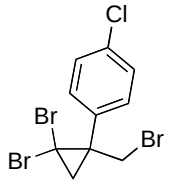
***N*-(1-(Bicyclo[1.1.0]but-1-yl)-2,2-dimethylpropyl)-*P,P*-diphenylphosphinic amide (120c).** According to the General Protocol G, 2,2-dibromo-1-(chloromethyl)-cyclopropane **119** (1.0 g, 4.2 mmol) was dissolved in dry Et_2O (20 mL), cooled to -78 ºC and treated dropwise with a solution of MeLi (2.8 mL, 4.2 mmol, c = 1.50 M in Et_2O). The reaction mixture was allowed to warm up to -50 ºC over 1 h, cooled to -78 ºC and treated with a solution of *t*-BuLi (2.9 mL, 4.2

mmol, c = 1.43 M in pentane). After 10 min, a solution of imine **83g** (0.48 g, 1.77 mmol) in THF (10 mL) was added, the reaction mixture was stirred at -78 ^{o}C for 10 min, allowed to warm up to rt, quenched with sat. NH_4Cl, and extracted (3 x 10 mL) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. The oil was purified by chromatography on SiO_2 (hexanes/EtOAc, 1:4) to afford **120c** (0.30 g, 52%) as a white solid: Mp. 158.8-160.5 ºC (hexanes/EtOAc); IR (neat) 3245, 2965, 2917, 1474, 1336, 1186, 1123, 1108 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92-7.76 (m, 4 H), 7.51-7.35 (m, 6 H), 2.99 (dd, *J* = 11.0, 8.8 Hz, 1 H), 2.87 (dd, *J* = 11.0, 6.2 Hz, 1 H), 1.66 (dd, *J* = 6.1, 2.7 Hz, 1 H), 1.42 (br s, 1 H), 1.34 (dd, *J* = 6.1, 2.7 Hz, 1 H), 1.00 (s, 9 H), 0.65 (s, 1 H), 0.44 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.75, 132.29, 132.16, 132.03, 131.91, 131.72, 131.57, 128.43, 128.29, 128.13, 59.80, 59.76, 37.35, 35.39, 28.36, 26.97, 11.78, -0.83; MS (EI) *m/z* (rel. intensity) 339 (2, M^+), 324 (2), 282 (90), 201 (100); HRMS (EI) calc for $C_{21}H_{26}NOP$ 339.1752, found 339.1740.



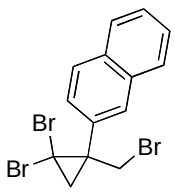
121a

1,1-Dibromo-2-(chloromethyl)-2-phenylcyclopropane (121a).[183] a-Bromomethylstyrener (1.0 g, 5.1 mmol) was dissolved in CH_2Cl_2 (10 mL), followed by $CHBr_3$ (1.0 mL, 11 mmol), cetrimide (0.18 g) and 50% aq NaOH (2.2 mL). The reaction mixture was vigorously stirred at rt for 16 h, diluted with water and extracted (3x) with CH_2Cl_2. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/Et_2O, 1:20) afforded **121a** (0.5 g, 27%) as a pale yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.34 (m, 5 H), 3.99 (dd, *J* = 11.6, 1.4 Hz, 1 H), 3.85 (d, *J* = 10.4 Hz, 1 H), 2.28 (dd, *J* = 8.0, 1.4 Hz, 1 H), 2.02 (d, *J* = 8.0 Hz, 1 H).



121b

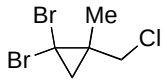
1-Chloro-4-(2,2-dibromo-1-(bromomethyl)cyclopropyl)benzene (121b). A solution of 1-(3-bromoprop-1-en-2-yl)-4-chlorobenzene[463] (5.2 g, 22 mmol) was dissolved in bromoform (5.8 mL, 0.19 mol), treated with cetrimide (0.30 g) and a solution of NaOH (10 mL, 50% aq) was added over 10 min. The reaction mixture was vigorously stirred at rt for 18 h, diluted with water and extracted (3x) with CH_2Cl_2. The organic layers were dried with Na_2SO_4 and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 100:1 to 95:5) afforded **121b** (3.65 g, 40%) as a colorless oil which solidified upon standing: Mp. 84.8-87.2 ^oC (hexane/EtOAc); IR (ATR) 3079, 1489, 1420, 1228 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, J = 8.4 Hz, 2 H), 7.33 (d, J = 8.4 Hz, 2 H), 3.94 (d, J = 10.5 Hz, 1 H), 3.83 (d, J = 10.5 Hz, 1 H), 2.24 (d, J = 8.1 Hz, 1 H), 2.04 (d, J = 8.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.5, 134.0, 131.1, 128.5, 42.1, 39.3, 34.7, 34.10; MS (EI) *m/z* (rel. intensity) 401 (M^+, 1), 323 (45), 243 (67), 229 (24), 207 (10), 162 (100), 149 (26), 128 (83); HRMS (EI) calc for $C_{10}H_8ClBr_3$ 399.7864, found 399.7869.



121c

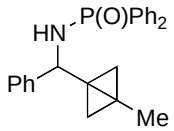
2-(2,2-Dibromo-1-(bromomethyl)cyclopropyl)naphthalene (121c). To a mixture of 2-(3-bromoprop-1-en-2-yl)naphthalene (5.9 g, 24 mmol), bromoform (6.2 mL, 120 mmol), and cetrimide (0.32 g), a solution of NaOH (11 mL, 50% aq.) was added at a rated that he internal temperature did not exceed 30 ^{o}C. The reaction mixture as vigorously stirred at rt for 21 h, poured into water (300 mL) and extracted (3 x 50 mL) with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4 and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 10:0 to 10:1) afforded **121c** (4.1 g, 40%) as a colorless oil: IR (ATR) 3041, 1597, 1502, 1418 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92-7.81 (m, 3 H), 7.78 (s, 1 H), 7.54-7.49 (m, 3 H), 4.09 (dd, *J* = 10.5, 1.5 Hz, 1 H), 3.92 (d, *J* = 10.5 Hz, 1 H), 2.41 (dd, *J* = 8.1, 1.4 Hz, 1 H), 2.10 (d, *J* = 8.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 132.9 (2), 129.1, 128.1, 128.0, 127.7, 127.0, 126.4, 126.3, 42.3, 40.2, 34.7, 34.1; MS (EI) *m/z* (rel. intensity) 418 (M^+, 1), 339 (10), 259 (40), 178 (100), 152 (35); HRMS (EI) calc for $C_{14}H_{11}Br_3$ 415.8411, found 415.8393.

2-(3-Bromoprop-1-en-2-yl)naphthalene was prepared by reaction of 2-(naphthalen-2-yl)prop-2-en-1-ol (6.0 g, 33 mmol) with PPh_3 (9.4 g, 35 mmol), Br_2 (1.8 mL, 36 mmol), and imidazole (3.3 g, 49 mmol) in CH_2Cl_2 (100 mL) at 0 ^{o}C in 74% yiel (6.0 g) as a colorless oil: IR (ATR) 3053, 2920, 2859, 1616, 1595, 1448, 1310, 1210 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 1 H), 7.91-7.85 (m, 3 H), 7.70-7.63 (m, 1 H), 7.56-7.48 (m, 2 H), 5.73 (s, 1 H), 5.61 (s, 1 H), 4.52 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 134.7, 133.3, 133.1, 128.3, 127.6, 126.3 (2), 125.2, 124.0, 117.6, 34.1; MS (EI) *m/z* (rel. intensity) 248 (M^+, 96), 165 (100), 152 (92), 139 (30), 115 (35); HRMS (EI) calc for $C_{13}H_{11}Br$ 246.0044, found 246.0054.



122

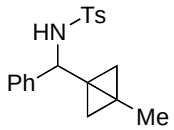
1,1-Dibromo-2-(chloromethyl)-2-methylcyclopropane (122).[464] A mixture of cetrimide (0.1 g), 2-methylallyl chloride (35 g, 0.39 mol), and bromoform (100 ml, 1.15 mol) was cooled to 0 ^{o}C, treated dropwise with 50% aq NaOH (500 mL) and vigorously stirred with a mechanical stirrer for 15 h. The mixture was diluted with water (ca. 2 L), extracted (3 x 500 mL) with Et_2O and the combined organic layers were dried ($MgSO_4$) and concentrated. Fractional distillation (1 mmHg, 60-75 ^{o}C) afforded **122** (79 g, 78%) as a clear, colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (d, *J* = 11.4 Hz, 1 H), 3.69 (d, *J* = 11.4 Hz, 1 H), 1.69 (d, *J* = 7.8 Hz, 1 H), 1.60 (d, *J* = 7.8 Hz, 1 H), 1.56 (s, 3 H).



123a

***N*-((3-methylbicyclo[1.1.0]but-1-yl)(phenyl)methyl)-*P*,*P*-diphenylphosphinic amide (123a).** A solution of **122** (1.0 g, 3.3 mmol) in dry Et_2O (10 mL) was cooled to -78 ^{o}C, treated with a solution of MeLi (2.0 mL, 3.3 mmol, c = 1.6 M in Et_2O). The mixture was warmed up to -50 ^{o}C over 1 h, cooled to -78 ^{o}C and treated with a solution of *t*-BuLi (1.9 mL, 3.3 mmol, c = 1.7 M in pentane). After 10 min at -78 ^{o}C, a solution of **83a** (0.40 g, 1.3 mmol) in THF (5.0 mL) was added *via* syringe. The mixture was stirred at -78 ^{o}C for 10 min, quenched with sat. NH_4Cl, warmed up to rt, and extracted (3 x 10 mL) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4 to 1:20) afforded **123a** (0.30 g, 62%) as a colorless solid: Mp. 150.5-153.1 ^{o}C

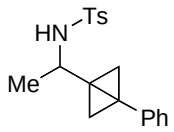
(hexane/CH_2Cl_2); IR (ATR) 3211, 1435, 1180 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 11.5, 7.6 Hz, 2 H), 7.78 (dd, *J* = 11.8, 7.9 Hz, 2 H), 7.51-7.42 (m, 4 H), 7.34-7.28 (m, 4 H), 7.25-7.22 (m, 3 H), 4.73 (app. t, *J* = 8.5 Hz, 1 H), 3.56 (br s, 1 H), 1.37 (d, *J* = 6.5 Hz, 1 H), 1.31 (s, 3 H), 0.97 (d, *J* = 6.5 Hz, 1 H), 0.48 (s, 1 H), 0.35 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.31, 142.27, 122.89, 133.11, 132.87, 132.25, 132.17, 132.08, 132.01, 131.59, 131.54, 128.34, 128.28, 128.24, 128.19, 128.14, 127.16, 127.00, 54.93, 34.19, 32.06, 17.14, 17.10, 12.40, 10.86; MS (EI) *m/z* (rel. intensity) 373 (M^+, 25), 306 (45), 218 (21), 201 (100), 172 (56); HRMS (EI) calc for $C_{24}H_{24}NOP$ 373.1596, found 373.1597.



123b

4-Methyl-*N*-((3-methylbicyclo[1.1.0]but-1-yl)(phenyl)methyl)benzenesulfonamide (123b). A solution of **122** (3.0 g, 12 mmol) in dry Et_2O (20 mL) was cooled to -78 °C, treated with a solution of MeLi (7.7 mL, 12 mmol, c = 1.5 M in Et_2O). After 1 h at -78 °C, the mixture was treated with a solution of *t*-BuLi (7.7 mL, 12 mmol, c = 1.5 M in pentane), stirred at this temperature for 20 min and a solution of **88a** (1.2 g, 4.6 mmol) in THF (10 mL) was added. The mixture was quenched with sat. NH_4Cl, warmed up to rt, diluted with water, and extracted (3 x 10 mL) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **123b** (0.36 g, 24%) as a colorless solid: Mp. 122.7-124.1 °C (pentane/Et_2O); IR (ATR) 3263, 2916, 1429, 1319, 1303, 1155 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.4 Hz, 2 H), 7.21-7.10 (m, 5 H), 7.06-7.03 (m, 2 H), 5.10 (d, *J* = 6.0 Hz, 1 H), 4.77 (d, *J* = 6.3 Hz, 1 H), 2.37 (s, 3 H), 1.30 (s,

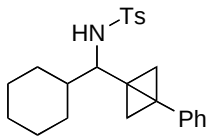
3 H), 1.19 (d, J = 6.3 Hz, 1 H), 0.94 (d, J = 6.6 Hz, 1 H), 0.55 (s, 1 H), 0.44 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 139.4, 138.0, 129.2, 128.2, 127.4, 127.1, 57.8, 33.4, 32.1, 21.4, 15.9, 11.8, 10.7; MS (EI) *m/z* (rel. intensity) 327 (M^+, 3), 260 (50), 172 (78), 155 (65), 145 (25), 104 (35), 91 (100); HRMS (EI) calc for $C_{19}H_{21}NO_2S$ 327.1293, found 327.1280.



123c

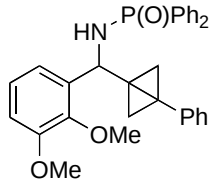
4-Methyl-*N*-(1-(3-phenylbicyclo[1.1.0]but-1-yl)ethyl)benzenesulfonamide (123c). A solution of **121a** (0.44 g, 1.20 mmol) in Et_2O (5.0 mL) was cooled to -78 °C, treated with a solution of MeLi (0.81 mL, 1.20 mmol, c = 1.49 M in Et_2O) and allowed to warm up to -50 °C over 1 h. The mixture was cooled to -78 °C, treated dropwise with a solution of *t*-BuLi (0.75 mL, 1.2 mmol, c = 1.6 M in pentane), stirred at this temperature for 10 min and a solution of **90a** (0.095 g, 0.48 mmol) in THF (5.0 mL) was added. The reaction was continued for 10 min, quenched with sat. NH_4Cl, warmed up to rt, extracted (3x5 mL) with EtOAc and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1 to 3:1) afforded unstable **123c** (0.094 g, 60%) as a light yellow oil. X-ray qulity crystal was obtained after recrystallized from pentane/Et_2O: IR (ATR) 3271, 2930, 1599, 1420, 1325, 1155, 1088 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 8.2 Hz, 2 H), 7.06 (t, J = 7.7 Hz, 2 H), 6.97 (app. t, J = 7.8 Hz, 3 H), 6.80 (d, J = 8.0 Hz, 2 H), 5.42 (d, J = 7.8 Hz, 1 H), 3.72 (quintet, J = 7.1 Hz, 1 H), 1.92 (d, J = 6.8 Hz, 1 H), 1.91 (s, 3 H), 1.79 (d, J = 6.7 Hz, 1 H), 0.72 (s, 1 H), 0.71 (s, 1 H), 0.69 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.6, 139.8, 136.3, 129.6, 128.7, 127.5, 125.8, 125.4, 49.5, 33.3, 29.6, 26.9, 21.1, 19.4, 18.9;

MS (EI) *m/z* (rel. intensity) 327 (M^+, 5), 312 (1), 97 (97), 172 (70), 155 (97), 91 (100); HRMS (EI) calc for $C_{19}H_{21}NO_2S$ 327.1293, found 327.1276.



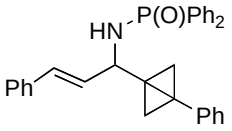
123d

Cyclohexyl(3-phenylbicyclo[1.1.0]but-1-yl)-*N*-tosylmethanamine (123d). According to the General Protocol G, 2,2-dibromo-1-bromomethylphenylcyclopropane **121a** (0.50 g, 1.4 mmol) in Et_2O (10.0 mL) was treated with MeLi (0.84 mL, 1.4 mmol, c = 1.6 M in Et_2O), followed by *t*-BuLi (0.81 mL, 2.2 mmol, c = 1.7 M in pentane) and a solution of imine **90b** (0.15 g, 0.54 mmol) in THF (5.0 mL). The reaction mixture was warmed up to rt, quenched with sat. NH_4Cl and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **123d** (0.16 g, 75%) as a light yellow oil: IR (neat) 3286, 2925, 2853, 1601, 1447, 1325, 1159 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50-7.48 (m, 2 H), 7.31-7.27 (m, 2 H), 7.22-7.10 (m, 5 H), 4.40 (d, *J* = 8.0 Hz, 1 H), 3.43 (dd, *J* = 8.0, 3.9 Hz, 1 H), 2.41 (s, 3 H), 1.94 (d, *J* = 6.7 Hz, 1 H), 1.87 (d, *J* = 6.7 Hz, 1 H), 1.67-1.53 (m, 6 H), 1.09-1.01 (m, 5 H), 0.97 (s, 1 H), 0.84 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 138.0, 135.8, 129.4, 128.4, 126.9, 125.6, 125.2, 56.9, 42.5, 32.3, 30.7, 28.9, 28.8, 26.2, 26.1, 26.0, 25.0, 21.4, 18.4; MS (EI) *m/z* (rel. intensity) 395 (M^+, 15), 312 (14), 266 (40), 240 (19), 91 (100); HRMS (EI) calc for $C_{24}H_{29}NO_2S$ 395.1919, found 395.1919.



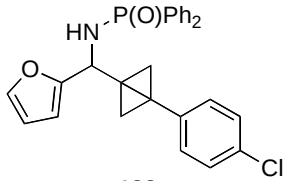
123e

***N*-((2,3-Dimethoxyphenyl)(3-phenylbicyclo[1.1.0]but-1-yl)methyl)-*P,P*-diphenylphosphinamide (123e)**. According to the General Protocol G, 2,2-dibromo-1-bromomethylphenylcyclopropane **121a** (0.50 g, 1.4 mmol) in Et_2O (10.0 mL) was treated with MeLi (0.84 mL, 1.4 mmol, c = 1.6 M in Et_2O), followed by *t*-BuLi (0.81 mL, 1.4 mmol, c = 1.7 M in pentane) and a solution of imine **83e** (0.20 g, 0.54 mmol) in THF (10 mL). The reaction mixture was warmed up to rt, quenched with sat. NH_4Cl, and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **123e** (0.32 g, 65%) as a colorless solid: IR (KBr) 2935, 1601, 1480, 1438, 1266, 1195, 1123 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69-7.56 (m, 4 H), 7.46-7.20 (m, 5 H), 7.12-6.90 (m, 6 H), 6.77-6.69 (m, 2 H), 6.01 (d, *J* = 6.4, 2.5 Hz, 1 H), 4.71 (app. t, *J* = 10.3 Hz, 1 H), 3.91-3.83 (m, 1 H), 3.77 (s, 3 H), 3.50 (s, 3 H), 2.14 (d, *J* = 6.6 Hz, 1 H), 2.04 (d, *J* = 6.6 Hz, 1 H), 1.04 (s, 1 H), 1.01 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.15, 145.96, 136.09, 134.46, 134.39, 133.51, 132.77, 132.28, 132.14, 131.81, 131.73, 131.60, 131.39, 131.04, 128.23, 128.07, 127.91, 125.49, 124.74, 123.32, 119.54, 111.32, 60.07, 55.45, 50.62, 32.73, 31.21, 28.48, 28.41, 20.08; MS (EI) *m/z* (rel. intensity) 495 (M^+, 11), 366 (81), 334 (14), 294 (34), 201 (84), 77 (100); HRMS (EI) calc for $C_{31}H_{30}NO_3P$ 495.1963, found 495.1939.



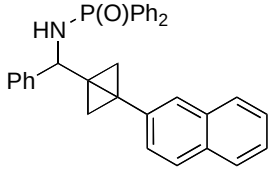
123f

***N*-((*E*)-3-Phenyl-1-(3-phenylbicyclo[1.1.0]but-1-yl)allyl)-*P*,*P*-diphenylphosphinamide (123f)**. According to the General Protocol G, 2,2-dibromo-1-bromomethylphenylcyclopropane **121a** (0.30 g, 0.81 mmol) in Et_2O (5.0 mL) was treated with MeLi (0.59 mL, 0.81 mmol, c = 1.38 M in Et_2O), followed by *t*-BuLi (0.56 mL, 0.81 mmol, c = 1.43 M in pentane) and a solution of imine **83h** (0.11 g, 0.32 mmol) in THF (5.0 mL). The reaction mixture was warmed up to rt, quenched with sat. NH_4Cl and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **123f** (0.14 g, 95%) as a colorless solid: Mp. 138-140 ^oC (hexane/CH_2Cl_2); IR (KBr) 1601, 1437, 1186, 1124 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88-7.79 (m, 4 H), 7.49-7.39 (m, 7 H), 7.33-7.11 (m, 9 H), 6.10 (d, *J* = 15.9 Hz, 1 H), 5.86 (dd, *J* = 15.8, 6.6 Hz, 1 H), 4.25 (app. q, *J* = 7.8 Hz, 1 H), 3.11 (dd, *J* = 8.2, 5.5 Hz, 1 H), 2.30 (AB, *J* = 6.5 Hz, 1 H), 2.26 (AB, *J* = 6.6 Hz, 1 H), 1.08 (s, 1 H), 1.01 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.45, 136.36, 132.27, 132.14, 132.07, 131.94, 131.83, 131.70, 131.00, 128.64, 128.46, 128.34, 128.10, 127.52, 126.55, 126.45, 125.58, 125.18, 52.97, 33.05, 30.91, 27.22, 27.13, 19.49; MS (EI) *m/z* (rel. intensity) 461 (M^+, 14), 260 (19), 201 (50), 86 (100); HRMS (EI) calc for $C_{31}H_{28}NOP$ 461.1909, found 461.1922.



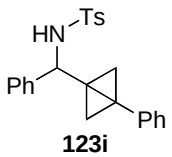
123g

***N*-((3-(4-Chlorophenyl)bicyclo[1.1.0]but-1-yl)(furan-2-yl)methyl)-*P*,*P*-diphenylphosphinic amide (123g).** A solution of **121b** (1.0 g, 2.5 mmol) in dry Et_2O (10 mL) was cooled to -78 ^oC, treated with a solution of MeLi (1.6 mL, 2.5 mmol, c = 1.5 M in Et_2O) and allowed to warm up to -40 ^oC over 1 h. The mixture was cooled to -78 ^oC, treated with a solution of *t*-BuLi (1.7 mL, 2.5 mmol, c = 1.45 M in pentane) and after 10 min at -78 ^oC, a solution of **83f** (0.29 g, 0.99 mmol) in THF (5.0 mL) was added *via* cannula. The mixture was stirred at -78 ^oC for 5 min, quenched with sat. NH_4Cl, warmed up to rt and extracted (3 x 10 mL) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **123g** (0.30 g, 67%) as a light yellow foam: IR (neat) 3399, 3151, 3056, 2928, 1484, 1438, 1190, 1107 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.83-7.66 (m, 4 H), 7.50-7.30 (m, 6 H), 7.21 (dd, *J* = 1.7, 0.87 Hz, 1 H), 7.21 (d, *J* = 8.3 Hz, 2 H), 6.95 (d, *J* = 8.4 Hz, 2 H), 6.15 (dd, *J* = 2.9, 1.6 Hz, 1 H), 5.69 (d, *J* = 3.2 Hz, 1 H), 4.71 (app. t, *J* = 9.3 Hz, 1 H), 3.44 (dd, *J* = 9.3, 7.3 Hz, 1 H), 2.13-2.08 (m, 2 H), 1.06 (s, 1 H), 1.04 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.92, 152.84, 141.49, 134.48, 133.46, 132.71, 132.13, 132.00, 131.81, 131.76, 131.68, 130.99, 130.67, 128.41, 128.33, 128.24, 128.16, 128.04, 126.95, 109.99, 106.45, 48.25, 33.25, 31.49, 27.73, 27.65, 19.65; MS (EI) *m/z* (rel. intensity) 459 (M^+, 61), 391 (12), 296 (46), 258 (35), 242 (47), 202 (46), 201 (100); HRMS (EI) calc for $C_{27}H_{23}NO_2PCl$ 459.1154, found 459.1157



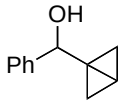
123h

***N*-((3-(Naphthalen-2-yl)bicyclo[1.1.0]but-1-yl)(phenyl)methyl)-*P*,*P*-diphenylphosphinic amide (123h).** A solution of **121c** (1.3 g, 3.1 mmol) in dry Et_2O (10 mL) was cooled to -78 ^oC, treated with a solution of MeLi (2.1 mL, 3.1 mmol, c = 1.5 M in Et_2O) and allowed to warm up to -40 ^oC over 1 h. The mixture was cooled to -78 ^oC, treated with a solution of *t*-BuLi (2.1 mL, 3.1 mmol, c = 1.45 M in pentane) and after 10 min at -78 ^oC, a solution of **83a** (0.38 g, 0.99 mmol) in THF (10 mL) was added *via* cannula. The mixture was stirred at -78 ^oC for 5 min, quenched with sat. NH_4Cl, warmed up to rt and extracted with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **123h** (0.50 g, 82%) as a white solid: Mp. 98.9-101.7 ^oC (hexane/CH_2Cl_2); IR (ATR) 3358, 3166, 3055, 2924, 1625, 1590, 1437, 1189 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80-7.73 (m, 3 H), 7.70-7.61 (m, 3 H), 7.46-7.39 (m, 5 H), 7.37-7.30 (m, 3 H), 7.27-7.22 (m, 2 H), 7.16-7.02 (m, 4 H), 6.79 (dd, *J* = 7.1, 0.9 Hz, 2 H), 4.73 (t, *J* = 8.6 Hz, 1 H), 3.46 (dd, *J* = 7.9, 5.3 Hz, 1 H), 2.26 (d, *J* = 6.7 Hz, 1 H), 2.16 (d, *J* = 6.7 Hz, 1 H), 1.04 (s, 1 H), 1.00 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.43, 140.36, 133.74, 133.58, 133.39, 133.07, 132.18, 132.05, 131.90, 131.78, 131.61, 131.52, 131.35, 128.37, 128.27, 128.20, 128.10, 128.00, 127.56, 127.22, 127.04, 126.07, 125.83, 124.24, 123.92, 54.98, 33.41, 31.37, 29.04, 28.96, 20.60; MS (EI) *m/z* (rel. intensity) 485 (M^+, 37), 306 (24), 268 (100), 252 (8), 218 (8), 201 (89); HRMS (EI) calc for $C_{22}H_{28}NOP$ 285.1909, found 485.1921.



123i

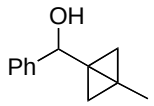
Phenyl(3-phenylbicyclo[1.1.0]but-1-yl)-*N*-tosylmethanamine (123i). According to the General Protocol G, 2,2-dibromo-1-bromomethylphenylcyclopropane **121a** (0.30 g, 0.81 mmol) in Et_2O (5.0 mL) was treated with MeLi (0.59 mL, 0.81 mmol, c = 1.38 M in Et_2O), followed by *t*-BuLi (0.56 mL, 0.81 mmol, c = 1.43 M in pentane) and a solution of imine **88b** (0.083 g, 0.32 mmol) in THF (2.0 mL). The reaction mixture was warmed up to rt, quenched with sat. NH_4Cl, and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded crude **123i** (0.074 g, 59%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-6.93 (m, 12 H), 6.69-6.66 (m, 2 H), 5.45 (d, *J* = 6.8 Hz, 1 H), 4.72 (d, *J* = 6.8 Hz, 1 H), 2.41 (s, 3 H), 2.06 (dd, *J* = 6.7, 0.7 Hz, 1 H), 1.83 (d, *J* = 6.6 Hz, 1 H), 1.07 (s, 1 H), 1.00 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.79, 137.63, 137.42, 134.96, 129.10, 128.01, 127.75, 127.13, 127.04, 126.96, 125.02, 125.24, 57.76, 32.41, 30.79, 26.44, 21.32, 19.46; MS (EI) *m/z* (rel. intensity) 390 (M^+, 1), 312 (1), 274 (2), 260 (68), 234 (17), 155 (50), 105 (63), 91 (100); HRMS (EI) calc for $C_{14}H_{14}NO_2S$ $[M-C_{10}H_9]^+$ 260.0745, found 260.0740



124a

Bicyclo[1.1.0]but-1-yl(phenyl)methanol (124a). A solution of MeLi (27 mL, 40 mmol, c = 1.5 M in Et_2O) was added to a solution of of 1,1-dibromo-2-(chloromethyl)cyclopropane (10 g, 40 mmol) in Et_2O (50 mL) at -78 ^{o}C. The reaction mixture was allowed to warm up to rt over 1 h, cooled to -78 ^{o}C, MeBr was removed by high vacuum and a solution of *t*-BuLi (27 mL, 40 mmol, c = 1.5 M in pentane) was added. After 1 h, neat PhCHO (2.0 mL, 20 mmol) was added,

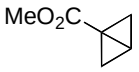
after 5 min the mixture was quenched with water, warmed up to rt and diluted with water. The mixture was extracted (3x) with Et_2O and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by Kugelrohr distillation (fractions collected at 110-120 ^oC, 1 mmHg) afforded **124a** (2.2g, 68%) as a clear, colorless oil: IR (neat) 3358, 2929, 1493, 1452, 1196 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.33 (m, 4 H), 7.32-7.29 (m, 1 H), 5.07 (d, *J* = 3.7 Hz, 1 H), 2.52 (d, *J* = 3.9 Hz, 1 H), 1.72 (dd, *J* = 6.2, 2.9 Hz, 1 H), 1.40 (dd, *J* = 6.2, 2.9 Hz, 1 H), 1.38 (t, *J* = 2.6 Hz, 1 H), 0.82 (s, 1 H), 0.70 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 128.2, 127.5, 126.2, 73.6, 32.4, 31.6, 14.9, 0.8; MS (EI) *m/z* (rel. intensity) 159 (16), 141 (31), 131 (97), 115 (77), 105 (99), 91 (100), 77 (95); HRMS (EI) calc for $C_{11}H_{12}O$ 160.0888, found 160.0887.



124b

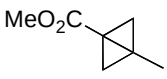
(3-Methylbicyclo[1.1.0]but-1-yl)(phenyl)methanol (124b). A solution of 1-chloromethyl-1-methyl-2,2-dibromocyclopropane **122** (10 g, 38 mmol) in Et_2O (50 mL) was cooled to -78 ^oC, treated with a solution of MeLi (25 mL, 38 mmol, c = 1.5 M in Et_2O). After 1 h, a solution of *t*-BuLi (25 mL, 38 mmol, c = 1.5 M in pentane) was added. The reaction mixture was stirred at -78 ^oC for 1 h and neat benzaldehyde (1.5 mL, 15 mmol) was added in one portion. The reaction mixture was quenched at -78 ^oC, warmed up to rt, extracted (3 x 10 mL) with Et_2O and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Product was purified by Kugelrohr distillation (1 mmHg, fractions collected at 105-115 ^oC oven temperature) to afford **124b** (2.13 g, 80 %) as a light-yellow oil: IR (ATR) 3383, 1493, 1450, 1088 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.26 (m, 5 H), 5.05 (d, *J* = 4.2 Hz, 1 H), 1.96 (d, *J* = 4.2 Hz, 1 H), 1.48 (d, *J* = 6.6 Hz, 1 H), 1.46 (s, 3 H), 1.13 (d, *J* = 6.6 Hz, 1 H), 0.73 (s, 1 H), 0.64 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1, 128.2, 127.5, 126.5, 73.3, 32.8, 32.6, 16.1, 11.1, 10.5; MS (EI) *m/z* (rel. intensity) 174 (M^+, 71), 159 (66), 141 (53), 115 (76), 105 (100), 91 (77), 77 (90); HRMS (EI) calc for $C_{12}H_{14}O$ 174.1045, found 174.1042.



125a

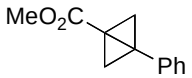
Methyl bicyclo[1.1.0]butane-1-carboxylate (125a).[98] A solution of **119** (35 g, 141 mmol) in Et_2O (50 mL) was cooled to -50 °C, treated with MeLi (88 mL, 141 mmol, c = 1.6 M in Et_2O) and after 1 h at this temperature with solution of *t*-BuLi (82 mL, 141 mmol, c = 1.6 M in pentane). The reaction was continued for 1 h, neat methyl chloroformate (22 mL, 282 mmol) was added in one portion, the mixture was warmed up to rt, quenched with sat. NH_4Cl, diluted with water, and extracted (3x50 mL) with Et_2O. Combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by Kugelrohr distillation (40-80 °C, water aspiration) afforded ester **125a** (4.0 g, 25%) as a clear, colorless oil: ^{1}H NMR (300 MHz, C_6D_6) δ 3.37 (s, 3 H), 2.17 (dt, *J* = 2.6, 0.8 Hz, 2 H), 1.55 (quintet, *J* = 3.1 Hz, 1 H), 0.81 (dt, *J* = 2.7, 0.8 Hz, 2 H).



125b

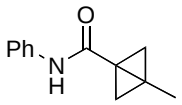
Methyl 3-methylbicyclo[1.1.0]butane-1-carboxylate (125b).[465] A solution of 2,2-dibromo-2-chloromethyl-2-methylcyclopropane **122** (5.0 g, 19 mmol) in Et_2O (50 mL) was cooled to -78

°C, treated with MeLi (13 mL, 20 mmol, c = 1.5 M in Et_2O) and stirred at -78 °C for 1 h. The mixture was then treated with *t*-BuLi (13 mL, 20 mmol, c = 1.5 M in pentane), stirred at -78 °C for 1 h, followed by methyl chloroformate (3.0 mL, 38 mmol). The mixture was allowed to warm up to rt, cooled to -78 °C, and quenched with sat. NH_4Cl. The mixture was warmed to rt, diluted with water, extracted with Et_2O (3x20 mL) and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by Kugelrohr distillation (2 mmHg, fractions collected at 80-100 °C) afforded **125b** (1.3 g, 54%) as a colorless oil: IR (ATR) 2950, 1707, 1439, 1325, 1148 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.71 (s, 3 H), 2.20 (s, 2 H), 1.54 (s, 3 H), 1.25 (s, 2 H).



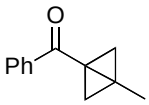
125c

Methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate (125c).[466] A solution of **121a** (1.0 g, 2.7 mmol) in Et_2O (10 mL) was cooled to -78 °C, treated with MeLi (1.9 mL, 2.7 mmol, c = 1.4 M in Et_2O) and the reaction mixture was allowed to warm to -50 °C, cooled to -78 °C and treated with *t*-BuLi (1.8 mL, 2.7 mmol, c = 1.5 M in pentane). The reaction mixture was stirred at -78 °C for 15 min, treated with $NCCO_2Me$ (0.29 mL, 5.4 mmol), warmed to rt and quenched with sat. NH_4Cl. The aqueous layer was extracted with Et_2O, the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **125c** (0.20 g, 39%) as a colorless solid: ^1H NMR (300 MHz, C_6D_6) δ 7.26-7.22 (m, 2 H), 7.18-7.05 (m, 3 H), 2.92 (t, *J* = 1.1 Hz, 2 H), 3.21 (s, 3 H), 1.34 (t, *J* = 1.1 Hz, 2 H); ^{13}C NMR (75 MHz, C_6D_6) δ 169.2, 134.2, 128.6, 127.1, 126.2, 51.3, 35.3, 32.3, 23.6.



126

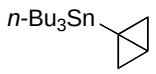
3-Methyl-*N*-phenylbicyclo[1.1.0]butane-1-carboxamide (126). A solution of 1,1-dibromo-2-(chloromethyl)-2-methylcyclopropane **122** (5.5 g, 21 mmol) in Et_2O (25 mL) was cooled to -78 ^oC, treated with MeLi (14 mL, 21 mmol, c = 1.5 M in Et_2O). After 1 h at -78 ^oC, *t*-BuLi (14 mL, 21 mmol, c = 1.5 M in pentane) was added. The mixture was stirred at -78 ^oC for 1 h, neat PhNCO (1.0 g, 8.4 mmol) was added. The mixture was quenched with sat. NH_4Cl, warmed up, and extracted (3 x 10mL) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. The product was precipitated from a crude mixture using Et_2O/pentane to afford **126** (1.2 g, 74%) colorless solid: Mp. 127-130 ^oC (pentane/Et_2O); IR (neat) 3259, 3125, 3043, 2947, 1638, 1595, 1527, 1493, 1442, 1410, 1375, 1332, 1251, 1179 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.53 (d, *J* = 7.8 Hz, 2 H), 7.44 (br s, 1 H), 7.30 (t, *J* = 7.9 Hz, 2 H), 7.08 (t, *J* = 7.4 Hz, 1 H), 2.22 (s, 2 H), 1.59 (s, 3 H), 1.24 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.1, 138.1, 128.8, 123.7, 119.6, 37.5, 25.9, 15.1, 12.2; MS (EI) *m/z* (rel. intensity) 187 (M^+, 30), 172 (10), 132 (50), 67 (100); HRMS (EI) calc for $C_{12}H_{13}NO$ 187.0997, found 187.1003.



127

(3-Methylbicyclo[1.1.0]butan-1-yl)(phenyl)methanone (127).[465] A solution of **122** (5.0 g, 19 mmol) in Et_2O (50 mL) was cooled to -78 ^oC, treated with MeLi (13 mL, 19 mmol, c = 1.5 M in

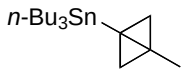
Et_2O) and after 1 h, with a solution of *t*-BuLi (13 mL, 19 mmol, c = 1.5 M in pentane). The reaction mixture was stirred at -78 ^oC, for 1 h, treated with benzoyl chloride (5.4 g, 38 mmol), quenched with sat. NH_4Cl, warmed to rt, and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 6:1) afforded **127** (1.1 g, 33%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.82-7.79 (m, 2 H), 7.54-7.32 (m, 3 H), 2.48 (s, 2 H), 1.56 (s, 2 H), 1.41 (s, 3 H); ^{13}C NMR (75 MHZ, $CDCl_3$) δ 198.7, 138.4, 131.8, 128.4, 128.0, 40.8, 33.6, 21.2, 12.4.



128a

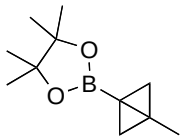
Bicyclo[1.1.0]but-1-yltributylstannane (128a). A solution of 2,2-dibromo-1-(chloromethyl)cyclopropane **119** (10 g, 40 mmoL) in dry Et_2O (40 mL) was cooled to -78 ^oC, treated with a solution of MeLi (27 mL, 40 mmol, c = 1.5 M in Et_2O) and stirred at this temperature for 1 h and a solution of *t*-BuLi (27 mL, 40 mmol, c = 1.5 M in pentane) was added. After 1 h, *n*-Bu_3SnCl (4.0 mL, 13 mmol, 90%) was added, the mixture was warmed up to rt, stirred for 3 h, carefully quenched with sat. NH_4Cl, diluted with water, extracted with Et_2O and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. The product was purified by Kugelrohr distillation: tributylmethyltin and other volatiles were removed at 30 mmHg, 130 ^oC (oven temperature) and the product was collected at 140-160 ^oC, 30 mmHg as a colorless oil (1.1 g, 24%): IR (neat) 3018, 2957, 2923, 2853, 1461, 1418, 1377 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.71 (t, *J* = 2.1 Hz, 1 H), 1.65-1.49 (m, 6 H), 1.35 (sextet, *J* = 7.4 Hz, 6 H), 1.28-1.26 (m, 2 H), 1.06-0.86 (m, 15 H), 0.49 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.2 (*J* = 6.9 Hz), 29.5 (*J* = 10.4 Hz), 27.6 (*J* = 26.5 Hz), 13.9, 9.8 (*J* = 165.8 Hz), 1.5 (*J* = 11.5 Hz), -9.7;

MS (EI) *m/z* (rel. intensity) 343 (4, M-1$^+$), 287 (60), 177 (100), 121 (42); HRMS (EI) calc for $C_{16}H_{32}{}^{120}Sn$ 344.1526, found 344.1530.



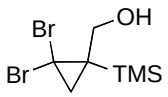
128b

Tributyl(3-methylbicyclo[1.1.0]but-1-yl)stannane (128b). A solution of 1,1-dibromo-2-(chloromethyl)-2-methylcyclopropane **122** (2.0 g, 7.4 mmol) in dry Et_2O (5.0 mL) was cooled to -78 ^oC, treated with a solution of MeLi (5.0 mL, 7.4 mmol, c = 1.5 M in Et_2O) and after 1 h, a solution of *t*-BuLi (5.0 mL, 7.4 mmol, c = 1.5 in pentane) was added. The reaction mixture was stirred at -78 ^oC for 1 h, neat *n*-Bu_3SnCl (0.70 mL, 2.5 mmol, 90%) was added, the mixture was warmed up to rt, stirred at this temperature for 3 h, carefully quenched with sat. NH_4Cl, diluted with water, extracted with Et_2O and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. The volatiles (including *n*-Bu_3SnMe) were removed *via* Kugelrohr distillation (oven temperature up to 105-110 ^oC, 2 mmHg) and the product was collected at 110-120 ^oC, 2 mmHg to afford **128b** (0.25 g, 29%) as a colorless oil: IR (neat) 2956, 2924, 2854, 1460, 1418, 1376, 1362 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.61 (s, 3 H), 1.56-1.46 (m, 6 H), 1.34 (sextet, J = 7.4 Hz, 6 H), 1.08 (s, J_{Sn-H} = 3.7 Hz, 2 H), 0.97-0.80 (m, 15 H), 0.31 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.2 (J_{Sn-C} = 6.7 Hz), 29.2 (J_{Sn-C} = 10 Hz), 27.3 (J_{Sn-C} = 27.6 Hz), 16.1 (J_{Sn-C} = 12.9 Hz), 10.9, 9.5 (J_{Sn-C} = 165.5, 173.3 Hz), -2.6; MS (EI) *m/z* (rel. intensity) 358 (2, M$^+$), 301 (21), 235 (5), 177 (100), 121 (82); HRMS (EI) calc for$C_{17}H_{34}{}^{120}Sn$ 358.1683, found 358.1695.



129b

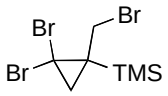
4,4,5,5-Tetramethyl-2-(3-methylbicyclo[1.1.0]but-1-yl)-1,3,2-dioxaborolane (129b). A solution of 2,2-dibromo-1-chloromethyl-1-methylcyclopropane **122** (5.0 g, 19 mmol) in Et_2O (20 mL) was cooled to -78 ^oC, treated with a solution of MeLi (13 mL, 20 mmol, c = 1.5 M in Et_2O) and stirred at -78 ^oC for 1 h. The mixture was then treated with a solution of *t*-BuLi (13 mL, 20 mmol, c = 1.5 M in pentane), stirred at -78 ^oC for 1 h, followed by 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.9 mL, 9.5 mmol). The mixture was allowed to warm up to rt, stirred for 3 h, cooled to -78 ^oC and quenched with sat. NH_4Cl. The mixture was warmed to rt, diluted with water, extracted with Et_2O (3x20 mL) and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Kugelrohr distillation at 2 mmHg, fractions 60-80 ^oC afforded **129b** (0.65 g, 35%) as a colorless oil: IR (ATR) 2974, 1513, 1455, 1438, 1381, 1341, 1139 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 1.78 (s, 2 H), 1.57 (s, 3 H) 1.06 (s, 12 H), 0.77 (s, 2 H); ^{13}C NMR (75 MHz, C_6D_6) δ 83.2, 37.2, 25.0, 24.6, 19.8, 14.4; MS (EI) *m/z* (rel. intensity) 194 (M^+, 75), 17 (63), 137 (76), 121 (44), 93 (83), 84 (98), 67 (87), 59 (100); HRMS (EI) calc for $C_{11}H_{19}BO$ 194.1478, found 194.1482.



131

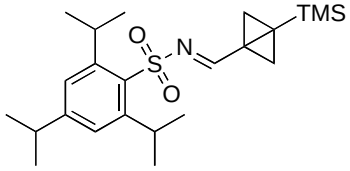
(2,2-Dibromo-1-(trimethylsilyl)cyclopropyl)methanol (131). A solution of 2-(trimethylsilyl)allyl alcohol (18 g, 138 mmol) and DHP (23.4 mL, 276 mmol) in dry CH_2Cl_2 (300 mL) was cooled to 0 ^oC and PPTS (3.5 g, 14 mmol) was added. The reaction mixture was stirred at 0 ^oC

for 1 h, warmed up to rt, stirred for additional 3 h and the solvent was removed to a total volume ca. 50 mL. The mixture was dissolved in Et_2O (200 mL), washed with water (3 x), sat. $NaHCO_3$, water, brine, dried ($MgSO_4$), and concentrated. The crude oil was dissolved in CH_2Cl_2 (100 mL), followed by 50% aq NaOH (1000 mL). This mixture was cooled on ice until the internal temperature reached 10 ^oC and cetrimide (0.50 g, 1.4 mmol) and bromoform (60 mL, 690 mmol) were added. The reaction mixture was vigorously stirred (mechanical stirrer) at 10-15 ^oC (internal temperature) for 1 h, allowed to warm up to rt and stirred for 15 h. The dark-brown solution was diluted with water (3 L), extracted (3x300 mL) with hexane and the combined organic layers were dried ($MgSO_4$), filtered through a pad of SiO_2, and concentrated. The cure oil was dissolved in MeOH (1000 mL) and *p*-TSA·H_2O (2.6 g, 14 mmol) was added. The mixture was stirred at rt for 10 h, the solvent was removed to a total volume of 100 mL and the mixture was diluted with Et_2O (400 mL), washed with water, sat $NaHCO_3$, again with water (3x), brine, dried ($MgSO_4$), and concentrated. The crude oil was purified by chromatography on SiO_2 (hexanes/EtOAc, 15:1 to 10:1) to afford light-yellow oil which was purified by Kugelrohr distillation (fractions collected at 100-120 ^oC, 2 mmHg) furnishing **131** (10 g, 25%) as a white solid. The product was recrystallized from boiling hexanes: Mp. 69.7-72.9 ^oC (hexanes); IR (KBr) 3374, 2963, 2890, 1434, 1402, 1257, 1215, 1158 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.01 (dd, *J* = 12.1, 10.6 Hz, 1 H), 3.42 (dd, *J* = 12.1, 3.5 Hz, 1 H), 1.99 (dd, *J* = 10.5, 3.5 Hz, 1 H), 1.62 (d, *J* = 6.7 Hz, 1 H), 1.38 (d, *J* = 6.7 Hz, 1 H), 0.27 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 70.9, 34.7, 29.0, 27.1, -0.30.



132

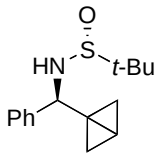
(2,2-Dibromo-1-(bromomethyl)cyclopropyl)trimethylsilane (132). A solution PPh_3 (6.5 g, 25 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 ^oC, treated with Br_2 (1.3 mL, 25 mmol) and stirred for 10 min. Solid imidazole (2.2 g, 33 mmol) was added followed by a solution of **131** (5.0 g, 17 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at 0 ^oC for 30 min, warmed up to rt, stirred for additional 30 min and poured into pentane (200 mL). The precipitate was filtered through a pad of SiO_2, washed with 10:1 hexane/Et_2O mixture, and concentrated. Purification by chromatography on SiO_2 (hexane) afforded **132** (4.9 g, 81%) as a colorless oil which solidified upon standing. The product was recrystallized from boiling hexane: Mp. 50.7-52.9 ^oC (hexane); IR (KBr) 2952, 2901, 1434, 1253, 1226, 1192, 1119 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.86 (d, *J* = 10.6 Hz, 1 H), 3.25 (d, *J* = 10.6 Hz, 1 H), 1.87 (d, *J* = 6.9 Hz, 1 H), 1.50 (d, *J* = 6.9 Hz, 1 H), 0.33 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.9, 34.4, 34.2, 25.4, -0.1; MS (EI) *m/z* (rel. intensity) 348 (90), 269 (36), 211 (46), 131 (100); HRMS (EI) calc for $C_6H_{10}SiBr_3$ $[M\text{-}CH_3]^+$ 346.8102, found 346.8094.



134

2,4,6-Triisopropyl-*N*-((3-(trimethylsilyl)bicyclo[1.1.0]butan-1-yl)methylene)benzenesulfonamide (134). A solution of **132** (1.5 g, 4.1 mmol) in dry Et_2O (10 mL) was cooled to -78 ^oC, treated with a solution of MeLi (1.37 mL, 4.1 mmol, c = 3.0 M in die-

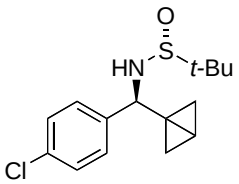
thoxymethane) and stirred at -78 °C for 1 h, warmed up to -45 °C, stirred for 10 min and cooled back to -78 °C. A solution of *t*-BuLi (2.6 mL, 4.1 mmol, c = 1.6 M in pentane) was added, the mixture was stirred for 1 h, diluted with dry THF (12 mL) and 1 M solution of DMF in THF (8.2 mL, 8.2 mmol) was added. The reaction mixture was warmed up to rt, quenched with sat. NH_4Cl, diluted with water and extracted (3x10 mL) with Et_2O. The combined organic layers were washed with water (4x), brine, and dried ($MgSO_4$). The mixture was concentrated to a total volume of ca. 3 mL and dissolved in dry THF (20 mL). 2,4,6-Triisopropylbenzenesulfonamide (1.2 g, 4.1 mmol) and Ti(O*i*-Pr)$_4$ (1.2 mL, 4.1 mmol) were added, the reaction mixture was stirred at rt for 10 min, heated under reflux for 2 h, cooled to rt, stirred for 10 h and the solvent was removed in vacuo. The crude oil was purified by chromatography on SiO_2 (hexanes/ EtOAc 9:1) to afford **134** (0.10 g, 6%) as a white solid. The product was recrystallized from hexane: Mp. 126.3-127.2 °C (hexanes); IR (KBr) 2959, 1589, 1316, 1252, 1152 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 8.87 (s, 1 H), 7.20 (s, 2 H), 4.82 (septet, *J* = 4.8 Hz, 2 H), 2.65 (septet, *J* = 6.9 Hz, 1 H), 1.80 (s, 2 H), 1.37 (d, *J* = 6.8 Hz, 12 H), 1.11 (d, *J* = 6.9 Hz, 6 H), 0.83 (s, 2 H), -0.15 (s, 9 H); ^{13}C NMR (125 MHz, C_6D_6) δ 176.8, 153.2, 151.3, 133.5, 123.8, 38.0, 34.5, 30.1, 25.1, 24.8, 23.7, 23.6, -1.9; MS (EI) *m/z* (rel. intensity) 419 (M^+, 33), 404 (100), 354 (7), 340 (57), 230 (6); HRMS (EI) calc for $C_{23}H_{37}NO_2SSi$ 419.2314, found 419.2308.



142a

(*R*)-*N*-((*S*)-Bicyclo[1.1.0]but-1-yl(phenyl)methyl)-2-methylpropane-2-sulfinamide (142a). A solution of **119** (0.10 g, 0.40 mmol) in dry Et_2O (0.25 mL) was cooled to -78 °C, treated with

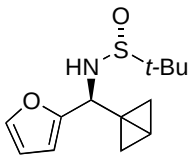
MeLi (0.31 mL, 0.40 mmol, c = 1.31 M in Et_2O) and allowed to warm up to -50 ^oC over 1 h. The reaction mixture was cooled to -78 ^oC, treated with *t*-BuLi (0.27 mL, 0.40 mmol, c = 1.5 M), stirred for 1 h and distilled TMEDA (0.12 mL, 0.80 mmol) was added, the mixture was stirred for additional 15 min and a solution of imine **141a**[467] (0.034 g, 0.16 mmol) in Et_2O (0.20 mL) was added *via* syringe over 17 min. The mixture was stirred -78 ^oC for 3 h, slowly wrmed up to rt, stirred overnight and quenched with EtOAc and water, and extracted (3 x 5 mL) with EtOAc. The combined organic layes were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:1 to 1:4) afforded **142a** (0.022 g, 51%) as a colorless oil: $[\alpha]_D$ +67.8 (c 1.0, $CHCl_3$); IR (ATR) 3235, 2920, 1490, 1452, 1045 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.35 (d, *J* = 7.4 Hz, 2 H), 7.14-7.12 (m, 2 H), 7.06 (t, *J* = 7.0 Hz, 1 H), 4.77 (d, *J* = 3.2 Hz, 1 H), 3.32 (br s, 1 H), 1.81 (dd, *J* = 6.2, 2.7 Hz, 1 H), 1.29 (br s, 1 H), 1.22 (dd, *J* = 6.2, 2.7 Hz, 1 H), 0.96 (s, 9 H), 0.83 (s, 1 H), 0.62 (s, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 142.4, 128.9, 128.7, 127.7, 58.1, 55.2, 32.7, 32.0, 22.5, 22.4, 14.2, 1.4; MS (EI) *m/z* (rel. intensity) 263 (M^+, 1), 245 (1), 143 (98), 128 (89), 105 (89), 57 (100); HRMS (EI) calc for $C_{15}H_{21}NOS$ 263.1344, found 263.1343.



142b

(*R*)-*N*-((*S*)-Bicyclo[1.1.0]but-1-yl(4-chlorophenyl)methyl)-2-methylpropane-2-sulfinamide (142b). A solution of **119** (0.26 g, 1.0 mmol) in dry Et_2O (0.62mL) was cooled to -78 ^oC, treated with MeLi (0.67 mL, 1.30 mmol, c = 1.5 M in Et_2O) and allowed to warm to -50 ^oC over 1 h.

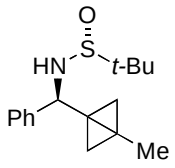
The mixture was cooled to -78 °C, treated with *t*-BuLi (0.67 mL, 1.0 mmol, c = 1.5 M in pentane), stirred at this temperature for 15 min, TMEDA (0.31 mL, 2.1 mmol) was added and after additional 15 min, a solution of imine **141b**[468] (0.10 g, 0.41 mmol) in Et_2O (0.20 mL) was added dropwise over 20 min. The reaction mixture was stirred at -78 °C for 10 h, warmed to rt over 2 h, and stirred at rt for 12 h. The mixture was quenched with sat. NH_4Cl, extracted (3x) with EtOAc and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:1) afforded **142d** (0.087 g, 71%) as a colorless oil: $[\alpha]_D$ +48.2 (c 1.0, $CHCl_3$); IR (ATR) 3213, 2924, 2864, 1489, 1362 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.30 (m, 5 H), 4.78 (d, *J* = 3.3 Hz, 1 H), 3.53 (d, *J* = 2.8 Hz, 1 H), 1.82 (dd, *J* = 6.2, 2.8 Hz, 1 H), 1.39 (app. t, *J* = 2.8 Hz, 1 H), 1.31-1.28 (m, 1 H), 1.25 (s, 9 H), 0.85 (s, 1 H), 0.65 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.8, 133.6, 128.7, 127.9, 57.8, 55.7, 32.6, 31.4, 22.6, 13.6, 1.4; MS (EI) *m/z* (rel. intensity) 297 (M^+, 1), 279 (1), 241 (15), 203 (30), 192 (25), 177 (60), 141 (100), 115 (50); HRMS (EI) calc for $C_{15}H_{20}NOSCl$ 297.0954, found 297.0942.



142c

(*R*)-*N*-((*S*)-Bicyclo[1.1.0]but-1-yl(furan-2-yl)methyl)-2-methylpropane-2-sulfinamide (142c). A solution of **119** (0.31 g, 1.3 mmol) in dry Et_2O (0.77 mL) was cooled to -78 °C, treated with MeLi (0.84 mL, 1.3 mmol, c = 1.5 M in Et_2O) and allowed to warm to -50 °C over 1 h. The mixture was cooed to -78 °C, treated with *t*-BuLi (0.84 mL, 1.3 mmol, c = 1.5 M in pentane), stirred at this temperature for 15 min, TMEDA (0.38 mL, 2.5 mmol) was added and after additional 15

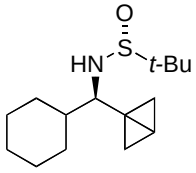
min, a solution of imine **141c**[469] (0.10 g, 0.50 mmol) in Et_2O (0.30 mL) was added dropwise over 20 min. The reaction mixture was stirred at -78 ^oC for 10 h, warmed to rt over 2 h, and stirred at rt for 10 h. The mixture was quenched with sat. NH_4Cl, extracted (3 x 10 mL) with EtOAc and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:1) afforded **142c** (0.091 g, 72%) as a colorless oil: $[\alpha]_D$ +30.1 (c 1.0, $CHCl_3$); IR (ATR) 3286, 2943, 1455, 1362 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (t, *J* = 1.1 Hz, 1 H), 6.34-6.32 (m, 1 H), 4.90 (d, *J* = 5.0 Hz, 1 H), 3.64 (d, *J* = 4.5 Hz, 1 H), 1.74-1.69 (m, 1 H), 1.55-1.50 (m, 2 H), 1.24 (s, 9 H), 0.77 (s, 1 H), 0.56 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 142.2, 110.2, 107.2, 56.0, 53.0, 31.9, 31.8, 22.6, 12.8, 1.5; MS (EI) *m/z* (rel. intensity) 253 (M^+, 1), 195 (20), 148 (54), 134 (95), 115 (57), 91 (71), 79 (97), 57 (100); HRMS (EI) calc for $C_{13}H_{19}NO_2S$ 253.1137, found 253.1130.



142d

(*R*)-2-Methyl-*N*-((*R*)-(3-methylbicyclo[1.1.0]but-1-yl)(phenyl)methyl)propane-2-sulfinamide (142d). A solution of **122** (0.30 g, 1.2 mmol) in dry Et_2O (0.74 mL) was cooled to -78 ^oC, treated with MeLi (0.74 mL, 1.2 mmol, c = 1.6 M in Et_2O) and allowed to warm to -50 ^oC over 1 h. The mixture was cooed to -78 ^oC, treated with *t*-BuLi (0.70 mL, 1.2 mmol, c = 1.7 M in pentane), stirred at this temperature for 15 min, TMEDA (0.36 mL, 2.4 mmol) was added and after additional 15 min, a solution of imine imine **141a**[467] (0.10 g, 0.48 mmol) in Et_2O (0.40 mL) was added dropwise over 20 min. The reaction mixture was stirred at -78 ^oC for 12 h, warmed to rt and

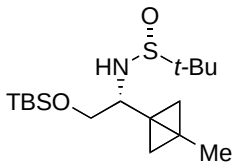
stirred for 10 h. The mixture was quenched with sat. NH_4Cl, extracted (3x10 mL) with EtOAc and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:1) afforded **142d** (0.074 g, 55%) as a colorless oil: $[\alpha]_D$ +90.1 (c 1.0, $CHCl_3$); IR (ATR) 2918, 1472, 1452, 1362, 1053 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31-7.27 (m, 5 H), 4.82 (d, *J* = 3.2 Hz, 1 H), 3.63 (br s, 1 H), 1.51 (d, *J* = 6.6 Hz, 1 H), 1.32 (s, 3 H), 1.25 (s, 9 H), 0.98 (d, *J* = 6.6 Hz, 1 H), 0.76 (s, 1 H), 0.52 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1, 128.4, 127.8, 127.6, 58.0, 55.5, 34.1, 31.9, 22.7, 15.4, 11.2 (2); MS (EI) *m/z* (rel. intensity) 277 (M^+, 3), 259 (3) 245 (3), 204 (14), 170 (38), 157 (100), 142 (83), 128 (92), 116 (75); HRMS (EI) calc for $C_{16}H_{23}NOS$ 277.1500, found 277.1489.



142e

(*R*)-*N*-((*R*)-Bicyclo[1.1.0]but-1-yl(cyclohexyl)methyl)-2-methylpropane-2-sulfinamide (142e). A solution of **119** (0.29 g, 1.2 mmol) in dry Et_2O (0.72 mL) was cooled to -78 ^oC, treated with MeLi (0.73 mL, 1.2 mmol, c = 1.6 M in Et_2O) and allowed to warm to -50 ^oC over 1 h. The mixture was cooed to -78 ^oC, treated with *t*-BuLi (0.68 mL, 1.2 mmol, c = 1.7 M in pentane), stirred at this temperature for 15 min, TMEDA (0.36 mL, 2.4 mmol) was added and after additional 15 min, a solution of imine imine **141d**[470] (0.10 g, 0.46 mmol) in Et_2O (0.30 mL) was added dropwise over 20 min. The reaction mixture was stirred at -78 ^oC for 12 h, warmed to rt and stirred for 10 h. The mixture was quenched with sat. NH_4Cl, extracted (3 x 5 mL) with EtOAc and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and

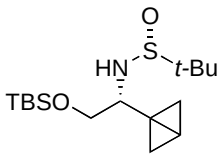
concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:1) afforded **142e** (0.060 g, 48%) as a colorless oil: ^{1}H NMR (300 MHz, C_6D_6) δ 3.34 (t, *J* = 5.1 Hz, 1 H), 2.98 (d, *J* = 3.5 Hz, 1 H), 1.83-1.78 (m, 2 H), 1.68-16.5 (m, 2 H), 1.60 (dd, *J* = 5.5, 3.2 Hz, 1 H), 1.35-1.32 (m, 2 H), 1.23-1.03 (m, 6 H), 0.98 (s, 9 H), 0.88 (br s, 1 H), 0.67 (d, *J* = 0.5 Hz, 1 H), 0.48 (s, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 59.0, 55.2, 45.4, 34.1, 30.6, 29.4, 28.8, 26.8, 26.4, 22.5, 12.4, -0.8; MS (EI) *m/z* (rel. intensity) 269 (M^+, 1), 253 (3), 231 (2), 213 (30), 149 (30), 81 (69), 67 (87), 57 (100); HRMS (EI) calc for $C_{15}H_{27}NOS$ 269.1813, found 269.1808.



142f

(*R*)-*N*-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-1-(3-methylbicyclo[1.1.0]but-1-yl)ethyl)-2-methylpropane-2-sulfinamide (142f). A solution of **122** (0.24 g, 0.90 mmol) in dry Et_2O (0.56 mL) was cooled to -78 ^{o}C with MeLi (0.56 mL, 0.90 mmol, c = 1.6 M in Et_2O) and allowed to warm up to -50 ^{o}C over 1 h. The reaction mixture was cooled to -78 ^{o}C, treated with *t*-BuLi (0.55 mL, 0.90 mmol, c = 1.6 M in pentane), stirred for 15 min and distilled TMEDA (0.27 mL, 1.8 mmol) was added, the mixture was stirred for additional 15 min and a solution of imine **141e**[188] (0.10 g, 0.36 mmol) in Et_2O (0.40 mL) was added *via* syringe over 20 min. The mixture was stirred -78 ^{o}C for 11 h, warmed up to rt, stirred for 12 h and quenched sat. NH_4Cl, and extracted (3 x 10 mL) with EtOAc. The comined organic layes were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:1) afforded **142f** (0.061 g, 50%) as a colorless oil: $[\alpha]_D$ +48.0 (c 1.0, $CHCl_3$); IR (ATR) 2924, 2883,

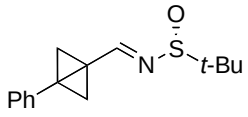
1470, 1461, 1360, 1252 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.97 (d, *J* = 6.5 Hz, 1 H), 3.92 (dd, *J* = 9.6, 4.0 Hz, 1 H), 3.79 (dt, *J* = 6.4, 4.6 Hz, 1 H), 3.66 (dd, *J* = 9.6, 4.9 Hz, 1 H), 1.50 (s, 3 H), 1.42 (d, *J* = 6.6 Hz, 1 H), 1.18 (d, *J* = 6.5 Hz, 1 H), 1.07 (s, 9 H), 0.96 (s, 9 H), 0.61 (s, 1 H), 0.55 (s, 1 H), 0.10 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 66.4, 55.5, 55.2, 32.5, 32.2, 26.0, 22.6, 18.4, 14.5, 12.1, 10.6, -5.2, -5.4; MS (EI) *m/z* (rel. intensity) 345 (M^+, 1), 288 (7), 225 (30), 73 (73), 57 (100); HRMS (EI) calc for $C_{17}H_{35}NO_2SiS$ 345.2158, found 345.2156.



142g

(*R*)-*N*-((*R*)-1-(Bicyclo[1.1.0]but-1-yl)-2-(*tert*-butyldimethylsilyloxy)ethyl)-2-methylpropane-2-sulfinamide (142g). A solution of **119** (0.22 g, 0.90 mmol) in dry Et_2O (0.55 mL) was cooled to -78 °C with MeLi (0.60 mL, 0.90 mmol, c = 1.5 M in Et_2O) and allowed to warm up to -50 °C over 1 h. The reaction mixture was cooled to -78 °C, treated with *t*-BuLi (0.60 mL, 0.90 mmol, c = 1.5 M in pentane), stirred for 15 min and distilled TMEDA (0.27 mL, 1.8 mmol) was added, the mixture was stirred for additional 15 min and a solution of imine **141e**[188] (0.10 g, 0.36 mmol) in Et_2O (0.30 mL) was added *via* syringe over 20 min. The mixture was stirred -78 °C for 10 h, warmed up to rt, stirred for 11 h and quenched sat. NH_4Cl, and extracted (3 x 10 mL) with EtOAc. The comined organic layes were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:1) afforded **142g** (0.073 g, 61%) as a colorless oil: $[\alpha]_D$ +70.4 (c 1.0, $CHCl_3$); IR (ATR) 2950, 2926, 1470, 1360, 1252 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 3.92 (d, *J* = 4.3 Hz, 1 H), 3.86 (dd, *J* = 9.7, 4.2 Hz, 1 H), 3.80 (dt, *J*

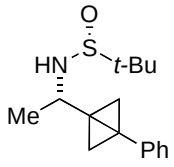
= 10.2, 4.7 Hz, 1 H), 3.61 (dd, *J* = 6.2, 3.6 Hz, 1 H), 1.67 (dd, *J* = 6.2, 2.7 Hz, 1 H), 1.49 (br s, 1 H), 1.42 (dd, *J* = 6.2, 2.8 Hz, 1 H), 1.05 (s, 9 H), 0.95 (s, 9 H), 0.59 (s, 1 H), 0.58 (s, 1 H), 0.08 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 66.3, 55.1, 54.9, 31.1, 30.3, 25.9, 22.5, 18.3, 11.2, 0.9, -5.3, -5.5; MS (EI) *m/z* (rel. intensity) 306 (6), 259 (3), 178 (9), 155 (7), 91 (100); HRMS (ESI) calc for $C_{16}H_{33}NO_2NaSiS$ (M+Na) 354.1899, found 354.1926



144

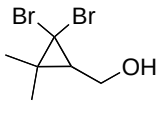
(*R*)-2-Methyl-*N*-((3-phenylbicyclo[1.1.0]but-1-yl)methylene)propane-2-sulfinamide (144). A solution of **121a** (2.0 g, 5.4 mmol) in dry Et_2O (5.0 mL) was cooled to -78 ^oC, treated with a solution of MeLi (3.6 mL, 5.4 mmol, 1.5 M in Et_2O). After warming up to -50 ^oC over 1 h, the mixture was coled to -78 ^oC, treated with *t*-BuLi (3.4 mL, 5.4 mmol, c = 1.6 M in pentane), stirred for 10 min and dry THF (20 mL) was added. The mixture was stirred for 5 min and neat DMF (0.84 mL, 11 mmol) was added in one portion. The mixture was stirred for 10 min, warmed up to rt, quenched with sat. NH_4Cl, extracted (3 x 10 mL) with Et_2O and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. The crude oil was dissoled in THF (10 mL), (*R*)-2-methylpropane-2-sulfinamide (0.33 g, 2.7 mmol) and Ti(O*i*-Pr)$_4$ (1.6 mL, 5.4 mmol) were added and the mixture was heated under reflux for 4.5 h. The solvent was removed in vacuo and the crude oil was purified by chromatography on SiO_2 (hexanes/EtOAc, 2:1) to afford **144** (0.37 g, 52%) as a light yellow oil: IR (neat) 2958, 1581, 1448, 1362, 1183 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (s, 1 H), 7.24-7.18 (m, 5 H), 3.05, 2.98 (AB_2, *J* = 6.5, 2.3 Hz, 2 H), 1.85 (d, *J* = 2.3 Hz, 1 H), 1.77 (d, *J* = 2.2 Hz, 1 H), 0.90 (s, 9 H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 164.6, 133.0, 128.5, 126.9, 125.9, 56.2, 37.0, 36.7, 35.7, 30.6, 21.7; MS (EI) *m/z* (rel. intensity) 261 (M^+, 2), 245 (1), 205 (60), 188 (20), 156 (100), 141 (54), 128 (85), 115 (49), 102 (34); HRMS (EI) calc for $C_{15}H_{19}NO_2$ 261.1187, found 261.1189.



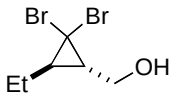
145

(*R*)-2-Methyl-*N*-((*S*)-1-(3-phenylbicyclo[1.1.0]but-1-yl)ethyl)propane-2-sulfinamide (145). A solution of imine **144** (0.070 g, 0.27 mmol) in dry CH_2Cl_2 (1.6 mL) was cooled to -50 ^oC, treated dropwise over 5 min with a solution of MeMgBr (0.18 mL, 0.57 mmol, c = 3.0 M in Et_2O). The reaction mixture was stirred at -50 ^oC, for 6 h, warmed up tor rt, and sirred for 12 h. The mixture was cooled to 0 ^oC, quenched with sat. NH_4Cl, extracted (3 x 5 mL) with EtOAc and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 2:1) afforded **145** (0.057 g, 77%) as a colorless oil: IR (ATR) 2976, 1712, 1448, 1133 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30-7.22 (m, 4 H), 7.17-7.13 (m, 1 H), 3.83 (quintet, *J* = 6.9 Hz, 1 H), 2.4 (d, *J* = 6.6 Hz, 1 H), 2.26, 2.22 (AB, *J* = 6.7 Hz, 2 H), 1.16-1.13 (m, 13 H), 1.02 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.5, 128.4, 125.4, 125.1, 55.6, 51.5, 32.4, 29.8, 27.5, 22.5, 20.8, 18.5.



147a

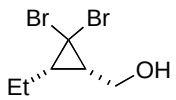
(2,2-Dibromo-3,3-dimethylcyclopropyl)methanol (147a). 3-Methyl-2-buten-1-ol (20 g, 232 mmol), DHP (29 g, 340 mmol), PPTS (5.8 g, 23 mmol) in CH_2Cl_2 (240 mL) were stirred at rt for 10 h. The solvent was removed and the crude material was dissolved in Et_2O, washed with water, sat. $NaHCO_3$, water, brine, dried, and concentrated. This material was dissolved in CH_2Cl_2 (100 mL), treated with NaOH (240 mL, 50% aq), cooled to 0 ^oC, treated with cetrimide (0.85 g, 2.3 mmol) and bromoform (102 mL, 293 mmol) was added slowly. The mixture was stirred at rt for 12 h, diluted with water, extracted (3x500 mL) with pentane and the combined organic layers were washed with water, dried ($MgSO_4$), and concentrated. The crude oil was dissolved in MeOH (300 mL) treated with TSA (4.0 g, 23.2 mmol) and stirred at rt for 1 h. Methanol was removed to ca. 100 mL total volume and ether (ca. 300 mL) was added. The mixture was washed with water (3x), sat. $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1 to 1:1) afforded **147a** (30 g, 51%) as a light brown oil: IR (neat) 3354, 2991, 2957, 2929, 1742, 1457, 1374, 1238 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.81-3.7 (m, 2 H), 2.61 (br s, 1 H), 1.67-1.61 (m, 1 H), 1.45 (s, 3 H), 1.29 (s, 3 H);^{13}C NMR (125 MHz, $CDCl_3$) δ 62.0, 44.4, 40.4, 29.0, 27.3, 19.5; MS (EI) *m/z* (rel. intensity) 256 (M^+, 2), 241 (13), 227 (6), 207 (2), 161 (10), 79 (69), 69 (77), 57 (100); HRMS (EI) calc for $C_6H_9Br_2$ [M-OH]$^+$ 238.9071, found 238.9064.



147b

((1*S,3*R**)-2,2-Dibromo-3-ethylcyclopropyl)methanol (147b).** A solution of *E*-2-penen-1-ol (10 g, 116 mmol) in dry DMF (24 mL) was treated with imidazole (12 g, 174 mmol), and TBSCl (18 g, 122 mmol). After stirring overnight at rt (12 h), the mixture was quenched with sat. NH_4Cl

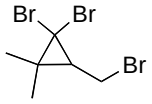
(100 ml), diluted with water, and extracted with Et_2O. The combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. The crude mixture was dissolved in pentane (50 mL), treated with KO*t*-Bu (26 g, 232 mmol), cooled to 0 ^oC, and a solution of bromoform (20 mL, 232 mmol) in pentane (50 mL) was added over 30 min. After warming up to rt, the mixture was stirred overnight (10 h), quenched with water, extracted with Et_2O, and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. The residual brown oil was taken up in THF (22 mL), cooled to 0 ^oC, treated with TBAF (130 mL, 0.13 mol, c = 1.0 M in THF), stirred for 1 h, quenched with sat NH_4Cl, and extracted with Et_2O. The organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **147b** (17 g, 58%) as a colorless oil.



147c

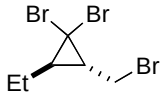
((1*S,3*S**)-2,2-Dibromo-3-ethylcyclopropyl)methanol (147c).** A solution of *Z*-2-penen-1-ol (10 g, 0.12 mol) in dry DMF (24 mL) was treated with imidazole (12 g, 0.17 mol) and TBSCl (18 g, 0.12 mol). After stirring overnight (12 h) at rt, the mixture was quenched with sat. NH_4Cl (100 mL), diluted with water, and extracted with Et_2O. The combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. The crude mixture was dissolved in pentane (50 mL), treated with KO*t*-Bu (26 g, 0.23 mol), cooled to 0 ^oC, and a solution of bromoform (20 mL, 0.23 mol) in pentane (50 mL) was added over 30 min. After warming up to rt, the mixture was stirred overnight (10 h), quenched with water, extracted with Et_2O, and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. The brown oil was then taken up in THF (22 mL), cooled to 0 ^oC, treated with TBAF (130 mL, 0.13

mol, c = 1.0 M in THF), stirred for 1 h, quenched with sat. NH_4Cl, and extracted with Et_2O. The organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **147b** (14 g, 45%) as a colorless oil: IR (ATR) 3332, 2963, 2872, 1718, 1456, 1375 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.74 (ABX, *J* = 12.0, 6.5 Hz, 1 H), 3.70 (ABX, *J* = 12.0, 8.1 Hz, 1 H), 2.24 (br s, 1 H), 1.94 (ddd, *J* = 14.5, 8.0, 6.5 Hz, 1 H)), 1.67 (dt, *J* = 11.0, 6.3 Hz, 1 H), 1.60-1.38 (m, 2 H), 1.07 (t, *J* = 7.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.0, 35.8, 34.7, 33.9, 20.7, 12.9; MS (EI) *m/z* (rel. intensity) 258 (M^+, 1), 240 (13), 214 (20), 199 (16), 135 (100); HRMS (EI) calc for $C_6H_{10}OBr_2$ 255.9098, found 255.9110.



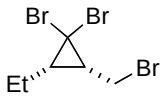
148a

1,1-Dibromo-3-(bromomethyl)-2,2-dimethylcyclopropane (148a). A solution of Ph_3P (15 g, 58 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C, treated with Br_2 (3.0 mL, 58 mmol) and after 10 min, solid imidazole (5.3 g, 77 mmol) was added in one portion. The reaction mixture was stirred for 5 min, neat **147a** (10 g, 39 mmol) was added and the reaction was contunued for 1 h. The mixture was poured into water, the layers were separated and the organic layer was washed with water (3x), brine, dried ($MgSO_4$), and concentrated. The white solid was suspended in pentane, filtered, washed with excess of pentane, and concentrated. Purification by chromatography on SiO_2 (hexanes) afforded **148a** (7.5 g, 60%) as a colorless oil: IR (neat) 2991, 2961, 2928, 1451, 1375, 1215, 1153 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.56 (t, *J* = 7.7 Hz, 1 H), 3.36 (t, *J* = 8.3 Hz, 1 H), 1.79 (t, *J* = 6.6 Hz, 1 H), 1.45 (s, 3 H), 1.30 (s, 3 H).



148b

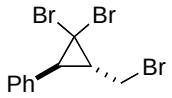
(2*S,3*R**)-1,1-Dibromo-2-(bromomethyl)-3-ethylcyclopropane (148b).** A solution of PPh_3 (9.2 g, 17 mmol) in dry CH_2Cl_2 (20 mL) was cooled to 0 ^oC, treated with Br_2 (1.8 mL, 17 mmol) and stirred for 10 min. Solid imidazole (3.2 g, 47 mmol) was added, the mixture was stirred for 10 min and a solution of **147b** (6.0 g, 23 mmol) in CH_2Cl_2 (5 mL) was added. The reaction mixture was stirred for 30 min, poured into dry pentane (300 mL), filtered through a pad of SiO_2 (washed with hexane), and the solvent was removed in vacuo. Product was obtained after purification by chromatography on SiO_2 (hexanes) to afford **148b** (3.2 g, 87%) as a colorless oil: IR (neat) 2965, 2931, 2874, 1457, 1439, 1378, 1218, 1180, 1143 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.55 (dd, *J* = 10.3, 7.9 Hz, 1 H), 3.46 (dd, *J* = 9.8, 8.5 Hz, 1 H), 1.72-1.60 (m, 2 H), 1.51 (app. septet, *J* = 7.2 Hz, 1 H), 1.32 (dd, *J* = 14.5, 7.3 Hz, 1 H), 1.10 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.5, 37.7, 36.6, 34.0, 25.6, 12.4; MS (EI) *m/z* (rel. intensity) 320 (M^+, 82), 280 (95), 239 (93), 197 (100), 159 (55), 133 (78); HRMS (EI) calc for $C_6H_9Br_3$ 317.8254, found 317.8257.



148c

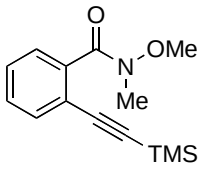
(2*S,3*S**)-1,1-Dibromo-2-(bromomethyl)-3-ethylcyclopropane (148c).** A solution of PPh_3 (4.6 g, 17 mmol) in dry CH_2Cl_2 (20 mL) was cooled to 0 ^oC, treated with Br_2 (0.90 mL, 17 mmol) and stirred for 10 min. Solid imidazole (1.6 g, 23 mmol) was added, the mixture was

stirred for 10 min and a solution of alcohol **147c** (3.0 g, 12 mmol) in CH_2Cl_2 (5 mL) was added. The reaction mixture was stirred for 30 min, poured in dry pentane (200 mL), filtered through a pad of SiO_2 (washed with hexane) and the solvent was removed in vacuo. Product was obtained after purification by chromatography on SiO_2 (hexanes) to afford **148c** (3.2 g, 87%) as a colorless oil: IR (neat) 2967, 2932, 2974, 1459, 1380, 1217, 1143 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.49 (dd, *J* = 10.8, 7.7 Hz, 1 H), 3.35 (dd, *J* = 10.8, 8.3 Hz, 1 H), 2.14 (td, *J* = 10.7, 7.9 Hz, 1 H), 1.75 (ddd, *J* = 14.6, 7.9 6.8 Hz, 1 H), 1.58-1.44 (m, 2 H), 1.13 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.4, 34.7, 34.6, 29.6, 20.2, 12.8; MS (EI) *m/z* (rel. intensity) 320 (M^+, 20), 278 (100), 199 (10), 161 (97), 133 (38); HRMS (EI) calc for $C_6H_9Br_3$ 317.8354, found 317.8261.



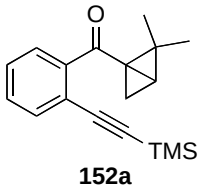
150

((1*S,3*S**)-2,2-Dibromo-3-(bromomethyl)cyclopropyl)benzene (150).**[471] A solution of cinnamyl bromide (5.0 g, 25 mmol), cetrimide (0.92 g, 2.5 mmol) and 50% aq NaOH (30 mL) was cooled to 0 ^oC, treated with bromoform (6.7 mL, 76 mmol) and vigorously stirred at rt for 24 h. The mixture was diluted with water, extracted (3x20 mL) with Et_2O and the combined organic layers were dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/Et_2O 10:0 to 10:1) gave **150** (3.7 g, 39%) as a light-yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.50-7.38 (m, 3 H), 7.36-7.30 (m, 2 H), 3.80-3.63 (m, 2 H), 2.77 (d, *J* = 8.1 Hz, 1 H), 2.42 (q, *J* = 7.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.9, 128.6, 128.4, 127.9, 43.1, 36.7, 35.7, 33.4.



151

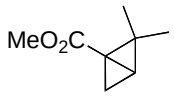
***N*-Methoxy-*N*-methyl-2-((trimethylsilyl)ethynyl)benzamide (151)**.[472] A solution of 2-iodo-*N*-methoxy-*N*-methylbenzamide[473] (4.5 g, 16 mmol), CuI (0.29 g, 1.5 mmol), $Pd(PPh_3)_4$ (0.89 g, 0.77 mmol) in *i*-Pr_2NH (50 mL) was cooled to 0 °C, treated with TMSCCH (2.6 mL, 19 mmol) and stirred at this temperature for 3 h. The mixture was quenched with sat. NH_4Cl, extracted with Et_2O and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purifiaction by chromatography on SiO_2 (hexanes/EtOAc, 1:1) afforded **151** (1.8, 44%) as a colorless oil: IR (neat) 3063, 2960, 2900, 2360, 2159, 1654, 1596, 1458, 1416 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49-7.46 (m, 2 H), 7.33-7.32 (m, 3 H), 3.75 (br s, 1 H), 3.48 (br s, 2 H), 3.29 (br s, 3 H), 0.21 (s, 9 H); MS (EI) *m/z* (rel. intensity) 261 (M^+, 4), 246 (2), 201 (100), 143 (10); HRMS (EI) calc for $C_{14}H_{19}NO_2Si$ 261.1185, found 261.1180.



152a

(2,2-Dimethylbicyclo[1.1.0]but-1-yl)(2-((trimethylsilyl)ethynyl)phenyl)methanone (152a). A solution of 3,3-dibromo-2-(bromomethyl)-1,1-dimethylcyclopropane (1.5 g, 4.6 mmol) in dry Et_2O (9.2 mL) was cooled to -78 °C, treated with a solution of MeLi (3.1 mL, 4.6 mmol, c = 1.5 M in Et_2O) and after 1 h at -78 °C, with a solution of *t*-BuLi (2.9 mL, 4.6 mmol, c = 1.6 M in pentane). The reaction mixture was stirred at -78 °C for 1 h and a solution of **151**[472] (0.40 g, 1.5

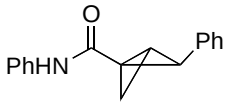
mmol) in THF (10 mL) was added in one portion. The mixture was stirred at -78 °C for 10 min, quenched with sat. NH_4Cl, warmed up to rt, diluted with water and extracted with Et_2O. The combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **152a** (0.15 g, 35%) as a colorless oil: IR (neat) 2961, 2925, 2158, 1651, 1475, 1442, 1389, 1249 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50-7.45 (m, 1 H), 7.37-7.30 (m, 3 H), 2.56 (dd, *J* = 2.9, 4.0 Hz, 1 H), 2.40 (t, *J* = 3.8 Hz, 1 H), 1.96 (t, *J* = 3.1 Hz, 1 H), 1.09 (s, 3 H), 1.05 (s, 3 H), 022 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 144.0, 133.0, 129.3, 128.2, 126.9, 120.7, 102.8, 98.9, 52.8, 36.6, 35.4, 28.3, 22.8, 15.2, -0.2; MS (EI) *m/z* (rel. intensity) 282 (M^+, 4), 267 (13), 201 (100), 149 (70), 73 (73); HRMS (EI) calc for $C_{18}H_{22}OSi$ 282.1440, found 282.1431.



152b

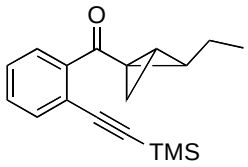
Methyl 2,2-dimethylbicyclo[1.1.0]butane-1-carboxylate (152b). A solution of 3,3-dibromo-2-(bromomethyl)-1,1-dimethylcyclopropane **148a** (1.0 g, 3.1 mmol) in dry Et_2O (5.0 mL) was cooled to -78 °C, treated with a solution of MeLi (1.9 mL, 3.1 mmol, c = 1.6 M in Et_2O) and after 1 h at -78 °C, with a solution of *t*-BuLi (2.1 mL, 3.1 mmol, c = 1.5 M in pentane). The reaction mixture was stirred at -78 °C for 1 h and methyl chloroformate (0.48 mL, 6.2 mmol) was added. The mixture was warmed up to rt, quenched with sat. NH_4Cl, extracted (3x) with Et_2O. The combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 10:1 to 4:1) afforded **152b** (0.21 g, 48%) as a colorless oil: IR (ATR) 2985, 2950, 1707, 1485, 1435, 1392, 1369, 1189 cm^{-1}; ^1H

NMR (500 MHz, $CDCl_3$) δ 3.65 (s, 3 H), 2.42 (d, *J* = 2.3 Hz, 1 H), 2.08 (app. t, *J* = 2.9 Hz, 1 H), 1.69 (s, 1 H), 1.34 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 51.3, 33.6, 31.5, 28.7, 22.3, 17.6, 14.9; MS (EI) *m/z* (rel. intensity) HRMS (EI) calc for $C_8H_{12}O_2$ 140.0837, found 140.0831.



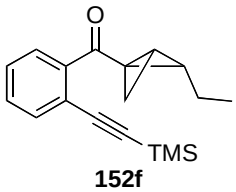
152d

(1*S,2*S**,3*R**)-*N*,2-Diphenylbicyclo[1.1.0]butane-1-carboxamide (152d).** A solution of **150** (1.0 g, 2.7 mmol) in Et_2O (20 mL) was cooled to -78 oC, treated with MeLi (0.090 mL, 2.7 mmol, 3.0 M in dimethoxymethane). After 1 h at -78 ^oC, a solution of *t*-BuLi (1.8 mL, 2.7 mmol, 1.5 M) was addded. After additional 1 h at this temperature, phenyl isocyanate (0.040 mL, 0.36 mmol) was added in one portion. The mixture was quenched with sat. NH_4Cl, diluted with water, extracted (3x10 mL) with EtOAc, and the combined organic layers were washed with water, brine, dried (MgSO4), and concentrated. Crystallization from Et_2O/pentane afforded **152d** (0.058 g, 65%) as a colorless solid: Mp. 124.1-125.0 ^oC (pentane/Et_2O); IR (ATR) 3295, 1646, 1526, 1439, 1243, 1155 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.27 (d, *J* = 7.7 Hz, 2 H), 7.03-6.95 (m, 5 H), 6.80-6.79 (m, 3 H), 6.26 (br s, 1 H), 2.49 (d, *J* = 3.1 Hz, 1 H), 2.32 (d, *J* = 1.5 Hz, 1 H), 2.00 (s, 1 H), 0.84 (s, 1 H), ^{13}C NMR (75 MHz, C_6D_6) 166.9, 138.9, 134.6, 129.0 (2), 127.9, 127.6, 123.6, 119.0, 49.6, 30.3, 19.1, 17.4; MS (EI) *m/z* (rel. intensity) 249 (M^+, 35), 196 (16), 157 (15), 129 (100), 86 (94); HRMS (EI) calc for $C_{17}H_{15}NO$ 249.1154, found 249.1150.



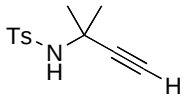
152e

((1*S,2*R**,3*R**)-2-Ethylbicyclo[1.1.0]but-1-yl)(2-((trimethylsilyl)ethynyl)phenyl)methanone (152e).** A solution of **148b** (1.0 g, 3.1 mmol) in Et_2O (10 ml) was cooled to -78 ^oC, treated with MeLi (1.9 mL, 3.1 mmol, c = 1.6 M in Et_2O) and after 1 h at -78 ^oC, with a solution of *t*-BuLi (1.8 mL, 3.1 mmol, c = 1.7 M in pentane). After additional 1 h, a solution of Weinreb amide **151** (0.41 g, 1.6 mmol) in THF (10 mL) was added. The mixture was stirred for 5 min, quenched at -78 ^oC with sat. NH_4Cl, warmed up to rt, extracted with Et_2O and the organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **152e** (0.30 g, 68%) as a colorless oil: IR (neat) 2962, 2876, 2158, 1711, 1651, 1463, 1442, 1384, 1250, 1212 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.39-7.33 (m, 1 H), 7.31-7.25 (m, 1 H), 6.90-6.81 (m, 2 H), 2.19 (dd, *J* = 3.6, 1.5 Hz, 1 H), 2.16 (dd, *J* = 5.6, 2.9 Hz, 1 H), 1.87-1.74 (m, 1 H), 1.43 (ddd, *J* = 10.1, 4.9, 2.3 Hz, 1 H), 1.38-1.24 (m, 1 H), 1.07 (dd, *J* = 2.6, 1.6 Hz, 1 H), 0.92 (t, *J* = 7.4 Hz, 3.H), 0.19 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 200.4, 144.5, 133.0, 129.5, 128.1, 127.5, 121.4, 103.9, 99.0, 54.0, 36.1, 26.9, 22.3, 22.1, 14.2, -0.1; MS (EI) *m/z* (rel. intensity) 282 (M^+, 13), 267 (32), 253 (100), 225 (26), 201 (60), 193 (30), 179 (33), 165 (34), 143 (44); HRMS (EI) calc for $C_{18}H_{22}OSi$ 282.1440, found 282.1440.



152f

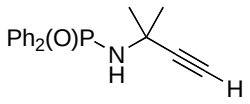
((1*S,2*S**,3*R**)-2-Ethylbicyclo[1.1.0]but-1-yl)(2-((trimethylsilyl)ethynyl)phenyl)methanone (152f).** A solution of **148c** (1.0 g, 3.1 mmol) in Et_2O (10 mL) was cooled to -78 ^oC, treated with MeLi (1.9 mL, 3.1 mmol, c = 1.6 M in Et_2O) and after 1 h at -78 ^oC, with a solution of *t*-BuLi (1.8 mL, 3.1 mmol). After additional 1 h, a solution of Weinreb amide **151** (0.41 g, 1.6 mmol) in THF (10 ml) was added. The mixture was stirred for 5 min, quenched at -78 ^oC with sat. NH_4Cl, warmed up to rt, extracted with Et_2O and the organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **152f** (0.17 g, 39%) as a colorless oil: IR (neat) 2962, 2900, 2874, 2159, 1655, 1593, 1476, 1443, 1343, 1250, 1202 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.42-7.36 (m, 1 H), 7.27-7.20 (m, 1 H), 6.88-6.79 (m, 2 H), 3.02 (app. septet, *J* = 3.0 Hz, 1 H), 2.56 (td, *J* = 3.8, 2.6 Hz, 1 H), 2.03 (q, *J* = 3.7 Hz, 1 H), 1.87 (t, *J* = 3.1 Hz, 1 H), 1.28 (dqd, *J* = 14.4, 7.3, 7.1 Hz, 1 H), 1.14 (dqd, *J* = 14.7, 7.3, 7.0 Hz, 1 H), 0.79 (t, *J* = 7.4 Hz, 3 H), 0.20 (s, 9 H); ^{13}C NMR (150 MHz, C_6D_6) δ 200.2 143.1, 133.1, 129.4, 128.4, 128.3, 128.2, 121.6, 104.0, 99.1, 54.7, 36.7, 28.1, 25.6, 16.8, 13.4, -0.2; MS (EI) *m/z* (rel. intensity) 282 (M^+, 8), 267 (15), 253 (32), 209 (9), 201 (39), 84 (61), 73 (100); HRMS (EI) calc for $C_{18}H_{22}OSi$ 282.1440, found 282.1444.



153a

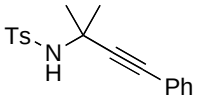
2-Methyl-*N*-tosylbut-3-yn-2-amine (153a).[474] *p*-Toluenesulfonyl chloride (0.86 g, 4.5 mmol) was dissolved in CH_2Cl_2 (20 mL), followed by 2-methylbut-3-yn-2-amine (0.75 g, 9.0 mmol) and Et_3N (2.5 mL, 18 mmol). The reaction mixture was stirred at rt for 16 h, quenched with sat. NH_4Cl, and extracted (3x) with CH_2Cl_2. The combined organic layers were washed with water,

brine, dried ($MgSO_4$) and evaporated. The product was obtained by precipitation from CH_2Cl_2 with an excess of hexanes to afford **153a** (0.83 g, 77%) as a colorless solid: Mp. 107.6-110.0 ^oC (CH_2Cl_2/hexanes).



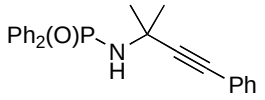
153b

2-Methyl-*N*-diphenylphosphinylbut-3-yn-2-amine (153b). Diphenylphosphinyl chloride (1.1 g, 4.5 mmol) was dissolved in CH_2Cl_2 (20 mL), followed by 2-methylbut-3-yn-2-amine (0.75 g, 9.0 mmol) and Et_3N (2.5 mL, 18 mmol). The reaction mixture was stirred at rt for 16 h, quenched with sat. NH_4Cl, and extracted (3x) with CH_2Cl_2. The combined organic layers were washed with water, brine, dried ($MgSO_4$) and evaporated. The product was obtained by precipitation from CH_2Cl_2 with an excess of hexanes to afford **153b** (0.35 g, 35%) as a colorless solid: Mp. 151.1-152.6 ^oC (CH_2Cl_2/hexanes); IR (KBr) 3300, 3161, 2982, 2360, 1591, 1438, 1381, 1195 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.94-7.88 (m, 4 H), 7.46-7.44 (m, 6 H), 3.18 (d, J = 5.7 Hz, 1 H), 2.25 (s, 1 H), 1.60 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.82, 134.51, 134.00, 132.80, 132.27, 131.60, 131.47, 131.32, 131.27, 131.04, 130.91, 130.47, 128.03, 127.70, 127.53, 88.22, 88.15, 70.19, 48.58, 48.56, 32.00, 31.95, 130.91; MS (EI) *m/z* (rel. intensity) 283 (M^+, 45), 268 (54), 216 (8), 201 (100), 187 (13); HRMS (EI) calc for $C_{17}H_{18}NOP$ 283.1126, found 283.1123.



154a

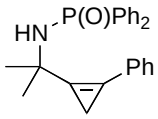
2-Methyl-4-phenyl-*N*-tosylbut-3-yn-2-amine (154a). A suspension of $Pd(PPh_3)_4$ (0.069 g, 0.06 mmol) and CuI (0.025 g, 0.013 mmol) in *i*-Pr_2NH was cooled to 0 ^oC, treated with PhI (0.071 mL, 0.63 mmol) and a solution of **153a** (0.15 g, 0.63 mmol) in a mixture of *i*-Pr_2NH (5.0 mL) and THF (5.0 mL) was added. The reaction mixture was stirred at 0 ^oC for 50 min, quenched with sat. NH_4Cl, and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried ($MgSO_4$), and evaporated. The remaining solid was purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to afford **154a** (0.16 g, 79%) as a colorless solid: IR (neat) 1324 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.7 Hz, 2 H), 7.27-7.02 (m, 7 H), 5.57 (s, 1 H), 2.24 (s, 3 H), 1.65 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 138.5, 131.5, 129.2, 128.0, 127.8, 127.5, 122.3, 90.4, 83.2, 50.3, 31.0, 21.3; MS (EI) *m/z* (rel. intensity) 313 (M^+, 16), 298 (17), 257 (29), 250 (54), 142 (57), 91 (100); HRMS (EI) calc for $C_{18}H_{19}NO_2S$ 313.1137, found 313.1132.



154b

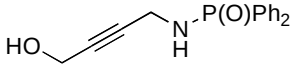
2-Methyl-4-phenyl-*N*-diphenylphosphinylbut-3-yn-2-amine (154b). **A** suspension of $Pd(PPh_3)_4$ (0.020 g, 0.018 mmol) and CuI (0.0070 g, 0.035 mmol) in *i*-Pr_2NH (5.0 mL) was cooled to 0 ^oC, and treated with PhI (0.040 mL, 0.35 mmol) and a solution of amide **153b** (0.10 g, 0.35 mmol) in THF (2.0 mL). The reaction mixture was stirred at 0 ^oC for 1 h, quenched with sat. NH_4Cl, and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried ($MgSO_4$), and evaporated. The remaining solid was purified by chromatography on SiO_2 (hexanes/EtOAc, 1:4) to afford **154b** (0.10 g, 81%) as a colorless solid: Mp. 147.9-150.0

°C (CH_2Cl_2/hexanes); IR (KBr) 3122, 1439, 1203, 1188, 1119, 1108 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98-7.91 (m, 4 H), 7.34-7.41 (m, 6 H), 7.24-7.18 (m, 5 H), 3.25 (d, *J* = 6.8 Hz, 1 H), 1.71 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.05, 133.36, 132.97, 131.84, 131.48, 128.52, 128.52, 128.39, 128.22, 127.91, 126.60, 122.73, 93.74, 93.67, 82.67, 49.56, 32.79; MS (EI) *m/z* (rel. intensity) 359 (M^+, 4), 344 (87), 216 (17), 201 (100); HRMS (EI) calc for $C_{23}H_{22}NOP$ 359.1439, found 359.1425.



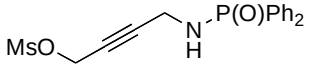
155

***N*-(2-(2-Phenylcycloprop-1-enyl)propan-2-yl)-*P,P*-diphenylphosphinamide (155).** According to the General Protocol E, imine **87** (0.50 g, 1.9 mmol), 1,2,3-tribromo-1-phenylcylopropane (0.83 g, 2.3 mmoL) and *n*-BuLi (3.2 mL, 5.1 mmol, c = 1.6 M in hexane) in THF (20 mL) afforded **155** (0.34 g, 47%) as a colorless oil: IR (neat) 3057, 2972, 2865, 1438, 1191, 1121 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92-7.85 (m, 4 H), 7.50-7.26 (m, 11 H), 3.27 (d, *J* = 6.1 Hz, 1 H), 1.66 (d, *J* = 1.1 Hz, 6 H), 1.20 (d, *J* = 1.1 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.29, 133.58, 131.82, 131.69, 131.46, 131.43, 129.78, 129,14, 128.60, 128.37, 128.28, 128.21, 128.05, 119.02, 118.93, 108.10, 53.36, 44.96, 29.56, 29.51, 7.38; MS (EI) *m/z* (rel. intensity) 373 (M^+, 86), 318 (15), 258 (48), 201 (100); HRMS (EI) calc for $C_{24}H_{24}NOP$ 373.1596, found 373.1595.



157

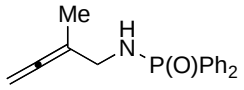
***N*-(4-Hydroxybut-2-ynyl)-*P,P*-diphenylphosphinamide (157).** Amide **91** (3.9 g, 15 mmol) was dissolved in THF (150 mL), cooled to -78 ^{o}C and treated with *n*-BuLi (27 mL, 43 mmol, c = 1.6 M in hexanes). The reaction mixture was stirred at -78 ^{o}C for 1 h and solid paraformaldehyde (0.90 g, 30 mmol) was added in one portion. The mixture was allowed to warm up to rt, stirred for 17 h, quenched with sat. NH_4Cl, and extracted (3x) with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc/MeOH, 1:8:1) afforded **157** (3.9, 90%) that was precipitated from CH_2Cl_2 with an excess of hexanes: Mp. 150.0-152.1 ^{o}C (hexanes/CH_2Cl_2); IR (KBr) 3215, 1440, 1186 cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.14, 132.08, 132.01, 130.41, 128.62, 128.47, 82.61, 82.57, 82.50, 50.50, 30.51; MS (EI) *m/z* (rel. intensity) 285 (M^+, 7), 284 (13), 267 (32), 230 (10), 201 (100); HRMS (EI) calc for $C_{16}H_{15}NO_2P$ (M-H) 284.0840, found 284.0839.



158

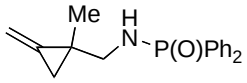
4-*P,P*-Diphenylphosphinamidobut-2-ynyl methanesulfonate (158). Alcohol **157** (0.14 g, 0.49 mmol) was dissolved in CH_2Cl_2 (50 mL), followed by Et_3N (0.14 mL, 0.98 mmol) and MsCl (0.057 mL, 0.74 mmol). The reaction mixture was stirred at rt for 15 min, quenched with sat NH_4Cl, and extracted (3 x) with CH_2Cl_2. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc/MeOH, 1:8:1) afforded **158** (0.13 g, 73%) as a light brown solid: IR (neat) 1439, 1355, 1174 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94-7.86 (m, 4 H), 7.57-7.44 (m, 6 H), 4.82 (t, *J* = 1.9 Hz, 2 H), 3.98-3.96 (m, 2 H), 3.32 (bs, 1 H), 3.09 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.34, 132.50, 132.27, 132.24, 132.12, 131.99, 131.88, 131.53, 131.22, 131.08, 130.15, 128.74,

128.57, 128.30, 128.13, 87.42, 87.30, 75.59, 57.66, 38.85, 30.31; MS (EI) *m/z* (rel. intensity) 364 (M^+, 7), 268 (41), 201 (100); HRMS (EI) calculated for $C_{17}H_{19}NO_4PS$ (M+H) 364.0772, found 364.0781.



159

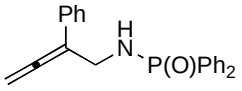
***N*-(2-Methylbuta-2,3-dienyl)-*P,P*-diphenylphosphinamide (159).** A suspension of CuBr·DMS (1.1 g, 5.5 mmol) in THF (50 mL) was cooled to 0 ^oC and treated with MeMgBr (3.7 mL, 11 mmol, c = 3.0 M in Et_2O). The reaction mixture was stirred at 0 ^oC for 20 min and solid amide **158** (0.50 g, 1.4 mmol) was added. Stirring was continued for 10 min and the reaction was quenched with sat NH_4Cl, and extracted (3 x) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **159** (0.33 g, 85%) as a colorless oil: IR (neat) 7.92-7.86 (m, 4 H), 7.48-7.42 (m, 6 H), 4.84-4.79 (m, 2 H), 3.47-3.40 (m, 2 H), 3.13-3.07 (m, 1 H), 1.68 (t, *J* = 3.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.09, 133.13, 132.09, 131.97, 131.78, 131.42, 128.56, 128.37, 98.48, 98.36, 42.43, 16.33; MS (EI) *m/z* (rel. intensity) 283 (M^+, 25), 269 (5), 230 (24), 216 (43), 201 (100); HRMS (EI) calc for $C_{17}H_{18}NOP$ 283.1126, found 283.1117.



160

***N*-((1-Methyl-2-methylenecyclopropyl)methyl)-*P,P*-diphenylphosphinamide (160).** Representative procedure: Amide **159** (0.039 g, 0.14 mmol) was dissolved in CH_2Cl_2 (2.0 mL), cooled

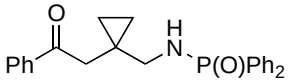
to 0 °C and treated with Me_2Zn (0.069 mL, 0.14 mmol). The reaction mixture was stirred at 0 °C for 1 h and transferred into a cold solution of CH_2I_2 (0.055 mL, 0.069 mmol) and Et_2Zn (0.042 g, 0.34 mmol) in CH_2Cl_2 (2.0 mL) and dimethoxyethane (0.036 mL). The reaction mixture was stirred at 0 °C for 6 h, quenched with sat. NH_4Cl and extracted (3x) with CH_2Cl_2. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **160** (0.024 g, 58%) as a colorless oil: IR (neat) 1438, 1181, 1123, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86-7.81 (m, 4 H), 7.43-7.37 (m, 6 H), 5.32 (s, 1 H), 5.27 (s, 1 H), 2.87-2.80 (m, 3 H), 1.19 (s, 3 H), 1.09-1.06 (m, 1 H), 0.60-0.55 (m 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.69, 133.19, 132.16, 132.03, 131.80, 128.57, 128.40, 103.12, 47.32, 20.94, 20.10, 15.24; MS (EI) *m/z* (rel. intensity) 297 (M^+, 35), 282 (33), 201 (100); HRMS (EI) calc for $C_{18}H_{20}NOP$ 297.1283, found 297.1278.



161

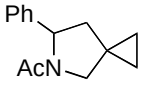
***N*-(2-Phenylbuta-2,3-dienyl)-*P,P*-diphenylphosphinamide (161).** A suspension of CuBr·DMS (0.23 g, 1.1 mmol) in THF (20 mL) was cooled to 0 °C and treated with PhMgCl (2.2 mL, 2.2 mmol, c = 1.0 M in THF). The reaction mixture was stirred at 0 °C for 20 min and solid amide **158** (0.10 g, 0.28 mmol) was added. Stirring was continued for 10 min and the reaction was quenched with sat NH_4Cl, and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **161** (0.078 g, 82%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 8.03-7.91 (m, 4 H), 7.58-7.50 (m, 7 H), 7.40-7.29 (m, 4 H), 5.47 (t, *J* = 3.3. Hz, 2 H),

4.10-4.07 (m, 2 H), 3.32-3.26 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.48, 133.78, 132.94, 132.07, 131.95, 131.85, 131.82, 131.22, 128.56, 128.49, 128.39, 127.77, 127.15, 126.20, 125.84, 105.08, 104.95, 81.16, 39.34; MS (EI) *m/z* (rel. intensity) 345 (M^+, 52), 269 (10), 230 (36), 201 (100); HRMS (EI) calc for $C_{22}H_{20}NOP$ 345.1283, found 345.1287.



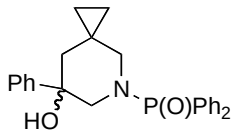
162

***N*-(1-(2-Oxo-2-phenylethyl)cyclopropylmethyl)-*P,P*-diphenylphosphinamide (162).** To a solution of **95** (0.16 g, 0.42 mmol) in dry THF (10 mL) was added OsO_4 (12 mg, 0.047 and $NaIO_4$ (0.45 g, 2.1 mmol). The reaction mixture was stirred for 4 h at rt, quenched with sat. NH_4Cl and extracted (3x) with EtOAc. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on deactivated SiO_2 (1:4, hexanes/EtOAc containing 1% v/v Et_3N) to afford **162** (0.13 g, 77%) as a colorless foam: IR (neat) 3201, 3058, 3003, 2922, 1686, 1596, 1580, 1438, 1448, 1353, 1310, 1277, 1211, 1186, 1123, 1110 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94-7.79 (m, 6 H), 7.49-7.26 (m, 9 H), 3.50 (b, 1 H), 3.20-18 (m, 2 H), 2.98-2.93 (m, 2 H), 0.58-0.50 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.66, 137.23, 133.41, 133.17, 132.09, 131.97, 131.71, 128.64, 128.54, 128.37, 128.10, 48.57, 43.62, 18.02, 11.45; MS (EI) *m/z* (rel. intensity) 389 (M+, 28), 371 (24), 284 (54), 218 (12), 201 (100), 172 (32); HRMS (EI) calc for $C_{24}H_{24}NO_2P$ 389.1545, found 389.1539.



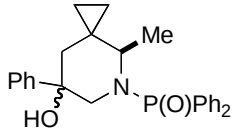
163

1-(6-Phenyl-5-aza-spiro[2.4]hept-5-yl)-ethanone (163). To a cooled (0 °C) solution of HCl (11 mL, 2.0 M in MeOH) was added a solution of **162** (99 mg, 0.26 mmol) in MeOH (1.0 mL). The reaction mixture was stirred for 1.5 h at 0 °C and concentrated. The residue was dissolved in MeOH (20 mL), treated with $NaBH_3CN$ (80 mg, 1.3 mmol), stirred for 48 h at rt and concentrated. The residue was dissolved in THF (5.0 mL) and DIPEA (5.0 mL) and treated with AcCl (0.10 g, 1.3 mmol). The reaction mixture was stirred for 4 h, quenched with sat. NH_4Cl and extracted (2x) with EtOAc. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on deactivated SiO_2 (EtOAc containing 1% v/v Et_3N) to afford **163** (48 mg, 87%) as a colorless oil: IR (neat) 3059, 3027, 2997, 2947, 2863, 1644, 1592, 1494, 1393, 1418, 1377, 1355, 1306, 1226, 1182, 1131, 1114 cm^{-1}; ^1H NMR (3.0:1 mixture of amide bond rotamers) major rotamer (300 MHz, $CDCl_3$) δ 7.37-7.17 (m, 6 H), 5.01 (dd, *J* = 8.0, 2.7 Hz, 1 H), 3.79 (d, *J* = 11.8 Hz, 1 H), 3.51 (d, *J* = 11.8 Hz, 1 H), 2.61 (dd, *J* = 12.4, 8.1 Hz, 1 H), 1.84 (s, 3 H), 1.66 (dd, *J* = 12.3, 2.6 Hz, 1 H), 0.66-0.32 (m, 4 H); minor rotamer (representative signals) δ 5.31 (dd, *J* = 8.2, 2.4 Hz, 1 H), 3.71 (d, *J* = 9.8 Hz, 1 H), 3.46 (d, *J* = 9.8 Hz, 1 H), 2.50 (dd, *J* = 12.5, 8.3 Hz, 1 H), 2.10 (s, 3 H); ^{13}C NMR major rotamer (75 MHz, $CDCl_3$) δ 170.3, 143.6, 128.8, 127.3, 125.7, 63.2, 54.9, 44.7, 22.4, 19.0, 14.1, 7.1; MS (EI) *m/z* (rel. intensity) 215 (M^+, 100), 172 (55), 158 (32), 145 (60), 129 (21); HRMS (EI) calc for $C_{14}H_{16}NO$ 214.1232, found 214.1236.



165a

5-(Diphenylphosphinoyl)-7-phenyl-5-azaspiro[2.5]octan-7-ol (165a). To a cooled (0 °C) solution of **95** (0.12 g, 0.31 mmol) in CH_2Cl_2 (5.0 mL) was added *m*-CPBA (0.23 g, 0.94 mmol, ~70 wt%). The reaction mixture was stirred for 3 h at rt, quenched with sat. NH_4Cl, and extracted (3 x) with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was dissolved in THF (5.0 mL), treated with HMPA (0.20 mL, 1.1 mmol) and NaH (0.026 g, 1.1 mmol) and heated at 70 ºC for 4 h, cooled to 0 ºC and quenched with sat. NH_4Cl. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on deactivated SiO_2 (hexanes/EtOAc, 1:4 containing 1% v/v Et_3N) to afford **165a** (0.069 g, 47%) as a colorless oil: IR (neat) 3357, 3057, 3027, 2995, 2914, 2847, 1601, 1591, 1495, 1488, 1439, 1391, 1377, 1349, 1315, 1286, 1244, 1220, 1198, 1177, 1121, 1105 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10-8.02 (m, 4 H), 7.67-7.32 (m, 11 H), 5.59 (s, 1 H), 3.54 (dd, *J* = 19.2, 13.7 Hz, 1 H), 3.41 (d, *J* = 14.7 Hz, 1 H), 3.48-3.34 (m, 1 H), 2.67 (d, *J* = 13.6 Hz, 1 H), 2.59 (dd, *J* = 13.4, 7.6 Hz, 1 H), 1.39 (d, *J* = 13.4 Hz, 1 H), 0.97-0.96 (m, 1 H), 0.82-0.75 (m, 1 H), 0.40-0.30 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.89, 132.74, 132.09, 131.40, 130.34, 129.6, 128.98, 128.90, 128.81, 128.73, 128.19, 127.01, 125.19, 71.38, 57.51, 54.11, 46.07, 15.88, 13.83, 8.30; MS (ESI) *m/z* (rel. intensity) 426 ($[M+Na]^+$, 100), 412 (12), 386 (3), 218 (10), 201 (2); HRMS (ESI) calc for $C_{25}H_{26}NO_2PNa$ (M+Na) 426.1599, found 426.1595.

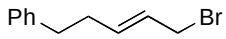


165b

5-(Diphenylphosphinoyl)-4-methyl-7-phenyl-5-azaspiro[2.5]octan-7-ol (165b). To a cooled (0 ºC) solution of **96** (0.15 g, 0.37 mmol) in CH_2Cl_2 (5.0 mL) was added *m*-CPBA (0.097 g, 0.56 mmol, ~70 wt%). The reaction mixture was warmed to rt, stirred for 6.5 h and quenched with sat. NH_4Cl. The aqueous layer was extracted (3x) with CH_2Cl_2 and the combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on deactivated SiO_2 (hexanes/EtOAc, 1:4 containing 1% v/v Et_3N) to afford **164b** (0.10 g, 64%) as an inseparable 1:1 mixture of distereoisomers. The mixture of epoxides (0.091 g, 0.22 mmol) was dissolved in dry THF (5.0 mL), treated with HMPA (0.19 mL, 1.1 mmol) and NaH (0.026 g, 1.1 mmol), heated at 70 ºC for 2.5 h, cooled to 0 ºC and quenched with sat. NH_4Cl. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were washed with water and brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (hexanes/EtOAc, 1:4 containing 1% v/v Et_3N) to afford **165b** (0.055 g, 57%) as a separable 1.3:1 mixture of diastereomers.

165b (major isomer), obtained as a colorless oil: IR (neat) 3288, 3059, 2974, 2920, 2851, 1738, 1591, 1495, 1483, 1463, 1338, 1374, 1337, 1310, 1253, 1183, 1121 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86-7.83 (m, 2 H), 7.87-7.68 (m, 2 H), 7.56-7.27 (m, 11 H), 3.66 (dd, *J* = 13.1, 9.6 Hz, 1 H), 3.38 (dd, *J* = 13.2, 3.9 Hz, 1 H), 2.94 (app. quintet *J* = 7.1 Hz, 1 H), 2.88 (b, 1 H), 2.24 (d, *J* = 13.7 Hz, 1 H), 1.82 (d, *J* = 13.7 Hz, 1 H), 1.25 (d, *J* = 7.2 Hz, 3 H), 0.40-0.31 (m, 3 H), 0.18-0.08 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.47, 132.91, 132.79, 132.59, 132.46, 131.92, 131.76, 131.08, 128.63, 128.48, 128.32, 128.03, 127.36, 126.39, 72.03, 71.93, 56.87, 51.37, 43.94, 20.69, 20.58, 15.57, 14.54, 9.64; MS (EI) *m/z* (rel. intensity) 417 (M^+, 24), 399 (43), 384 (30), 230 (7), 201 (100); HRMS (EI) calc for $C_{26}H_{28}NO_2P$ 417.1872, found 417.1858.

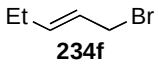
165b (minor isomer), obtained as a colorless oil: IR (neat) 3364, 3058, 3026, 2974, 2935, 1493, 1488, 1439, 1446, 1427, 1380, 1362, 1325, 1311, 1255, 1202, 1179, 1163, 1135, 1121, 1103 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.94-7.90 (m, 4 H), 7.56-7.28 (m, 11 H), 5.72 (s, 1 H), 3.49 (dd, *J* = 21.0, 14.5 Hz, 1 H), 3.10 (ddd, *J* = 14.4, 8.8, 1.7 Hz, 1 H), 2.68 (d, *J* = 14.0 Hz, 1 H), 2.59-2.49 (m, 1 H), 1.41 (d, *J* = 6.8 Hz, 3 H), 1.05 (bd, *J* = 14.0 Hz, 1 H), 0.91-0.84 (m, 1 H), 0.73-0.66 (m, 1 H), 0.25-0.10 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.20, 132.81, 132.69, 132.41, 132.29, 132.12, 131.98, 131.77, 130.53, 128.97, 128.81, 128.16, 126.96, 125.27, 71.34, 56.00, 51.33, 41.48, 18.93, 15.83, 15.45, 9.14; MS (EI) *m/z* (rel. intensity) 417 (M^+, 72), 399 (44), 334 (5), 298 (10), 258 (21), 230 (76), 201 (100), 186 (25); HRMS (EI) calc for $C_{26}H_{28}NO_2P$ 417.1872, found 417.1856.



234e

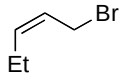
(*E*)-(5-Bromopent-3-enyl)benzene (234e). A solution of PPh_3 (2.4 g, 9.2 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C, treated with Br_2 (0.47 mL, 9.2 mmol) and after 10 min at this temperature, solid imidazole (0.84 g, 12 mmol) was added. The mixture was stirred for 5 min and neat (*E*)-5-phenylpent-2-en-1-ol[475] (1.0 g, 6.2 mmol, 94:6 mixture of diastereomers) was added. The mixture was stirred at 0 °C for 20 min, poured into pentane (100 mL), filtered through a short pad of silica, washed with pentane and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:0 to 20:1) afforded **234e** (0.97 g, 70%, 85:15 mixture of diastereomers) as a colorless oil: IR (ATR) 3023, 1659, 1601, 1493, 1452, 1202 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55-732 (m, 2 H), 7.24-7.7.19 (m, 3 H), 5.88-5.72 (m, 2 H), 3.96 (t, *J* = 8.6 Hz, 2 H), 2.73 (t, *J* =

8.2 Hz, 2 H), 2,45-2.38 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 135.4, 128.4, 128.3, 126.9, 125.9, 35.2, 33.8, 33.0.



234f

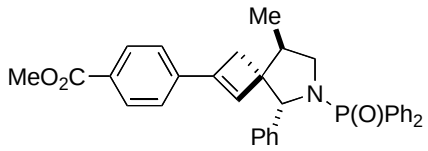
(*E*)-1-Bromopent-2-ene (234f). A solution of PPh_3 (9.1 g, 35 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 oC, treated with Br_2 (1.8 mL, 35 mmol) and after 10 min, solid imidazole (3.2 g, 46 mmol) was added. The reaction mixture was tirred at 0 ^{o}C for 10 min, (*E*)-pent-2-en-1-ol (2.0 g, 23 mmol) was added, the reaction was stirred for 30 min, poured into pentane (150 mL), filtered through a pad of SiO_2, washed with pentane and concentated to afford **234f** (2.1 g, 60%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (td, *J* = 15.3, 6.0 Hz, 1 H), 5.79 (td, *J* = 15.3, 7.2 Hz, 1 H), 3.95 (d, *J* = 7.2 Hz, 2 H), 2.11 (quintet, *J* = 6.9 Hz, 2 H), 1.02 (t, *J* = 7.2 Hz, 3 H). The crude bromide was used in the subsequent reactions.



234g

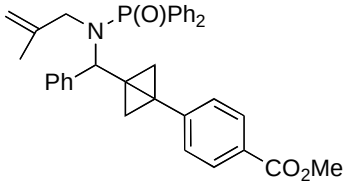
(*Z*)-1-Bromopent-2-ene (234g). A solution of PPh_3 (9.1 g, 35 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 oC, treated with Br_2 (1.8 mL, 35 mmol) and after 10 min, solid imidazole (3.2 g, 46 mmol) was added. The reaction mixture was tirred at 0 ^{o}C for 10 min, (*Z*)-pent-2-en-1-ol (2.0 g, 23 mmol) was added, the reaction was stirred for 30 min, poured into pentane (150 mL), filtered through a pad of SiO_2, washed with pentane and concentrated to afford **234g** (1.9 g, 56%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79-5.57 (m, 2 H), 4.01 (d, *J* = 8.0 Hz, 2 H), 2.18

(quintet, J = 7.5 Hz, 2 H), 1.04 (t, J = 7.5 Hz, 3 H). The crude bromide was used in the subsequent reactions.



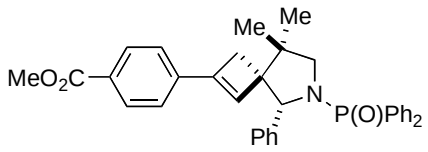
235

(*4S*,5R*,8R)-6-(*N*-(*P,P*-Diphenylphosphinyl))-2-((4-ethoxycarbonyl)phenyl)-8-methyl-5-phenyl-6-azaspiro[3.4]oct-1-ene (235). General Protocol I.** Amide **113** (0.10 g, 0.20 mmol), allyl bromide (0.12 g, 1.0 mmol) and Bu_4NHSO_4 (0.034 g, 0.10 mmol) were dissolved in PhMe (10.0 mL) and treated with 50% aq NaOH (10.0 mL). The reaction mixture was vigorously stirred at rt for 36 h, diluted with water, and extracted (3x) with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 1:4) to afford **235** (0.090 g, 83%) as a colorless oil: IR (neat) 3058, 2954, 2925, 2871, 1719, 1617, 1428, 1453, 1438, 1410, 1359, 1280, 1193, 1121, 1109 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05-7.97 (m, 4 H), 7.63 (dd, J = 11.1, 8.1 Hz, 2 H), 7.52-7.48 (m, 3 H), 7.40 (d, J = 8.2 Hz, 2 H), 7.31-7.24 (m, 4 H), 7.15-7.11 (m, 4 H), 6.96 (s, 1 H), 4.58 (d, J = 11.5 Hz, 1 H), 3.94 (s, 3 H), 3.59 (app t, J = 7.3 Hz, 1 H), 3.26 (q, J = 10.3 Hz, 1 H), 2.82-2.79 (m, 1 H), 2.45 (d, J = 13.3 Hz, 1 H), 2.30 (d, J = 13.3 Hz, 1 H), 0.97 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.77, 148.03, 143.84, 143.35, 138.09, 134.75, 132.53, 132.41, 132.32, 132.20, 131.57, 131.33, 129.66, 129.16, 128.55, 128.39, 127.86, 127.68, 127.26, 126.79, 124.56, 68.93, 57.06, 57.01, 52.72, 51.99, 51.90, 36.84, 36.76, 32.41, 11.91; MS (EI) *m/z* (rel. intensity) 533 (M^+, 15), 332 (24), 306 (43), 230 (11), 215 (14), 201 (80), 118 (100); HRMS (EI) calc for $C_{34}H_{32}NO_3P$ 533.2120, found 533.2129.



236

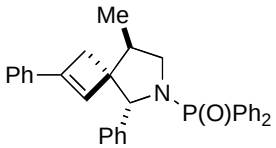
***N*-((3-(4-Methoxycarbonylphenyl)bicyclo[1.1.0]but-1-yl)(phenyl)methyl)-*N*-(2-methylallyl)-*P,P*-diphenylphosphinamide (236).** According to General Protocol I, a solution of amide **113** (0.10 g, 0.20 mmol), 3-bromo-2-methylpropene (0.10 mL, 1.0 mmol) and Bu_4NHSO_4 (0.013 g, 0.10 mmol) in PhMe (10 mL) and 50% aq NaOH (10 mL) was vigorously stirred at rt for 1 h. The reaction mixture was diluted with water and extracted (3x) with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **105** (0.10 g, 90%) as a colorless oil: IR (neat) 3059, 2948, 1718, 1607, 1437, 1311, 1280, 1181, 1117 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.99-7.89 (m, 6 H), 7.67 (d, *J* = 8.3 Hz, 2 H), 7.43-7.42 (m, 3 H), 7.10 (d, *J* = 7.2 Hz, 2 H), 7.01 (t, *J* = 7.6 Hz, 2 H), 6.89 (d, *J* = 7.2 Hz, 2 H), 6.63 (d, *J* = 7.2 Hz, 2 H), 4.87 (d, *J* = 6.2 Hz, 2 H), 4.38 (d, *J* = 11.7 Hz, 1 H), 3.88 (s, 3 H), 3.53 (dd, *J* = 16.1, 10.8 Hz, 1 H), 3.27 (dd, *J* = 16.3, 10.5 Hz, 1 H), 2.27 (d, *J* = 6.0 Hz, 1 H), 1.86 (d, *J* = 6.3 Hz, 1 H), 1.57 (s, 3 H), 0.58 (s, 1 H), 0.51 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.32, 142.20, 141.87, 141.82, 137.19, 137.15, 134.66, 133.67, 132.81, 132.69, 132.42, 132.30, 129.12, 128.99, 128.38, 128.17, 127.86, 127.38, 126.49, 125.25, 113.54, 63.10, 53.12, 52.02, 37.47, 34.31, 28.89, 28.83, 23.18, 20.60; MS (EI) *m/z* (rel. intensity) 547 (M^+, 19), 346 (27), 319 (14), 306 (10), 272 (9), 230 (23), 215 (18), 201 (96), 183 (6), 118 (100); HRMS (EI) calc for $C_{35}H_{34}NO_3P$ 547.2276, found 547.2277.



237

(*4S*,5R)-6-(*P,P*-diphenylphosphinyl)-2-((4-ethoxycarbonyl)phenyl)-8,8-dimethyl-5-phenyl-6-azaspiro[3.4]oct-1-ene (237).** Table 18, entry 5. A mixture of amide **119** (0.030 g, 0.061 mmol), 3-bromo-2-methylpropene (0.030 mL, 0.030 mmol), Bu_4NHSO_4 (0.010 g, 0.030 mmol), powdered NaOH (0.012 g, 0.61 mmol) and K_2CO_3 (0.042 g, 0.30 mmol) in PhMe (3.0 mL) was vigorously stirred at rt for 2.5 h and at 110 ºC for an additional 12 h. The reaction mixture was diluted with water and extracted (3x) with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 1:4) to afford a mixture (2.3:1) of diastereoisomers of **237** (0.022 g, 66%) as a colorless oil. Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03-7.84 (m, 3 H), 7.53-7.46 (m, 3 H), 7.20-7.11 (m, 5 H), 7.04-6.92 (m, 6 H), 6.32 (s, 1 H), 4.74 (d, *J* = 11.0 Hz, 1 H), 3.86 (s, 3 H), 3.53-3.30 (m, 2 H), 2.75 (d, *J* = 12.9 Hz, 1 H), 2.36 (d, *J* = 12.9 Hz, 1 H), 1.38 (s, 3 H), 0.94 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.70, 145.97, 141.48, 141.30, 133.46, 132.59, 132.47, 132.30, 132.18, 131.87, 131.59, 129.49, 128.55, 128.39, 128.30, 127.53, 127.36, 127.22, 127.17, 126.36, 124.28, 68.21, 60.52, 59.89, 51.98, 42.48, 31.60, 23.15, 21.78; IR(neat) 2955, 1720, 1605, 1438, 1280, 1193, 1122, 1109 cm^{-1}; MS (EI) *m/z* (rel. intensity) 547 (M^+, 52), 532 (9), 500 (10), 470 (8), 346 (53), 230 (15), 201 (100); HRMS (EI) calc for $C_{35}H_{34}NO_3P$ 547.2276, found 547.2251. Minor isomer (representative signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.40 (s, 1 H), 4.81 (d, *J* = 11.5 Hz, 1 H), 3.87 (s, 3 H), 3.31 (app d, *J* = 10.8 Hz, 1 H), 2.50 (d, *J* = 13.2 Hz, 1 H), 1.36 (s, 3 H), 1.07 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 67.87, 43.49, 32.24, 23.98, 21.51.

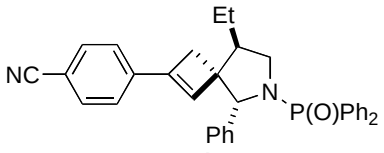
Synthesis of **237** from *N*-((3-(4-methoxycarbonylphenyl)bicyclo[1.1.0]but-1-yl)(phenyl)methyl)-*N*-(2-methylallyl)-*P*,*P*-diphenylphosphinamide (**236**). A solution of amide **236** (0.025 g, 0.047 mmol) in PhMe (1.5 mL) was heated at reflux (110 ºC) for 6.5 h. The solvent was evaporated, and purification of the residue by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded a diastereomeric mixture (2.5:1) of **236** (0.020 g, 80%).



239a

(*4S*,5R*,8R)-6-(*N*-(*P*,*P*-Diphenylphosphinyl))-8-methyl-2,5-diphenyl-6-azaspiro[3.4]oct-1-ene (239a).** According to the General Protocol I, amide **98** (0.049 g, 0.11 mmol), allyl bromide (0.068 g, 0.56 mmol) and Bu_4NHSO_4 (0.020 g, 0.056 mmol) were dissolved in PhMe (5.0 mL), and treated with 50% aq NaOH (5.0 mL). The reaction mixture was vigorously stirred at rt for 36 h, diluted with water, and extracted (3x) with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated. The product was purified by chromatography on SiO_2 (hexanes/EtOAc, 1:4) to afford **239a** (0.033 g, 63%) as a colorless oil: IR (neat) 2922, 1489, 1438, 1200, 1108 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (ddd, *J* = 11.7, 4.8, 1.6 Hz, 3 H), 7.61 (ddd, *J* = 11.8, 8.3, 1.3 Hz, 3 H), 7.49-7.44 (m, 5 H), 7.35-7.20 (m, 4 H), 7.15-7.06 (m, 5 H), 6.77 (s, 1 H), 4.54 (d, *J* = 11.3 Hz, 1 H), 3.59-3.49 (m, 1 H), 3.27-3.17 (m, 1 H), 2.81-2.69 (m, 2 H), 2.39 (d, *J* = 13.4 Hz, 1 H), 2.25 (d, *J* = 13.4 Hz, 1 H), 0.94 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.08, 144.04, 134.02, 132.56, 132.43, 132.32, 132.20, 131.67, 131.29, 128.54, 128.43, 128.37, 128.26, 127.85, 127.79, 127.67, 127.26, 126.67, 124.67, 69.25, 56.68, 56.63, 52.66, 36.69, 32.37, 11.89; MS (EI) *m/z* (rel. intensity) 475 (M^+, 29), 318

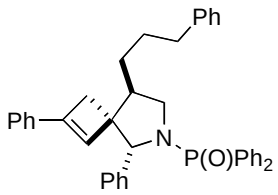
(9), 306 (52), 274 (28), 230 (20), 201 (100); HRMS (EI) calc for $C_{32}H_{30}NOP$ 475.2065, found 475.2095.



239b

(*4S*,5R*,8R)-2-(4-Cyanophenyl)-6-(*P,P*-diphenylphosphinyl)-8-ethyl-5-phenyl-6-azaspiro[3.4]oct-1-ene (239b).** A suspension of amide **114b** (0.11 g, 0.24 mmol), crotyl bromide (0.12 mL, 1.2 mmol), Bu_4NHSO_4 (0.041 g, 0.12 mmol), powdered NaOH (0.10 g, 2.4 mmol) and K_2CO_3 (0.17 g, 1.2 mmol) in PhMe (10 mL) was vigorously stirred at rt for 4 h, and at 50 ^oC for an additional 14 h. The reaction mixture was diluted with water and extracted (3x) with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **239b** (0.063 g, 51%) as a colorless oil: IR (neat) 3060, 2960, 2925, 2873, 2225, 1612, 1558, 1497, 1454, 1439, 1299, 1194, 1109 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (ddd, *J* = 11.8, 7.7, 1.9 Hz, 2 H), 7.62-7.56 (m, 4 H), 7.50-7.44 (m, 4 H), 7.39-7.36 (m, 2 H), 7.31-7.23 (m, 3 H), 7.15-7.06 (m, 4 H), 7.00 (s, 1 H), 4.51 (d, *J* = 11.6 Hz, 1 H), 3.64 (ddd, *J* = 11.0, 8.0, 3.0 Hz, 1 H), 3.26 (td, *J* = 12.3, 10.0 Hz, 1 H), 2.57 (ddd, *J* = 18.2, 10.4, 3.8 Hz, 1 H), 2.42 (d, *J* = 13.4 Hz, 1 H), 2.30 (d, *J* = 13.4 Hz, 1 H), 1.49-1.35 (m, 1 H), 1.30-1.18 (m, 1 H), 0.86 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.68, 142.22, 138.00, 136.82, 133.28, 132.54, 132.41, 132.31, 132.20, 131.65, 131.44, 131.41, 128.66, 128.49, 127.94, 127.77, 127.27, 126.94, 125.18, 118.92, 110.98, 69.33, 56.96, 56.92, 51.49, 44.17, 44.10, 32.67, 21.92, 13.09; MS (ES) *m/z* (rel. intensity) 1051

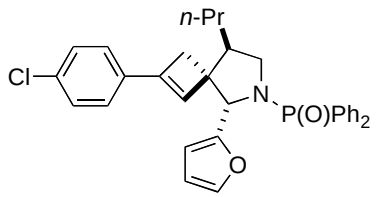
([2M+Na]$^+$, 15), 537 ([M+Na]$^+$, 72), 515 ([M+H]$^+$, 100); HRMS (ES) calc for $C_{34}H_{32}N_2OP$ (M+H) 515.2252, found 515.2251.



239c

(4*S,5*R**,8*R**)-6-(Diphenylphosphoryl)-2,5-diphenyl-8-(3-phenylpropyl)-6-azaspiro[3.4]oct-1-ene (239c).** A solution of **114b** (0.050 g, 0.11 mmol), powdered K_2CO_3 (0.079 g, 0.57 mmol), powdered NaOH (0.046 g, 1.1 mmol), Bu_4NHSO_4 (0.020g, 0.057 mmol) and bromide **234e** (0.13 g, 0.57 mmol) in dry PhMe (5.0 mL) was heated at 60 ^oC with vigorous stirring for 14 h. The mixture was cooled to rt, diluted with water (10 mL), extracted (3 x 10 mL) with EtOAc and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on silca (hexanes/EtOAc, 1:4) afforded **239c** (0.038 g, 57%) as a colorless oil: IR (neat) 3059, 2927, 2855, 1683, 1452, 1439, 1197, 1121 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.93 (ddd, *J* = 11.6, 7.8, 1.1 Hz, 2 H); 7.49-7.43(m, 3 H), 7.36-7.34 (m, 3 H), 7.32-7.27 (m, 3 H), 7.26-7.22 (m, 4 H), 7.17-7.13 (m, 3 H), 7.10-7.03 (m, 4 H), 7.80 (s, 1 H), 4.52 (d, *J* = 11.1 Hz, 1 H), 3.63 (td, *J* = 8.6, 2.7 Hz, 1 H), 3.27 (q, *J* = 10.0 Hz, 1 H), 2.71-2.63 (m, 1 H), 2.59-2.48 (m, 1 H), 2.41 (d, *J* = 13.3 Hz, 1 H), 2.29 (d, *J* = 13.3 Hz, 1 H), 1.80-1.69 (m, 1 H), 1.63-1.56 (m, 1 H), 1.51-1.45 (m, 1 H), 1.401.27 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.13, 144.09, 143.91, 142.31, 134.02, 132.94, 132.53, 132.45, 132.28, 132.21, 132.05, 131.91, 131.78, 131.60, 131.57, 131.36, 131.34, 131.02, 128.56, 128.46, 128.30, 128.25, 128.21, 127.91, 127.86, 127.78, 127.27, 126.73, 125.67, 124.72, 69.72, 56.40, 56.37, 51.52, 42.22, 42.17, 36.28,

32.65, 30.79, 28.69; MS (EI) *m/z* (rel. intensity) 579 (M^+, 4), 378 (10), 306 (20), 219 (55), 201 (76), 105 (100); HRMS (EI) calc for $C_{40}H_{38}NOP$ 579.2691, found 579.2668.

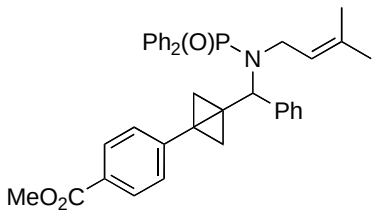


239d

(4*S,5*S**,8*R**)-2-(4-Chlorophenyl)-6-(diphenylphosphoryl)-5-(furan-2-yl)-8-propyl-6-azaspiro[3.4]oct-1-ene (239d).** Table 18, entry 7. A suspension of amide **123h** (0.030 g, 0.065 mmol), bromide **234f** (0.050 g, 0.033 mmol), K_2CO_3 (0.046 g, 0.33 mmol), NaOH (0.026 g, 0.65 mmol) and Bu_4NHSO_4 (0.011 g, 0.033 mmol) in PhMe (3.0 mL) was vigorously stirred at 60 ^oC for 21 h. After cooling to rt, the mixture was diluted with water and extracted (3 x 10 mL) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), filtered through a pad of SiO_2, and concentrated. Purification by column chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **239d** (0.024 g, 69%) as a colorless oil.

A suspension of amide **123h** (0.030 g, 0.065 mmol), bromide **234g** (0.050 g, 0.033 mmol), K_2CO_3 (0.046 g, 0.33 mmol), NaOH (0.026 g, 0.65 mmol) and Bu_4NHSO_4 (0.011 g, 0.033 mmol) in PhMe (3.0 mL) was vigorously stirred at 60 ^oC for 21 h. After cooling to rt, the mixture was diluted with water and extracted (3 x 10 mL) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), filtered through a pad of SiO_2, and concentrated. Purification by column chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **239d** (0.024 g, 69%) as a colorless oil: IR (neat) 2957, 2928, 1487, 1439, 1232, 1200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (ddd, *J* = 11.7, 7.5, 1.5 Hz, 2 H), 7.69 (ddd, *J* = 11.7, 8.1, 1.2 Hz, 1 H), 7.52-7.42

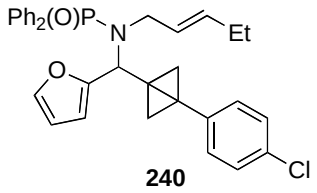
(m, 3 H), 7.43-7.37 (m, 2 H), 7.33-7.23 (m, 6 H), 6.71 (s, 1 H), 6.15 (dd, *J* = 3.3, 1.8 Hz, 1 H), 5.83 (d, *J* = 3.0 Hz, 1 H), 4.50 (d, *J* = 9.9 Hz, 1 H), 3.55 (td, *J* = 8.1, 3.3 Hz, 1 H), 3.11 (q, *J* = 9.6 Hz, 1 H), 2.75-2.73 (m, 1 H), 2.43 (s, 2 H), 1.38-1.16 (m, 4 H), 0.84 (t, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.24, 156.14, 143.23, 141.22, 133.63, 133.20, 132.70, 132.53, 132.41, 132.31, 132.18, 131.69, 131.60, 131.52, 131.48, 130.99, 128.57, 128.50, 128.40, 128.13, 127.96, 126.03, 110.04, 107.23, 63.04, 56.01, 55.96, 51.31, 42.82, 42.75, 32.48, 31.13, 21.82, 14.35; MS (EI) *m/z* (rel. intensity) 527 (M^+, 56), 460 (20), 417 (16), 326 (67), 296 (80), 230 (49), 218 (80), 201 (100), 154 (56); HRMS (EI) calc for $C_{32}H_{31}NO_2PCl$ 527.1781, found 527.1777.



239e

***N*-((3-(4-Methoxycarbonylphenyl)bicyclo[1.1.0]but-1-yl)(phenyl)methyl)-*N*-(2,2-dimethylallyl)-*P,P*-diphenylphosphinamide (239e).** Amide **113** (0.030 g, 0.061 mmol), 4-bromo-2-methyl-2-butene **234h** (0.035 mL, 0.030 mmol) and Bu_4NHSO_4 (0.010 g, 0.030 mmol) were dissolved in PhMe (3.0 mL) and treated with 50 % aq NaOH (3.0 mL). The reaction mixture was vigorously stirred at rt for 1.5 h, diluted with water, and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **239e** (0.034 g, 99%) as a colorless oil: IR (neat) 1718, 1606, 1437, 1278, 1179, 1117 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90-7.80 (m, 4 H), 7.73 (d, *J* = 8.2 Hz, 2 H), 7.40-7.36 (m, 6 H), 7.15-7.10 (m, 1 H), 7.04 (t, *J* = 7.4 Hz, 2 H), 6.75 (t, *J* = 8.6 Hz, 4 H), 5.26 (bs, 1 H), 4.45 (d, *J* = 8.9 Hz, 1 H), 3.89 (s, 3 H),

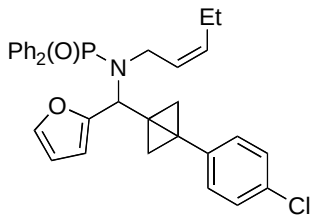
3.58-3.52 (m, 2 H), 2.42 (d, J = 6.3 Hz, 1 H), 1.74 (d, J = 6.4 Hz, 1 H), 1.61 (s, 3 H), 1.06 (s, 3 H), 0.85 (s, 1 H), 0.57 (s, 1 H); MS (EI) *m/z* (rel. intensity) 561 (M^+, 41), 360 (38), 319 (18), 306 (55), 201 (100), 118 (88); HRMS (EI) calc for $C_{36}H_{36}NO_3P$ 561.2433, found 561.2437.



240

(*E*)-*N*-((3-(4-Chlorophenyl)bicyclo[1.1.0]but-1-yl)(furan-2-yl)methyl)-*N*-(pent-2-enyl)-*P*,*P*-diphenylphosphinic amide (240). Amide **123h** (0.089 g, 0.19 mmol), bromide **234f** (0.14 g, 0.097 mmol), and Bu_4NHSO_4 (0.034 g, 0.097 mmol) were suspended in PhMe (9.0 mL) and 50% solution of NaOH (9.0 mL) was added. The mixture was vigorously stirred at rt for 30 min, diluted with water (10 mL) and extracted (3 x 5 mL) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **240** (0.099 g, 97%) as a colorless oil: IR (neat) 3055, 2961, 2930, 2871, 1592, 1501, 1484, 1438, 1366, 1310, 1201, 1119 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86-7.72 (m, 5 H), 7.47-7.34 (m, 6 H), 7.08 (d, J = 7.3 Hz, 2 H), 6.81 (d, J = 7.3 Hz, 2 H), 6.17 (t, J = 1.4 Hz, 1 H), 5.66 (d, J = 3.1 Hz, 1 H), 5.37-5.28 (m, 1 H), 5.19-5.10 (m, 1 H), 4.66 (d, J = 8.4 Hz, 1 H), 3.91-3.69 (m, 2 H), 2.34 (d, J = 6.6 Hz, 1 H), 1.97 (d, J = 6.6 Hz, 1 H), 1.88 (quintet, J = 6.6 Hz, 1 H), 1.17 (s, 1 H), 0.98 (s, 1 H), 0.87 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.71, 152.64, 141.27, 134.54, 134.10, 133.56, 133.03, 132.61, 132.48, 131.98, 131.86, 131.71, 131.57, 131.41, 130.57, 128.50, 128.23, 128.15, 128.06, 127.99, 127.88, 126.99, 126.95, 126.88, 109.94, 108.13, 53.17, 53.11, 47.58, 47.53, 35.44, 33.79, 25.44, 25.38, 25.13, 21.26, 13.38; MS (EI) *m/z* (rel. intensity) 527 (M^+, 36), 328 (20), 326 (56), 309 (84), 296

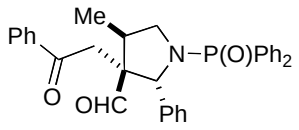
(90), 218 (44), 202 (47), 201 (100); HRMS (EI) calc for $C_{32}H_{31}NO_2PCl$ 527.1780, found 527.1792.



241

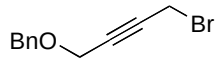
(*Z*)-*N*-((3-(4-Chlorophenyl)bicyclo[1.1.0]butan-1-yl)(furan-2-yl)methyl)-*N*-(pent-2-enyl)-*P*,*P*-diphenylphosphinic amide (241). Amide **123h** (0.083 g, 0.18 mmol), bromide **234g** (0.13 g, 0.097 mmol), and Bu_4NHSO_4 (0.032 g, 0.090 mmol) were suspended in PhMe (8.0 mL) and 50% solution of NaOH (8.0 mL) was added. The mixture was vigorously stirred at rt for 30 min, diluted with water (10 mL) and extracted (3 x 5 mL) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **241** (0.090 g, 95%) as a colorless oil: IR (neat) 3056, 2961, 2931, 2872, 1501, 1484, 1438, 1201, 1148, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88-7.73 (m, 5 H), 7.48-7.33 (m, 6 H), 7.08 (dd, *J* = 6.7, 1.6 Hz, 2 H), 6.81 (dd, *J* = 6.9, 1.6 Hz, 2 H), 6.17 (dd, *J* = 3.1, 1.8 Hz, 1 H), 5.65 (d, *J* = 3.2 Hz, 1 H), 5.39-5.32 (m, 1 H), 5.24-5.16 (m, 1 H), 4.04-4.92 (m, 1 H), 3.87-3.76 (m, 1 H), 2.34 (d, *J* = 6.5 Hz, 1 H), 1.97 (d, *J* = 6.6 Hz, 1 H), 1.66 (quintet, *J* = 7.1 Hz, 2 H), 1.18 (s, 1 H), 0.97 (s, 1 H), 0.76 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.68, 152.61, 141.34, 134.50, 133.33, 132.58, 132.45, 131.96, 131.62, 131.43, 131.22, 130.59, 128.25, 128.22, 128.09, 128.05, 127.87, 126.88, 109.94, 108.07, 53.38, 53.32, 42.43, 42.39, 35.42, 33.82, 25.33, 25.27, 21.24, 20.15, 13.81; MS (EI) *m/z* (rel. intensity)

527 (M^+, 26), 326 (19), 309 (42), 296 (53), 218 (17), 202 (21), 201 (100); HRMS (EI) calc for $C_{32}H_{31}NO_2PCl$ 527.1780, found 527.1790.



242

***(2R*,3S*,4R*)-N*-(3-((Benzoyl)methyl)-3-formyl-4-methyl-2-phenyl-pyrrolidine)-*P,P*-diphenylphosphinamide (242).** To a solution of **239a** (0.017 g, 0.035 mmol) in 2:1 mixture of THF and water (6.0 mL) was added $NaIO_4$ (0.023 g, 0.11 mmol) followed by OsO_4 (1.0 mg, 3.5 μmol). The reaction mixture was stirred at rt for 3 h, diluted with water, and extracted (3x) with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:6) afforded **242** (0.013 g, 73%) as a colorless solid: Mp. 117.9-119.2 ºC (Et_2O); IR (KBr) 3060, 2963, 2928, 2861, 1521, 1679, 1598, 1450, 1439, 1198, 1122 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.12 (s, 1 H), 7.87-7.73 (m, 4 H), 6.54-7.27 (m, 13 H), 7.05-7.02 (m, 3 H), 5.24 (d, *J* = 6.5 Hz, 1 H), 3.73 (td, *J* = 8.8, 3.1 Hz, 1 H), 3.48 (d, *J* = 18.3 Hz, 1 H), 3.10-3.01 (m, 1 H), 2.77-2.68 (m, 1 H), 2.37 (d, *J* = 18.3 Hz, 1 H), 1.05 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.92, 198.23, 140.91, 136.15, 133.18, 132.69, 132.23, 131.61, 128.34, 128.01, 127.68, 127.29, 67.03, 60.78, 51.84, 42.07, 40.25, 11.60; MS (EI) *m/z* (rel. intensity) 507 (M^+, 13), 505 (31), 489 (7), 478 (35), 451 (90), 388 (15), 306 (23), 288 (17), 278 (14), 230 (11), 201 (100); HRMS (EI) calc for $C_{32}H_{30}NO_3P$ 507.1963, found 507.1930.



243b

((4-Bromobut-2-ynyloxy)methyl)benzene (243b). A solution of PPh_3 (1.4 g, 5.5 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C, treated with Br_2 (0.28 mL, 5.5 mmol) and after 10 min at this temperature, solid imidazole (0.50 g, 7.4 mmol) was added. The mixture was stirred for 5 min and neat 4-(benzyloxy)but-2-yn-1-ol[476] (0.70 g, 3.7 mmol) was added. The mixture was stirred at 0 °C for 20 min, poured into pentane (100 mL), filtered through a short pad of silica, washed with pentane, and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:0 to 10:1) afforded **243b** (0.62 g, 67%) as a colorless oil: IR (ATR) 3084, 2850, 1495, 1452, 1351, 1208, 1139, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54-7.30 (m, 5 H), 4.63 (s, 2 H), 4.26 (t, J = 2.0 Hz, 2 H), 3.99 (t, J = 2.0 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.0, 128.3, 127.9, 127.8, 82.7, 81.4, 71.5, 57.1, 14.2.

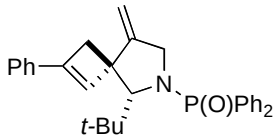
243c

1-Bromo-4,4-dimethylpent-2-yne (243c). A solution of PPh_3 (5.8 g, 22 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C, treated with Br_2 (1.1 mL, 22 mmol) and after 5 min, solid imidazole (2.0 g, 29 mmol) was added. The mixture was stirred at 0 °C for 5 min, neat 4,4-dimethylpent-2-yn-1-ol[477] (1.6 g, 15 mmol) was added, the mixture was stirred for 30 min, poured into pentane (100 mL), filtered through a pad of SiO_2, washed with pentane, and concentrated to afford **243c** (1.0 g, 40%) as a colorless oil. Analytical sample was prepared by Kugelrohr distillation (60-80 °C oven temperature, water aspirator): IR (ATR) 2967, 2235, 1455, 1360, 1267, 1206 cm^{-1}; ^1H

NMR (300 MHz, $CDCl_3$) δ 3.91 (s, 2 H), 1.20 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 95.9, 74.0, 30.6, 27.5, 15.7.

243d

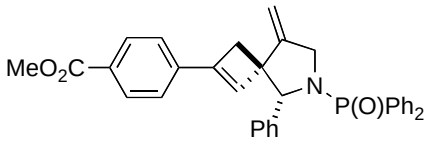
1-Bromohept-2-yne (243d). A solution of PPh_3 (7.0 g, 27 mmol) in CH_2Cl_2 (70 mL) was cooled to 0 °C, treated with Br_2 (1.4 mL, 27 mmol) and after 10 min at this temperature, solid imidazole (2.4 g, 36 mmol) was added. The mixture was stirred for 15 min and neat alcohol (2.0 g, 18 mmol) was added. The mixture was stirred at 0 °C for 35 min, poured into pentane, filtered through a short pad of silica, and concentrated to afford **243d** (2.2 g, 70%) as a colorless oil. Analytical sample was prepared by Kugelrohr distillation (80-100 °C oven temperature, water aspirator). **243d**: IR (ATR) 2954, 2927, 2868, 2231, 1457, 1426, 1206 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.94 (t, J = 2.4 Hz, 2 H), 2.25 (tt, J = 6.9, 2.3 Hz, 2 H), 1.55-1.34 (m, 4 H), 0.92 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 88.3, 75.2, 30.4, 21.9, 18.6, 15.8, 13.6.



244a

(4*R,5*R**)-5-*tert*-Butyl-6-(diphenylphosphoryl)-8-methylene-2-phenyl-6-azaspiro[3.4]oct-1-ene (244a).** Amide **118a** (0.15 g, 0.35 mmol), propargyl bromide (0.26 mL, 1.8 mmol, 80% in PhMe) and Bu_4NHSO_4 (0.060 g, 0.18 mmol) were dissolved in PhMe (10 mL) and treated with 50% aq NaOH (10 mL). The reaction mixture was vigorously stirred at rt for 24 h, diluted with water (20 mL) and extracted (3 x 10 mL) with EtOAc. The combined organic layers were

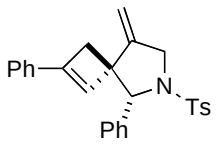
washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **244a** (0.11 g, 67%) as a clear oil which was recrystallized from CH_2Cl_2/hexane: Mp. 168.5-170.7 ^oC (CH_2Cl_2/hexane); IR (neat) 3071, 3053, 2953, 2870, 1737, 1480, 1435, 1370, 1198 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.05-7.99 (m, 2 H), 7.92-7.86 (m, 2 H), 7.62-7.35 (m, 11 H), 6.44 (s, 1 H), 5.09 (s, 1 H), 4.76 (s, 1 H), 4.18 (app. t, *J* = 13.8 Hz, 1 H), 4.00 (t, *J* = 12.4 Hz, 1 H), 3.87 (d, *J* = 10.3 Hz, 1 H), 3.17 (d, *J* = 12.5 Hz, 1 H), 2.73 (d, *J* = 12.4 Hz, 1 H), 0.97 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.99, 154.95, 144.84, 133.98, 133.32, 133.01, 132.79, 132.67, 132.38, 132.26, 131.68, 131.60, 131.51, 131.33, 128.43, 128.30, 128.21, 128.03, 126.56, 124.72, 102.03, 73.75, 55.76, 51.78, 48.97, 37.30, 37.24, 28.46; MS (EI) *m/z* (rel. intensity) 453 (M^+, 12), 437 (12), 397 (45), 396 (100), 201 (98), 194 (37); HRMS (EI) calc for $C_{30}H_{32}NOP$ 453.2221, found 453.2201.



244b

Methyl 4-((4*R,5*R**)-6-(diphenylphosphoryl)-8-methylene-5-phenyl-6-azaspiro[3.4]oct-1-en-2-yl)benzoate (244b).** A solution of **113** (0.32 g, 0.62 mmol), propargyl bromide (0.50 mL, 3.1 mmol, 80% in PhMe), and Bu_4NHSO_4 (0.11 g, 0.32 mmol) in PhMe (30 mL) was treated with 50% aq NaOH (30 mL). The reaction mixture was vigorously stirred at rt for 24 h, diluted with water and extracted (3x) with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated. The residual oil was purified by chromatography on SiO_2 (hexanes/EtOAc, 1:4) to afford **244b** (0.29 g, 87%) as a colorless oil: IR (neat) 3058, 2959, 1721, 1603, 1438, 1280, 1195, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 6.8, 1.7

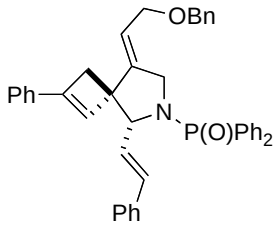
Hz, 2 H), 7.92 (ddd, *J* = 11.7, 7.9, 1.7 Hz, 2 H), 7.71 (ddd, *J* = 11.8, 8.3, 1.4 Hz, 2 H), 7.52-7.44 (m, 4 H), 7.40-7.34 (m, 4 H), 7.30-7.20 (m, 3 H), 7.03-7.00 (m, 2 H), 5.77 (s, 1 H), 4.93 (d, *J* = 1.4 Hz, 2 H), 4.58 (d, *J* = 10.3 Hz, 1 H), 4.34 (ddt, *J* = 14.4, 12.1, 2.4 Hz, 1 H), 4.04 (dd, *J* = 14.3, 5.5 Hz, 1 H), 3.91 (s, 3 H), 3.28 (d, *J* = 12.6 Hz, 1 H), 2.92 (d, *J* = 12.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.71, 150.76, 146.39, 142.72, 142.66, 137.88, 132.53, 132.49, 132.40, 132.37, 131.67, 130.82, 129.73, 129.57, 128.65, 128.49, 128.30, 128.21, 128.05, 128.00, 127.02, 126.56, 124.85, 105.56, 69.91, 57.59, 52.03, 50.71, 46.42; MS (EI) *m/z* (rel. intensity) 531 (M^+, 27), 417 (6), 330 (65), 217 (21), 201 (100); HRMS (EI) calc for $C_{30}H_{34}NO_3P$ 531.1963, found 531.1941.



244c

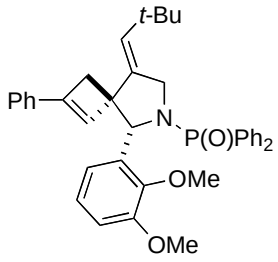
(4*R,5*R**)-8-Methylene-2,5-diphenyl-6-tosyl-6-azaspiro[3.4]oct-1-ene (244c).** Amide **123j** (0.050 g, 0.0.13 mmol), Bu_4NHSO_4 (0.022 g, 0.064 mmol) and propargyl bromide (0.077 mL, 0.64 mmol) were dissolved in PhMe (5.0 mL), treated with 50% aq NaOH (5.0 mL) and stirred at rt for 36 h. The reaction mixture was diluted with water, extracted (3x) with EtOAc, and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. The residual oil was purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to afford **244c** (0.024 g, 42%) as a colorless oil: IR (neat) 1346, 1162 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.53 (m, 2 H), 7.35-7.21 (m, 9 H), 7.12-7.06 (m, 2 H), 5.59 (s, 1 H), 4.99-4.95 (m, 3 H), 4.40 (dt, *J* = 13.4, 1.5 Hz, 1 H), 4.20 (d, *J* = 13.6 Hz, 1 H), 2.61, 2.54 (AB, *J* = 12.2 Hz, 2 H), 2.43 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 147.0, 143.1, 140.4, 135.9, 133.6, 129.4, 128.5, 128.4,

128.3, 128.1, 127.3, 126.8, 124.9, 124.4, 106.4, 70.3, 56.2, 51.4, 45.8, 21.5; MS (EI) *m/z* (rel intensity) 427 (M^+, 12), 298 (7), 272 (44), 245 (19), 168 (65), 91 (100); HRMS (EI) calc for $C_{27}H_{25}NO_2S$ 427.1606, found 427.1602.



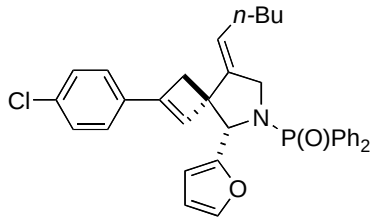
244d

(4*R,5*R**,*Z*)-8-(2-(Benzyloxy)ethylidene)-6-(diphenylphosphoryl)-2-phenyl-5-styryl-6-azaspiro[3.4]oct-1-ene (244d).** Amide **123f** (0.037 g, 0.080 mmol), Bu_4NHSO_4 (0.014 g, 0.040 mmol) and bromide **243b** (0.096g, 0.40 mmol) were dissolved in PhMe (4.0 mL), treated with 50% aq NaOH (4.0 mL) and stirred at rt for 24 h. The reaction mixture was diluted with water (20 mL), extracted (3 x 5 mL) with EtOAc, and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. The residual oil was purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to afford crude **244d** (0.035 g, 70%) as a colorless oil: IR (ATR) 3067, 1650, 1446, 1159 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00-7.82 (m, 6 H), 7.55-7.43 (m, 10 H), 7.40-7.05 (m, 9 H), 6.21-6.01 (m, 4 H), 5.63 (t, *J* = 6.0 Hz, 1 H), 4.49-4.41 (m, 2 H), 4.18-3.88 (m, 4 H), 3.12 (d, *J* = 12.5 Hz, 1 H), 2.88 (d, *J* = 12.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.81, 145.74, 139.97, 138.06, 136.73, 133.73, 132.71, 132.59, 132.40, 131.78, 131.42, 131.28, 128.50, 128.35, 128.17, 127.69, 127.57, 127.33, 126.55, 124.90, 117.26, 74.74, 72.31, 68.72, 56.53, 46.79, 46.30; MS (ES) *m/z* (rel. intensity) 642 ($[M+Na]^+$, 100), 620 ($[M+H]^+$, 20), 512 (17), 441 (2); HRMS (EI) calc for $C_{42}H_{38}NO_2NaP$ (M+Na) 642.2538, found 642.2509.



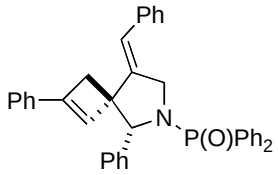
244e

(4*R,5*S**,*Z*)-5-(2,3-Dimethoxyphenyl)-8-(2,2-dimethylpropylidene)-6-(diphenylphosphoryl)-2-phenyl-6-azaspiro[3.4]oct-1-ene (244e).** A suspension of amide **123e** (0.049 g, 0.099 mmol), bromide **243c** (0.087 g, 0.50 mmol), powdered K_2CO_3 (0.068 g, 0.50 mmol), NaOH (0.040 g, 0.99 mmol) and Bu_4NHSO_4 (0.017 g, 0.050 mmol) in PhMe (5.0 mL) was degassed and vigorously stirred at 60 ^oC for 15 h. After cooling to rt, the mixture was diluted with water and extracted (3 x 5 mL) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by column chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **244e** (0.030 g, 51%) as a colorless oil: IR (ATR) 2952, 1478, 1437, 1183 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95-7.89 (m, 2 H), 7.78-7.72 (m, 2 H), 7.48-7.43 (m, 4 H), 7.37-7.33 (m, 4 H), 7.30 (br s, 1 H), 7.27-7.22 (m, 2 H), 5.58 (s, 1 H), 5.26 (s, 1 H), 4.99 (d, *J* = 10.4 Hz, 1 H), 4.38-4.20 (m, 2 H), 3.81 (s, 3 H), 3.22 (d, *J* = 12.2 Hz, 1 H), 3.01 (s, 3 H), 2.77 (d, *J* = 12.2 Hz, 1 H), 1.00 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.02, 146.14, 146.05, 138.73, 138.66, 137.55, 137.48, 134.32, 133.56, 132.99, 132.61, 132.49, 132.44, 132.31, 131.84, 131.59, 131.55, 131.50, 131.26, 128.59, 128.43, 128.29, 128.19, 128.05, 127.87, 125.78, 125.04, 123.34, 119.29, 111.06, 62.14, 59.70, 58.14, 58.10, 55.73, 47.71, 47.68, 46.56, 32.69, 30.98, 30.35; MS (EI) *m/z* (rel. intensity) 589 (M^+, 61), 549 (7), 532 (15), 388 (70), 201 (100); HRMS (EI) calc for $C_{38}H_{40}NOP$ 589.2746, found 589.2728.



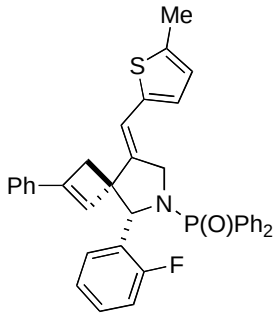
244f

(4*R,5*S**,*Z*)-2-(4-Chlorophenyl)-6-(diphenylphosphoryl)-5-(furan-2-yl)-8-pentylidene-6-azaspiro[3.4]oct-1-ene (244f).** A suspension of amide **123h** (0.030 g, 0.065 mmol), bromide **243d** (0.057 g, 0.33 mmol), powdered K_2CO_3 (0.046 g, 0.33 mmol), powdered NaOH (0.026 g, 0.65 mmol) and Bu_4NHSO_4 (0.011 g, 0.033 mmol) in PhMe (3.0 mL) was degassed and vigorously stirred at 60 ^oC for 21 h. After cooling to rt, the mixture was diluted with sat. NH_4Cl and extracted (3 x 5 mL) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by column chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **244f** (0.028 g, 79%) as a colorless oil: IR (neat) 3056, 2955, 2925, 2855, 1590, 1487, 1438, 1334, 1202, 1120, 1069 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.94-7.78 (m, 4 H), 7.54-7.43 (m, 4 H), 7.40-7.34 (m, 2 H), 7.30-7.25 (m, 4 H), 6.29 (dd, *J* = 3.0, 1.8 Hz, 1 H), 6.00 (d, *J* = 3.3 Hz, 1 H), 5.31 (app. t, *J* = 7.2 Hz, 1 H), 4.48 (d, *J* = 8.4 Hz, 1 H), 4.08, 4.02 (AB, *J* = 14.7 Hz, 2 H), 3.05 (d, *J* = 12.6 Hz, 1 H), 2.79 (d, *J* = 12.6 Hz, 1 H), 1.96-1.78 (m, 2 H), 1.47-1.17 (m, 4 H), 0.82 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.40, 155.32, 146.08, 141.43, 141.37, 133.91, 133.17, 132.64, 132.49, 132.42, 132.36, 132.30, 131.82, 131.77, 131.73, 131.44, 130.92, 128.64, 128.54, 128.47, 128.44, 128.38, 128.28, 126.38, 126.25, 120.96, 110.01, 106.43, 63.69, 63.67, 56.42, 56.38, 47.70, 47.67, 46.50, 31.43, 28.88, 22.22, 13.94; MS (EI) *m/z* (rel. intensity) 553 (M^+, 75), 485 (15), 417 (21), 352 (67), 296 (57), 218 (70), 217 (72), 202 (80), 201 (100), 139 (65); HRMS (EI) calc for $C_{34}H_{33}NO_2PCl$ 553.1937, found 553.1920.



244g

(4*R,5*R**,*Z*)-8-Benzylidene-6-(diphenylphosphoryl)-2,5-diphenyl-6-azaspiro[3.4]oct-1-ene (244g).** Amide **98** (0.20 g, 0.45 mmol), Bu_4NHSO_4 (0.072 g, 0.21 mmol) and bromide **243e** (0.41 mL, 2.1 mmol) were dissolved in PhMe (10 mL), treated with 50% aq NaOH (10 mL) and stirred at rt for 24 h. The reaction mixture was diluted with water (20 mL), extracted (3 x 10 mL) with EtOAc, and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. The residual oil was purified by chromatography on SiO_2 (hexanes/EtOAc, 1:4) to afford **244c** (0.13 g, 51%) as a colorless oil: IR (ATR) 3058, 1707, 1686, 1439, 1178 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.91 (ddd, *J* = 11.9, 7.1, 1.2 Hz, 2 H), 7.76 (ddd, *J* = 11.8, 7.2, 1.1 Hz, 2 H), 7.54-7.50 (m, 2 H), 7.47-7.42 (m, 5 H), 7.37 (t, *J* = 7.2 Hz, 1 H), 7.34-7.28 (m, 4 H), 7.25-7.22 (m, 3 H), 7.14 (d, *J* = 7.4 Hz, 2 H), 6.97 (dd, *J* = 6.4, 2.9 Hz, 2 H), 6.37 (s, 1 H), 5.76 (s, 1 H), 4.68 (ddd, *J* = 13.9, 10.8, 2.7 Hz, 1 H), 4.55 (d, *J* = 9.6 Hz, 1 H), 4.42 (ddd, *J* = 15.2, 4.9, 1.9 Hz, 1 H), 3.30 (d, *J* = 12.4 Hz, 1 H), 3.03 (d, *J* = 12.4 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.27, 143.93, 143.88, 142.82, 142.78, 136.88, 133.84, 132.80, 132.50, 132.43, 132.38, 132.21, 131.81, 131.77, 131.18, 128.69, 128.59, 128.43, 128.33, 128.23, 128.03, 126.97, 126.74, 126.61, 125.04, 125.01, 121.09, 69.23, 58.66, 58.64, 48.97, 46.94; MS (EI) *m/z* (rel. intensity) 549 (M^+, 73), 349 (28), 348 (90), 244 (21), 202 (33), 201 (100); HRMS (EI) calc for $C_{38}H_{32}NOP$ 549.2221, found 549.2229.



244h

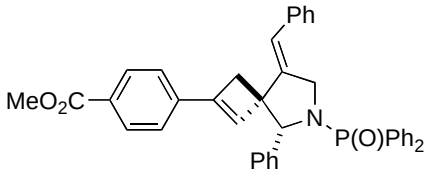
(4*R,5*S**,*Z*)-6-(Diphenylphosphoryl)-5-(2-fluorophenyl)-8-((5-methylthiophen-2-yl)methylene)-2-phenyl-6-azaspiro[3.4]oct-1-ene (244h).** Amide **118c** (0.40 g, 0.088 mmol), Bu_4NHSO_4 (0.016 g, 0.044 mmol) and bromide **243f** (0.095 g, 0.44 mmol) were dissolved in PhMe (4.0 mL), treated with 50% aq NaOH (4.0 mL) and stirred at rt for 24 h. The reaction mixture was diluted with water, extracted (3 x 5 mL) with EtOAc, and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. The residual oil was purified by chromatography on SiO_2 (hexanes/EtOAc, 1:4) to afford **244c** (0.012 g, 23%) as a colorless oil: IR (neat) 3057, 2918, 1588, 1487, 1438, 1362, 1226, 1198, 1121, 1109 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.62 Hz, 1 H), 7.86 (d, *J* = 7.4 Hz, 1 H), 7.78 (d, *J* = 7.8 Hz, 1 H), 7.74 (d, *J* = 7.7 Hz, 1 H), 7.54-7.43 (m, 4 H), 7.39-7.27 (m, 7 H), 7.23-7.16 (m, 1 H), 7.10 (t, *J* = 7.4 Hz, 1 H), 6.61 (dd, *J* = 6.21, 3.2 Hz, 1 H), 6.44 (s, 1 H), 5.68 (s, 1 H), 4.98 (d, *J* = 9.2 Hz, 1 H), 4.52-4.38 (m, 2 H), 3.30 (d, *J* = 12.5 Hz, 1 H), 2.96 (d, *J* = 12.4 Hz, 1 H), 2.44 (s, 3 H); δ ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.00, 157.73, 147.77, 140.93, 140.85, 140.33, 138.73, 133.82, 132.95, 132.47, 132.38, 132.34, 132.25, 132.21, 131.85, 131.81, 131.77, 131.74, 131.23, 130.75, 130.30, 130.12, 128.67, 128.59, 128.50, 128,38, 128.36, 128.22, 127.93, 127.88, 126.38, 125.62, 125.05, 124.28, 124.14, 124.10, 114.99, 114.69, 114.25, 62.49, 58.12, 58.08, 49.74, 47.12,

15.34; MS (EI) *m/z* (rel. intensity) 587 (M^+, 35), 386 (52), 384 (78), 288 (15), 217 (33), 201 (100), 111 (43); HRMS (EI) calc for $C_{37}H_{31}NOFPS$ 587.1848, found 587.1825.

3-(5-Methylthiophen-2-yl)prop-2-yn-1-ol. A suspension of $Pd(Ph_3P)_4$ (0.77 g, 0.67 mmol) and CuI (0.26 g, 1.3 mmol) in *i*-Pr_2NH (50 mL) was degassed, cooled to 0 ^oC, and treated with 2-iodo-5-methylthiophene (1.6 mL, 13 mmol) and propargyl alcohol (0.78 mL, 13 mmol). The reaction mixture was stirred at 0 ^oC for 10 min, quenched with sat. NH_4Cl, and extracted (3x20 mL) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. 3-(5-Methylthiophen-2-yl)prop-2-yn-1-ol was obtained as a light-brown oil (1.7 g, 84%) after Kugelrohr distillation (120 ^oC oven temperature, 1 mmHg): IR (ATR) 3342, 2917, 2857, 2218, 1435, 1353, 1193, 1010 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.02 (d, *J* = 3.5 Hz, 1 H), 6.62 (dt, *J* = 2.5, 1.1 Hz, 1 H), 4.47 (s, 2 H), 2.50 (br s, 1 H), 2.45 (d, *J* = 0.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.3, 142.7, 125.3, 119.9, 90.5, 79.4, 51.6, 15.4; MS (EI) *m/z* (rel. intensity) 152 (M^+, 2), 137 (10), 84 (100); HRMS (EI) calc for C_7H_5OS $(M\text{-}CH_3)^+$ 137.0061, found 137.0058.

2-(3-Bromoprop-1-ynyl)-5-methylthiophene (243f). A solution of PPh_3 (2.6 g, 9.8 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 ^oC, treated with Br_2 (0.50 mL, 9.8 mmol), and after 10 min, with imidazole (0.89 g, 13 mmol). The mixture was stirred at 0 ^oC for 10 min, 3-(5-methylthiophen-2-yl)prop-2-yn-1-ol (1.0 g, 9.8 mmol) was added and the reaction was continued at 0 ^oC for 1 h. The mixture was poured into pentane (100 mL), filtered through a pad of SiO_2, washed with pentane and the solvent was removed in vacuo. Purification by Kugelrohr distillation (100 ^oC oven temp, 1 mmHg) afforded **234f** (0.82 g, 58%) as a light-brown oil: IR

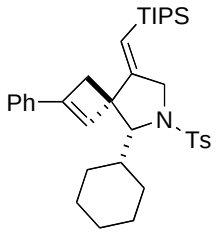
(ATR) 2916, 2214, 1536, 1463, 1444, 1202, 1159 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, *J* = 3.6 Hz, 1 H); 6.66 (dt, *J* = 2.5, 1.1 Hz, 1 H), 4.21 (s, 2 H), 2.49 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0, 133.3, 125.3, 119.4, 87.4, 80.6, 15.6, 15.4; MS (EI) *m/z* (rel. intensity) 214 (M^+, 7), 135 (100), 69 (85); HRMS (EI) calc for C_8H_7SBr 213.9451, found 312.9447.



244i

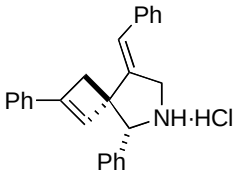
Methyl 4-((4*R,5*R**,*Z*)-8-benzylidene-6-(diphenylphosphoryl)-5-phenyl-6-azaspiro[3.4]oct-1-en-2-yl)benzoate (244i)**. A solution of amide **113** (0.050 g, 0.10 mmol), Bu_4NHSO_4 (0.017 g, 0.051 mmol), and 1-phenyl-3-bromopropyne (0.099 g, 0.51 mmol) in PhMe (5.0 mL) was treated with 50% aq NaOH (5.0 mL). The reaction mixture was vigorously stirred at rt for 36 h, diluted with water and extracted (3x) with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated. The residual oil was purified by chromatography on SiO_2 (hexanes/EtOAc, 1:4) to afford **244i** (0.030 g, 49%) as a colorless oil: IR (neat) 3059, 2950, 1720, 1666, 1603, 1494, 1455, 1438, 1410, 1310, 1281, 1194, 1111 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.4 Hz, 2 H), 7.89 (ddd, *J* = 11.8, 8.2, 1.5 Hz, 2 H), 7.73 (ddd, *J* = 11.8, 8.3, 1.3 Hz, 2 H), 7.54-7.38 (m, 7 H), 7.32-7.18 (m, 7 H), 7.11 (d, *J* = 7.8 Hz, 2 H), 6.95 (dd, *J* = 6.7, 2.8 Hz, 2 H), 6.33 (s, 1 H), 5.88 (s, 1 H), 4.65 (ddd, *J* = 14.7, 11.1, 2.7 Hz, 1 H), 4.55 (d, *J* = 9.8 Hz, 1 H), 4.39 (ddd, *J* = 15.1, 5.1, 1.9 Hz, 1 H), 3.92 (s, 3 H), 3.32 (d, *J* = 12.6 Hz, 1 H), 3.02 (d, *J* = 12.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.73, 146.54, 143.57, 142.56, 137.82, 136.73, 133.10, 132.48, 132.35, 131.78, 131.38, 130.79, 129.78, 129.66, 128.73, 128.41, 128.32,

128.09, 127.07, 126.84, 126.56, 124.94, 121.32, 69.09, 58.89, 52.10, 49.00, 46.89; MS (EI) *m/z* (rel. intensity) 607 (M^+, 40), 407 (70), 307 (9), 217 (18), 201 (100); HRMS (EI) calc for $C_{28}H_{24}NO_2$ (M-$C_{12}H_{10}OP$) 406.1807, found 406.1814.



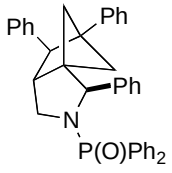
244j

(4*R,5*R**,*Z*)-5-Cyclohexyl-2-phenyl-6-tosyl-8-((triisopropylsilyl)methylene)-6-azaspiro[3.4]oct-1-ene (244j).** A solution of amide **123d** (0.068 g, 0.17 mmol), (3-bromoprop-1-ynyl)triisopropylsilane[478] (0.24 g, 0.86 mmol) and Bu_4NHSO_4 (0.029 g, 0.086 mmol) in PhMe (5.0 mL) was treated with 50 % aq NaOH (5.0 mL). The reaction mixture was vigorously stirred at rt for 24 h, diluted with water and extracted (3x) with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **244k** (0.062 g, 62%) as a colorless foam: IR (neat), 1626, 1449, 1349, 1162 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.2 Hz, 2 H), 7.36-7.30 (m, 5 H), 7.29 (m, 2 H), 6.12 (s, 1 H), 5.45 (app. t, *J* = 2.1 Hz, 1 H), 4.29 (dd, *J* = 16.0, 2.0 Hz, 1 H), 4.13 (dd, *J* = 16.0, 1.9 Hz, 1 H), 3.77 (d, *J* = 3.2 Hz, 1 H), 2.49 (s, 3 H), 1.96 (d, *J* = 12.2 Hz, 1 H), 1.83 (d, *J* = 12.2 Hz, 1 H), 1.77-1.68 (m, 7 H), 1.85-0.91 (m, 25 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 146.9, 143.4, 136.1, 133.6, 129.6, 128.4, 127.7, 125.3, 124.7, 112.7, 71.1, 57.2, 52.8, 47.3, 43.6, 31.1, 28.2, 26.5 (2x), 26.2, 21.5, 19.0, 18.8, 11.8; MS (EI) *m/z* (rel. intensity) 589 (M^+, 30), 506 (100), 434 (17); HRMS (EI) calc for $C_{36}H_{51}NO_2SSi$ 589.3410, found 589.3397.



245

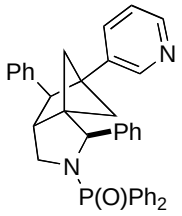
(4*R*,5R*,Z*)-8-Benzylidene-2,5-diphenyl-6-azaspiro[3.4]oct-1-ene hydrogenchloride salt (245). Amide **244g** (0.031 g, 0.056 mmol) was dissolved in MeOH (1.0 mL), cooled to 0 ^{o}C and gaseous HCl was bubbled for ca. 5 min. The reaction mixture was stirred at 0 ^{o}C for 1 h, Et_2O (10 mL) was added and the precipitate was colleted to afford **245** (0.016 g, 71%) as a white solid: Mp. 223.7 ^{o}C (decomp., MeOH/Et_2O); IR (KBr) 3432, 3025, 2831, 2697, 2568, 2463, 2362, 1627, 1489, 1457, 1410 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.7 (br s, 1 H), 7.35-7.29 (m, 13 H), 7.21 (d, *J* = 7.5 Hz, 1 H), 6.59 (s, 1 H), 6.05 (s, 1 H), 4.84 (s, 1 H), 4.51 (app. t, *J* = 17.2 Hz, 1 H), 3.29 (d, *J* = 13.0 Hz, 1 H), 3.01 (d, *J* = 12.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.88, 137.18, 135.73, 133.53, 133.09, 129.21, 128.90, 128.86, 128.77, 128.46, 128.39, 127.84, 127.71, 125.18, 124.45, 123.72, 67.37, 56.04, 46.71, 44.60; HRMS (TOF-ES) calc for $C_{26}H_{24}N$ ((M-Cl)+H) 350.1909, found 350.1880.



247a

(2*S*,5R*,6S)-3-(*N*-(*P,P*-Diphenylphosphinyl))-2,6,7-triphenyl-3-azatricyclo[5.1.1.0^{1,5}]nonane (247a).** Amide **98** (0.038 g, 0.088 mmol), (*E*)-cinnamyl bromide (0.0.087 g, 0.44 mol), Bu_4NHSO_4 (0.015 g, 0.044 mmol) were dissolved in PhMe (4.0 mL) and

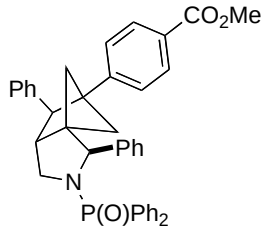
treated with 50% aq NaOH (4.0 mL). The reaction mixture was vigorously stirred at rt for 2 h, diluted with water, and extracted (3x) with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **274a** (0.029 g, 59%) as a colorless oil: IR (neat) 1601, 1496, 1439, 1202, 1120, 1111 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.04-7.99 (m, 2 H), 7.81-7.75 (m, 2 H), 7.52-7.48 (m, 2 H), 7.39-7.22 (m, 9 H), 7.15-7.06 (m, 6 H), 6.90-6.89 (m, 4 H), 4.63 (d, *J* = 9.6 Hz, 1 H), 3.68 (app. t, *J* = 8.4 Hz, 1 H), 3.51 (app. q, *J* = 9.2 Hz, 1 H), 3.34 (bs, 1 H), 3.06 (bs, 1 H), 2.52 (t, *J* = 6.9 Hz, 1 H), 1.98 (d, *J* = 6.3 Hz, 1 H), 1.92 (d, *J* = 6.7 Hz, 1 H), 1.78 (t, *J* = 8.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.61, 141.57, 141.29, 141.09, 132.43, 132.31, 132.25, 132.12, 131.60, 128.52, 128.36, 128.29, 128.26, 127.97, 127.78, 126.62, 126.05, 125.98, 125.92, 62.60, 59.26, 58.94, 58.88, 53.79, 51.34, 51.26, 49.09, 48.59, 39.22; MS (EI) *m/z* (rel. intensity) 551 (M^+, 59), 434 (7), 350 (30), 306 (25), 230 (28), 201 (100); HRMS (EI) calc for $C_{38}H_{34}NOP$ 551.2378, found 551.2360.



247b

(*2S*,5R*,6S)-3-(*N*-(*P,P*-Diphenylphosphinyl))-2,6-diphenyl-7-(pyridin-3-yl)-3-azatricyclo[5.1.1.0^{1,5}]nonane (247b).** A solution of amide **114c** (0.051 g, 0.12 mmol), (*E*)-cinnamyl bromide (0.012 g, 0.59 mmol) and Bu_4NHSO_4 (0.020 g, 0.058 mmol) in PhMe (5.0 mL) and 50 % aq NaOH (5.0 mL) was vigorously stirred at rt for 1 h, diluted with water, and extracted (3x) with EtOAc. The combined organic layers were washed with water and brine, dried

(Na_2SO_4), and evaporated. Purification of the residue by chromatography on SiO_2 (hexanes/EtOAc/MeOH, 1:8:1) afforded **247b** (0.021 g, 32%) as a colorless oil: IR (neat) 3057, 3028, 2974, 2880, 1601, 1495, 1481, 1451, 1439, 1416, 1350, 1300, 1264, 1234, 1197, 1121 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (bs, 1 H), 8.03 (bs 1 H), 7.93-7.86 (m, 2 H), 7.67-7.60 (m, 2 H), 7.37-7.33 (m, 3 H), 7.24-7.16 (m, 4 H), 7.13-7.06 (m, 4 H), 6.97-6.90 (m, 5 H), 6.46 (dd, *J* = 6.1, 3.1 Hz, 2 H), 4.51 (d, *J* = 9.9 Hz, 1 H), 3.55 (app t, *J* = 8.6 Hz, 1 H), 3.38 (q, *J* = 9.9 Hz, 1 H), 3.21 (d, *J* = 4.0 Hz, 1 H), 2.97 (bs, 1 H), 2.42 (t, *J* = 7.0 Hz, 1 H), 1.89 (d, *J* = 6.9 Hz, 1 H), 1.80 (d, *J* = 7.0 Hz, 1 H), 1.70 (t, *J* = 7.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.89, 147.56, 141.38, 140.59, 133.66, 132.48, 132.36, 132.28, 132.16, 131.66, 131.56, 128.61, 128.45, 128.30, 128.12, 128.05, 127.98, 127.89, 126.83, 126.54, 125.96, 122.75, 62.53, 59.57, 59.51, 57.25, 54.03, 51.27, 51.19, 49.07, 48.33, 39.41; MS (EI) *m/z* (rel. intensity) 552 (M^+, 31), 461 (6), 434 (7), 351 (46), 320 (21), 232 (25), 201 (61), 91 (100); HRMS (EI) calc for $C_{37}H_{33}N_2OP$ 552.2331, found 552.2309.

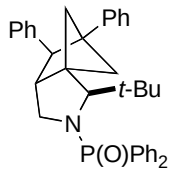


247c

(*2S*,5R*,6S)-3-(*N*-(*P*,*P*-Diphenylphosphinyl))-7-((4-methoxycarbonyl)phenyl)-2,6-diphenyl-3-azatricyclo[5.1.1.0^{1,5}]nonane (247c) from (*E*)-cinnamyl bromide.** According to General Protocol I, a solution of amide **113** (0.030 g, 0.061 mmol), (*E*)-cinnamyl bromide (0.069 g, 0.30 mmol) and Bu_4NHSO_4 (0.010 g, 0.030 mmol) in PhMe (3.0 mL) was treated with 50% aq NaOH (3.0 mL). The reaction mixture was vigorously stirred at rt for 2 h, diluted with water, and

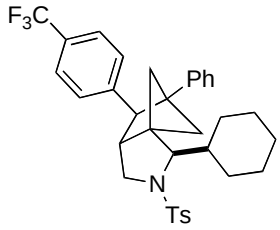
extracted (3x) with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **111** (0.034 g, 93%) as a colorless oil: IR (neat) 3059, 3027, 2949, 1720, 1611, 1495, 1451, 1438, 1310, 1280, 1196, 1111 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 10.5, 7.6 Hz, 2 H), 7.69 (d, *J* = 8.5 Hz, 2 H), 7.64 (dd, *J* = 11.5, 7.5 Hz, 2 H), 7.40-7.35 (m, 3 H), 7.21 (t, *J* = 7.7 Hz, 3 H), 7.16 (d, *J* = 8.0 Hz, 1 H), 7.11 (dd, *J* = 7.6, 2.8 Hz, 4 H), 6.95-6.94 (m, 3 H), 6.81 (d, *J* = 8.2 Hz, 2 H), 6.71 (s, 2 H), 4.50 (d, *J* = 9.8 Hz, 1 H), 3.75 (s, 3 H), 3.55 (t, *J* = 8.5 Hz, 1 H), 3.38 (q, *J* = 9.9 Hz, 1 H), 3.23 (d, *J* = 4.1 Hz, 1 H), 2.96 (bs, 1 H), 2.42 (t, *J* = 8.3 Hz, 1 H), 1.87 (d, *J* = 6.4 Hz, 1 H), 1.80 (d, *J* = 6.9 Hz, 1 H), 1.68 (t, *J* = 8.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.14, 146.65, 141.60, 141.54, 140.93, 132.60, 132.48, 132.40, 132.28, 131.70, 129.41, 128.76, 128.60, 128.45, 128.23, 128.12, 128.04, 126.92, 126.47, 126.28, 126.06, 62.66, 59.40, 59.32, 59.26, 54.21, 52.07, 51.38, 51.30, 49.24, 48.78, 48.35, 39.42; MS (EI) *m/z* (rel. intensity) 609 (M^+, 61), 532 (3), 408 (33), 344 (19), 333 (21), 320 (21), 306 (27), 230 (41), 201 (100); HRMS (EI) calc for $C_{40}H_{36}NO_3P$ 609.2433, found 609.2432.

Synthesis of 247c from (*Z*)-cinnamyl bromide 268. According to General Protocol C, a solution of amide **113** (0.036 g, 0.073 mmol), freshly prepared (*Z*)-cinnamyl bromide **268** (0.071 g, 0.36 mmol) and Bu_4NHSO_4 (0.012 g, 0.036 mmol) in PhMe (3.0 mL) and 50% aq NaOH (3.0 mL) was vigorously stirred at rt for 1 h. The reaction mixture was diluted with water and extracted (3x) with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated. Purification of the residue by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **247c** (0.023 g, 52%).



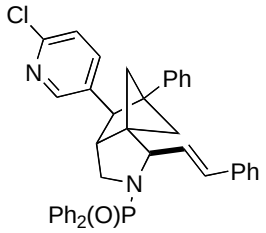
247d

(*2R*,5R*,6S)-3-(*N*-(*P,P*-Diphenylphosphinyl))-2-*tert*-butyl-6,7-diphenyl-3-azatricyclo[5.1.1.0^{1,5}]nonane (247d)**. Amide **118a** (0.027 g, 0.065 mmol), (*E*)-cinnamyl bromide (0.064 g, 0.32 mmol) and Bu_4NHSO_4 (0.016 g, 0.032 mmol) were dissolved in PhMe (3.0 mL), followed by addition of 50% aq NaOH (3.0 mL). The reaction mixture was stirred at rt for 2 h, diluted with water, extracted (3x) with EtOAc and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexane/EtOAc, 1:4) afforded **247d** (0.019 g, 54%) as a colorless oil: IR (neat) 1479, 1437, 1201, 1121, 1108 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85-7.79 (m, 4 H), 7.57-7.46 (m, 6 H), 7.12-7.05 (m, 6 H), 6.95-6.93 (m, 2 H), 6.84-6.82 (m, 2 H), 3.81 (d, *J* = 8.6 Hz, 1 H), 3.46-3.42 (m, 2 H), 3.23-3.22 (m, 1 H), 3.08 (d, *J* = 4.1 Hz, 1 H), 3.04-2.94 (m, 1 H), 2.48 (dd, *J* = 9.3, 7.2 Hz, 1 H), 2.24 (d, *J* = 6.9 Hz, 1 H), 1.81 (dd, *J* = 14.5, 6.8 Hz, 1 H), 1.70 (d, *J* = 6.5 Hz, 1 H), 0.97 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.71, 141.22, 133.73, 132.60, 132.48, 132.34, 132.21, 131.51, 128.31, 128.27, 128.24, 128.14, 128.08, 127.95, 127.83, 127.70, 126.02, 125.97, 125.90, 67.69, 59.36, 56.41, 56.35, 55.60, 53.74, 53.65. 51.05, 50.11, 41.15, 36.57, 28.41; MS (EI) *m/z* (rel. intensity) 475 (65), 280 (32), 201 (100); HRMS (EI) calc for $C_{32}H_{29}NOP$ (M-C_4H_9) 474.1987, found 474.2001.



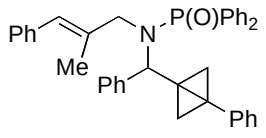
247e

(2*R,5*R**,6*S**)-3-(*N*-Tosyl)-2-cyclohexyl-7-phenyl-6-(4-trifluoromethylphenyl)-3-azatricyclo[5.1.1.0^{1,5}]nonane (247e).** Amide **123d** (0.038 g, 0.088 mmol), (*E*)-1-(3-bromoprop-1-enyl)-4-(trifluoromethyl)benzene **246b**[479] (0.0.087 g, 0.44 mol) and Bu_4NHSO_4 (0.015 g, 0.044 mmol) were dissolved in PhMe (4.0 mL) and treated with 50% aq NaOH (4.0 mL). The reaction mixture was vigorously stirred at rt for 2 h, diluted with water, and extracted (3x) with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **247e** (0.029 g, 59%) as a colorless oil: IR (neat) 2928, 2854, 1618, 1326, 1164 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 7.95 (d, *J* = 8.0 Hz, 2 H), 7.22-7.17 (m, 2 H), 6.98-6-94 (m, 5 H), 6.76 (d, *J* = 8.0 Hz, 2 H), 6.61-6.58 (m, 2 H), 3.79 (t, *J* = 8.0 Hz, 1 H), 3.69 (d, *J* = 5.4 Hz, 1 H), 3.07 (t, *J* = 9.7 Hz, 1 H), 2.91 (d, *J* = 4.0 Hz, 1 H), 2.76-2.73 (m, 1 H), 2.1-1.7 (m, 4 H), 1.99 (s, 3 H), 1.46-1.25 (m, 7 H), 1.06-1.04 (m, 4 H); ^{13}C NMR (75 MHz, C_6D_6) δ 145.6, 143.0, 140.5, 135.9, 130.2, 129.5, 128.6, 128.5, 127.9, 126.7, 126.2, 125.2, 66.4 (C2), 59.8 (C7), 55.7, 53.2, 52.6, 51.1, 49.1, 42.9, 40.6, 30.9, 30.0, 27.0, 26.8, 21.1; MS (EI) *m/z* (rel. intensity) 579 (M^+, 2), 496 (100), 424 (7); HRMS (EI) calc for $C_{34}H_{36}NO_2FS$ 579.2419, found 579.2418.



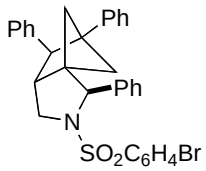
247f

(*2R*,5R*,6S)-3-(*N*-(*P,P*-Diphenylphosphinyl))-6-(6-chloro-3-pyridyl)-7-phenyl-2-(1-styryl)-3-azatricyclo[5.1.1.0^{1,5}]nonane (247f).** Amide **123f** (0.035 g, 0.076 mmol), bromide **246c**[480] (0.088 g, 0.38 mmol), and Bu_4NHSO_4 (0.013 g, 0.038 mmol) were suspended in PhMe (4.0 mL), treated with 50% aq NaOH (4.0 mL) and vigorously stirred at rt for 2 h. The reaction mixture was diluted with water (10 mL), extracted (2 x 10 mL) with EtOAc and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **247f** (0.037 g, 78%) as a colorless oil: IR (ATR) 3077, 1459, 1436, 1105 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32-8.12 (m, 4 H), 7.63-7.22 (m, 17 H), 7.04-7.02 (m, 2 H), 6.21-6.13 (m, 2 H), 4.29 (t, *J* = 6.8 Hz, 1 H), 3,69-3.64 (m, 1 H), 3.47-3.42 (m, 1 H), 3.16 (s, 1 H), 2.56 (d, *J* = 8.2 Hz, 1 H), 2.24 (t, *J* = 8.6 Hz, 1 H), 2.16 (d, *J* = 7.2 Hz, 1 H), 2.07 (d, *J* = 7.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.41, 149.25, 140.09, 138.13, 136.67, 135.71, 132.68, 132.57, 132.46, 131.78, 131.49, 128.63, 128.51, 128.47, 128.31, 128.17, 127.61, 126.73, 126.50, 125.92, 123.43, 60.95, 60.20, 57.98, 57.92, 52.42, 52.33, 50.91, 48.70, 48.35, 38.72; MS (EI) *m/z* (rel. intensity) 612 (M$^+$, 25), 411 (81), 244 (67), 201 (100); HRMS (EI) calc for $C_{39}H_{22}N_2OPCl$ [M-H] 611.2019, found 611.2040.



247g

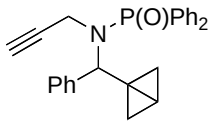
***N*-((*E*)-2-Methyl-3-phenylallyl)-*N*-(phenyl(3-phenylbicyclo[1.1.0]but-1-yl)methyl)-*P,P*-diphenylphosphinamide (247g).** Amide **98** (0.060 g, 0.14 mmol), 3-bromo-1-phenyl-2-methylpropene (0.15 g, 0.69 mmol) and Bu_4NHSO_4 (0.029 g, 0.069 mmol) were dissolved in PhMe (6.0 mL) and treated with 50% aq NaOH (6.0 mL). The reaction mixture was vigorously stirred at rt for 2 h, diluted with water, and extracted (3x) with EtOAc. The combined organic layers were washed with water, brined, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **247g** (0.056 g, 71%) as a colorless oil: IR (neat) 3059, 2930, 1712, 1601, 1493, 1439, 1266, 1179 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98-7.95 (m, 4 H), 7.45-6.93 (m, 19 H), 6.67-6.64 (m, 2 H), 6.25 (s, 1 H), 4.47 (d, *J* = 10.8 Hz, 1 H), 3.82 (dd, *J* = 15.7, 11.0 Hz, 1 H), 3.63 (dd, *J* = 16.0, 10.6 Hz, 1 H), 2.29 (d, *J* = 6.3 Hz, 1 H), 1.80 (d, *J* = 6.6 Hz, 1 H), 1.74 (s, 3 H), 0.68 (s, 1 H), 0.57 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.73, 132.70, 132.58, 132.41, 132.29, 131.09, 128.97, 128.70, 128.16, 128.14, 128.00, 127.76, 127.68, 127.60, 126.98, 126.23, 125.35, 124.80, 63.20, 55.19, 36.37, 33.40, 25.99, 25.92, 22.43, 15.88; MS (EI) *m/z* (rel. intensity) 565 (M^+, 23), 474 (19), 364 (25), 346 (11), 319 (19), 230 (22), 201 (98), 118 (100); HRMS (EI) calc for $C_{39}H_{36}NOP$ 565.2534, found 565.2540.



247i

(*4S*,5R*,8S)-7-(*N*-(4-Bromobenzenesulfonyl))-3,4,8-triphenyl-7-azatricyclo[3.3.1^{1,3}.0]octane (247i).** Amide **247a** (0.038 g, 0.069 mmol) was dissolved in MeOH

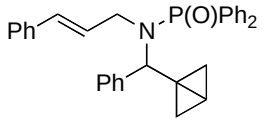
(1.0 mL), cooled on ice and HCl was bubbled through for 10 min. The reaction mixture was stirred at 0 ^{o}C for additional 45 min, the solvent was removed in vacuo and Et_3N (0.096 mL, 0.69 mmol) and 4-$BrC_6H_4SO_2Cl$ (0.036 g, 0.14 mmol) were added. The reaction mixture was stirred at rt for 14 h, quenched with sat. NH_4Cl, extracted (3 x 5 mL) with CH_2Cl_2 and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **247i** (0.020 g, 51%) as a white solid: Mp. 230.0-231.8 ^{o}C (CH_2Cl_2/hexanes); IR (ATR) 3024, 1601, 1573, 1494, 1469, 1344 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.5 Hz, 2 H), 7.70 (d, *J* = 8.5 Hz, 2 H), 7.41-7.33 (m, 5 H), 7.18-7.10 (m, 6 H), 6.87-6.84 (m, 4 H), 4.93 (s, 1 H), 4.06 (t, *J* = 8.3 Hz, 1 H), 3.35 (t, *J* = 9.5 Hz, 1 H), 3.30-3.27 (m, 1 H), 2.90 (app. t, *J* = 10.6 Hz, 1 H), 2.04 (d, *J* = 7.2 Hz, 1 H), 1.82 (t, *J* = 7.4 Hz, 1 H), 1.63 (d, *J* = 6.5 Hz, 1 H), 1.57 (dt, *J* = 9.3, 7.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.5, 140.3, 138.8, 137.1, 132.2, 128.8, 128.3, 128.0, 127.9 (2), 127.6, 127.3, 126.3 (2), 126.0, 125.9, 64.1, 59.1, 57.6, 53.0, 51.1, 50.1, 47.9, 40.0; MS (EI) *m/z* (rel. intensity) 571 (M^+, 5), 350 (61), 232 (79), 118 (100); HRMS (EI) calc for $C_{32}H_{28}NO_2SBr$ 569.1024, found 569.1019.



248a

***N*-((Bicyclo[1.1.0]but-1-yl)(phenyl)methyl)-*N*-(prop-2-ynyl)-*P,P*-diphenylphosphinamide (248a).** Amide **120a** (0.11 g, 0.31 mmol), propargyl bromide (0.23 mL, 1.5 mmol, c = 80% in PhMe) and Bu_4NHSO_4 (0.052 g, 0.15 mmol) were dissolved in PhMe (10 mL) and treated with 50% aq NaOH (10 mL). The reaction mixture was vigorously stirred at rt for 12 h, diluted with

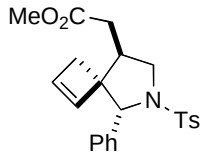
water and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **248a** (0.076 g, 63%) as a colorless oil: IR (neat) 3058, 2936, 2222, 1493, 1438, 1200, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.06-7.99 (m, 4 H), 7.64-7.30 (m, 11 H), 4.96 (d, *J* = 8.9 Hz, 1 H), 3.88 (dd, *J* = 11.1, 2.4 Hz, 2 H), 2.30 (t, *J* = 2.4 Hz, 1 H), 1.83 (dd, *J* = 6.3, 2.9 Hz, 1 H), 1.32 (s, 1 H), 1.26 (dd, *J* = 6.3, 2.8 Hz, 1 H), 0.56 (s, 1 H), 0.43 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.40, 139.37, 133.46, 133.07, 132.57, 132.44, 132.39, 132.26, 131.74, 131.58, 131.37, 128.30, 128.23, 128.16, 128.10, 128.00, 127.85, 127.16, 81.51, 81.44, 71.78, 62.65, 62.64, 37.05, 36.11, 36.04, 32.71, 12.80, 12.73, 5.20; MS (EI) *m/z* (rel. intensity) 397 (M^+, 9), 358 (23), 256 (6), 201 (100), 196 (32), 158 (49); HRMS (EI) calc for $C_{26}H_{24}NOP$ 397.1596, found 397.1607.



248b

***N*-((Bicyclo[1.1.0]but-1-yl)(phenyl)methyl)-*P*,*P*-diphenylphosphinamide (248b).** Amide **120a** (0.090 g, 0.25 mmol), *(E)*-cinnamyl bromide (0.25 g, 1.3 mmol) and Bu_4NHSO_4 (0.044 g, 0.13 mmol) were dissolved in PhMe (9.0 mL) and treated with 50% aq NaOH (9.0 mL). The reaction mixture was vigorously stirred at rt for 2 h, diluted with water and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **248b** (0.080 g, 67%) as a colorless oil: IR (neat) 2924, 1438, 1199 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88-7.82 (m, 4 H), 7.44-7.12 (m, 16 H), 6.00 (dt, *J* = 15.8, 6.6 Hz, 1 H), 5.81 (d, *J* = 15.9 Hz, 1 H), 4.76

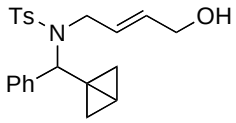
(d, *J* = 8.6 Hz, 1 H), 3.91-3-71 (m, 2 H), 1.76 (dd, *J* = 6.3, 2.8 Hz, 1 H), 1.26 (s, 1 H), 1.04 (dd, *J* = 6.3, 2.8 Hz, 1 H), 0.56 (s, 1 H), 0.19 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.49, 140.43, 136.97, 132.83, 132.70, 132.57, 132.38, 132.26, 131.78, 131.51, 128.54, 128.47, 128.37, 128.30, 128.22, 127.47, 127.32, 126.42, 62.17, 62.13, 48.91, 48.87, 36.45, 32.78, 13.22, 13.15, 5.24; MS (EI) *m/z* (rel. intensity) 475 (M^+, 14), 358 (24), 332 (22), 306 (17), 274 (37), 201 (100), 158 (29); HRMS (EI) calc for $C_{32}H_{30}NOP$ 475.2065, found 475.2067.



249

Methyl 2-((4*S,5*R**,8*R**)-5-phenyl-6-tosyl-6-azaspiro[3.4]oct-1-en-8-yl)acetate (249).** A solution of amide **120b** (0.055 g, 0.18 mmol) in DMF (1.0 mL) was cooled to 0 °C, treated with NaH (8.9 mg, 0.35 mmol), stirred for 10 min and methyl bromocrotonate (0.048 mL, 0.35 mmol) was added. The mixture was stirred at 0 °C for 2 h, warmed up to rt, stirred for 1 h and placed in an oil bath (50 °C) and stirred at this temperature for 22 h. The reaction miture was cooled to rt, quenched with sat. NH_4Cl, extracted (3 x 15 mL) with EtOAc and the combined organic layers were washed with water (3x), brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **249** (0.036 g, 51%) as a colorless oil: IR (ATR) 2948, 1726, 1435, 1347, 1161 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.2 Hz, 2 H), 7.34-7.24 (m, 7 H), 6.07 (d, *J* = 2.8 Hz, 1 H), 5.52 (d, *J* = 2.9 Hz, 1 H), 4.75 (s, 1 H), 3.99 (dd, *J* = 9.6, 7.0 Hz, 1 H), 3.71 (s, 3 H), 3.16 (t, *J* = 9.5 Hz, 1 H), 2.92-2.82 (m, 1 H), 2.46 (s, 3 H), 2.32 (dd, *J* = 16.2, 3.5 Hz, 1 H), 2.24 (d, *J* = 14.2 Hz, 1 H), 2.02 (dd, *J* = 16.2, 10.7 Hz, 1 H), 1.97 (d, *J* = 10.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 143.3, 140.8, 138.4, 136.7, 134.8,

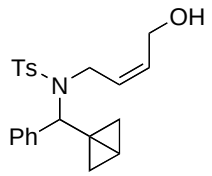
129.4, 128.0, 127.5, 127.4, 127.2, 68.5, 59.7, 52.4, 51.8, 38.0, 35.3, 33.0, 21.5; HRMS (TOF-ES) calc for $C_{23}H_{26}NO_4S$ (M+H) 412.1583, found 412.1583.



251a

(*E*)-*N*-(Bicyclo[1.1.0]but-1-yl(phenyl)methyl)-*N*-(4-hydroxybut-2-enyl)-4-methylbenzenesulfonamide (251a). A solution of amide **120b** (0.20 g, 0.64 mmol) in DMF 5.0 mL) was cooled to 0 ^{o}C, treated with NaH (51 mg, 1.3 mmol), stirrd for 30 min and *(E)*-(4-bromobut-2-enyloxy)(*tert*-butyl)dimethylsilane (0.34 g, 1.3 mmol) was added in one portion. The raction mixture was sirred at 0 ^{o}C for 2 h, quenched with sat. NH_4Cl, extracted (3 x 10 mL) with EtOAc and the combined organic layers were washed with water (3x), brine, dried (Na_2SO_4), and concentrated. The crude mixture was dissolved in THF (5.0 mL), treated with TBAF (1.6 mL, 1.6 mmol, c = 1.0 M in THF), stirred for 30 min and quenched with sat. NH_4Cl. The mixture was extracted with EtOAc, the combined oranic layers were washd with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hex-anes/EtOAc, 1:1) afforded **251a** (0.15 g, 60%) as a colorless oil: IR (ATR) 3530, 2924, 1597, 1449, 1329, 1154 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.3 Hz, 2 H), 7.32-7.09 (m, 7 H), 5.65-5.52 (m, 2 H), 5.35 (s, 1 H), 4.08 (app. t, *J* = 4.2 Hz, 2 H), 3.96 (s, 2 H), 2.39 (s, 3 H), 1.80 (s, 1 H), 1.57 (dd, *J* = 6.3, 2.9 Hz, 1 H), 1.44 (s, 1 H), 1.24 (dd, *J* = 6.3, 2.8 Hz, 1 H), 0.71 (s, 1 H), 0.56 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 139.1, 138.1, 131.8, 129.3, 128.8, 128.3, 127.7, 127.4 (2), 62.8, 62.5, 47.9, 34.4, 31.9, 21.5, 12.2, 3.8; MS (EI) *m/z* (rel. intensity)

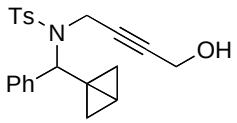
383 (M^+, 1), 366 (2), 352 (2), 324 (3), 306 (1), 298 (2), 28 (15), 91 (100); HRMS (EI) calc for $C_{22}H_{25}NO_2S$ 383.1555, found 383.1537.



251b

(*Z*)-*N*-(Bicyclo[1.1.0]but-1-yl(phenyl)methyl)-*N*-(4-hydroxybut-2-enyl)-4-methylbenzenesulfonamide (251b). A solution of amide **120b** (0.20 g, 0.64 mmol) in DMF 5.0 mL) was cooled to 0 ^oC, treated with NaH (51 mg, 1.3 mmol), stirrd for 30 min and *(Z)*-(4-bromobut-2-enyloxy)(*tert*-butyl)dimethylsilane (0.34 g, 1.3 mmol) was added in one portion. The raction mixture was sirred at 0 ^oC for 2 h, quenched with sat. NH_4Cl, extracted (3 x 10 mL) with EtOAc and the combined organic layers were washed with water (3x), brine, dried (Na_2SO_4), and concentrated. The crude mixture was dissolved in THF (5.0 mL), treated with TBAF (1.6 mL, 1.6 mmol, c = 1.0 M in THF), stirred for 30 min and quenched with sat. NH_4Cl. The mixture was extracted with EtOAc, the combined oranic layers were washd with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:1) afforded **251b** (0.13 g, 52%) as a colorless oil: IR (ATR) 3532, 2971, 1718, 1677, 1344, 1159 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.1 Hz, 2 H), 7.27-7.15 (m, 5 H), 7.13-7.09 (m, 2 H), 5.46 (dtt, *J* = 10.8, 6.9, 1.4 Hz, 1 H), 5.38 (dtt, *J* = 11.1, 6.6, 1.2 Hz, 1 H), 5.27 (s, 1 H), 4.24-4.04 (m, 4 H), 2.64 (t, *J* = 5.7 Hz, 1 H), 2.36 (s, 3 H), 1.52 (dd, *J* = 6.3, 3.0 Hz, 1 H), 1.45 (app. t, *J* = 2.4 Hz, 1 H, 1.22 (dd, *J* = 6.3, 2.7 Hz, 1 H), 0.69 (s, 1 H), 0.55 (s, 1 H); ^{13}C NMR (75 Mz, $CDCl_3$) δ 143.0, 138.7, 137.7, 130.2, 129.7, 129.5, 129.2, 129.0, 128.9,

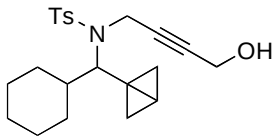
128.8, 128.6, 128.3, 128.1, 127.8, 127.3, 127.1, 62.2, 57.6, 57.4, 42.8, 34.0, 31.5, 21.3, 11.9, 3.5; MS (EI) *m/z* (rel. intensity) 383 (M^+, 1), 366 (7), 352 (6), 324 (7), 298 (6), 228 (45), 155 (60), 143 (62), 128 (71), 91 (100); HRMS (EI) calc for $C_{22}H_{25}NO_3S$ 383.1555, found 383.1543.



253a

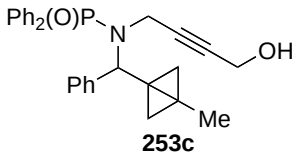
***N*-(Bicyclo[1.1.0]but-1-yl(phenyl)methyl)-*N*-(4-hydroxybut-2-ynyl)-4-methylbenzenesulfonamide (253a).** A solution of amide **120b** (0.50 g, 1.6 mmol) in DMF (10 mL) was cooled to 0 ^oC, treated with NaH (0.13 g, 3.1 mmol) and after 30 min, with bromide **252**[481] (0.82 g, 3.1 mmol). The reaction mixture was stirred at 0 ^oC for 15 min, warmed to rt, stirred for 1 h, quenched with sat. NH_4Cl, and extracted (3 x 10 mL) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. The crude oil was dissolved in THF (10 mL), cooled to 0 ^oC, treated with TBAF (4.0 mL, 4.0 mmol, 1.0 M in THF), stirred for 1 h, and quenched with sat. NH_4Cl. The mixture was extracted with EtOAc and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1 to 1:1) afforded **253a** (0.37 g, 61%) as a colorless oil: IR (ATR) 3543, 22924, 1493, 1331, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.2 Hz, 2 H), 7.32-7.29 (m, 2 H), 7.23 (t, *J* = 0.6 Hz, 2 H), 7.18-7.08 (m, 3 H), 6.90 (d, *J* = 8.0 Hz, 2 H), 5.41 (s, 1 H), 4.24 (qt, *J* = 18.2, 1.7 Hz, 2 H), 3.86 (d, *J* = 5.7 Hz, 2 H), 1.91 (s, 3 H) 1.86 (t, *J* = 5.5 Hz, 1 H), 1.45 (dd, *J* = 6.3, 2.8 Hz, 1 H), 1.31 (br s, 1 H), 1.17 (dd, *J* = 6.3, 2.8 Hz, 1 H), 0.61 (s, 1 H), 0.51 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 138.5, 137.8, 129.1, 128.3, 127.7, 127.7, 127.5, 82.2, 81.7, 62.5, 50.8, 35.6, 34.5, 31.9, 21.5,

11.9, 3.9; MS (EI) *m/z* (rel. intensity) (381, M^+), 328 (5), 304 (12), 260 (7), 226 (27), 208 (36), 194 (28), 167 (46), 155 (54); HRMS (EI) calc for $C_{22}H_{23}NO_3S$ 381.1399, found 381.1387.



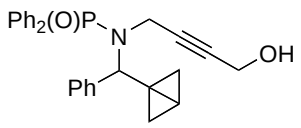
253b

***N*-(Bicyclo[1.1.0]but-1-yl(cyclohexyl)methyl)-*N*-(4-hydroxybut-2-ynyl)-4-methylbenzenesulfonamide (253b).** A solution of **341e** (0.38 g, 1.2 mmol) in DMF (5.0 mL) was cooled to 0 ^oC, treated with NaH (0.094 g, 2.4 mmol, 60%) and after 30 min, neat bromide **252**[481] (0.62 g, 2.4 mmol) was added. The reaction mixture was stirred at 0 ^oC for 1 h, warmed up to rt, stirred for 2 h, quenched with sat. NH_4Cl, and extracted (3x) with EtOAc. The combined organic layers were washed with water (3 x 5 mL), brine, dried (Na_2SO_4), and concentrated. The crude oil was dissolved in dry THF (5.0 mL), cooled to 0 ^oC and treated with TBAF (3.0 mL, 3.0 mmol, 1.0 M in THF). After 30 min, the mixture was quenched with sat. NH_4Cl, extracted (3 x 5 mL) with EtOAc and the organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:1) afforded **253b** (0.37 g, 81%) as a colorless oil: IR (ATR) 2973, 2924, 2851, 1737, 1371, 1336, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.1 Hz, 2 H), 7.27 (d, *J* = 8.1 Hz, 2 H), 4.34-4.27 (m, 1 H), 4.25-4.08 (m, 4 H), 4.03-3.81 (m, 1 H), 2.42 (s, 3 H), 2.03-1.89 (m, 1 H), 1.75-1.43 (m, 7 H), 1.33-0.98 (m, 4 H), 0.98-0.80 (m, 1 H), 0.42 (s, 1 H), 0.12 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 138.6, 129.1, 127.8, 81.9, 81.7, 63.1, 50.9, 40.1, 33.6, 31.0, 30.9, 30.6, 30.2, 26.2 (2), 26.0, 21.5, 10.8, 5.2; HRMS (ESI) calc for $C_{22}H_{29}NO_3NaS$ (M+Na) 410.1777, found 410.1786.



253c

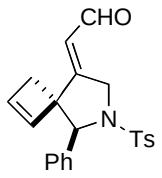
***N*-(4-Hydroxybut-2-ynyl)-*N*-((3-methylbicyclo[1.1.0]but-1-yl)(phenyl)methyl)-*P*,*P*-diphenylphosphinic amide (253c).** A solution of amide **123a** (0.086 g, 0.23 mmol) in dry DMF (5.0 mL) was cooled to 0 ^{o}C, treated with NaH (0.018 g, 0.46 mmol, 60%) ad after 10 min, bromide **252**[482] (0.12 g, 0.46 mmol) was added and the reaction mixture was stirred at 0 ^{o}C for 1 h, quenched with sat. NH_4Cl, diluted with water (10 mL), and extracted (3x 10 mL) with EtOAc. The combined organic layers were washed with water (3 x 10 mL), brine, dried (Na_2SO_4), and concentrated. The crude oil was dried on high vacuum, dissolved in THF (5.0 mL) and treated with TBAF (0.63 mL, 0.63 mmol). After 10 min, the mixture was quenched with water and extracted (3 x 10 mL) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc/MeOH, 1:6:0 to 1:10:1) afforded **253c** (0.074 g, 73%) as a colorless oil: IR (ATR) 3360, 2915, 1437, 1118 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97-7.84 (m, 4 H), 7.47-7.37 (m, 5 H), 7.32-7.22 (m, 5 H), 4.88 (d, *J* = 7.1 Hz, 1 H), 4.20 (app. t, *J* = 1.8 Hz, 2 H), 3.88-3.68 (m, 2 H), 2.48 (br s, 1 H), 1.48 (d, *J* = 6.7 Hz, 1 H), 1.15 (s, 3 H), 0.86 (s, 1 H), 0.42 (s, 1 H), 0.02 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.87, 139.80, 133.56, 133.31, 132.56, 132.43, 132.35, 132.23, 131.83, 131.60, 131.52, 131.48, 131.43, 131.40, 128.34, 128.31, 128.26, 128.22, 128.17, 128.11, 127.37, 83.08, 83.03, 62.28, 62.24, 50.83, 37.88, 36.44, 36.39, 33.68, 14.77, 14.46, 14.40, 11.06; MS (ES) *m/z* (rel. intensity) 464 ([M+Na]$^{+}$, 100), 442 ([M+H]$^{+}$, 15), 404 (5), 202 (19), 186 (64); HRMS (ES) calc for $C_{28}H_{29}NO_2P$ [M+1] 442.1936, found 442.1939.



253d

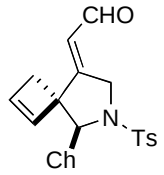
***N*-(Bicyclo[1.1.0]but-1-yl(phenyl)methyl)-*N*-(4-hydroxybut-2-ynyl)-*P,P*-diphenylphosphinic amide (253d).** A solution of **120a** (0.50 g, 1.4 mmol) in dry DMF (10 mL) was cooled to 0 oC and treated with NaH (0.084 g, 2.1 mmol, 60%) and stirred at 0 ^{o}C for 30 min. Bromide **252**[482] (0.79 g, 2.8 mmol) was added via syringe and the reaction mixture was allowed to warm up to rt, stirred for 2.5 h, quenched with sat. NH_4Cl and extracted (3x40 mL) with EtOAc. The organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded alkylated product (0.66 g, 91%) as a colorless oil. This oil (0.65 g, 1.2 mmol) was dissolved in dry THF (25 mL), cooled on ice and treated with TBAF (2.4 mL, 2.4 mmol, c = 1.0 M in THF). After 10 min at 0 ^{o}C, the reaction mixture was quenched with sat. NH_4Cl, diluted with water, extracted (2x20 mL) with EtOAc and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (Hexanes/EtOAc, 1:6) afforded **253d** (0.40 g, 71% over two steps) as a coloress oil: IR (ATR) 3358, 2924, 1437, 1183, 1105 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01-7.90 (m, 4 H), 7.49-7.38 (m, 6 H), 7.36-7.22 (m, 4 H), 4.89 (d, *J* = 7.3 Hz, 1 H), 4.21 (s, 2 H), 3.83-3.80 (m, 1 H), 3.77-3.69 (m, 1 H), 1.87 (dd, *J* = 6.3, 2.8 Hz, 1 H), 1.29 (s, 1 H), 1.05 (dd, *J* = 6.3, 2.7 Hz, 1 H), 0.62 (s, 1 H), 0.16 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.53, 139.43, 133.30, 132.99, 132.54, 132.41, 132.28, 131.56, 131.61, 131.57, 131.53, 131.27, 128.42, 128.34, 128.25, 128.17, 127.85, 127.29, 83.12, 82.80, 82.74, 62.58, 62.54, 50.69, 37.23, 36.43, 36.38, 32.40, 12.92, 12.86, 5.35; MS (EI) *m/z* (rel. intensity) 427 (M^+, 6), 374 (4), 306

(20), 273 (17), 201 (100), 174 (76), 158 (62); HRMS (EI) calc for $C_{27}H_{26}NO_2P$ 427.1701, found 427.1692.



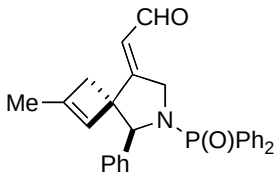
254

(*Z*)-2-((4*S,5*S**)-5-Phenyl-6-tosyl-6-azaspiro[3.4]oct-1-en-8-ylidene)acetaldehyde (254).** A solution of **253a** (0.020 g, 0.054 mmol) in CH_2Cl_2 (1.0 mL) was cooled to 0 ^oC, treated with 2,6-lutidine (31 μL, 0.27 mmol) and solid DMP (0.045 g, 0.11 mmol) was added. The reaction mixture was stirred at 0 ^oC for 4 h, diluted with Et_2O (10 mL), filtered through a pad of SiO_2, and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 2:1 to 1:1) afforded **254** (0.013 g, 64%) as a colorless oil: IR (ATR) 2922, 1675, 1618, 1346, 1161 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.80 (d, *J* = 5.2 Hz, 1 H), 7.55 (d, *J* = 8.2 Hz, 2 H), 7.27-7.19 (m, 5 H), 7.01 (d, *J* = 7.4 Hz, 2 H), 6.36 (d, *J* = 2.9 Hz, 1 H), 6.11-6.09 (m, 1 H), 5.42 (d, *J* = 2.9 Hz, 1 H), 5.08 (s, 1 H), 4.78 (dd, *J* = 17.6, 2.2 Hz, 1 H), 4.73 (dd, *J* = 17.6, 2.2 Hz, 1 H), 2.62 (d, *J* = 13.1 Hz, 1 H), 2.41 (s, 3 H), 2.38 (d, *J* = 13.2 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.8, 164.5, 143.5, 139.3, 135.5, 134.1, 129.5, 128.4, 127.8, 127.2, 126.6, 119.1, 68.8, 61.8, 50.3, 49.0, 21.5; MS (EI) *m/z* (rel. intensity) 379 (M^+, 20), 366 (11), 350 (9), 260 (34), 24 (18), 194 (34), 155 (41), 134 (37); HRMS (EI) calc for $C_{22}H_{21}NO_3S$ 379.1242, found 379.1227.



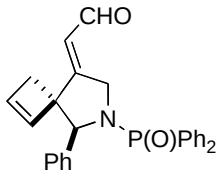
255

(*Z*)-2-((4S*,5*S**)-5-Cyclohexyl-6-tosyl-6-azaspiro[3.4]oct-1-en-8-ylidene)acetaldehyde (255).** A solution of **253d** (0.052 g, 0.13 mmol) in CH_2Cl_2 (1.0 mL) was cooled to 0 ^oC, treated with 2,6-lutidine (78 μL) and solid DMP (0.11 g, 0.27 mmol) was added. The reaction mixture was stirred at 0 ^oC for 3 h, quenched with sat. $NaHCO_3$ and sat. $Na_2S_2O_3$, stirred at rt for 20 min, and extracted (3 x 5 mL) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. The crude mixture showed 91:9 mixture of diastereomers (^1H NMR, aldehyde peak). Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1 to 1:1) gave unstable **255** (0.027 g, 53%) as a colorless oil: IR (ATR) 2922, 2850, 1674, 1448, 1346, 1161, 1092 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.71 (d, *J* = 5.6 Hz, 1 H), 7.75 (d, *J* = 8.5 Hz, 12 H), 7.30 (d, *J* = 8.2 Hz, 2 H), 6.24-6.23 (m, 1 H), 6.01 (dt, *J* = 5.6, 2.4 Hz, 1 H), 5.87 (d, *J* = 2.9 Hz, 1 H), 4.60, 4.54 (ABX, *J* = 19.0, 2.2 Hz, 2 H), 3.89 (d, *J* = 3.1 Hz, 1 H), 2.40 (s, 3 H), 1.95 (d, *J* = 13.1 Hz, 1 H), 1.78-1.63 (m, 5 H), 1.54-1.53 (m, 1 H), 1.39-1.16 (m, 1 H), 1.15-0.84 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.1, 168.1, 143.8, 139.0, 136.0, 134.2, 129.8, 127.6, 117.3, 70.3, 60.5, 51.7, 49.5, 43.4, 30.8, 28.1, 26.3 (2), 26.1, 21.6; HRMS (EI) calc for $C_{22}H_{27}NO_3S$ 385.1712, found 385.1725.



256

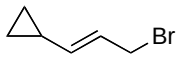
(*Z*)-2-((4*S,5*S**)-6-(Diphenylphosphoryl)-2-methyl-5-phenyl-6-azaspiro[3.4]oct-1-en-8-ylidene)acetaldehyde (256).** A solution of alcohol **253c** (0.020 g, 0.045 mmol) in CH_2Cl_2 (0.50 mL) was cooled to 0 ^oC, treated with 2,6-lutidine (31 μL) and solid DMP (0.048 g, 0.11 mmol). The reaction mixture was stirred at 0 ^oC for 2.5 h, quenched with sat. NH_4Cl and sat. $NaHCO_3$, and extracted (3 x 2 mL) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. The crude mixture showed 94:6 ratio of diastereomers (^1H NMR, aldehyde peak). Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **256** (0.010 g, 51%) as a colorless oil: IR (ATR) 3055, 2940, 1670, 1614, 1437, 1196, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.69 (d, *J* = 6.2 Hz, 1 H), 7.91-7.84 (m, 2 H), 7.76-7.68 (m, 2 H), 7.57-713 (m, 4 H), 7.31-7.23 (m, 5 H), 6.95-6.92 (m, 2 H), 6.01-5.99 (m, 1 H), 5.10 (d, *J* = 1.44 Hz, 1 H), 4.70-4.56 (m, 3 H), 2.98 (d, *J* = 13.0 Hz, 1 H), 2.54 (d, *J* = 13.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.28, 169.23, 169.17, 149.50, 141.68, 141.61, 132.66, 132.45, 132.41, 132.32, 132.29, 132.17, 132.07, 132.04, 131.95, 131.92, 128.85, 128.68, 128.58, 128.43, 128.27, 127.28, 126.37, 125.93, 118.81, 68.61, 59.14, 59.10, 51.42, 49.42, 49.39, 16.95; LC-MS (ESI) *m/z* (rel. intensity) 462.0 ($[M+Na]^+$, 40), 446.0 (61), 440.0 ($[M+H]^+$, 41), 201.1 (100).



257

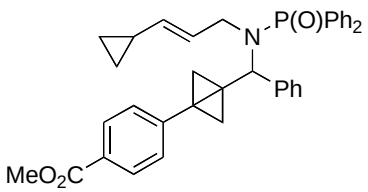
(*Z*)-2-((4*S,5*S**)-6-(Diphenylphosphoryl)-5-phenyl-6-azaspiro[3.4]oct-1-en-8-ylidene)acetaldehyde (257).** A solution of **253d** (0.035 g, 0.08 mmol) and 2,6-lutidine (0.047

mL, 0.40 mmol) in CH_2Cl_2 (3.0 mL) was cooled to 0 °C, and treated with solid DMP (0.069 g, 0.16 mmol). The reaction mixture was stirred at rt for 8 h, quenched with sat. $Na_2S_2O_3$, and sat. $NaHCO_3$ and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded crude, unstable **257** (0.021 g, 59%) as colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (d, *J* = 5.9 Hz, 1 H), 7.89 (dd, *J* = 11.7, 7.8 Hz, 2 H), 7.74 (dd, *J* = 11.7, 8.0 Hz, 2 H), 7.48-7.37 (m, 4 H), 7.32-7.15 (m, 5 H), 7.96 (dd, *J* = 5.6, 7.2 Hz, 2 H), 6.41 (s, 1 H), 6.05 (dd, *J* = 5.7, 3.1 Hz, 1 H), 5.43 (d, *J* = 2.5 Hz, 1 H), 5.35 (br s, 1 H), 4.69-4.59 (m, 2 H), 3.11 (d, *J* = 13.4 Hz, 1 H), 2.69 (d, *J* = 13.3 Hz, 1 H).



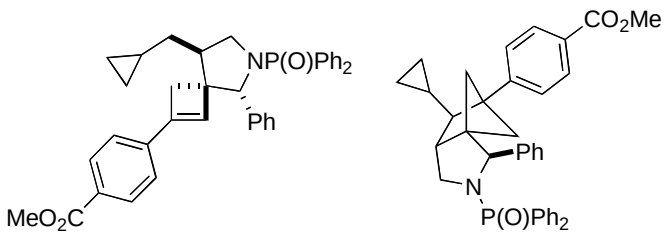
265a

(*E*)-3-Bromo-1-cyclopropylpropene (265a). Triphenylphosphine (2.1 g, 8.2 mmol) was dissolved in CH_2Cl_2 (40 mL), cooled to 0 °C and treated with Br_2 (0.42 mL, 8.2 mmol). The mixture was stirred at 0 °C for 10 min (precipitate formed), imidazole was added (0.69 g, 10 mmol) and after an additional 10 min, a solution of (*E*)-3-cyclopropylprop-2-en-1-ol[482] (0.50 g, 5.1 mmol) in CH_2Cl_2 (20 ml) was added. The reaction mixture was stirred at 0 °C for 25 min, poured into dry pentane and filtered through a pad of SiO_2 (washed with pentane). The solvent was removed *in vacuo* and the crude bromide **265a** (0.72 g, 88%) was used immediately for the next step: ^{1}H NMR (300 MHz, $CDCl_3$) δ (characteristic signals) 5.77-5.68 (m, 1 H), 4.07 (dd, *J* = 15.2, 8.8 Hz, 1 H), 4.07 (d, *J* = 5.0 Hz, 2 H), 0.76-0.71 (m, 3 H), 0.41-0.36 (m, 2 H).



266

***N*-((3-(4-Methoxycarbonylphenyl)bicyclo[1.1.0]but-1-yl)(phenyl)methyl)-*N*-(3-cyclopropylallyl)-*P,P*-diphenylphosphinamide (266).** According to General Protocol C, a solution of amide **113** (0.078 g, 0.15 mmol), freshly prepared cyclopropylallyl bromide **265a** (0.13 g, 0.79 mmol) and Bu_4NHSO_4 (0.027 g, 0.080 mmol) in PhMe (7.0 mL) was treated with 50% aq NaOH (7.0 mL), and vigorously stirred at rt for 1 h. The reaction mixture was diluted with water and extracted (3x) with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated. The resulting oil was purified by chromatography on a short pad of SiO_2 (hexanes/EtOAc, 1:4) to afford crude, unstable amide **266** (0.062 g, 68%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08-7.93 (m, 6 H), 7.87-7.84 (m, 7 H), 7.54-7.53 (m, 3 H), 6.89-6.86 (m, 3 H), 5.63 (dd, *J* = 14.4, 6.7 Hz, 1 H), 4.69 (dd, *J* = 15.9, 8.9 Hz, 1 H), 4.61 (d, *J* = 9.0 Hz, 1 H), 4.02 (s, 3 H), 3.75-3.90 (m, 1 H), 3.57-3.50 (m, 1 H), 2.55 (d, *J* = 6.5 Hz, 1 H), 1.87 (d, *J* = 6.5 Hz, 1 H), 1.00 (s, 1 H), 0.78-0.75 (m, 4 H), 0.72 (s, 1 H), 0.31-0.30 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 166.75, 142.55, 138.99, 137.76, 134.16, 133.00, 132.89, 132.71, 132.59, 131.05, 129.49, 128.87, 128.32, 128.19, 128.00, 127.68, 127.51, 127.24, 125.84, 125.41, 62.02, 51.40, 49.79, 37.60, 34.06, 29.69, 29.64, 23.59, 13.68, 6.80, 6.74.

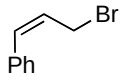


267a **267b**

(*4S*,5R*,8R)-8-Cyclopropyl-(6-*N*-(*P,P*-diphenylphosphinamido)-2-((4-ethoxycarbonyl)phenyl)-5-phenyl-6-azaspiro[3.4]oct-1-ene (267a) and (*4R*,5R*,8S**)-3-Cyclopropyl-7-(*N*-(*P,P*-diphenylphosphinamido))-8-phenyl-7-azatricyclo[3.3.1^{1,3}.0]octane (267b)**. A solution of amide **266** (0.054 g, 0.094 mmol) in PhMe (5.0 mL) was stirred at rt for 12 h. The solvent was removed in vacuo and the residual oil was purified by chromatography on SiO_2 (hexanes/EtOAc, 1:4) to afford **267a** (0.018 g, 33%) and **267b** (0.017 g, 31%).

267a. Obtained as a colorless oil: IR (neat) 2919, 1720, 1604, 1438, 1279, 1196, 1109 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99-7.91 (m, 3 H), 7.64-7.57 (m, 2 H), 7.51-7.42 (m, 4 H), 7.36-7.23 (m, 6 H), 7.16-7.08 (m, 4 H), 6.92 (s, 1 H), 4.51 (d, *J* = 11.3 Hz, 1 H), 3.91 (s, 3 H), 3.78-3-71 (m, 1 H), 3.33 (app q, *J* = 10.1 Hz, 1 H), 2.82-2.71 (m, 1 H), 2.42 (d, *J* = 13.4 Hz, 1 H), 2.30 (d, *J* = 13.5 Hz, 1 H), 1.22-1.19 (m, 2 H), 0.57-0.53 (m, 1 H), 0.38-0.33 (m, 2 H), -0.06--0.09 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.81, 143.94, 143.88, 143.04, 138.02, 135.12, 133.15, 132.53, 132.40, 132.29, 132.17, 131.62, 131.42, 130.54, 129.68, 129.10, 128.60, 128.43, 127.92, 127.75, 127.30, 126.82, 124.57, 69.27, 56.65, 56.60, 52.08, 51.61, 42.88, 42.81, 33.75, 32.62, 9.95, 4.95, 4.22; MS (EI) *m/z* (rel. intensity) 573 (M^+, 52), 486 (27), 372 (73), 319 (19), 306 (56), 230 (31), 212 (48), 201 (100); HRMS (EI) calc for $C_{37}H_{36}NO_3P$ 573.2433, found 573.2393.

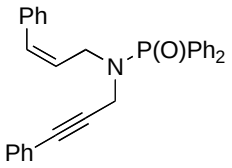
267b. Obtained as a colorless oil: IR (neat) 2949, 1721, 1610, 1438, 1278, 1179 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.03-7.96 (m, 2 H), 7.94-7.91 (m, 2 H), 7.75-7.44 (m, 3 H), 7.35-7.13 (m, 12 H), 4.50 (d, *J* = 9.7 Hz, 1 H), 3.90 (s, 3 H), 3.57 (td, *J* = 9.8, 2.0 Hz, 1 H), 3.24 (app q, *J* = 10.0 Hz, 1 H), 2.53-2.46 (m, 1 H), 2.27 (dd, *J* = 9.4, 6.8 Hz, 1 H), 1.82 (dd, *J* = 6.9, 1.5 Hz, 1 H), 1.79 (d, *J* = 6.9 Hz), 1.56 (dd, *J* = 9.5, 6.9 Hz, 1 H), 1.27 (dd, *J* = 9.6, 3.4 Hz, 1 H), 0.49-0.37 (m, 1 H), 0.28-0.19 (m, 1 H), 0.06--0.05 (m, 1 H), -0.14--0.22 (m, 1 H), -0.49--0.57 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.15, 147.83, 141.60, 141.54, 133.48, 132.47, 132.34, 132.27, 132.15, 131.58, 130.84, 129.25, 128.57, 128.40, 128.02, 127.94, 127.86, 127.81, 126.64, 126.12, 125.96, 62.58, 59.27, 59.21, 57.71, 55.34, 51.97, 50.76, 48.81, 46.68, 39.77, 12.46, 5.53, 2.09; MS (EI) *m/z* (rel. intensity) 573 (M^+, 6), 436 (9), 372 (34), 320 (8), 306 (19), 218 (22), 201 (100); HRMS (EI) calc for $C_{37}H_{36}NO_3P$ 573.2433, found 573.2463



268

(*Z*)-cinnamyl bromide (268). $Ni(OAc)_2 \cdot 4\ H_2O$ (0.32 g, 1.3 mmol) was suspended in EtOH (22 mL) and treated with $NaBH_4$ (0.048 h, 1.3 mmol). After 10 min 1,2-diaminoethane (0.17 mL, 1.3 mmol) was added, stirring was continued for 20 min followed by addition of 3-phenylprop-2-yn-1-ol (0.84 g, 0.36 mmol). A balloon with H_2 was connected to the reaction flask and the mixture was stirred rt for 12 h, quenched with water and extracted (3x) with Et_2O. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 3:1) to afford alcohol (0.19 g, 23%) as a colorless oil. Triphenylphosphine (0.91 g, 3.5 mmol) was dissolved in dry CH_2Cl_2 (20 mL), cooled to 0 ^oC and treated with Br_2 (0.18 mL, 3.5 mmol). After 10 min at 0 ^oC, solid imidazole (0.32 g,

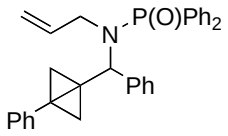
4.6 mmol) was added followed by (*Z*)-cinnamyl alcohol (0.30 g, 2.2 mmol). The reaction mixture was stirred at 0 ^{o}C for 1 h, poured into pentane (50 mL) and filtered through a pad of SiO_2. The solvent was removed *in vacuo* and the product was purified by Kugelrohr distillation to afford **268** (0.19 g, 42%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.22 (m, 5 H), 6.61 (d, *J* = 11.2 Hz, 1 H), 6.05-5.95 (m, 1 H), 3.34 (dd, *J* = 8.5 Hz, 0.5 Hz, 2 H).



270

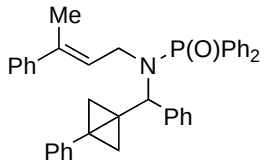
***N*-Cinnamyl-*N*-(3-phenylprop-2-ynyl)-*P,P*-diphenylphosphinamide (270).** To a solution of *N*-(3-phenylprop-2-ynyl)-*N*-diphenylphosphinamide **92** (0.050 g, 0.15 mmol) in PhMe (5.0 mL) was added freshly prepared (*Z*)-cinnamyl bromide **268** (0.15 g, 0.76 mmol) followed by Bu_4NHSO_4 (0.025 g, 0.076 mmol) and 50% aq NaOH (5.0 mL). The reaction mixture was vigorously stirred at rt for 1 h, diluted with water and extracted (3x) with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated. The crude oil was purified by chromatography on SiO_2 (hexanes/EtOAc, 1:4) to afford **270** (0.046 g, 67%) as a colorless oil: IR (neat) 3056, 1598, 1490, 1439, 1357, 1203, 1122, 1109 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 7.7, 4.2 Hz, 6 H), 7.61-7.51 (m, 9 H), 7.40-7.25 (m, 5 H), 6.74 (d, *J* = 11.6 Hz, 1 H), 5.94 (td, *J* = 12.1, 5.9 Hz, 1 H), 4.18 (dd, *J* = 9.0, 7.7 Hz, 2 H), 4.08 (d, *J* = 9.7 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.30, 132.68, 132.44, 132.31, 132.11, 131.97, 131.93, 131.64, 130.40, 128.72, 128.65, 128.48, 128.14, 128.10, 128.06, 128.03, 126.92, 122.67, 85.11, 85.02, 84.39, 43.95, 43.91, 36.33, 36.26; MS (EI) *m/z* (rel. intensity) 447 (M^+, 12), 446 (29), 332

(29), 246 (21), 230 (10), 217 (7), 210 (100); HRMS (EI) calc for $C_{30}H_{25}NOP$ (M-H) 446.1674, found 446.1661.



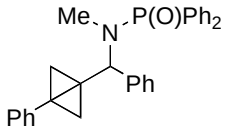
271a

***N*-allyl-*P*,*P*-diphenyl-*N*-(phenyl(3-phenylbicyclo[1.1.0]butan-1-yl)methyl)phosphinic amide (271a).** A solution of **98** (0.10 g, 0.23 mmol), allyl bromide (0.50 mL, 1.2 mmol), Bu_4NHSO_4 (0.039 g, 0.12 mmol) in PhMe (2.0 mL) was treated with 50% aq NaOH (10 mL) was vigorously stirred at rt for 20 min, diluted with water, extracted with EtOAc and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **271a** (0.087 g, 80%) containing ca. 13% of the rearranged product as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ (characteristic signals) 5.94-5.88 (m, 1 H), 5.02 (d, *J* = 10.2 Hz, 1 H), 4.81 (dd, *J* = 17.1, 1.3 Hz, 1 H), 0.81 (s, 1 H), 0.54 (s, 1 H). A solution of **271a** (0.020 g, 0.042 mmol) in PhMe (2.0 mL) was stirred at rt for 36 h, the solvent was removed *in vacuo* and purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded unstable **239a** (0.016 g, 80%, containing ca. 13% of the rearranged product) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ (characteristic signals) 5.92-5.88 (m, 1 H), 5.02 (d, *J* = 10.2 Hz, 1 H), 4.81 (d, *J* = 17.1 Hz, 1 H), 4.54 (d, *J* = 9.0 Hz, 1 H), 2.36 (d, *J* = 6.7 Hz, 1 H), 1.71 (d, *J* = 6.7 Hz, 1 H), 0.81 (s, 1 H), 0.54 (s, 1 H).



271b

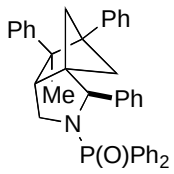
(*E*)-*P*,*P*-Diphenyl-*N*-(phenyl(3-phenylbicyclo[1.1.0]butan-1-yl)methyl)-*N*-(3-phenylbut-2-enyl)phosphinic amide (271b). A solution of **98** (0.072 g, 0.17 mmol) in PhMe (5.0 mL) was treated with Bu_4NHSO_4 (0.020 g, 0.083 mmol), (*E*)-1-bromo-3-phenylbut-2-ene (0.17 g, 0.83 mmol) and 50% aq NaOH (5.0 mL). The reaction mixture was vigorously stirred at rt for 15 min, diluted with water, and extracted (3x2 mL) with Et_2O. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. The oil was purified by a flash column to afford crude, unstable **271b** (0.063 g, 68%, ca. 80-90% pure). This material was used immediately for the subsequent transformations: ^{1}H NMR (600 MHz, $CDCl_3$) δ (representative signals) 5.91 (t, *J* = 5.9 Hz, 1 H), 4.57 (d, *J* = 8.8 Hz, 1 H), 2.42 (d, *J* = 6.5 Hz, 1 H), 1.69 (d, *J* = 6.6 Hz, 1 H), 0.90 (s, 1 H), 0.61 (s, 1 H).



271c

***N*-Methyl-*P*,*P*-diphenyl-*N*-(phenyl(3-phenylbicyclo[1.1.0]butan-1-yl)methyl)phosphinic amide (271c).** A solution of amide **98** (0.034 g, 0.078 mmol) in PhMe (1.0 mL) was treated with Bu_4NHSO_4 (0.013 g, 0.039 mmol), distilled Me_2SO_4 (0.040 mL, 0.39 mmol) and 50% aq NaOH (1.0 mL). The reaction mixture was vigorously stirred at rt for 30 min, diluted with water, and extracted (3 x 5 mL) with Et_2O. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc,

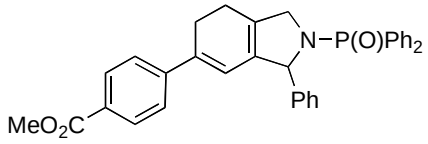
1:4) afforded **271c** (0.033 g, 94%) as a clear oil: IR (neat) 3057, 3028, 2923, 1489, 1438, 1218, 1192, 1119 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81-7.75 (m, 2 H), 7.71-7.64 (m, 2 H), 7.49-7.40 (m, 4 H), 7.37-7.28 (m, 2 H), 7.21-7.06 (m, 6 H), 6.96 (d, *J* = 6.8 Hz, 2 H), 6.85-6.83 (m, 2 H), 4.59 (d, *J* = 8.9 Hz, 1 H), 2.82 (d, *J* = 10.9 Hz, 3 H), 2.40 (d, *J* = 6.6 Hz, 1 H), 1.73 (d, *J* = 6.6 Hz, 1 H), 1.21 (s, 1 H), 0.95 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.51, 139.45, 136.12, 133.27, 133.01, 132.50, 132.37, 131.56, 31.44, 142.41, 131.31, 128.45, 128.34, 128.29, 128.17, 128.05, 128.00, 127.96, 127.07, 125.92, 125.19, 60.05, 60.01, 34.01, 32.30, 32.02, 31.98, 26.47, 26.41, 21.16; MS (ES) *m/z* (rel. intensity) 472 ($[M+Na]^+$, 100), 450 ($[M+H]^+$, 32), 32 (20), 201 (10); HRMS (ES) calc for $C_{30}H_{29}NO_2$ (M+H) 450.1987, found 450.1971.



272

((*6S*,2R)-6-Methyl-2,6,7-triphenyl-3-azatricyclo[5.1.1.0^{1,5}]non-3-yl)diphenylphosphino-1-one (272).** Crude amide **271b** (0.028 g, 0.050 mmol) was dissolved in PhMe (1.0 mL) and stirred at room temperature for 12 h. The solvent was removed in vacuo and the crude oil was purified by a chromatopgraphy on SiO_2 (hexanes/EtOAc, 1:4) to afford crude **272** (0.019 g, 68%) as a colorless oil. Further purification afforded analytically pure sample (0.0090 g): IR (ATR) 3056, 1437, 1189, 1120, 1109, 1023 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05-8.01 (m, 2 H), 7.77-7.73 (m, 2 H), 7.51-7.49 (m, 4 H), 7.29-7.20 (m, 9 H), 7.07-7.-6 (m, 4 H), 6.98-6.96 (m, 2 H), 6.93-6.91 (m, 2 H), 4.55 (d, *J* = 9.9 Hz, 1 H), 3.61-3.53 (m, 2 H), 3.51-3.44 (m, 1 H), 2.79 (dd, *J* = 9.8, 7.6 Hz, 1 H), 1.83 (dd, *J* = 7.5, 1.6 Hz, 1 H), 1.76 (d, *J* = 6.9 Hz, 2 H), 1.48 (s, 3 H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 147.31, 141.77, 141.66, 132.54, 132.25, 132.13, 131.68, 128.63, 128.47, 127.97, 127.82, 127.72, 127.58, 127.43, 127.39, 126.59, 126.20, 125.94, 125.49, 63.14, 60.59, 57.54, 51.92, 51.83, 49.78, 46.37, 45.35, 41.44, 24.54; MS (EI) 565 (M^+, 87), 201 (97), 169 (54), 131 (87), 119 (100); HRMS (EI) calc for $C_{39}H_{36}NOP$ 565.2535, found 565.2534.



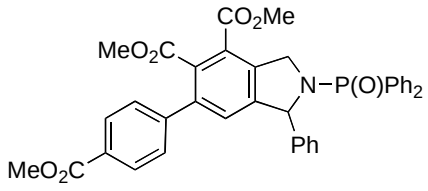
284

Methyl 4-(2-(*P*,*P*-diphenylphosphinyl)-2,3,4,5-tetrahydro-1-phenyl-1*H*-isoindol-6-yl)benzoate (284). A suspension of amide **113** (0.030 g, 0.061 mmol), Bu_4NHSO_4, (0.010g, 0.030 mmol), powdered NaOH (0.024g, 0.61 mmol) and K_2CO_3 (0.042g, 0.30 mmol) in xylenes (3.0 mL) was treated with propargyl bromide (0.044 mL, 0.30 mmol, 80% in PhMe) and warmed to 55 ºC. After 2 h (starting material was consumed), the reaction mixture was warmed to 140 ºC, and heated at reflux for 6.5 h, cooled to rt, and diluted with water. The aqueous layer was extracted (3x) with EtOAc and the combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 1:4) to afford **284** (0.010 g, 32%) as a colorless oil: IR (neat) 2926, 1718, 1606, 1437, 1282, 1206 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96-7.89 (m, 4 H), 7.61-7.54 (m, 2 H), 7.50-7.43 (m, 3 H), 7.35-7.32 (m, 4 H), 7.19-7.12 (m, 4 H), 6.87-6.79 (m, 2 H), 5.94 (s, 1 H), 5.35-5.30 (m, 1 H), 4.40-4.32 (m, 1 H), 4.25-4.20 (m, 1 H), 3.88 (s, 3 H), 2.75 (t, *J* = 9.6 Hz, 2 H), 2.45 (t, *J* = 9.7 Hz, 2 H); ^{13}C NMR (125 MHz, C_6D_6) δ 166.48, 145.16, 143.92, 135.93, 133.01, 132.95, 132.86, 131.62, 129.96, 129.14, 128.75, 128.75, 128.65, 128.51, 128.51, 128.42, 127.49, 127.34, 125.14, 118.81, 69.91, 56.61, 51.49, 26.17, 21.67; MS (ES) *m/z* (rel. intensity) 616 (3), 554 (55), 532

([M+1]$^+$, 100), 483 (2), 461 (4); HRMS (ES) calc for $C_{34}H_{30}NNaO_3P$ (M+Na) 554.1861, found 554.1865.

Synthesis of **284** from **74** under microwave conditions. A solution of amide **113** (0.010 g, 0.020 mmol) in chlorobenzene (1.0 mL) was treated with powdered NaOH (0.0080 g, 0.20 mmol), K_2CO_3 (0.014 g, 0.10 mmol), Bu_4NHSO_4 (0.0030 g, 0.010 mmol) and propargyl bromide (0.015 mL, 0.10 mmol, 80% in PhMe). The reaction mixture was warmed to 65 ºC, stirred for 1 h, and heated in the microwave reactor (200 ºC, 300 W) for 1 h. The inorganic salts were dissolved in water, the aqueous layer was extracted (3x) with EtOAc, and the combined organic layers were washed with water and brine, dried (Na_2SO_4) and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4) afforded **284** (0.0041 g, 38%).

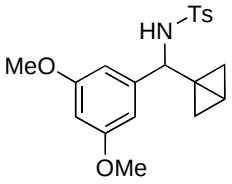
Synthesis of **284** from **244c**. A solution of **244c** (0.021 g, 0.040 mmol) in 1,2-dichlorobenzene (2.0 mL) was heated at 150 ºC for 3 h. The reaction mixture was cooled to rt, the solvent was removed *in vacuo*, and the remaining oil was purified by chromatography on SiO_2 (hexanes/EtOAc, 1:4) to afford **284** (0.012 g, 58%).



285

Dimethyl 2-(diphenylphosphoryl)-6-(4-(methoxycarbonyl)phenyl)-1-phenylisoindoline-4,5-dicarboxylate (285). A solution of **284** (0.0060 g, 11 μmol) and DMAD (0.013 mL, 0.11 mmol) in PhCl (0.5 mL) was heated in microwave reactor (200 ^{o}C, 300 W) for 20 min. The solvent was evaporated and purification on preparative TLC (hexanes/EtOAc, 1:4) afforded crude **285**

(0.0030 g, 42%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01-6.87 (m, 19 H), 5.84 (d, *J* = 9.9 Hz, 1 H), 5.03 (bs, 2 H), 3.92 (s, 3 H), 3.82 (s, 3 H), 3.60 (s, 3 H).

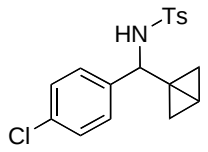


341a

***N*-(Bicyclo[1.1.0]but-1-yl(3,5-dimethoxyphenyl)methyl)-4-methylbenzenesulfonamide (341).** A solution of 1,1,-dibromo-2-(chloromethyl)cyclopropane **119** (3.0 g, 12 mmol) in dry Et_2O (10 mL) was cooled to -78 ^oC and treated with a solution of MeLi (8.1 mL, 12 mmol, c = 1.5 M in Et_2O). After slow warming to ca. -50 ^oC over 1 h, the mixture was cooled to -78 ^oC, MeBr was removed by high vacuum and a solution of *t*-BuLi (8.1 ml, 12 mmol, c = 1.5 M in pentane) was added dropwise. The mixture was stirred at -78 ^oC for 1 h and a solution of *N*-(3,5-dimethoxybenzylidene)-4-methylbenzenesulfonamide (1.5 g, 4.8 mmol) in dry THF was added. The mixture was quenched with sat. NH_4Cl, warmed up to rt, diluted with water and extracted with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **341a** (0.90, 50%) as a clear, colorless oil that solidified upon standing: IR (neat) 3276, 2933, 1598, 1462, 1431, 1326, 1204, 1158 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.1 Hz, 2 H), 7.21 (d, *J* = 8.1 Hz, 2 H), 6.27 (t, *J* = 2.1 Hz, 1 H), 6.22 (d, *J* = 2.1 Hz, 2 H), 5.10 (d, *J* = 6.9 Hz, 1 H), 4.68 (d, *J* = 7.0 Hz, 1 H), 3.68 (s, 6 H), 2.40 (s, 3 H), 1.53 (dd, *J* = 6.3, 2.9 Hz, 1 H), 1.36-1.31 (m, 2 H), 0.64 (s, 1 H), 0.50 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 143.2, 141.8, 137.8, 129.4, 127.1, 105.0, 99.4, 58.0, 55.2, 32.2, 31.8, 21.4, 13.9, 1.9; MS (ESI) *m/z* (rel. inten-

sity) 396 (100), 203 (20); HRMS (ESI) calc for $C_{20}H_{23}NO_4NaS$ (M+Na) 396.1245, found 396.1232.

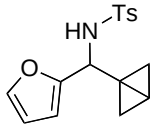
***N*-(3,5-Dimethoxybenzylidene)-4-methylbenzenesulfonamide.** A solution of Et_3N (13 mL, 90 mmol), 3,5-dimethoxybenzaldehyde (5.0 g, 30 mmol) and *p*-toluenesulfonamide (5.2 g, 30 mmol) in CH_2Cl_2 (50 mL) was cooled on ice and treated dropwise over 20 min with a solution of $TiCl_4$ (2.1 mL, 19 mmol) in CH_2Cl_2. The reaction mixture was stirred at 0 ^oC for 2 h, poured into dry Et_2O (200 mL) and filtered through a short pad of silica (washed with excess of EtOAc). The solvent was removed in vacuo and *N*-(3,5-dimethoxybenzylidene)-4-methylbenzenesulfonamide was obtainted by precipitation with hexanes from CH_2Cl_2 (5.1 g, 53%) as a white solid: Mp. 132.1-136.6 ^oC (Hexanes/CH_2Cl_2); IR (ATR) 3014, 1593, 1569, 1452, 1293, 1152 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.92 (s, 1 H), 7.88 (dd, *J* = 6.6, 1.7 Hz, 2 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.05 (d, *J* = 2.3 Hz, 2 H), 6.68 (t, *J* = 2.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 161.1, 144.6, 134.1, 129.8, 128.1, 126.5, 108.6, 107.7, 55.7, 21.7; LC-MS (ESI) *m/z* (rel. intensity) 320.0 ($[M+H]^+$, 100), 181 (37).



341b

***N*-(Bicyclo[1.1.0]but-1-yl(4-chlorophenyl)methyl)-4-methylbenzenesulfonamide (341b).** A solution of 1,1-dibromo-2-(chloromethyl)cyclopropane **119** (2.0 g, 8.1 mmol) in dry Et_2O (10 mL) was cooled to -78 ^oC and treated with a solution of MeLi (5.0 mL, 8.1 mmol, c = 1.6 M in Et_2O). After 1 h, MeBr was removed by high vacuum and a solution of *t*-BuLi (4.7 mL, 8.1

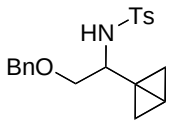
mmol, c = 1.7 M in pentane) was added. The mixture was stirred at -78 °C for 1 h, followed by a solution of *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide[483] (0.94 g, 3.2 mmol) in dry THF (10 mL). The mixture was stirred at -78 °C for 5 min, quenched with sat. NH_4Cl, warmed up to rt and extracted (3x) with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **341b** (0.56 g, 50%) as a colorless oil that solidified upon standing: IR (neat) 3272, 292, 1597, 1492, 1329, 1160 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.3 Hz, 2 H), 7.21 (d, *J* = 8.1 Hz, 2 H), 7.16 (dd, *J* = 6.6, 1.9 Hz, 2 H), 7.03 (dd, *J* = 6.8, 1.7 Hz, 2 H), 5.41 (d, *J* = 6.8 Hz, 1 H), 4.75 (d, *J* = 6.9 Hz, 1 H), 2.42 (s, 3 H), 1.48 (dd, *J* = 6.3, 2.9 Hz, 1 H), 1.26 (t, *J* = 2.9 Hz, 1 H), 1.23 (dd, *J* = 6.3, 2.9 Hz, 1 H), 0.65 (s, 1 H), 0.55 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 137.9, 137.6, 133.3, 129.4, 128.4, 128.3, 127.1, 57.3, 32.4, 31.3, 21.5, 14.0, 1.7; MS (ESI) *m/z* (rel. intensity) 370 (12), 142 (18); HRMS (ESI) calc for $C_{18}H_{18}NO_2NaSCl$ (M+Na) 370.0644, found 370.0633.



341c

***N*-(Bicyclo[1.1.0]but-1-yl(fur-2-yl)methyl)-4-methylbenzenesulfonamide (341c).** A solution of 1,1-dibromo-2-(chloromethyl)cyclopropane **119** (2.0 g, 8.1 mmol) in Et_2O (10 mL) was cooled to -78 °C, treated with MeLi (5.4 mL, 8.1 mmol, c = 1.5 M in Et_2O) and allowed to warm up to -50 °C. After 1 h, the mixture was cooled to -78 °C, MeBr was removed by high vacuum and a solution of *t*-BuLi (5.4 mL, 8.1 mmol, c = 1.5 M in pentane) was added. The reaction was stirred for 1 h and a solution of *N*-(furan-2-ylmethylene)-4-methylbenzenesulfonamide[484] (0.80

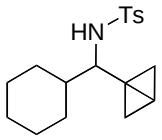
g, 3.2 mmol) in THF (5 mL + 5 mL for washing) was added. The reaction mixture was stirred for 5 min, quenched with sat. NH_4Cl, warmed up to rt and extracted (3x) with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **341c** (0.49 g, 50%) as a white solid: Mp. 96.0-98.4 ^oC (CH_2Cl_2); IR (neat) 3252, 1599, 1500, 1431, 1321, 1228, 1162, 1143 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.2 Hz, 2 H), 7.22 (d, *J* = 8.2 Hz, 2 H), 7.16 (t, *J* = 0.7 Hz, 1 H), 6.16 (dd, *J* = 3.0, 2.0 Hz, 1 H), 6.05 (d, *J* = 3.1 Hz, 1 H), 5.43 (d, *J* = 8.4 Hz, 1 H), 4.92 (d, *J* = 8.4 Hz, 1 H), 2.39 (s, 3 H), 1.45-1.44 (m, 2 H), 1.42-1.41 (m, 1 H), 0.57 (s, 1 H), 0.56 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1, 142.1, 142.0, 137.7, 129.3, 127.0, 110.0, 107.1, 51.9, 32.2, 31.8, 21.4, 12.7, 1.7; MS (EI) *m/z* (rel. intensity) 303 (M^+, 2), 289 (1), 250 (4), 148 (59), 91 (100); HRMS (EI) calc for $C_{16}H_{17}NO_3S$ 303.0929, found 303.0927.



341d

***N*-(2-(Benzyloxy)-1-(bicyclo[1.1.0]but-1-yl)ethyl)-4-methylbenzenesulfonamide (341d).** A solution of 1,1-dibromo-2-(chloromethyl)cyclopropane **119** (1.3 g, 5.4 mmol) in dry Et_2O (10 mL) was cooled to -78 ^oC and treated with a solution of MeLi (3.6 mL, 5.4 mmol, c = 1.5 M in Et_2O). After 1 h, MeBr was removed by high vacuum and a solution of *t*-BuLi (3.6 mL, 5.4 mmol, c = 1.5 M in pentane) was added. The reaction mixture was stirred at -78 ^oC for 1 h, then treated with a solution of *N*-(2-(benzyloxy)ethylidene)-4-methylbenzenesulfonamide[485] (0.65 g, 2.1 mmol) in dry THF (5 mL + 5 mL for washing). The mixture was stirred at -78 ^oC for 5 min, quenched with sat. NH_4Cl, warmed up to rt and extracted (3x) with EtOAc. The combined organ-

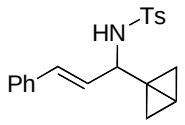
ic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **341d** (0.23 g, 30%) as a colorless oil: IR (neat) 3278, 2925, 2866, 1598, 1495, 1453, 1328, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.2 Hz, 2 H), 7.39-7.31 (m, 3 H), 7.29-7.21 (m, 4 H), 5.03 (d, *J* = 7.5 Hz, 1 H), 4.46-4.33 (m, 2 H), 3.85 (dt, *J* = 7.5, 4.9 Hz, 1 H), 3.51 (dd, *J* = 9.6, 4.9 Hz, 1 H), 3.43 (dd, *J* = 9.6, 5.0 Hz, 1 H), 2.42 (s, 3 H), 1.53 (dd, *J* = 6.3, 2.7 Hz, 1 H), 1.45 (dd, *J* = 6.3, 2.9 Hz, 1 H), 1.41 (app. t, *J* = 2.5 Hz, 1 H), 0.50 (s, 1 H), 0.44 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 138.0, 137.6, 129.5, 128.4, 127.8, 127.6, 127.1, 73.2, 71.7, 52.8, 31.4, 31.2, 21.5, 11.0, 1.6; MS (ESI) *m/z* (rel. intensity) 380 (5); HRMS (ESI) calc for $C_{20}H_{23}NO_3NaS$ (M+Na) 380.1296, found 380.1278.



341e

***N*-(Bicyclo[1.1.0]but-1-yl(cyclohexyl)methyl)-4-methylbenzenesulfonamide (341e).** A solution of 1,1-dibromo-2-(chloromethyl)cyclopropane **119** (1.7 g, 6.7 mmol) in dry Et_2O (10 mL) was cooled to -78 °C and treated with a solution of MeLi (4.5 mL, 6.7 mmol, c = 1.5 M in Et_2O). After 1 h, MeBr was removed by high vacuum and a solution of *t*-BuLi (4.5 mL, 6.7 mmol, c = 1.5 M in pentane) was added. The mixture was stirred at -78 °C for 1 h, and treated with a solution of *N*-(cyclohexylmethylene)-4-methylbenzenesulfonamide (0.71 g, 2.7 mmol) in dry THF (5 mL + 5 mL for washing). The mixture was stirred at -78 °C for 5 min, quenched with sat. NH_4Cl, warmed up to rt and extracted (3x) with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2

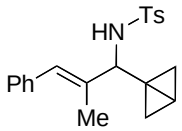
(hexanes/EtOAc, 4:1) afforded **341e** (0.40 g, 47%) as a colorless oil that solidified upon standing: IR (neat) 3281, 2926, 2852, 1599, 1496, 1448, 1322, 1162 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2 H), 7.30 (d, *J* = 8.1 Hz, 2 H), 5.00 (d, *J* = 8.9 Hz, 1 H), 3.40 (dd, *J* = 8.9, 5.9 Hz, 1 H), 2.45 (s, 3 H), 1.74-1.62 (m, 5 H), 1.50-1.46 (m, 1 H), 1.43 (dd, *J* = 6.3, 2,8 Hz, 1 H), 1.39 (dd, *J* = 6.3, 2.8 Hz, 1 H), 1.19-0.97 (m, 5 H), 0.83 (t, *J* = 2.7 Hz, 1 H), 0.58 (s, 1 H), 0.36 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1, 138.6, 129.5, 126.8, 58.1, 44.5, 33.7, 29.4, 29.2, 28.7, 26.2, 26.0 (2), 21.5, 11.8, -0.1; MS (ESI) *m/z* (rel. intensity) 342 (15), 320 (4), 155 (23); HRMS (ESI) calc for $C_{18}H_{25}NO_2NaS$ (M+Na) 342.1504, found 342.1496.



341f

(*E*)-*N*-(1-(Bicyclo[1.1.0]but-1-yl)-3-phenylallyl)-4-methylbenzenesulfonamide (341f). A solution of 1,1-dibromo-2-(chloromethyl)cyclopropane **119** (2.0 g, 8.1 mmol) in Et_2O (10 mL) was cooled to -78 ^oC, treated with a solution of MeLi (5.4 mL, 8.1 mmol, c = 1.5 M in Et_2O) and allowed to warm up to -50 ^oC over ca.1 h. After cooling to -78 ^oC, MeBr was removed by high vacuum and a solution of *t*-BuLi (5.4 mL, 8.1 mmol, c = 1.5 M in pentane) was added. The mixture was stirred for 1 h and a solution of 4-methyl-*N*-((*E*)-3-phenylallylidene)benzene- sulfonamide[486] (0.92 g, 3.2 mmol) in THF (5+5 mL for washing) was added. The reaction mixture was quenched with sat. NH_4Cl, warmed up to rt, extracted (3x) with EtOAc, and the combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (Hexanes/EtOAc, 4:1) afforded **341f** (0.72 g, 66%) as a clear, colorless oil: IR (neat) 3271, 2929, 1428, 1160 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3 Hz, 2 H),

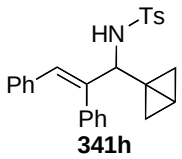
7.30-7.28 (m, 2 H), 7.27-7.22 (m, 3 H), 7.17 (d, *J* = 8.1 Hz, 2 H), 6.40 (d, *J* = 15.9 Hz, 1 H), 5.84 (ddd, *J* = 15.8, 6.7, 0.9 Hz, 1 H), 5.38 (d, *J* = 7.7 Hz, 1 H), 4.42 (app. t, *J* = 7.3 Hz, 1 H), 2.34 (s, 3 H), 1.57 (dd, *J* = 6.2, 2.8 Hz, 1 H), 1.51 (dd, *J* = 6.3, 2.9 Hz, 1 H), 1.38 (app. t, *J* = 2.0 Hz, 1 H), 0.59 (s, 1 H), 0.58 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 138.1, 136.1, 129.4, 128.3, 127.7, 127.2, 126.6, 126.4, 55.9, 32.6, 31.0, 21.3, 12.8, 1.1; MS (EI) *m/z* (rel. intensity) 339 (M^+, 9), 298 (1), 286 (7), 273 (3), 127 (15), 115 (100); HRMS (EI) calc for $C_{20}H_{21}NO_2S$ 339.1293, found 339.1280.



341g

(*E*)-*N*-(1-(Bicyclo[1.1.0]butan-1-yl)-2-methyl-3-phenylallyl)-4-methylbenzenesulfonamide (341g). A solution of 1,1-dibromo-2-(chloromethyl)cyclopropane **119** (3.0 g, 12 mmol) in Et_2O (10 mL) was cooled to -78 °C, treated with a solution of MeLi (8.0 mL, 12 mmol, c = 1.5 M in Et_2O) and allowed to warm up to -50 °C over ca.1 h. After cooling to -78 °C, a solution of *t*-BuLi (8.0 mL, 12 mmol, c = 1.5 M in pentane) was added. The mixture was stirred for 1 h and a solution of 4-methyl-*N*-((*E*)-2-methyl-3-phenylallylidene)benzenesulfonamide[487] (1.5 g, 4.8 mmol) in THF (10 mL) was added. The reaction mixture was warmed up to rt, quenched with sat. NH_4Cl, extracted (3x) with EtOAc, and the combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (Hexanes/EtOAc, 4:1) afforded **341g** (0.97 g, 57%) as a clear oil: IR (neat) 3278, 2927, 1598, 1493, 1326, 1160 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 2 H), 7.33-7.14 (m, 5 H), 7.06 (d, *J* = 7.4 Hz, 2 H), 6.33 (s, 1 H), 4.87 (br s, 1 H), 4.30 (d, *J* = 7.6 Hz, 1 H), 2.39 (s, 3 H),

1.68 (s, 3 H), 1.57-1.50 (m, 2 H), 1.41 (s, 1 H), 0.65 (s, 1 H), 0.63 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 138.0, 136.9, 135.9, 129.5, 128.9, 128.0, 127.9, 127.3, 126.6, 60.9, 32.2, 31.2, 21.5, 15.1, 12.7, 2.2; MS (ESI) *m/z* (rel. intensity) 376 (100), 354 (3), 322 (26); HRMS (ESI) calc for $C_{21}H_{23}NO_2NaS$ (M+Na) 376.1347, found 376.1380.

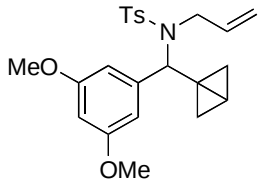


341h

(*E*)-*N*-(1-(Bicyclo[1.1.0]but-1-yl)-2,3-diphenylallyl)-4-methylbenzenesulfonamide (341h). A solution of 1,1-dibromo-2-(chloromethyl)cyclopropane **119** (3.0 g, 12 mmol) in dry Et_2O (10 mL) was cooled to -78 ^oC and treated with a solution of MeLi (8.1 mL, 12 mmol, c = 1.5 M in Et_2O). After 1 h, MeBr was removed by high vacuum and a solution of *t*-BuLi (8.1 mL, 12 mmol, c = 1.5 M in pentane) was added. The mixture was stirred at -78 ^oC for 1 h, then treated with a solution of *N*-((*E*)-2,3-diphenylallylidene)-4-methylbenzenesulfonamide (1.7 g, 4.8 mmol) in dry THF (10 mL). The mixture was stirred at -78 ^oC for 5 min, quenched with sat. NH_4Cl, warmed up to rt and extracted with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **341h** (1.1 g, 54%) as a white solid: Mp. 148.8-150.2 ^oC (CH_2Cl_2/Hex); IR (neat) 3285, 2924, 1495, 1408, 1328, 1161 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.2 Hz, 2 H), 7.28-7.18 (m, 5 H), 7.07-7.00 (m, 5 H), 6.78-6.74 (m, 2 H), 6.45 (s, 1 H), 4.73 (d, *J* = 8.0 Hz, 1 H), 4.56 (d, *J* = 8.0 Hz, 1 H), 2.35 (s, 3 H), 1.66 (dd, *J* = 6.2, 2.8 Hz, 1 H), 1.50 (dd, *J* = 6.2, 2.9 Hz, 1 H), 1.33 (br s, 1 H), 0.71 (s, 1 H), 0.59 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 140.0, 138.0, 137.8, 136.0, 130.0, 129.2, 129.1, 128.7, 127.8, 127.6,

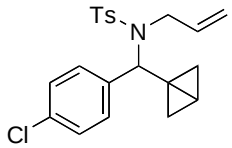
127.1, 126.9, 60.6, 32.7, 31.2, 21.4, 13.3, 2.3; MS (ESI) *m/z* (rel. intensity) 438 (100), 245 (10); HRMS (ESI) calc for $C_{26}H_{25}NO_2NaS$ (M+Na) 438.1504, found 438.1487.

***N*-((*E*)-2,3-Diphenylallylidene)-4-methylbenzenesulfonamide.** A solution of Et_3N (6.1 mL, 43 mmol), *p*-toluenesulfonamide (2.5 g, 14 mmol) and (*E*)-2,3-diphenylacrylaldehyde[488] (3.0 g, 14 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C and treated dropwise over 20 with a solution of $TiCl_4$ (1.0 mL, 9.0 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was continued at 0 °C for 2 h, poured into dry Et_2O (150 mL) and filtered through a short pad of silica (washed with EtOAc). The solvent was removed in vacuo, the light yellow solid was dissolved in CH_2Cl_2 and precipitation with hexane afforded *N*-((*E*)-2,3-diphenylallylidene)-4-methylbenzenesulfonamide (3.7 g, 71%) as a colorless solid: Mp. 153.8-156.6 °C (Hexane/CH_2Cl_2); IR (ATR) 3068, 1592, 1560, 1446, 1314, 1150 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.92 (s, 1 H), 7.81 (d, *J* = 8.3 Hz, 2 H), 7.47 (s, 1 H), 7.39 (dd, *J* = 4.6, 3.3 Hz, 3 H), 7.36-7.29 (m, 3 H), 7.24-7.18 (m, 4 H), 7.13 (d, *J* = 7.4 Hz, 2 H), 2.45 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 151.0, 144.2, 138.1, 135.5, 134.1, 133.8, 131.1, 130.4, 129.6, 129.4, 128.8, 128.5, 128.3, 127.8, 21.6; LC-MS (ESI) *m/z* (rel. intensity) 384.1 ($[M+Na]^+$, 59), 361.9 ($[M+H]^+$, 100), 206.1 (24), 191.1 (35).



342a

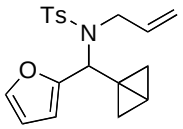
***N*-Allyl-*N*-(bicyclo[1.1.0]butan-1-yl(3,5-dimethoxyphenyl)methyl)-4-methylbenzenesulfonamide (342a).** A solution of **341a** (0.58 g, 1.6 mmol), Bu_4NHSO_4 (0.038 g, 0.16 mmol) and allyl bromide (0.68 mL, 7.8 mmol) in PhMe (20 ml) was treated with 50% aq NaOH (20 mL) and stirred vigorously at rt for 30 min. The reaction mixture was diluted with water, extracted with Et_2O and the combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **342a** (0.56 g, 87%) as a clear, colorless oil: IR (neat) 2931, 1598, 1461, 1340, 1204, 1158 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.2 Hz, 2 H), 7.21 (d, *J* = 8.1 Hz, 2 H), 6.30 (t, *J* = 2.0 Hz, 1 H), 6.24 (d, *J* = 1.9 Hz, 2 H), 5.78-5.69 (m, 1 H), 5.24 (s, 1 H), 5.08 (dd, *J* = 17.3, 1.1 Hz, 1 H), 5.03 (dd, *J* = 10.2, 1.1 Hz, 1 H), 4.07 (d, *J* = 6.3 Hz, 2 H), 3.66 (s, 6 H), 2.40 (s, 3 H), 1.60 (dd, *J* = 6.2, 5.9 Hz, 1 H), 1.50 (br s, 1 H), 1.31 (dd, *J* = 6.3, 2.8 Hz, 1 H), 0.71 (s, 1 H), 0.58 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 142.9, 141.3, 138.2, 135.7, 129.2, 127.4, 116.9, 105.9, 99.3, 62.7, 55.2, 49.0, 34.5, 32.3, 21.4, 12.1, 4.1; MS (ESI) *m/z* (rel. intensity) 436 (90); HRMS (ESI) calc for $C_{23}H_{27}NO_4NaS$ (M+Na) 436.1559, found 436.1542.



342b

***N*-Allyl-*N*-(bicyclo[1.1.0]but-1-yl(4-chlorophenyl)methyl)-4-methylbenzenesulfonamide (342b).** A solution of **341b** (0.32 g, .092 mmol), Bu_4NHSO_4 (0.092 g, 0.023 mmol) and allyl bromide (0.40 mL, 4.56 mmol) in PhMe (20 mL) was treated with 50 % aq NaOH (20 mL). The reaction mixture was stirred vigorously at rt for 1 h, diluted with water and extracted (3x) with Et_2O. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and con-

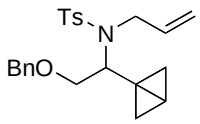
centrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **342b** (0.27 g, 76%) as a clear colorless oil: IR (neat) 2928, 1597, 1492, 1340, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.2 Hz, 2 H), 7.23-7.19 (m, 4 H), 7.08 (d, *J* = 8.5 Hz, 2 H), 5.79-5.66 (m, 1 H), 5.27 (s, 1 H), 5.07 (dd, *J* = 17.5, 1.2 Hz, 1 H), 5.03 (dd, *J* = 10.2, 1.0 Hz, 1 H), 4.17-4.09 (m, 2 H), 2.42 (s, 3 H), 1.55 (dd, *J* = 6.2, 3.2 Hz, 1 H), 1.49 (br s, 1 H), 1.22 (dd, *J* = 6.3, 2.9 Hz, 1 H), 0.70 (s, 1 H), 0.56 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 138.1, 137.7, 135.4, 133.3, 129.3, 129.0, 128.4, 127.3, 117.1, 62.2, 49.1, 34.7, 31.9, 21.5, 12.1, 4.0; MS (ESI) *m/z* (rel. intensity) 410 (91), 365 (75), 142 (25); HRMS (ESI) calc for $C_{21}H_{22}NO_2NaSCl$ (M+Na) 410.0957, found 410.0951.



342c

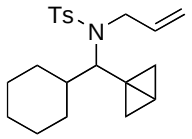
***N*-Allyl-*N*-(bicyclo[1.1.0]but-1-yl(furan-2-yl)methyl)-4-methylbenzenesulfonamide (342c).** A solution of **341c** (0.30 g, 1.0 mmol), Bu_4NHSO_4 (0.034 g, 0.10 mmol) and allyl bromide (0.43 mL) in PhMe (10 mL) was treated with 50% aq NaOH (10 mL) and vigorously stirred at rt for 1 h. The reaction mixture was diluted with water, extracted (3x) with Et_2O and the combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **342c** (0.29g, 86%) as a clear, colorless oil: IR (neat) 2929, 1598, 1498, 1343, 1161 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.3 Hz, 2 H), 7.29-7.19 (m, 3 H), 6.24 (dd, *J* = 3.3, 1.9 Hz, 1 H), 6.13 (d, *J* = 3.3 Hz, 1 H), 5.77-5.64 (m, 1 H), 5.48 (s, 1 H), 5.06 (dd, *J* = 15.9, 1.4 Hz, 1 H), 4.98 (dd, *J* =10.1, 1.4 Hz, 1 H), 4.10-3.96 (m, 2 H), 2.40 (s, 3 H), 1.60-1.57 (m, 2 H), 1.48 (dd, *J* = 4.0, 5.3 Hz, 1 H), 0.65 (s, 1

H), 0.60 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1, 142.9, 141.7, 137.8, 135.3, 129.2, 127.4, 116.4, 110.1, 108.3, 56.7, 48.2, 34.1, 32.7, 21.4, 11.1, 3.6; MS (EI) *m/z* (rel. intensity) 343 (M^+, 14), 290 (6), 188 (32), 91 (100); HRMS (EI) calc for $C_{19}H_{21}NO_3S$ 343.1242, found 343.1236.



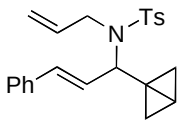
342d

***N*-Allyl-*N*-(2-(benzyloxy)-1-(bicyclo[1.1.0]but-1-yl)ethyl)-4-methylbenzenesulfonamide (342d).** A solution of **341d** (0.063 g, 0.18 mmol), Bu_4NHSO_4 (0.018 g, 0.044 mmol) and allyl bromide (0.080 mL, 0.88 mmol) in PhMe (5 mL) was treated with 50 % aq NaOH (5 mL) and vigorously stirred at rt for 1 h. The mixture was diluted with water, extracted (3x5 mL) with Et_2O and the combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **342d** (0.0567 g, 81%) as a clear colorless oil: IR (neat) 2926, 1598, 1495, 1342, 1161 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2 H), 7.38-716 (m, 7 H), 5.89 -5.75 (m, 1 H), 5.15 (dd, *J* = 17.2, 1.4 Hz, 1 H), 5.06 (dd, *J* = 10.2, 1.2 Hz, 1 H), 4.44-4.32 (m, 3 H), 4.12-3.93 (m 2 H), 3.63 (dd, *J* = 9.6, 5.9 Hz, 1 H), 3.53 (dd, *J* = 9.7, 8.2 Hz, 1 H), 2.41 (s, 3 H), 1.62-1.57 (m, 3 H), 1.03 (dd, *J* = 6.3, 2.9 Hz, 1 H), 0.49 (s, 1 H), 0.35 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9, 138.2. 137.8, 136.1, 129.3, 128.3, 127.6 (2), 127.4, 116.8, 73.0, 70.7, 57.9, 47.9, 32.7, 31.2, 21.5, 8.6, 3.5; MS (ESI) *m/z* (rel. intensity) 420 (100); HRMS (ESI) calc for $C_{23}H_{27}NO_3NaS$ (M+Na) 420.1609, found 420.1598.



342e

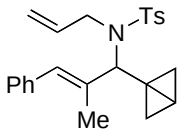
***N*-Allyl-*N*-(bicyclo[1.1.0]but-1-yl(cyclohexyl)methyl)-4-methylbenzenesulfonamide (342e).** A solution of **341e** (0.40 g, 1.3 mmol), allyl bromide (0.54 mL, 6.3 mmol), Bu_4NHSO_4 (0.042 g, 0.13 mmol) in PhMe (10 mL) was treated with 50% aq NaOH (10 mL) and vigorously stirred at rt for 1.5 h. The reaction mixture was diluted with water, extracted (3x) with Et_2O and the combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (Hexanes/EtOAc, 4:1) afforded **342e** (0.39 g, 88%) as a clear colorless oil: IR (neat) 3029, 2925, 2852, 1449, 1337, 1160 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.2 Hz, 2 H), 7.42 (d, *J* = 8.1 Hz, 2 H), 5.86-5.78 (m, 1 H), 5.13 (d, *J* = 17.2 Hz, 1 H), 5.03 (d, *J* = 10.2 Hz, 1 H), 3.96-3.88 (m, 3 H), 2.38 (s, 3 H), 1.92-1.90 (m, 1 H), 1.74-1.66 (m, 2 H), 1.61-1.54 (m, 5 H), 1.15-0.97 (m, 4 H), 0.89 (dd, *J* = 6.4, 2.6 Hz, 1 H), 0.34 (s, 1 H), 0.07 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.6, 138.7, 135.8, 129.1, 127.3, 116.7, 62.9, 47.6, 40.0, 30.9, 30.6, 30.3, 29.9, 26.1, 25.8, 21.3, 10.9, 5.2; MS (ESI) *m/z* (rel. intensity) 382 (25), 234 (3), 155 (7); HRMS (ESI) calc for $C_{21}H_{29}NO_2S$ (M+Na) 382.1817, found 382.1798.



342f

(*E*)-*N*-Allyl-*N*-(1-(bicyclo[1.1.0]but-1-yl)-3-phenylallyl)-4-methylbenzenesulfonamide (342f). A solution of **341f** (0.23 g, 0.68 mmol), Bu_4NHSO_4 (0.023 g, 0.068 mmol) and allyl bro-

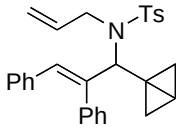
mide (0.30 mL, 3.4 mmol) in PhMe (10 mL) was treated with 50% aq NaOH (10 mL). The reaction mixture was stirred vigorously at rt for 20 min, diluted with water and extracted with Et_2O. The combined organic layers were washed with water and brine, dried (Na_2SO_4), concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to yield **342f** (0.16 g, 64%) as a clear, colorless oil: IR (neat) 3028, 2927, 1642, 1598, 1495, 1448, 1341, 1159 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 2 H), 7.34-7.31 (m, 2 H), 7.29-7.23 (m, 5 H), 6.41 (d, *J* = 15.9 Hz, 1 H), 5.96 (ddd, *J* = 15.9, 7.3, 0.7 Hz, 1 H), 5.93-5.87 (m, 1 H), 5.23 (dt, *J* = 17.2, 1.1 Hz, 1 H), 5.14 (dt, *J* = 10.1, 1.1 Hz, 1 H), 4.91 (d, *J* = 7.3 Hz, 1 H), 4.15 (dd, *J* = 16.6, 6.5 Hz, 1 H), 4.09 (ddd, *J* = 16.2, 5.7, 0.8 Hz, 1 H), 2.39 (s, 3 H), 1.64 (dd, *J* = 6.3, 2.8 Hz, 1 H), 1.51 (dd, *J* = 6.3, 2.9 Hz, 1 H), 1.40 (br s, 1 H), 0.65 (s, 1 H), 0.61 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9, 138.2, 136.2, 135.8, 132.8, 129.3, 128.4, 127.8, 127.4, 126.4, 124.8, 116.8, 61.4, 47.9, 35.2, 31.6, 21.4, 11.4, 2.7; MS (ESI) *m/z* (rel. intensity) 402 (29), 325 (2), 272 (8), 250 (3), 169 (3); HRMS (ESI) calc for $C_{23}H_{25}NO_2NaS$ (M+Na) 402.1504, found 402.1496.



342g

(*E*)-*N*-Allyl-*N*-(1-(bicyclo[1.1.0]but-1-yl)-2-methyl-3-phenylallyl)-4-methylbenzenesulfonamide (342g). A solution of **341g** (0.95 g, 2.7 mmol), allyl bromide (1.2 mL, 14 mmol) and Bu_4NHSO_4 (0.065 g, 0.27 mmol) in PhMe (30 mL) was treated with 50 % aq NaOH (30 mL). The mixture was stirred vigorously at rt for 30 min, diluted with water, and extracted (3x) with Et_2O. The combined organic layers were washed with water and brine, dried (Na_2SO_4), concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1)

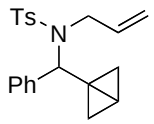
to afford **342g** (1.0 g, 95%) as a clear, colorless oil: IR (neat) 3027, 2929, 1641, 1598, 1493, 1446, 1345, 1305, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.0 Hz, 2 H), 7.39-7.20 (m, 5 H), 7.15 (d, *J* = 7.6 Hz, 2 H), 6.59 (s, 1 H), 5.90-5.80 (m, 1 H), 5.11 (d, *J* = 17.1 Hz, 1 H), 5.05 (d, *J* = 10.1 Hz, 1 H), 4.77 (s, 1 H), 4.12-4.05 (m, 2 H), 2.42 (s, 3 H), 1.67 (s, 3 H), 1.58-1.51 (m, 3 H), 0.69 (s, 1 H), 0.67 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 137.6, 135.6, 133.9, 131.4, 129.2 (2), 128.3, 128.2, 128.1, 127.6, 116.8, 65.7, 48.7, 33.7, 32.6, 21.5, 17.0, 11.0, 4.6; MS (ESI) *m/z* (rel. intensity) 416 (100), 183 (3); HRMS (ESI) calc for $C_{24}H_{27}NO_2NaS$ (M+Na) 416.1660, found 416.1653.



342h

(*E*)-*N*-Allyl-*N*-(1-(bicyclo[1.1.0]but-1-yl)-2,3-diphenylallyl)-4-methylbenzenesulfonamide (342h). A solution of **341h** (0.39 g, 0.93 mmol), allyl bromide (0.41 mL, 4.6 mmol) and Bu_4NHSO_4 (0.093 g, 0.093 mmol) in PhMe (30 mL) was treated with 50% aq NaOH (30 mL). The reaction mixture was stirred vigorously at rt for 1 h, diluted with water and extracted (3x) with Et_2O. The combined organic layers were washed with water and brine, dried (Na_2SO_4), concentrated *in vacuo*, and the crude oil was purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to afford **342h** (0.42g, 99%) as a light yellow oil: IR (neat) 3054, 3025, 2926, 1598, 1493, 1444, 1341, 1304, 1159 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.2 Hz, 2 H), 7.32-7.24 (m, 3 H), 7.18-7.15 (m, 2 H), 7.08-7.05 (m, 5 H), 6.81-6.78 (m, 2 H), 6.52 (s, 1 H), 5.89-5.76 (m, 1 H), 5.32 (s, 1 H), 5.18 (dd, *J* = 17.2, 1.3 Hz, 1 H), 5.06 (dd, *J* = 10.1, 1.2 Hz, 1 H), 4.27-2.11 (m, 2 H), 2.26 (s, 3 H), 1.67 (dd, *J* = 6.3, 2.8 Hz, 1 H), 1.38 (dd, *J* = 6.3, 2.8 Hz, 1 H), 1.02 (br s, 1 H), 0.57 (s, 1 H), 0.53 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 139.4,

139.2, 137.9, 136.3, 136.0, 129.5, 129.2 (2), 128.7, 128.7, 127.7, 127.6, 127.3, 126.7, 116.9, 65.2, 48.8, 33.3, 31.9, 21.3, 11.3, 4.3; MS (ESI) *m/z* (rel. intensity) 478 (100), 463 (12), 245 (3); HRMS (ESI) calc for $C_{29}H_{29}NO_2NaS$ (M+Na) 478.1817, found 478.1839.

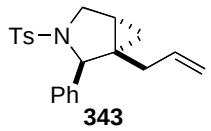


342i

***N*-Allyl-*N*-(bicyclo[1.1.0]but-1-yl(phenyl)methyl)-4-methylbenzenesulfonamide (342i).** A solution of **120b** (0.19 g, 0.62 mmol), allyl bromide (0.27 mL, 3.1 mmol) and Bu_4NHSO_4 (0.11 g, 0.31 mmol) in PhMe (10 mL) was treated with 50% aq NaOH (10 mL). The reaction mixture was stirred vigorously at rt for 10 min, diluted with water, extracted (3x) with EtOAc and the combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **342i** (0.22 g, quant.) as a clear, colorless oil: IR (neat) 3030, 2926, 1598, 1494, 1342, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.1 Hz, 2 H), 7.26-7.20 (m, 5 H), 7.16-7.14 (m, 2 H), 5.77-5.69 (m, 1 H), 5.34 (s, 1 H), 5.08 (d, *J* = 17.2 Hz, 1 H), 5.02 (d, *J* = 10.2 Hz, 1 H), 4.12 (d, *J* = 6.3 Hz, 1 H), 2.42 (s, 3 H), 1.60 (dd, *J* = 6.3, 2.8 Hz, 1 H), 1.48 (br s, 1 H), 1.27 (dd, *J* = 6.4, 2.7 Hz, 1 H), 0.72 (s, 1 H), 0.57 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 139.0, 138.2, 135.6, 129.2, 128.2, 127.6, 127.4, 116.8, 62.3, 49.0, 34.6, 32.0, 21.4, 12.3, 3.9; MS (ESI) *m/z* (rel. intensity) 443 (100); HRMS (ESI) calc for $C_{21}H_{23}NO_2NaS$ (M+Na) 376.1347, found 376.1359.

General Optimization Protocol (Tables 26, 27, and 28). An oven-dried test tube equipped with a magnetic stirrer and capped with a rubber septum was charged with N_2 and a solution of pre-

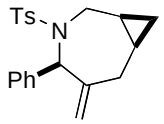
catalyst (4.2 μmol, 5 mol%) in PhMe was added, followed by a solution of ligand (8.5 μmol, 10 mol%) in PhMe and an additional amount of PhMe for a total volume of 1.40 mL. The reaction mixture was stirred at rt for 10 min and a solution of **342i** (0.030 g, 0.085 mmol) in PhMe (0.30 mL) was added. The solution was degassed, and the tube was placed in an oil bath (110 °C) and stirred at this temperature until the substrate disappeared (usually 15-30 min, monitored by TLC). The mixture was then cooled to rt, filtered through a short pad of SiO_2, washed with EtOAc, and concentrated. The crude mixture was added to a solution of $CHBr_3$ in $CDCl_3$ and the yield of the reaction was estimated by comparison of the chemical shifts of bromoform (^{1}H NMR: 6.85, s) with the shifts of **343** or **344**.



343

(1*S,2*S**,5*R**)-1-Allyl-2-phenyl-3-tosyl-3-azabicyclo[3.1.0]hexane (343).** A solution of $[Rh(CH_2CH_2)_2Cl]_2$ (1.7 mg, 4.2 μmol, 5 mol %) in PhMe (0.17 mL) was added to PhMe (1.01 mL) followed by a solution of Ph_3P (2.2 mg, 8.5 μmol, 10 mol %) in PhMe (0.22 mL). The reaction mixture was stirred at room temperature for 10 min and a solution of **342i** (30 mg, 0.085 mmol) in PhMe (0.30 mL) was added. The reaction mixture was degassed, placed in an oil bath (110 ^oC) and stirred at this temperature for 15 min. After cooling to room temperature, the mixture was filtered through a pad of SiO_2, washed with EtOAc, and concentrated *in vacuo*. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **2** (0.023 g, 77%) as a clear, colorless oil: IR (neat) 2926, 1598, 1454, 1341, 1161, 1106 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.19 (m, 5 H), 7.09-7.05 (m, 4 H), 5.57-5.50 (m, 1 H), 4.92 (d, *J* = 10.1 Hz, 1 H), 4.84 (s, 1

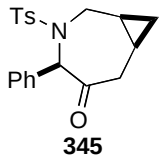
H), 4.71 (dd, *J* = 17.2, 1.7 Hz, 1 H), 3.72 (d, *J* = 9.7 Hz, 1 H), 3.66 (dd, *J* = 9.7, 3.6 Hz, 1 H), 2.35 (s, 3 H), 2.13 (dd, *J* = 15.0, 7.3 Hz, 1 H), 1.60 (dd, *J* = 15.0, 6.1 Hz, 1 H), 1.52 (dt, *J* = 7.8, 3.7 Hz, 1 H), 0.72 (dd, *J* = 7.7, 5.0 Hz, 1 H), 0.50 (t, *J* = 4.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 139.5, 136.6, 134.7, 129.1, 128.2, 128.0, 127.5, 126.7, 116.6, 67.8, 50.3, 35.2, 31.3, 21.8, 21.4, 13.5; MS (EI) *m/z* (rel. intensity) 352 (17), 274 (23), 258 (17), 196 (85), 154 (80), 116 (26), 89 (100); HRMS (EI) calc for $C_{21}H_{22}NO_2S$ (M-2H) 352.1371, found 352.1360.



344

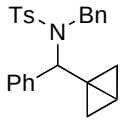
(1*S,4*S**,7*S**)-5-Methylene-4-phenyl-3-tosyl-3-azabicyclo[5.1.0]octane (344).** A solution of $[Rh(CO)_2Cl]_2$ (1.7 mg, 4.2 μmol, 5 mol %) in PhMe (0.17 mL) was added to PhMe (0.89 mL) followed by a solution of dppe (3.3 mg, 8.5 μmol) in PhMe (0.33 mL). The reaction mixture was stirred at room temperature for 10 min and a solution of **342i** (30 mg, 0.085 mmol) in PhMe (0.30 mL) was added. The reaction mixture was degassed, placed in an oil bath (110 ^{o}C) and stirred at this temperature for 30 min. After cooling to room temperature, the mixture was filtered through a pad of SiO_2, washed with EtOAc, and concentrated *in vacuo*. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **344** (0.023 g, 77%) as a clear, colorless oil: IR (neat) 2927, 1598, 149, 1340, 1158 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.3 Hz, 2 H), 7.35-7.20 (m, 7 H), 5.81 (s, 1 H), 5.14 (d, *J* = 1.5 Hz, 1 H), 4.99 (d, *J* = 1.3 Hz, 1 H), 4.35 (ddd, *J* = 16.0, 5.9, 1.5 Hz, 1 H), 2.72 (dd, *J* = 14.0, 6.2 Hz, 1 H), 2.44 (s, 3 H), 2.40 (dd, *J* = 11.3, 5.5 Hz, 1 H), 1.51 (dd, *J* = 13.9, 9.9 Hz, 1 H), 1.12-1.04 (m, 1 H), 0.81-0.74 (m, 1 H), 0.70 (td, *J* = 8.0, 5.0 Hz, 1 H), 0.05 (q, *J* = 4.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 142.9,

138.8, 137.7, 129.3, 128.5, 127.4, 127.2, 126.9, 117.5, 66.3, 46.8, 34.5, 21.5, 15.7, 15.3, 15.0; MS (ESI) *m/z* (rel. intensity) 376 (2), 321 (10); HRMS (ESI) calc for $C_{21}H_{23}NO_2NaS$ (M+Na) 376.1347, found 376.1330.



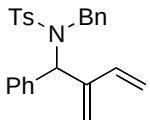
345

(1*S,4*R**,7*S**)-4-Phenyl-3-tosyl-3-azabicyclo[5.1.0]octan-5-one (345).** A solution of **344** (0.020 g, 0.057 mmol) in CH_2Cl_2 (5.0 mL) was cooled to -78 ^oC and ozone was bubbled through the mixture until it turned light blue. Neat Me_2S (0.021 mL, 0.28 mmol) was added and the reaction mixture was allowed to warm up to room temperature overnight. The solvent was removed *in vacuo*, and purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1 to 2:1) afforded **345** (0.014 g, 68%) as a clear solid that was crystallized from EtOAc to afford x-ray quality crystals: Mp. 164.4-166.5 ^oC (EtOAc); IR (KBr) 3026, 1711, 1341, 1186 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.2 Hz, 2 H), 7.38-7.28 (m, 5 H), 7.10 (d, *J* = 7.1 Hz, 2 H), 5.78 (s, 1 H), 4.58 (dd, *J* = 15.9, 5.3 Hz, 1 H), 2.81 (dd, *J* = 12.3, 6.2 Hz, 1 H), 2.57 (dd, *J* = 16.1, 11.3 Hz, 1 H), 2.42 (s, 3 H), 2.01 (dd, *J* = 12.3, 10.2 Hz, 1 H), 1.30-1.15 (m, 1 H), 0.93 (td, *J* = 8.0, 5.3 Hz, 1 H), 0.81-0.68 (m, 1 H), 0.19 (q, *J* = 5.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 143.5, 138.2, 133.9, 129.7, 129.1, 128.1, 127.3, 125.8, 69.9, 47.0, 41.4, 21.5, 16.7, 16.6, 9.9; MS (ESI) *m/z* (rel. intensity) 378 (15), 343 (4); HRMS (ESI) calc for $C_{10}H_{21}NO_3NaS$ (M+Na) 378.1140, found 378.1127.



352

***N*-Benzyl-*N*-(bicyclo[1.1.0]but-1-yl(phenyl)methyl)-4-methylbenzenesulfonamide (352).** A solution of **120b** (0.15 g, 0.48 mmol), benzyl bromide (0.28 mL, 2.4 mmol) and Bu_4NHSO_4 (0.016 g, 0.048 mmol) in PhMe (5.0 mL) was treated with 50% aq NaOH (5.0 mL). The reaction mixture was stirred vigorously at rt for 20 min, diluted with water and extracted (3x) with Et_2O. The combined organic layers were washed with water and brine, dried (Na_2SO_4), concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexanes/EtOAc, 6:1 to 4:1) to afford **352** (0.17 g, 90%) as a clear, colorless oil: IR (neat) 3030, 2928, 1495, 1453, 1338, 1159 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.2 Hz, 2 H), 7.31-7.26 (m, 5 H), 7.23-7.09 (m, 5 H), 7.00-6.97 (m, 2 H), 5.31 (s, 1 H), 4.78, 4.71 (AB, *J* = 16.0 Hz, 2 H), 2.37 (s, 3 H), 1.44 (dd, *J* = 6.3, 2.9 Hz, 1 H), 1.29 (br s, 1 H), 1.15 (dd, *J* = 6.3, 2.9 Hz, 1 H), 0.38 (s, 1 H) 0.36 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 138.5, 138.4, 137.9, 129.1, 128.1 (2), 128.0, 127.7, 127.3, 127.1, 127.0, 63.9, 50.2, 35.4, 32.1, 21.4, 12.5, 3.7; MS (ESI) *m/z* (rel. intensity) 426 (100); HRMS (ESI) calc for $C_{25}H_{25}NO_2NaS$ (M+Na) 426.1504, found 426.1498.



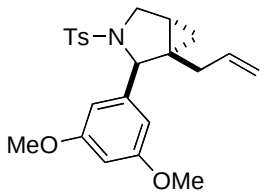
353

Method A. A suspension of $[Rh(CH_2CH_2)_2Cl]_2$ (2.4 mg, 6.3 μmol) in PhMe (0.24 mL) was added to PhMe (1.4 mL), followed by a solution of Ph_3P (3.3 mg, 12 μmol) in PhMe (0.33 mL). The reaction mixture was stirred at rt for 10 min and a solution of **352** (50 mg, 0.12 mmol) in PhMe

(0.50 mL) was added. The reaction mixture was degassed and placed in an oil bath (110 ^{o}C). After 30 min, the mixture was cooled to rt, concentrated *in vacuo*, and the dark-brown oil was purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to afford **353** (30 mg, 60 %) as a clear, colorless oil.

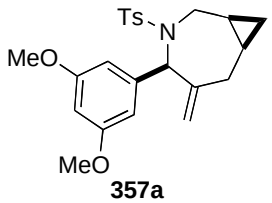
Method B. A solution of $[Rh(CO)_2Cl]_2$ (2.4 mg, 6.3 μmol) in PhMe (0.25 mL) was added to PhMe (1.23 mL), followed by a solution of dppe (4.9 mg, 12 μmol) in PhMe (0.49 mL). The reaction mixture was stirred at rt under N_2 for 10 min, followed by addition of a solution of **352** (50 mg, 0.12 mmol) in PhMe (0.50 mL). The mixture was degassed, placed in an oil bath (110 ^{o}C) and stirred for 1.5 h. After cooling to rt, the mixture was concentrated *in vacuo*, and the crude light yellow oil was purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to afford **353** (29 mg, 58%) as a clear, colorless oil.

***N*-Benzyl-4-methyl-*N*-(2-methylene-1-phenylbut-3-enyl)benzenesulfonamide (353).** IR (neat) 2925, 1598, 1495, 1453, 1339, 1204 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.3 Hz, 2 H), 7.20-7.09 (m, 9 H), 7.04-7.01 (m, 2 H), 6.95 (dd, *J* = 7.2, 2.2 Hz, 2 H), 6.21 (dd, *J* = 17.8, 11.2 Hz, 1 H), 5.99 (s, 1 H), 5.32 (s, 1 H), 5.06 (d, *J* = 7.7 Hz, 1 H), 5.05 (s, 1 H), 4.98 (d, *J* = 11.3 Hz, 1 H), 4.49, 4.41 (AB, *J* = 15.9 Hz, 2 H), 2.40 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 143.0, 137.9, 137.5, 137.2, 136.9, 129.5, 129.2, 128.6, 128.4, 127.8 (2), 127.5, 127.0, 119.7, 115.6, 63.1, 49.9, 21.5; MS (ESI) *m/z* (rel. intensity) 426 (70), 404 (5), 325 (5), 272 (3); HRMS (ESI) calc for $C_{25}H_{25}NO_2NaS$ (M+Na) 426.1504, found 426.1493.



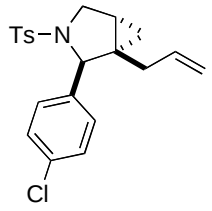
356a

(1*S,2*S**,5*R**)-1-Allyl-2-(3,5-dimethoxyphenyl)-3-tosyl-3-azabicyclo[3.1.0]hexane (356a).** A solution of $[Rh(CH_2CH_2)_2Cl]_2$ (1.4 mg, 3.6 μmol) in PhMe (0.14 mL) was added to PhMe (0.82 mL) followed by a solution of Ph_3P (1.9 mg, 7.3 μmol) in PhMe (0.19 mL). The reaction mixture was stirred at room temperature for 10 min and a solution of **342a** (0.030 g, 0.073 mmol) in PhMe (0.30 mL) was added in one portion. The mixture was degassed, placed in an oil bath (110 ^oC) and stirred at under N_2 for 10 min. After cooling to room temperature the mixture was filtered through a short pad of SiO_2, washed with EtOAc and concentrated *in vacuo*. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **356a** (0.020 g, 67%) as a colorless oil：IR (neat) 2935, 1598, 1463, 1343, 1204, 1161, 1107 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.1 Hz, 2 H), 7.08 (d, *J* = 8.01 Hz, 2 H), 6.32 (t, *J* = 2.0 Hz, 1 H), 6.16 (br s, 2 H), 5.63-5.49 (m, 1 H), 4.93 (d, *J* = 10.1 Hz, 1 H), 4.83 (d, *J* = 17.1 Hz, 1 H), 4.75 (s, 1 H), 3.77-3-71 (m, 1 H), 3.70 (s, 6 H), 3.62 (dd, *J* = 9.5, 3.5 Hz, 1 H), 2.35 (s, 3 H), 2.17 (dd, *J* = 14.8, 7.1 Hz, 1 H), 1.61 (dd, *J* = 15.0, 6.0 Hz, 1 H), 1.48 (dt, *J* = 7.7, 3.6 Hz, 1 H), 0.71 (dd, *J* = 7.6, 5.2 Hz, 1 H), 0.52 (t, *J* = 4.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 142.4, 141.6, 136.6, 135.0, 129.0, 126.8, 116.6, 106.1, 99.4, 68.0, 55.2, 50.5, 35.0, 31.5, 21.8, 21.4, 13.5; MS (ESI) *m/z* (rel. intensity) 436 (100), 397 (12); HRMS (ESI) calc for $C_{23}H_{27}NO_4NaS$ (M+Na) 436.1559, found 436.1537.



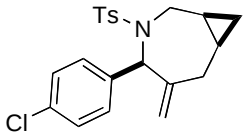
357a

(1*S,4*S**,7*S**)-4-(3,5-Dimethoxyphenyl)-5-methylene-3-tosyl-3-azabicyclo[5.1.0]octane (357a).** A solution of $[Rh(CO)_2Cl]_2$ (1.4 mg, 3.6 μmol) in PhMe (0.14 mL) was added to PhMe (0.72 mL) followed by a solution of dppe (2.9 mg, 7.3 μmol) in PhMe (0.29 mL). The reaction mixture was stirred at room temperature for 10 min and a solution of **242a** (0.030 g, 0.073 mmol) in PhMe (0.20 mL) was added in one portion. The mixture was degassed, placed in an oil bath (110 ^oC) and stirred at under N_2 for 30 min. After cooling to room temperature, the mixture was filtered through a short pad of SiO_2, washed with EtOAc and concentrated *in vacuo*. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **357a** (0.026 g, 87%) as a colorless oil: IR (neat) 2939, 1597, 1460, 1340, 1204, 1158 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, 2 H), 7.27 (d, *J* = 8.2 Hz, 2 H), 6.32 (s, 3 H), 5.71 (s, 1 H), 5.10 (s, 1 H), 4.97 (s, 1 H), 4.30 (dd, *J* = 16.0, 5.7 Hz, 1 H), 3.70 (s, 6 H), 2.70 (dd, *J* = 14.0, 6.1 Hz, 1 H), 2.44 (dd, *J* = 16.0, 11.2 Hz, 1 H), 2.43 (s, 3 H) 1.54 (dd, *J* = 14.0, 9.8 Hz, 1 H), 1.14-1.10 (m, 1 H), 0.80-0.67 (m, 2 H), 0.07 (q, *J* = 4.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 144.5, 142.9, 140.5, 138.8, 129.4, 127.4, 117.5, 105.1, 99.2, 66.5, 55.2, 47.0, 34.7, 21.5, 16.0, 15.4, 15.0; MS (ESI) *m/z* (rel. intensity) 436 (100), 397 (17); HRMS (ESI) calc for $C_{23}H_{27}NO_4NaS$ (M+Na) 436.1559, found 436.1542.



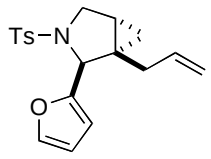
356b

(1*S,2*S**,5*R**)-1-Allyl-2-(4-chlorophenyl)-3-tosyl-3-azabicyclo[3.1.0]hexane (356b).** A suspension of $[Rh(CH_2CH_2)_2Cl]_2$ (1.0 mg, 2.6 μmol) in PhMe (0.10 mL) was added to PhMe (0.59 mL) followed by a solution of Ph_3P (1.4 mg, 5.2 μmol) in PhMe (0.14 mL). The reaction mixture was stirred at room temperature for 10 min and a solution of **342b** (0.020 g, 0.052 mmol) in PhMe (0.20 mL) was added in one portion. The mixture was degassed, placed in an oil bath (110 ^oC) and stirred at under N_2 for 10 min. After cooling to room temperature, the mixture was filtered through a short pad of SiO_2, washed with EtOAc and concentrated *in vacuo*. Purification by chromatography on SiO_2 (Hexanes/EtOAc, 4:1) afforded **356b** (0.011 g, 55%) as a clear, colorless oil: IR (neat) 2925, 1492, 1344, 1162, 1104 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 7.8 Hz, 2 H), 7.17 (d, *J* = 8.3 Hz, 2 H), 7.10 (d, *J* = 8.3 Hz, 2 H), 7.00 (d, *J* = 7.8 Hz, 2 H), 5.56-5.49 (m, 1 H), 4.94 (d, *J* = 10.2 Hz, 1 H), 4.79 (s, 1 H), 4.78 (dd, *J* = 14.9, 1.3 Hz, 1 H), 3.73 (d, *J* = 9.8 Hz, 1 H), 3.65 (dd, *J* = 9.8, 3.5 Hz, 1 H), 2.39 (s, 3 H), 2.11 (dd, *J* = 15.2, 7.5 Hz, 1 H), 1.60 (dd, *J* = 15.2, 5.8 Hz, 1 H), 1.52 (dt, *J* = 7.8, 3.7 Hz, 1 H), 0.73 (dd, *J* = 7.7, 5.1 Hz, 1 H), 0.50 (t, *J* = 3.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 138.1, 136.4, 134.5, 133.4, 129.3, 129.1, 128.3, 126.6, 116.9, 67.1, 50.3, 35.2, 31.2, 21.8, 21.4, 13.6; MS (ESI) *m/z* (rel. intensity) 410 (100), 398 (12), 214 (8); HRMS (ESI) calc for $C_{21}H_{22}NO_2NaSCl$ (M+Na) 410.0957, found 410.0977.



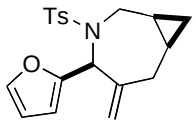
357b

(1*S,4*S**,7*S**)-4-(4-Chlorophenyl)-5-methylene-3-tosyl-3-azabicyclo[5.1.0]octane (357b).** A solution of $[Rh(CO)_2Cl]_2$ (1.0 mg, 2.6 μmol) in PhMe (0.10 mL) was added to PhMe (0.52 mL), followed by a solution of dppe (2.1 mg, 5.2 μmol) in PhMe (0.21 mL). The reaction mixture was stirred at room temperature for 10 min and a solution of **342b** (20 g, 0.052 mmol) in PhMe (0.20 mL) was added in one portion. The mixture was degassed, placed in an oil bath (110 ^oC) and stirred at under N_2 for 30 min. After cooling to room temperature, the mixture was filtered through a short pad of SiO_2, washed with EtOAc and concentrated *in vacuo*. Purification by chromatography on SiO_2 (Hexanes/EtOAc, 4:1) afforded **357b** (16 mg, 80%) as a clear, colorless oil: IR (neat) 2928, 1489, 1341, 1158 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.3 Hz, 2 H), 7.28-7.26 (m, 4 H), 7.15 (d, *J* = 8.3 Hz, 2 H), 5.74 (s, 1 H), 5.12 (s, 1 H), 4.97 (s, 1 H), 4.33 (dd, *J* = 16.0, 5.8 Hz, 1 H), 2.69 (dd, *J* = 14.0, 6.0 Hz, 1 H), 2.43 (s, 3 H), 2.34 (dd, *J* = 15.8, 11.4 Hz, 1 H), 1.46-1.42 (m, 1 H), 1.07-0.98 (m, 1 H), 0.77-0.68 (m, 2 H), 0.04 (q, *J* = 4.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 143.1, 138.6, 133.2, 129.4, 128.7, 128.4, 127.4, 117.9, 66.0, 46.8, 34.5, 21.5, 15.7, 15.4, 14.9; MS (ESI) *m/z* (rel. intensity) 410 (100); HRMS (ESI) calc for $C_{21}H_{22}NO_2NaSCl$ (M+Na) 410.0957, found 410.0958.



356c

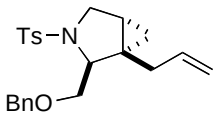
(1*S,2*S**,5*R**)-1-Allyl-2-(furan-2-yl)-3-tosyl-3-azabicyclo[3.1.0]hexane (356c).** A solution of $[Rh(CH_2CH_2)_2Cl]_2$ (2.3 mg, 5.8 μmol) in PhMe (0.23 mL) was added to PhMe (1.4 mL) followed by a solution of Ph_3P (3.1 mg, 12 μmol) in PhMe (0.31 mL). The reaction mixture was stirred at room temperature for 10 min, a solution of **342c** (40 mg, 0.12 mmol) in PhMe (0.40 mL) was added, and the mixture was degassed and placed in an oil bath (110 ^oC) for 7 min. After cooling to room temperature, the mixture was filtered through a pad of SiO_2, washed with EtOAc, concentrated *in vacuo* and purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to afford **356c** (30 mg, 75%) as a clear, colorless oil: IR (neat) 2923, 1341, 1162, 1106 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.3 Hz, 2 H), 7.10 (d, *J* = 8.3 Hz, 2 H), 7.05 (d, *J* = 0.5 Hz, 1 H), 6.25 (d, *J* = 3.2 Hz, 1 H), 6.21 (dd, *J* = 3.1, 1.8 Hz, 1 H), 5.62-5.54 (m, 1 H), 4.93 (d, *J* = 10.1 Hz, 1 H), 4.91 (s, 1 H), 4.85 (dd, *J* = 17.1, 1.5 Hz, 1 H), 3.63 (d, *J* = 8.8 Hz, 1 H), 3.53 (dd, *J* = 8.8, 3.5 Hz, 1 H), 2.36 (s, 3 H), 2.02 (dd, *J* = 14.8, 7.5 Hz, 1 H), 1.62 (dd, *J* = 14.9, 6.1 Hz, 1 H), 1.46 (td, *J* = 7.6, 3.8 Hz, 1 H), 0.70-0.64 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2, 142.3, 142.0, 136.2, 134.9, 129.1, 126.8, 116.6, 109.7, 109.4, 60.1, 49.5, 34.9, 30.1, 21.4, 21.3, 12.5; MS (ESI) *m/z* (rel. intensity) 366 (100), 212 (3), 195 (2), 119 (1); HRMS (ESI) calc for $C_{19}H_{21}NO_3NaS$ (M+Na) 366.1140, found 366.1138.



357c

(1*S,4*S**,7*S**)-4-(Furan-2-yl)-5-methylene-3-tosyl-3-azabicyclo[5.1.0]octane (357c).** A solution of $[Rh(CO)_2Cl]_2$ (2.3 mg, 5.8 μmol) in PhMe (0.23 mL) was added to PhMe (1.24 mL) followed by a solution of dppe (4.6 mg, 12 μmol) in PhMe (0.46 mL). The reaction mixture was

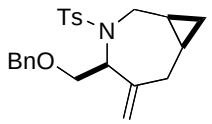
stirred at room temperature for 10 min, then placed in an oil bath (110-120 ^{o}C). When the mixture started to reflux, a solution of **342a** (40 mg, 0.12 mmol) was added in one batch, and the subsequent mixture was allowed to react for an additional 20 min at reflux temperature. The mixture was cooled to room temperature, concentrated *in vacuo* and purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to afford **357c** (23 mg, 58%) as a colorless oil: IR (neat) 2927, 1341, 1158 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2 H), 7.29-7.22 (m, 3 H), 6.26 (dd, *J* = 3.1, 1.9 Hz, 1 H), 6.00 (dd, *J* = 3.0, 0.9 Hz, 1 H), 5.76 (s, 1 H), 5.04 (s, 1 H), 4.98 (s, 1 H), 4.18 (dd, *J* = 16.0, 6.2 Hz, 1 H), 2.77 (dd, *J* = 14.0, 6.0 Hz, 1 H), 2.65 (dd, *J* = 16.0, 10.8, Hz, 1 H), 2.41 (s, 3 H), 1.88 (dd, *J* = 13.9, 8.8 Hz, 1 H), 1.21-1.11 (m, 1 H), 0.92-0.80 (m, 1 H), 0.73 (td, *J* = 7.9, 5.0 Hz, 1 H), 0.18 (q, *J* = 5.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 143.7, 142.8, 142.2, 138.4, 129.3, 127.3, 117.2, 110.2, 108.2, 61.5, 46.8, 34.7, 21.5, 16.3, 15.0, 14.5; MS (ESI) *m/z* (rel. intensity) 366 (7), 343 (3), 163 (7); HRMS (ESI) calc for $C_{19}H_{21}NO_3NaS$ (M+Na) 366.1140, found 366.1126 .



356d

(1*S,2*S**,5*R**)-1-Allyl-2-(benzyloxymethyl)-3-tosyl-3-azabicyclo[3.1.0]hexane (356d).** A solution of $[Rh(CH_2CH_2)_2Cl]_2$ (2.0 mg, 5.0 μmol) in PhMe (0.40 mL) was added to PhMe (0.94 mL) followed by a solution of Ph_3P (2.6 mg, 10 μmol) in PhMe (0.26 mL). The reaction mixture was stirred at room temperature for 10 min and placed in an oil bath (110-120 ^{o}C) until the solvent started to reflux. A solution of **342d** (40 mg 0.10 mmol) in PhMe (0.40 mL) was added via syringe and the reaction mixture was stirred for 10 min, cooled to room temperature and concen-

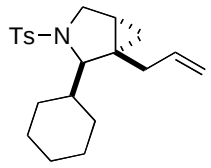
trated *in vacuo*. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **356d** (25 mg, 63%) as a clear, colorless oil: IR (neat) 3065, 3031, 2924, 2884, 1598, 1453, 1342, 1163, 1109 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 8.2, 1.6 Hz, 2 H), 7.38-7.32 (m, 2 H), 7.31-7.27 (m, 5 H), 5.75-5.66 (m, 1 H), 4.99 (d, *J* = 10.7 Hz, 1 H), 4.96 (dd, *J* = 17.0, 1.4 Hz, 1 H), 4.48, 4.41 (AB, *J* = 11.9 Hz, 2 H), 3.89 (t, *J* = 2.4 Hz, 1 H), 3.76-3-71 (m, 2 H), 3.65 (dd, *J* = 9.6, 3.3 Hz, 1 H), 3.47 (d, *J* = 9.7 Hz, 1 H), 2.64 (dd, *J* = 15.3, 7.7 Hz, 1 H), 2.43 (s, 3 H), 1.85 (ddd, *J* = 15.2, 5.6, 1.7 Hz, 1 H), 1.31-1.28 (m, 2 H), 0.37 (dd, *J* = 7.6, 5.4 Hz, 1 H), -0.23 (t, *J* = 4.1 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0, 138.3, 137.3, 135.7, 129.6, 128.3, 127.5, 127.4, 126.8, 116.4, 73.3, 71.0, 63.2, 50.5, 35.0, 27.8, 21.8, 21.5, 12.0; MS (ESI) *m/z* (rel. intensity) 420 (100), 163 (6); HRMS (ESI) calc for $C_{23}H_{27}NO_3NaS$ (M+Na) 420.1609, found 420.1617.



357d

(1*S,4*S**,7*S**)-4-(Benzyloxymethyl)-5-methylene-3-tosyl-3-azabicyclo[5.1.0]octane (357d).** A solution of $[Rh(CO)_2Cl]_2$ (2.0 mg, 5.0 μmol) in PhMe (0.20 mL) was added to PhMe (1.0 mL) followed by a solution of dppe (4.0 mg, 10 μmol) in PhMe (0.40 mL), and the reaction mixture was stirred at rt for 10 min and placed in an oil bath (110-120 ^oC). When the solvent started to reflux, a solution of **342d** (40 mg, 0.10 mmol) in PhMe (0.40 mL) was added in one portion. The mixture was stirred in the oil bath under N_2 for 25 min, cooled to rt, filtered through a short pad of SiO_2, washed with EtOAc, concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to afford **357d** (27 mg, 68%) as a clear, colorless oil: IR (neat) 2926, 2861,

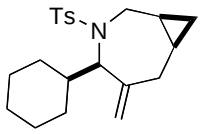
1598, 1453, 1338, 1158 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.1 Hz, 2 H), 7.35-7.30 (m, 3 H), 7.28-7.18 (m, 3 H), 5.00 (s, 1 H), 4.90 (s, 1 H), 4.74 (t, *J* = 5.9 Hz, 1 H), 4.45. 4.42 (AB, *J* = 12.0 Hz, 2 H), 4.20 (dd, *J* = 16.1, 6.4 Hz, 1 H), 3.57-3.44 (m, 2 H), 2.62 (dd, *J* = 16.1, 10.5 Hz, 1 H), 2.51 (dd, *J* = 14.2, 4.9 Hz, 1 H), 2.39 (s, 3 H), 1.82 (dd, *J* = 13.5, 7.2 Hz, 1 H), 1.17-1.07 (m, 1 H), 0.73-0.66 m, 2 H), 0.17-0.16 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 142.7, 138.7, 137.9, 129.2, 128.3, 127.6, 127.4, 116.4, 72.9, 69.8, 61.7, 46.1, 34.5, 21.5, 15.8, 14.9, 14.3; MS (ESI) *m/z* (rel. intensity) 420 (100); HRMS (ESI) calc for $C_{23}H_{27}NO_3NaS$ (M+Na) 420.1609, found 420.1601.



356e

(1*S,2*R**,5*R**)-1-Allyl-2-cyclohexyl-3-tosyl-3-azabicyclo[3.1.0]hexane (5e).** A solution of $[Rh(CH_2CH_2)_2Cl]_2$ (1.1 mg, 2.8 μmol) in PhMe (0.22 mL) was added to PhMe (0.72 mL), followed by a solution of Ph_3P (1.5 mg, 5.6 μmol) in PhMe (0.15 mL). The reaction mixture was stirred at rt for 10 min and a solution of **342e** (0.020 g, 0.056 mmol) in PhMe (0.20 mL) was added in one portion. The mixture was degassed, placed in an oil bath (110-120 ^oC) and stirred at under N_2 for 5 min. After cooling to rt the mixture was filtered through a short pad of SiO_2, washed with EtOAc, concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to afford **356e** (13 mg, 65%) as a clear, colorless oil: IR (neat) 2927, 2852, 1450, 1346, 1161, 1103 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.2 Hz, 2 H), 7.30 (d, *J* = 8.1 Hz, 2 H), 5.77-5.64 (m, 1 H), 5.09-5.02 (m, 2 H), 3.83 (s, 1 H), 3.46-3.36 (m, 2 H), 2.57

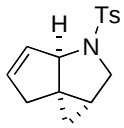
(dd, *J* = 15.3, 7.2 Hz, 1 H), 2.43 (s, 3 H), 1.81-1.66 (m, 7 H), 1.27-1.11 (m, 6 H), 0.20 (dd, *J* = 7.5, 5.6 Hz, 1 H), -0.42 (t, *J* = 3.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 137.6, 135.5, 129.6, 127.3, 116.5, 68.4, 51.2, 41.4, 45.8, 32.1, 28.1, 27.4, 27.0, 26.5 (2), 22.0, 21.5. 11.5; MS (ESI) *m/z* (rel. intensity) 382 (20), 311 (8), 203 (4); HRMS (ESI) calc for $C_{21}H_{29}NO_2NaS$ (M+Na) 382.1817, found 382.1812.



357e

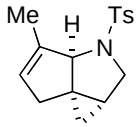
(1*S,4*R**,7*S**)-4-Cyclohexyl-5-methylene-3-tosyl-3-azabicyclo[5.1.0]octane (357e).** A solution of $[Rh(CO)_2Cl]_2$ (1.1 mg, 2.8 μmol) in PhMe (0.11 mL) was added to PhMe (0.58 mL), followed by a solution of dppe (2.2 mg, 5.6 μmol) in PhMe (0.22 mL). The reaction mixture was stirred at rt for 10 min, and treated with a solution of **342e** (20 mg, 0.056 mmol) in PhMe (0.20 mL). The reaction mixture was degassed, placed in an oil bath (110 ^{o}C), stirred for 30 min, cooled to rt, concentrated *in vacuo*, and the crude mixture was purified by a chromatography on SiO_2 (hexanes/EtOAc, 4:1) to afford **357e** (15 mg, 75%) as a clear, colorless oil: IR (neat) 2928, 2852, 1449, 1337, 1157 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 2 H), 7.24 (d, *J* = 8.1 Hz, 2 H), 4.82 (s, 1 H), 4.75 (d, *J* = 1.4 Hz, 1 H), 4.28 (dd, *J* = 16.1, 5.8 Hz, 1 H), 4.20 (d, *J* = 10.4 Hz, 1 H), 2.59 (dd, *J* = 14.0, 6.5 Hz, 1 H), 2.51 (dd, *J* = 16.1, 11.4 Hz, 1 H), 2.41 (s, 3 H), 1.80-1.72 (m, 3 H), 1.65-164 (m, 1 H), 1.52 (dd, *J* = 13.9, 10.3 Hz, 1 H), 1.47-1.34 (m, 2 H), 1.16-1.13 (m, 3 H), 1.00-0.94 (m, 1 H), 0.92-0.79 (m, 2 H), 0.74 (td, *J* = 8.0, 5.0 Hz, 1 H), 0.63-0.58 (m, 1 H), 0.19 (q, *J* = 4.8 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7, 142.5, 139.4, 129.1, 127.5, 115.1, 68.7, 45.4, 35.4, 33.7, 30.5, 29.9, 26.2, 26.1, 21.5, 16.1, 15.4, 15.2; MS

(ESI) *m/z* (rel. intensity) 382 (11), 325 (5), 155 (3); HRMS (ESI) calc for $C_{21}H_{29}NO_2SNa$ (M+Na) 382.1817, found 382.1804.



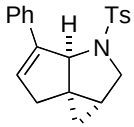
358a

(1*S,3*R**,6*R**)-*N*-Tosyl-5-azatricyclo[4.3.0.0^{1,3}]non-7-ene (358a).** A solution of $[Rh(CH_2{=}CH_2)_2Cl]_2$ (1.5 mg, 4.0 μmol) in PhMe (0.15 mL) was added to PhMe (0.92 mL), followed by a solution of Ph_3P (2.1 mg, 7.9 μmol) in PhMe (0.21 mL). The reaction mixture was stirred at rt for 10 min and a solution of **342f** (30 mg, 0.079 mmol) in PhMe (0.30 mL) was added. The reaction mixture was degassed, placed in an oil bath (110 ^{o}C) and stirred at this temperature for 10 min. The mixture was cooled to rt, Grubbs II catalyst (CAS Number: 246047-72-3, 1.7 mg, 2.0 μmol) was added, and the mixture was degassed and placed in an oil bath (70 ^{o}C). After 40 min, the mixture was cooled to rt, filtered through a short pad of SiO_2, washed with EtOAc, concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to yield **358a** (12 mg, 55%) as a colorless oil: IR (neat) 2924, 1598, 1446, 1344, 1162 cm^{-1}; ^{1}H NMR; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2 H), 7.31 (d, *J* = 8.1 Hz, 2 H), 6.00-5.95 (m, 1 H), 5.93-5.92 (m, 1 H), 4.50 (s, 1 H), 3.63 (dd, *J* = 10.5, 4.9 Hz, 1 H), 3.36 (d, *J* = 10.5 Hz, 1 H), 2.56 (dd, *J* = 16.7, 1.8 Hz, 1 H), 2.44 (s, 3 H), 2.14 (d, *J* = 16.7 Hz, 1 H), 1.17 (dt, *J* = 8.1, 4.4 Hz, 1 H), 0.89 (dd, *J* = 8.0, 5.9 Hz, 1 H), -0.07 (t, *J* = 5.2 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 136.1, 133.7, 132.7, 129.6, 127.1, 71.8, 50.3, 36.1, 34.0, 23.9, 21.5, 13.2; MS (ESI) *m/z* (rel. intensity) 298 (28), 276 (4), 156 (3), 155 (8); HRMS (ESI) calc for $C_{15}H_{17}NO_2NaS$ (M+Na) 298.0878, found 298.0897.



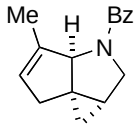
358b

(1*S,3*R**,6*R**)-*N*-Tosyl-7-methyl-5-azatricyclo[4.3.0.0^{1,3}]non-7-ene (358b).** A solution of $[Rh(CH_2{=}CH_2)_2Cl]_2$ (1.5 mg, 3.8 μmol) in PhMe (0.15 mL) was added to PhMe (0.87 mL) followed by a solution of Ph_3P (2.0 mg, 7.6 μmol) in PhMe (0.20 mL). The reaction mixture was stirred at rt for 10 min, and a solution of **342g** (30 mg, 0.076 mmol) in PhMe (0.30 mL) was added in one portion. The reaction mixture was degassed, placed in an oil bath (110 ^{o}C) and stirred for 10 min. The reaction mixture was cooled to rt, Grubbs II catalyst (CAS Number: 246047-72-3, 1.6 mg, 1.8 μmol) was added, and the reaction mixture was degassed and placed in oil bath (70 ^{o}C). After 40 min, the mixture was cooled to rt, filtered through a pad of SiO_2, washed with EtOAc, concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to afford **358b** (13 mg, 59%) as a clear, colorless oil: IR (neat) 3037, 2921, 2888, 2849, 1597, 1445, 1345, 1305, 1207, 1100 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.4 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 5.56 (t, *J* = 1.3 Hz, 1 H), 4.42 (s, 1 H), 3.61 (dd, *J* = 11.4, 4.7 Hz, 1 H), 3.40 (d, *J* = 11.5 Hz, 1 H), 2.49 (d, *J* = 16.1 Hz, 1 H), 2.44 (s, 3 H), 2.01 (dd, *J* = 16.2, 1.2 Hz, 1 H), 1.89 (app. t, *J* = 1.2 Hz, 1 H), 1.04 (dt, *J* = 8.0, 4.6 Hz, 1 H), 0.68 (app. t, *J* = 7.0 Hz, 1 H), -0.55 (t, *J* = 5.1 Hz, 1 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 143.3, 141.4, 136.3, 129.7, 127.3, 126.9, 73.8, 50.4, 35.0, 34.5, 23.7, 21.5, 14.7, 11.9; MS (ESI) *m/z* (rel. intensity) 312 (12), 272 (5), 261 (2), 155 (5); HRMS (ESI) calc for $C_{16}H_{19}NO_2NaS$ (M+Na) 312.1034, found 312.1021.



358c

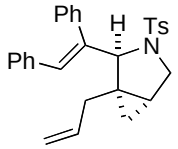
(1*S,3*R**,6*S**)-*N*-Tosyl-7-phenyl-5-azatricyclo[4.3.0,0^{1,3}]non-7-ene (358c).** A suspension of $[Rh(CH_2{=}CH_2)_2Cl]_2$ (2.2 mg, 5.4 μmol) in PhMe (0.22 mL) was added to PhMe (1.19 mL), followed by a solution of Ph_3P (2.9 mg, 11 μmol) in PhMe (0.29 mL). The reaction mixture was stirred at rt for 10 min and a solution of **342h** (0.050 g, 0.11 mmol) in PhMe (0.50 mL) was added in one portion. The mixture was degassed, placed in an oil bath (110 ^{o}C), and stirred under N_2 for 10 min. After cooling to rt, Grubbs II catalyst was added (CAS Number: 246047-72-3, 2.3 mg, 2.7 μmol), the mixture was degassed and placed in an oil bath (70 ^{o}C). After 30 min, the solution was cooled to rt, filtered through a short pad of 1:1 mixture of Florosil and Celite, washed with EtOAc, concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to afford **358c** (0.027 g, 71%) as a clear colorless oil: IR (neat) 3055, 2924, 2889, 2846, 1597, 1494, 1445, 1346, 1160 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63-7.62 (m, 2 H), 7.56 (d, *J* = 8.3 Hz, 2 H), 7.35-7.32 (m, 2 H), 7.29-7.26 (m, 1 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 6.15-6.14 (m, 1 H), 5.37 (s, 1 H), 3.54 (d, *J* = 11.7 Hz, 1 H), 3.33 (dd, *J* = 11.7, 4.2 Hz, 1 H), 2.75 (d, *J* = 16.7 Hz, 1 H), 2.39 (s, 3 H), 2.21 (dt, *J* = 16.8, 2.1 Hz, 1 H), 1.08 (dt, *J* = 8.1 4.2 Hz, 1 H), 0.86 (dt, *J* = 7.9, 6.4 Hz, 1 H), 0.23 (app q, *J* = 5.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 143.2, 137.5, 135.9, 130.8, 129.5, 128.0, 127.4, 127.3, 71.1, 49.5, 34.9, 34.1, 23.8, 21.4, 10.4; MS (ESI) *m/z* (rel. intensity) 374 (10), 272 (7), 261 (3), 155 (2); HRMS (ESI) calc for $C_{21}H_{21}NO_2NaS$ (M+Na) 374.1191, found 374.1183.



359

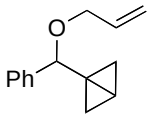
(1*S,3*R**,*6R**)-*N*-Benzoyl-7-methyl-5-azatricyclo[4.3.0.0^{1,3}]non-7-ene (359).** A solution of sodium naphthalenide was prepared by dissolving sodium (32 mg) in a solution of naphthalene (0.20 g) in dry THF (4.7 mL) at room temperature. A solution of **358b** (20 mg, 0.069 mmol) in THF (1.0 mL) was cooled to -78 ^{o}C and treated dropwise with the solution of sodium naphthalenide until the mixture remained dark brown/green (ca. 0.60 mL). The reaction mixture was stirred for an additional 5 min, quenched with sat. NH_4Cl, warmed up to rt and extracted (3x) with EtOAc. The aqueous layer was basified to pH 10 with aq. NaOH, extracted (2x) with EtOAc, and the combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The crude residue was dissolved in dry CH_2Cl_2 (2.0 mL), cooled on ice and treated with DMAP (3.4 mg, 0.028 mmol), Et_3N (0.050 mL, 0.34 mmol) and benzoyl chloride (0.016 mL, 0.14 mmol). The reaction mixture was stirred at 0 ^{o}C for 2 h, quenched with sat. NH_4Cl, and extracted (3x) with CH_2Cl_2. The combined organic layers were washed with water and brine, dried (Na_2SO_4), concentrated *in vacuo*, and purified by chromatography on SiO_2 (Hexanes/EtOAc 4:1 to 1:1) to afford **359** (0.0088 g, 53%) as a clear oil: IR (neat) 2925, 2851, 1631, 1446, 1405, 1376, 1221 cm^{-1}; Major Rotamer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.47 (m, 2 H), 7.41-7.39 (m, 3 H), 5.63 (s, 1 H), 5.23 (s, 1 H), 3.78 (dd, *J* = 10.8, 4.7 Hz, 1 H), 3.36 (d, *J* = 10.8 Hz, 1 H), 2.71 (d, *J* = 15.8 Hz, 1 H), 2.14 (d, *J* = 17.2 Hz, 1 H), 1.86 (s, 3 H), 1.18-1.10 (m, 1 H), 1.04 (dd, *J* = 8.0, 6.5 Hz, 1 H), 0.60 (t, *J* = 4.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 142.0, 137.3, 129.9, 128.2, 127.2, 127.0, 70.4, 51.8, 35.5, 32.7, 23.3, 15.0, 12.8; Minor rotamer (representative signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.54 (s, 1 H), 4.67 (s, 1

H), 4.04 (d, *J* = 12.2 Hz, 1 H), 3.54 (dd, *J* = 12.1, 4.3 Hz, 1 H), 2.56 (d, *J* = 16.3 Hz, 1 H), 1.42 (s, 3 H), 0.76 (t, *J* = 4.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 72.0, 47.6, 34.9, 21.7, 12.2; MS (ESI) *m/z* (rel. intensity) 262 (53), 240 (23), 119 (68); HRMS (ESI) calc for $C_{16}H_{17}NO$ (M+H) 240.1388, found 240.1382.



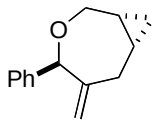
360

(1*S,2*S**,5*R**)-1-Allyl-2-((*E*)-1,2-diphenylvinyl)-3-tosyl-3-azabicyclo[3.1.0]hexane (360).** A base washed test tube was oven dried, cooled to room temperature, equipped with a magnetic stirrer and rubber septum and placed under N_2. Degassed PhMe (0.72 mL) was added and a solution of $[Rh(CH_2{=}CH_2)_2Cl]_2$ (1.3 mg, 0.0022 mmol) in PhMe (0.13 mL) was added followed by a solution of Ph_3P (1.7 mg, 0.0044 mmol) in PhMe (0.17 mL). The reaction mixture was stirred at room temperature for 10 min and a solution of **342h** (0.030 g, 0.0658 mmol) in PhMe (0.20 mL) was added in one portion. The mixture was degassed and placed in an oil bath (110 ^{o}C) and stirred at under N_2 for 7 min. After cooling to room temperature the mixture was filtered through a short pad of SiO_2, washed with EtOAc and the solvent was removed *in vacuo*. Purification by chromoatgraphy on SiO_2 (hexanes/EtOAc, 4:1) afforded **360** (0.017 g, 83%) as a colorless oil: IR (neat) 3056, 2925, 1598, 1344, 1162 cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0, 140.5, 138.0, 136.3, 135.1, 130.3, 129.7, 129.5, 129.3, 128.4, 127.8, 127.3, 126.9, 126.8, 116.9, 71.7, 50.7, 35.3, 30.6, 22.2, 12.1.

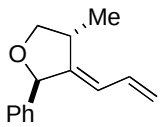


361

1-(Allyloxy(phenyl)methyl)bicyclo[1.1.0]butane (361). A solution of alcohol **124a** (1.3 g, 7.8 mmol) in PhMe (10 mL) was treated with Bu_4NHSO_4 (1.3 g, 3.9 mmol), allyl bromide (1.4 mL, 16 mmol) and 50 % aq NaOH (10 mL). The reaction mixture was vigorously stirred at rt for 1 h, diluted with water and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. The product was purified by Kugelrohr distillation (fractions collected at 85-95 ^oC, 1 mmHg) to afford **361** (1.4 g, 89%) as a clear, colorless oil: IR (neat) 3029, 2929, 2861, 1492, 1452 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.38-7.34 (m, 2 H), 7.31-7.27 (m, 3 H), 6.02-5.92 (m, 1 H), 2.59 (dq, *J* = 17.3, 1.7 Hz, 1 H), 5.20 (dt, *J* = 10.4, 1.3 Hz, 1 H), 4.77 (s, 1 H), 4.09-4.00 (m, 2 H), 1.67 (dd, *J* = 6.2, 2.9 Hz, 1 H), 1.32 (dd, *J* = 6.2, 2.9 Hz, 1 H), 1.25-1.24 (m, 1 H), 0.88 (s, 1 H), 0.65 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.0, 135.0, 128.2, 127.5, 126.9, 116.7, 80.9, 69.6, 34.1, 31.1, 13.7, 0.7; MS (EI) *m/z* (rel. intensity) 159 (15), 141 (36), 131 (98), 105 (99), 91 (100); HRMS (EI) calc for $C_{14}H_{16}O$ 200.1201, found 200.1200.



362



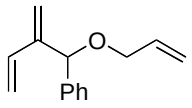
363

To a solution of $[Rh(CH_2{=}CH_2)_2Cl]_2$ (1.9 mg, 5.0 μmol) in PhMe (0.19 mL) was added PhMe (0.35 mL) followed by a solution of Ph_3P (2.6 mg, 10 μmol) in PhMe (0.20 mL). After 5 min at rt, the reaction mixture was placed in an oil bath (110 ^oC) and a solution of **361** (20 mg, 0.10

mmol) in PhMe (0.20 mL) was added in one portion. The mixture was kept at this temperature for 15 min, cooled to rt, filtered through a short pad of SiO_2 (washed with CH_2Cl_2) and the solvent was removed *in vacuo*. The yields (^{1}H NMR) were determined using an internal standard ($CHBr_3$): **363** (46%), **362** (20%). Analytically pure samples were prepared by SFC purification: Chiralpak-IB, 5% *i*-PrOH at 8.5 mL/min, **363**: R_t = 3.65, 6.55 min, **362**: R_t = 4.25, 6.21 min; Chiralpak-IA, 5% *i*-PrOH at 8.5 mL/min, **363**: R_t = 5.36, 4.24 min; **362**: R_t = 4.67, 3.65 min.

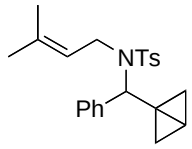
(1*R,4*S**,7*R**)-5-Methylene-4-phenyl-3-oxabicyclo[5.1.0]octane (362).** Clear, colorless oil: IR (neat) 2997, 2923, 2855, 1449 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (t, *J* = 7.6 Hz, 1 H), 7.41 (d, *J* = 7.8 Hz, 2 H), 7.25 (d, *J* = 7.2 Hz, 2 H), 4.96 (s, 2 H), 4.92 (s, 1 H), 4.46 (dd, *J* = 13.5, 7.8 Hz, 1 H), 3.35 (dd, *J* = 13.5, 8.5 Hz, 1 H), 2.82 (dd, *J* = 13.2, 5.2 Hz, 1 H), 2.25 (dd, *J* = 13.2, 4.4 Hz, 1 H), 1.33-1.26 (m, 1 H), 1.14-1.08 (m, 1 H), 0.76 (td, *J* = 8.2, 4.6 Hz, 1 H), 0.49 (q, *J* = 5.1 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.0, 141.1, 128.0, 127.1, 126.3, 117.2, 87.9, 70.2, 33.2, 16.7, 15.2, 11.6.

(2*R,4*R**,*E*)-3-Allylidene-4-methyl-2-phenyltetrahydrofuran (363).** Clear, colorless oil: IR (neat) 2921, 1738, 1242 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 7.1, 1.2 Hz, 2 H), 7.35 (t, *J* = 7.8 Hz, 2 H), 7.29-7.28 (m 1 H), 6.13 (dd, *J* = 12.0, 2.3 Hz, 1 H), 5.59 (d, *J* = 12.1 Hz, 1 H), 5.31 (s, 1 H), 5.08 (s, 1 H), 4.81 (s 1 H), 4.04 (ddd, *J* = 12.1, 4.6, 1.5 Hz, 1 H), 3.56 (dd, *J* = 11.9, 10.5 Hz, 1 H), 2.81-2.77 (m, 1 H), 1.00 (d, *J* = 7.3 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.7, 142.6, 136.1, 128.2, 127.5, 127.3, 127.2, 118.0, 87.2, 74.1, 38.8, 16.9.



364

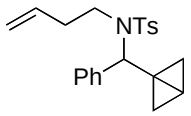
(1-(Allyloxy)-2-methylenebut-3-enyl)benzene (364). A solution of $[Rh(CO)_2Cl]_2$ (1.9 mg, 5.0 μmol) in degassed PhMe (0.19 mL) was added to PhMe (1.21 mL) followed by a solution of dppe (4.0 mg, 10 mmol) in PhMe (0.40 mL). After stirring at rt for 10 min, the mixture was placed in an oil bath (120-130 ^oC) and once the solution started refluxing, a solution of **361** (20 mg, 0.10 mmol) in PhMe (0.20 mL) was added in one portion. The reaction mixture was stirred at this temperature for 20 min, cooled to rt, diluted with CH_2Cl_2 (ca. 10 mL), filtered through a short pad of silica (washed with excess of CH_2Cl_2) and the solvent was removed *in vacuo*. The yields (^1H NMR) were determined using an internal standard ($CHBr_3$): **362** (18%) and **364** (23%). **364** (characteristic signals): ^1H NMR (300 MHz, $CDCl_3$) δ 6.31 (dd, J = 17.9, 6.7 Hz, 1 H).



368

***N*-(Bicyclo[1.1.0]but-1-yl(phenyl)methyl)-4-methyl-*N*-(3-methylbut-2-enyl)benzenesulfonamide (368).** A solution of **120b** (0.40 g, 1.3 mmol), Bu_4NHSO_4 (0.23 g, 0.64 mmol), prenyl bromide (0.95 g, 6.4 mmol) in PhMe (10 mL) was treated with NaOH (50% aq, 10 mL) and vigorously stirred at rt for 20 min. The mixture was diluted with water, extracted (3x20 mL) with Et_2O and thecombined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) af-

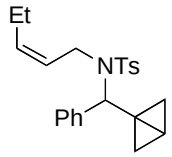
forded **368** (0.45 g, 93%) as a colorless oil: IR (neat) 3029, 2967, 1673, 1494, 1378, 1339 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 8.2, 1.3 Hz, 2 H), 7.28-7.21 (m, 7 H), 5.34 (s, 1 H), 5.07-4.99 (m, 1 H), 4.13-4.00 (m, 2 H), 2.41 (s, 3 H), 1.60 (br s, 4 H), 1.67 (s, 3 H), 1.51 (br s, 1 H), 1.30 (dd, *J* = 6.3, 2.8 Hz, 1 H), 0.71 (s, 1 H), 0.59 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 139.3, 138.7, 133.9, 129.1, 128.2, 127.7, 127.3, 122.1, 62.4, 44.3, 34.0, 31..9, 25.6, 21.4, 17.7, 12.2, 3.5; MS (ESI) *m/z* (rel. intensity) 785 ($[2M+Na]^+$, 8), 404 ($[M+Na]^+$, 100); HRMS (ESI) calc for $C_{23}H_{27}NO_2NaS$ $(M+Na)^+$ 404.1660, found 404.1678.



369

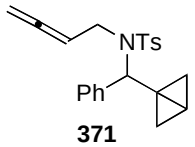
***N*-(Bicyclo[1.1.0]butan-1-yl(phenyl)methyl)-*N*-(but-3-enyl)-4-methylbenzenesulfonamide (369).** A solution of **120b** (0.30 g, 0.96 mmol), Bu_4NHSO_4 (0.033 g, 0.096 mmol), and 4-bromobut-1-ene (0.64 g, 4.8 mmol) in PhMe (3.0 mL) was treated with NaOH (50% aq, 3.0 mL) and vigorously stirred at rt for 24 h. The mixture was diluted with water, extracted with Et_2O and thecombined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **369** (0.10 g, 28%) as a colorless oil: IR (ATR) 2924, 1597, 1450, 1336, 1157 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.2 Hz, 2 H), 7.33-7.17 (m, 3 H), 5.71-5.63 (m, 1 H), 5.34 (s, 1 H), 5.00-4.96 (m, 2 H), 3.57-3.47 (m, 2 H), 2.46-2.40 (m, 4 H), 2.31-2.23 (m, 1 H), 1.63 (dd, *J* = 6.2, 2.7 Hz, 1 H), 1.46 (s, 1 H), 1.28 (dd, *J* = 6.3, 2.9 Hz, 1 H), 0.79 (s, 1 H), 0.58 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 138.9, 137.9, 135.0, 129.2, 128.2, 127.6, 127.4, 127.3, 127.1, 116.6, 62.4, 46.2, 35.5, 34.5, 31.2, 21.4, 12.1, 3.5; MS (EI) *m/z* (rel. intensity) 367 (M^+, 5), 326 (20), 212 (15), 143

(100), 128 (54), 115 (24), 91 (69), 84 (85); HRMS (EI) calc for $C_{22}H_{25}NO_2S$ 367.1606, found 367.1605.



370

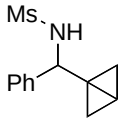
(*Z*)-*N*-(Bicyclo[1.1.0]but-1-yl(phenyl)methyl)-4-methyl-*N*-(pent-2-enyl)benzenesulfonamide (370). A solution of **120b** (0.40 g, 1.3 mmol), Bu_4NHSO_4 (0.23 g, 0.64 mmol), and crude (*Z*)-1-bromopent-2-ene (0.95 g, 6.4 mmol) in PhMe (10 mL) was treated with NaOH (50% aq, 10 mL) and vigorously stirred at rt for 20 min. The mixture was diluted with water, extracted (3x20 mL) with Et_2O and thecombined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatograpgy on SiO_2 (hexanes/EtOAc, 4:1) afforded **370** (0.47 g, 95%) as a colorless oil: IR (neat) 3029, 2964, 2930, 1599, 1494, 1341, 1159 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.8 Hz, 2 H), 7.28-7.17 (m, 7 H), 5.38-5.21 (m, 3 H), 4.20 - 4.07 (m, 2 H), 2.42 (s, 3 H), 2.00 (quintet, *J* = 7.2 Hz, 2 H), 1.59 (dd, *J* = 6.3, 3.2 Hz, 1 H), 1.50 (br s, 1 H), 1.28 (dd, *J* = 6.3, 3.0 Hz, 1 H), 0.95 (t, *J* = 7.5 Hz, 3 H), 0.71 (s, 1 H), 0.58 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 139.2, 138.5, 133.2, 129.2, 128.3, 127.7, 127.4, 126.5, 62.6, 43.3, 34.3, 32.0, 21.5, 20.5, 14.0, 12.2, 3.7; MS (ESI) *m/z* (rel. intensity) 785 ($[2M+Na]^+$, 10), 404 ($[M+Na]^+$, 100); HRMS (ESI) calc for $C_{23}H_{27}NO_2NaS$ $(M+Na)^+$ 404.1660, found 404.1642.



371

***N*-(Bicyclo[1.1.0]butan-1-yl(phenyl)methyl)-*N*-(buta-2,3-dienyl)-4-methylbenzenesulfonamide (371).** A solution of **120b** (0.42 g, 1.3 mmol), Bu_4NHSO_4 (0.045 g, 0.13 mmol) and 4-bromobuta-1,2-diene (0.89 g, 6.7 mmol) in PhMe (10 mL) was treated with 50% aq NaOH (10 mL), vigorously stirred at rt for 1 h, diluted with water, extracted with Et_2O (3x10 mL) and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **371** (0.40 g, 82%) as a colorless oil: IR (neat) 3030, 2928, 1955, 1598, 1340, 1159 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, 2 H), 7.35-7.20 (m, 5 H), 7.19-7.15 (m, 2 H), 5.37 (s, 1 H), 5.07 (quintet, *J* = 6.1 Hz, 1 H), 4.67-466 (m, 2 H), 4.17 (dt, *J* = 6.9, 2.4 Hz, 1 H), 2.42 (s, 3 H), 1.61 (dd, *J* = 6.3, 2.9 Hz, 1 H), 1.48 (s, 1 H), 1.27 (dd, *J* = 6.3, 2.8 Hz, 1 H), 0.76 (s, 1 H), 0.62 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.5, 142.9, 138.8, 138.1, 129.2, 128.2, 127.6, 127.3, 127.2, 88.7, 75.9, 62.6, 45.3, 34.3, 31.6, 21.4, 12.0, 3.6.

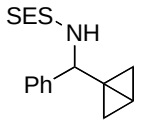
4-bromobuta-1,2-diene.



372

***N*-(bicyclo[1.1.0]but-1-yl(phenyl)methyl)methanesulfonamide (372).** A solution of 2,2-dibromo-1-chloromethylcyclopropane **119** (1.7 g, 6.5 mmol) in dry Et_2O (5.0 mL) was cooled to

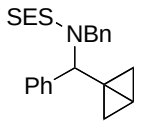
-78 °C, treated with MeLi (4.4 mL, 6.5 mmol, c = 1.5 M in Et_2O) and after 1 h at -78 °C, a solution of *t*-BuLi (4.4 mL, 6.5 mmol, c = 1.5 M in pentane) was added. The reaction mixture was stirred at this temperature for 1 h, a solution of *N*-benzylidenemethanesulfonamide (0.40 g, 1.2 mmol) in THF (4.0 mL) was added. The mixture was quenched with sat. NH_4Cl, warmed up to rt, diluted with water, extracted with EtOAc and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purifiction by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **372** (0.36 g, 69%) as a colorless oil: IR (neat) 3278, 3031, 2931, 2871, 1495, 1453, 1435, 1412, 1318, 1197, 1153, 1101 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.26 (m, 5 H), 5.62 (d, *J* = 7.3 Hz, 1 H), 4.97 (d, *J* = 7.4 Hz, 1 H), 2.72 (s, 3 H), 1.65 (dd, *J* = 6.2, 2.8 Hz, 1 H), 1.45 (s, 1 H), 1.39 (dd, *J* = 6.3, 2.7 Hz, 1 H), 0.77 (s, 1 H), 0.63 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3, 128.6, 127.9, 126.8, 57.9, 41.9, 33.0, 31.1, 14.2, 1.6; MS (EI) *m/z* (rel. intensity) 237 (2, M^+), 184 (28), 158 (56), 142 (30), 131 (33), 117 (54), 106 (100); HRMS (EI) calc for $C_{12}H_{15}NO_2S$ 237.0823, found 237.0835.



373

***N*-(bicyclo[1.1.0]but-1-yl(phenyl)methyl)-2-(trimethylsilyl)ethanesulfonamide (373).** A solution of 2,2-dibromo-1-chloromethylcyclopropane **119** (1.4 g, 5.4 mmol) in dry Et_2O (5.0 mL) was cooled to -78 °C, treated with MeLi (3.7 mL, 5.4 mmol, c = 1.5 M in Et_2O) and after 1 h at -78 °C, a solution of *t*-BuLi (3.3 mL, 5.4 mmol, c = 1.7 M in pentane) was added. The reaction mixture was stirred at this temperature for 1 h, a solution of *N*-benzylidene-2-(trimethylsilyl)ethanesulfonamide[489] (0.50 g, 1.2 mmol) in THF (4.0 mL) was added. The mix-

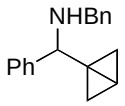
ture was quenched with sat. NH_4Cl, warmed up to rt, diluted with water, extracted with EtOAc and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purifiction by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **373** (0.36 g, 60%) as a colorless oil: IR (neat) 3276, 3032, 2953, 1431, 1320, 1252, 1145 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.21 (m, 5 H), 4.91 (d, *J* = 6.5 Hz, 1 H), 4.84 (d, *J* = 6.4 Hz, 1 H), 2.79-2.57 (m, 2 H), 1.70 (dd, *J* = 6.2, 2.9 Hz, 1 H), 1.42 (s, 1 H), 1.36 (dd, *J* = 6.3, 2.9 Hz, 1 H), 0.98-0.84 (m, 2 H), 0.80 (s, 1 H), 0.63 (s, 1 H), -0.09 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7, 128.7, 128.1, 127.0, 58.2, 50.1, 33.3, 31.3, 14.3, 10.4, 1.9, 0.0, -2.1; MS (EI) *m/z* (rel. intensity) 323 (M^+, 7), 259 (57), 178 (75), 158 (87), 143 (92), 128 (95), 75 (100); HRMS (EI) calc for $C_{16}H_{25}NO_2SSi$ 323.1375, found 323.1373.



374

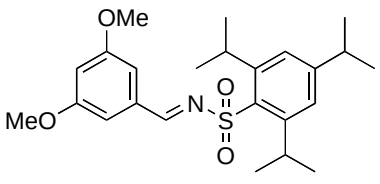
***N*-benzyl-*N*-(bicyclo[1.1.0]but-1-yl(phenyl)methyl)-2-(trimethylsilyl)ethanesulfonamide (374).** A solution of **373** (0.10 g, 0.32 mmol) in PhMe (10 mL) was treated with BnBr (75 μL, 0.63 mmol), Bu_4NHSO_4 (0.011 g, 0.032 mmol) and 50% aq NaOH (10 mL). The reaction mixture was vigorously stirred at rt for 30 min, diluted with water, extracted (3x10mL) with Et_2O and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 6:1) afforded **374** (0.11 g, 83%) as a colorless oil: IR (neat) 3031, 2952, 1603, 1495, 1453, 1331, 1140 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.24 (m, 10 H), 5.31 (s, 1 H), 4.81 (s, 2 H), 2.47-2.45 (m, 1 H), 2.42-2.41 (m, 2 H), 1.70 (dd, *J* = 6.3, 2.8 Hz, 1 H), 1.42 (s, 1 H), 1.34 (dd, *J* = 6.3, 2.9 Hz, 1 H), 0.92-0.90

(m, 1 H), 0.87-0.85 (m, 1 H), 0.54 (s, 2 H), -0.13 (s, 9 H); MS (EI) *m/z* (rel. intensity) 413 (M^+, 34), 385 (21), 349 (17), 316 (53), 249 (87), 181 (97), 167 (96), 136 (98), 89 (100); HRMS (EI) calc for $C_{23}H_{31}NO_2SSi$ 413.1845, found 413.1844.



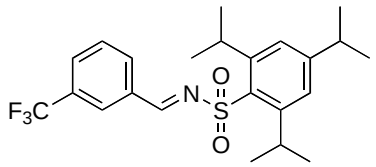
375

***N*-benzyl-1-(bicyclo[1.1.0]but-1-yl)-1-phenylmethanamine (375).** A solution of **374** (0.10 g, 0.25 mmol) in MeCN (10 mL) was treated with TBAF (0.76 mL, 0.76 mmol, 1.0 M in THF) and stirred under reflux for 12 h. After cooling to rt, the mixture was diluted with sat. NH_4Cl and water, extracted (3 x 10 mL) with EtOAc and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **375** (0.052 g, 82%) as a colorless oil: IR (neat) 3026, 2924, 1602, 1493, 1453, 1301, 1198, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.33 (m, 7 H), 7.30-7.23 (m, 3 H), 4.11 (s, 1 H), 3.81, 3.75 (AB, *J* = 13.3 Hz, 2 H), 1.82 (br s, 1 H, 1.61 (dd, *J* = 6.2, 2.8 Hz, 1 H), 1.28 (dd, *J* = 6.3, 2.8 Hz, 1 H), 1.24-1.23 (m, 1 H), 0.73 (s, 1 H), 0.55 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9, 140.6, 128.3, 128.2, 128.1, 127.5, 127.1, 126.9, 61.5, 51.8, 32.8, 30.6, 15.2, 0.5; MS (EI) *m/z* (rel. intensity) 249 (M^+, 2), 121 (31), 117 (100); HRMS (EI) calc for $C_{18}H_{19}N$ 249.1518, found 249.1518.



376a

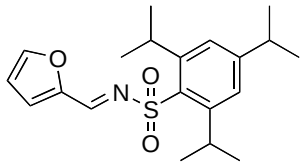
***N*-(3,5-Dimethoxybenzylidene)-2,4,6-triisopropylbenzenesulfonamide (376a).** A solution of 3,5-dimethoxybenzaldehyde (0.59 g, 3.5 mmol), 2,4,6-triisopropylbenzenesulfonamide (1.0 g, 3.5 mmol) and DIPEA (1.8 mL, 10.6 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 ^oC, treated with a solution of $TiCl_4$ (0.23 mL, 2.2 mmol) in CH_2Cl_2 (2.0 mL). After 2 h at 0 ^oC, the reaction mixture was poured into dry ether, filtered through a pad of SiO_2, washed with EtOAc and the solvent was removed in vacuo. Crystallization from CH_2Cl_2/hexane afforded **376a** (1.0 g, 66%) as a white solid: Mp. 131.8-133.1 ^oC (hexanes/CH_2Cl_2); IR (neat) 2959, 1581, 1459, 13001, 1154 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.91 (s, 1 H), 7.22 (s, 2 H), 7.07 (d, *J* = 2.3 Hz, 2 H), 6.69 (d, *J* = 2.3 Hz, 1 H), 4.37 (septet, *J* = 6.8 Hz, 2 H), 3.83 (s, 6 H), 2.93 (septet, *J* = 6.9 Hz, 1 H), 1.30 (d, *J* = 6.8 Hz, 12 H), 1.27 (d, *J* = 6.9 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 161.1, 153.7, 151.2, 134.5, 130.8, 123.9, 108.4, 107.4, 55.6, 34.6, 34.2, 29.8, 24.7, 23.5; MS (EI) *m/z* (rel. intensity) 431 (M^+, 25), 352 (100), 267 (7), 230 (14), 203 (27), 187 (18), 164 (37); HRMS (EI) calc for $C_{24}H_{33}NO_4S$ 431.2130, found 431.2129.



376b

2,4,6-Triisopropyl-*N*-(3-(trifluoromethyl)benzylidene)benzenesulfonamide (376b). A solution of 3-(trifluoromethyl)benzaldehyde (0.61 g, 3.5 mmol), 2,4,6-triisopropylbenznene sulfonamide (1.0 g, 3.5 mmol) and DIPEA (1.8 mL, 11 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 ^oC, treated with a solution of $TiCl_4$ (0.23 mL, 2.2 mmol) in CH_2Cl_2 (10 mL) over 10 min. The reaction mixture was stirred at 0 ^oC for 1 h, poured into Et_2O (120 mL), filtered through a pad of

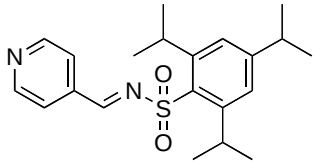
SiO_2 (washed with EtOAc), and concentrated. Precipitation from CH_2Cl_2 with excess of hexanes afforded **376b** (0.96 g, 62%) as a white solid: Mp. 166.6-167.1 ^oC (CH_2Cl_2/hexane); IR (ATR) 2958, 2866, 1621, 1603, 1457, 1331, 1308, 1276 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.11 (s, 1 H), 8.25 (s, 1 H), 8.13 (d, *J* = 7.7 Hz, 1 H), 7.87 (d, *J* = 7.8 Hz, 1 H), 7.67 (t, *J* = 7.8 Hz, 1 H), 7.25 (s, 2 H), 4.41 (septet, *J* = 6.7 Hz, 2 H), 2.94 (septet, *J* = 6.9 Hz, 1 H), 1.33 (d, *J* = 6.8 Hz, 12 H), 1.29 (d, *J* = 6.9 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.98, 154.03, 131.35, 134.10, 133.44, 132.51, 132.07, 131.63, 131.19, 130.75, 130.70 130.40, 129.84, 128.78, 127.18, 127.13, 125.16, 123.95, 121.55, 117.94, 34.24, 29.81, 24.69, 23.47; MS (EI) *m/z* (rel. intensity) 439 (M^+, 1), 420 (44), 406 (33), 360 (100), 332 (19), 317 (16) 267 (41), 251 (51), 202 (76), 187 (77); HRMS (ES) calc for $C_{23}H_{28}NO_2F_3NaS$ (M+Na) 462.1691, found 462.1728.



376c

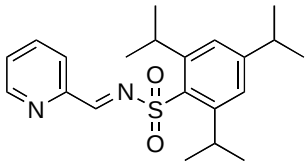
***N*-(Fur-2-ylmethylene)-2,4,6-triisopropylbenzenesulfonamide (376c).** A solution of 2-furfural (0.25 g, 2.6 mmol), 2,4,6-triisopropylbenznene sulfonamide (0.75 g, 2.6 mmol), DIPEA (1.4 mL, 7.9 mmol) in CH_2Cl_2 (5.0 mL) was cooled to 0 ^oC, treated with a solution of $TiCl_4$ (0.31 g, 1.7 mmol) in CH_2Cl_2 (2.0 mL) and stirred at 0 ^oC for 2 h. The mixture was poured into dry ether, filtered through a pad of SiO_2, washed with EtOAc and concentrated. Crystallization from CH_2Cl_2/hexane afforded **376c** (0.48g, 50%) as a white solid: Mp. 150.7-152.3 ^oC (hexanes/CH_2Cl_2); IR (neat) 2956, 1599, 1538, 1460, 1287, 1147 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.81 (s, 1 H), 7.74 (d, *J* = 1.5 Hz, 1 H), 7.32 (d, *J* = 3.6 Hz, 1 H), 7.19 (s, 2 H), 6.64 (dd, *J* =

3.6, 1.7 Hz, 1 H), 4.32 (septet, *J* = 6.8 Hz, 2 H), 2.91 (septet, *J* = 6.9 Hz, 1 H), 1.29 (d, *J* = 6.8 Hz, 12 H), 1.26 (d, *J* = 6.8 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 153.6, 151.0, 149.5, 149.4, 131.1, 123.8, 123.3, 113.5, 34.3, 29.8, 24.7, 23.6; MS (EI) *m/z* (rel. intensity) 361 (M^+, 1), 346 (1), 282 (78), 187 (22), 95 (100).



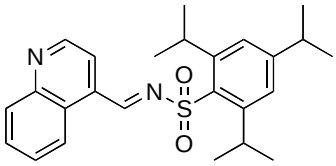
376d

2,4,6-Triisopropyl-*N*-(pyridin-4-ylmethylene)benzenesulfonamide (376d). A solution of 4-pyridine carboxaldehyde (0.38 g, 3.5 mmol), 2,4,6-triisopropylbenzenesulfonamide (1.0 g, 3.5 mmol) and DIPEA (1.8 mL, 10.6 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 ^oC, treated with a solution of $TiCl_4$ (0.23 mL, 2.2 mmol) in CH_2Cl_2 (2.0 mL) and after 2 h at 0 ^oC, the reaction mixture was poured into dry ether, filtered through a pad of SiO_2, washed with EtOAc and the solvent was removed in vacuo. Crystallization from CH_2Cl_2/hexane afforded **376d** (0.69 g, 53%) as an off-white solid: Mp. 190-192 ^oC (CH_2Cl_2/hexanes); IR (ATR) 2954, 1610, 1558, 1310, 1152 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.05 (s, 1 H), 8.83 (d, *J* = 4.7 Hz, 2 H), 7.75 (d, *J* = 5.6 Hz, 2 H), 7.23 (s, 2 H), 4.32 (septet, *J* = 6.7 Hz, 2 H), 2.93 (septet, *J* = 6.8 Hz, 1 H), 1.31-1.26 (m, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 154.3, 151.6, 151.1, 139.3, 130.0, 124.1, 123.3, 34.3, 29.9, 24.8, 23.5.



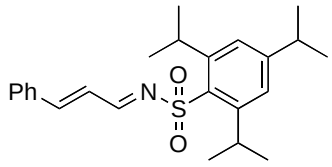
376e

2,4,6-Triisopropyl-*N*-(pyridin-2-ylmethylene)benzenesulfonamide (376e). A solution of 2-pyridine carboxaldehyde (0.38 g, 3.5 mmol), 2,4,6-triisopropylbenzenesulfonamide (1.0 g, 3.5 mmol) and DIPEA (1.8 mL, 10.6 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 ^oC, treated with a solution of $TiCl_4$ (0.23 mL, 2.2 mmol) in CH_2Cl_2 (2.0 mL). After 2 h at 0 ^oC, the reaction mixture was poured into dry ether, filtered through a pad of SiO_2, washed with EtOAc and the solvent was removed in vacuo. Crystallization from CH_2Cl_2/hexane afforded **376e** (0.59 g, 49%) as a yellow solid: Mp. 117-120 ^oC (hexane/CH_2Cl_2); IR (neat) 2961, 2930, 2870, 1612, 1464, 1323, 1164 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.99 (s, 1 H), 8.77 (d, J = 4.7 Hz, 1 H), 8.24 (d, J = 7.9 Hz, 1 H), 7.86 (td, J = 7.9, 1.6 Hz, 1 H), 7.50 (ddd, J = 7.6, 4.9, 1.1 Hz, 1 H), 7.24 (s, 2 H), 4.26 (septet, J = 6.8 Hz, 2 H), 2.94 (septet, J = 6.9 Hz, 1 H), 1.29 (d, J = 6.8 Hz, 6 H), 1.28 (d, J = 6.8 Hz, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 154.2, 151.7, 151.6, 150.4, 137.1, 129.6, 127.5, 124.1, 123.8, 34.3, 29.9, 24.8, 23.6; MS (EI) *m/z* (rel. intensity) 372 (M^+, 12), 294 (100), 265 (45), 251 (55), 203 (77), 187 (92), 159 (59); HRMS (EI) calc for $C_{21}H_{28}N_2O_2S$ 372.1872, found 372.1856.



376f

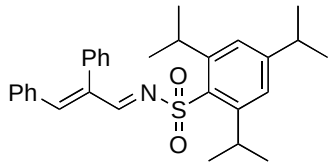
2,4,6-Triisopropyl-*N*-(quinolin-4-ylmethylene)benzenesulfonamide (376f). A solution of quinoline-4-carboxaldehyde (0.55 g, 3.5 mmol), 2,4,6-triisopropylbenzenesulfonamide (1.0 g, 3.5 mmol) and DIPEA (1.8 mL, 10.6 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 ^oC, treated with a solution of $TiCl_4$ (0.23 mL, 2.2 mmol) in CH_2Cl_2 (2.0 mL). After 2 h at 0 ^oC, the reaction mixture was poured into dry ether, filtered through a pad of SiO_2, washed with EtOAc and the solvent was removed in vacuo. Crystallization from CH_2Cl_2/hexane afforded **376f** (2.4 g, 69%) as a colorless solid: Mp. 149.2-150.5 ^oC (CH_2Cl_2/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 9.67 (s, 1 H), 9.11 (d, *J* = 4.4 Hz, 1 H), 8.82 (d, *J* = 8.4 Hz, 1 H), 8.23 (d, *J* = 8.4 Hz, 1 H), 7.92 (d, *J* = 4.4 Hz, 1 H), 7.83 (td, *J* = 8.3, 1.2 Hz, 1 H), 7.74-7.69 (m, 1 H), 7.24 (s, 2 H), 4.41 (septet, *J* = 6.8 Hz, 2 H), 2.94 (septet, *J* = 6.9 Hz, 1 H), 1.33 (d, *J* = 6.8 Hz, 12 H), 1.27 (d, *J* = 6.9 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 154.4, 151.7, 150.1, 149.3, 135.0, 130.6, 130.2, 130.1, 128.9, 125.3, 124.1, 124.0, 123.8, 34.3, 30.0, 24.8, 23.5; IR (ATR) 2954, 1599, 1573, 1316, 1295, 1152 cm^{-1}; MS (EI) *m/z* (rel. intensity) 421 (M^+, 5), 407 (24), 389 (26), 343 (100), 267 (50), 251 (46), 230 (75), 203 (77), 187 (76), 155 (72), 128 (85); HRMS (EI) calc for $C_{25}H_{30}N_2O_2S$ 422.2028, found 422.2019.



376g

2,4,6-Triisopropyl-*N*-((*E*)-3-phenylallylidene)benzenesulfonamide (376g). A solution of *E*-cinnamaldehyde (0.35 g, 2.6 mmol), 2,4,6-triisopropylbenznene sulfonamide (0.75 g, 2.6 mmol), DIPEA (1.4 mL, 7.9 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 ^oC, treated with a solu-

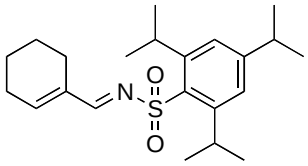
tion of $TiCl_4$ (0.46 mL, 1.7 mmol) in CH_2Cl_2 (10 mL) and stirred at 0 ^oC for 2 h. The mixture was poured into dry ether, filtered through a pad of SiO_2, washed with EtOAc and concentrated. Crystallization from CH_2Cl_2/hexane afforded **376g** (0.82, 78%) as a white solid: Mp. 166.4-167.6 ^oC (CH_2Cl_2/hexane); IR (KBr) 2956, 1624, 1600, 1581, 1461, 1425, 1363, 1307, 1257, 1154 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.76 (d, *J* = 9.3 Hz, 1 H), 7.58-756 (m, 2 H), 7.45-7.41 (m, 4 H), 7.20 (s, 2 H), 7.01 (dd, *J* = 15.8, 9.3 Hz, 1 H) 4.26 (septet, *J* = 6.8 Hz, 2 H), 2.92 (septet, *J* = 6.9 Hz, 1 H), 1.29 (d, *J* = 6.8 Hz, 12 H), 1.27 (d, *J* = 7.0 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 153.6, 152.9, 151.1, 134.3, 131.5, 131.1, 129.2, 128.6, 125.1, 123.9, 34.3, 29.8, 24.8, 23.6; MS (EI) *m/z* (rel. intensity) 397 (M^+, 17), 382 (21), 333 (15), 318 (100), 267 (17), 230 (17), 203 (22), 187 (34), 130 (72); HRMS (EI) calc for $C_{24}H_{31}NO_2S$ 397.2076, found 397.2090.



376h

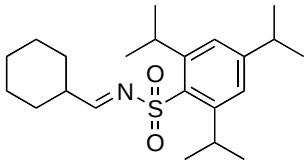
***N*-((*E*)-2,3-Diphenylallylidene)-2,4,6-triisopropylbenzenesulfonamide (376h).** A solution of *(E)*-2,3-diphenylacrylaldehyde (0.50 g, 2.4 mmol), 2,4,6-triisopropylbenzenesulfonamide (.68 g, 2.4 mmol) and DIPEA (1.3 mL, 7.2 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 ^oC, treated with a solution of $TiCl_4$ (1.5 mL, 1.5 mmol, c = 1.0 M in CH_2Cl_2). After 2 h at 0 ^oC, the reaction mixture was poured into dry ether, filtered through a pad of SiO_2, washed with EtOAc and the solvent was removed in vacuo. Crystallization from CH_2Cl_2/hexane afforded **376h** (0.98, 86%) as a white solid: Mp. 170.7-172.8 ^oC (hexane/CH_2Cl_2), IR (ATR) 2959, 1560, 1310, 1293, 1150 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.93 (s, 1 H), 7.42 (s, 1 H), 7.36 (br s, 3 H), 7.28-7.27 (m, 1 H)

7.22-7.19 (m, 4 H), 7.13-7.12 (m, 4 H), 4.24 (septet, J = 6.7 Hz, 2 H), 2.89 (septet, J = 6.9 Hz, 1 H), 1.24 (d, J = 6.9 Hz, 6 H), 1.15 (d, J = 6.8 Hz, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 153.3, 151.1, 150.3, 138.6, 134.3, 134.1, 131.3, 131.0, 130.3, 129.6, 128.7, 128.5, 128.2, 123.6, 34.2, 29.6, 24.6, 23.6; MS (EI) *m/z* (rel. intensity) 473 (M^+, 5), 458 (3), 430 (5), 394 (40), 230 (100), 206 (83); HRMS (EI) calc for $C_{30}H_{35}NO_2S$ 473.2389, found 473.2387.



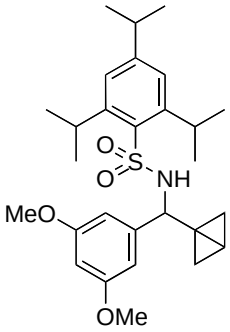
376i

***N*-(Cyclohexenylmethylene)-2,4,6-triisopropylbenzenesulfonamide (376i).** A solution of cyclohex-1-enecarboxaldehyde (0.47 g, 4.2 mmol), 2,4,6-triisopropylbenzenesulfonamide (1.2 g, 4.2 mmol) and DIPEA (2.2 mL, 13 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 ^{o}C, treated with a solution of $TiCl_4$ (2.6 mL, 2.6 mmol, c = 1.0 M in CH_2Cl_2). After 2 h at 0 ^{o}C, the reaction mixture was poured into dry ether, filtered through a pad of SiO_2, washed with EtOAc and the solvent was removed in vacuo. Crystallization from CH_2Cl_2/hexane afforded **376i** (1.1, 68%) as a white solid: Mp. 117.6-119.0 ^{o}C (CH_2Cl_2/hexane); IR (ATR) 2950, 2864, 1625, 1565, 1461, 1312, 1150 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (s, 1 H), 7.18 (s, 2 H), 6.79 (t, J = 3.8 Hz, 1 H), 4.30 (septet, J = 6.8 Hz, 2 H), 2.91 (septet, J = 6.9 Hz, 1 H), 2.35-2.31 (m, 4 H), 1.68-1.66 (m, 4 H), 1.26 (d, J = 6.5 Hz, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 153.3, 152.7, 150.9, 137.5, 131.4, 123.7, 34.2, 29.7, 27.3, 24.7, 23.6, 22.9, 21.7, 21.4; MS (EI) *m/z* (rel. intensity) 375 (M^+, 10), 360 (22), 296 (100), 230 (75), 203 (30), 187 (45), 161 (39); HRMS (EI) calc for $C_{22}H_{33}NO_2S$ 375.2232, found 375.2222.



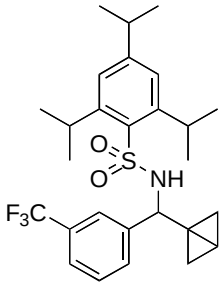
376j

***N*-(Cyclohexylmethylene)-2,4,6-triisopropylbenzenesulfonamide (376j).** A suspension of 2,4,6-triisopropylbenzenesulfonamide (1.0 g 3.5 mmol), cyclohexanecarboxaldehyde (0.40 g, 3.5 mmol) and $PhSO_2Na$ (0.64 g, 3.9 mmol) in 10 mL of 1:1 mixture of formic acid (98%) and water was stirred at rt for 36 h. The mixture was diluted with water, extracted (3x) with CH_2Cl_2 and the organic layers were washed with water, transferred into a flask and stirred vigorously for 30 min with sat. $NaHCO_3$. The phases were separated, the organic layer was washed with brine, dried ($MgSO_4$), and concentrated to obtain **376j** (0.99 g, 74%) as a white solid: Mp. 93.0-95.8 ^oC (CH_2Cl_2/hexanes); IR (neat) 2927, 2853, 1621, 1600, 1450, 113, 1296, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, *J* = 4.2 Hz, 1 H), 7.18 (s, 2 H), 4.17 (septet, *J* = 6.8 Hz, 2 H), 2.91 (septet, *J* = 7.0 Hz, 1 H), 2.48-2.42 (m, 1 H), 1.93-1.89 (m, 2 H), 1.78 (br s, 1 H), 1.71-1.67 (m, 2 H), 1.40-1.27 (m, 23 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.6, 141.1, 128.4, 128.3, 126.0, 40.4, 35.7, 30.3, 19.8, 18.9; MS (EI) *m/z* (rel. intensity) 377 (M^+, 1), 267 (20), 251 (25), 230 (100), 218 (24), 202 (27), 187 (85); HRMS (EI) calc for $C_{22}H_{35}NO_2S$ 377.2389, found 377.2380.



377a

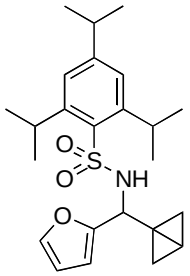
***N*-(Bicyclo[1.1.0]but-1-yl(3,5-dimethoxyphenyl)methyl)-2,4,6-triisopropylbenzenesulfonamide (377a).** A solution of 2,2-dibromo-1-(chloromethyl)cyclopropane **119** (0.86 g, 3.5 mmol) in Et_2O (5.0 mL) was cooled to -78 ^oC, treated with MeLi (2.3 mL, 3.4 mmol, c = 1.5 M in Et_2O) and stirred at -78 ^oC for 1 h. *t*-BuLi (2.3 mL, 3.4 mmol, c = 1.5 M in pentane) was added, the mixture was stirred for 1 h followed by a solution of **376a** (0.50 g, 1.2 mmol) in THF (5.0 mL). The mixture was quenched with sat. NH_4Cl, warmed to rt, extracted with EtOAc and the organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **377a** (0.35 g, 62%) as a colorless oil which solidified upon standing: IR (ATR) 3299, 2956, 2932, 1597, 1457, 1428, 1159 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.14 (s, 2 H), 6.27 (t, *J* = 1.3 Hz, 1 H), 6.24 (d, *J* = 2.3 Hz, 2 H), 4.83 (d, *J* = 5.7 Hz, 1 H), 4.75 (d, *J* = 5.7 Hz, 1 H), 3.62 (s, 6 H), 4.03 (septet, *J* = 6.8 Hz, 2 H), 2.89 (septet, *J* = 6.9 Hz, 1 H), 1.60 (dd, *J* = 6.2, 3.0 Hz, 1 H), 1.36 (t, *J* = 2.7 Hz, 1 H), 1.33 (dd, *J* = 6.2, 3.0 Hz, 1 H), 1.25 (d, *J* = 6.9 Hz, 6 H), 1.20 (app. dd, *J* = 6.8, 0.6 Hz, 12 H), 0.66 (s, 1 H), 0.58 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7, 152.6, 149.7, 142.1, 134.0, 123.6 (2), 105.0 (2), 99.6, 58.1, 55.2, 34.1, 32.6, 32.0, 29.8, 24.8, (2), 24.7 (2), 23.6, 14.0, 2.0; MS (EI) *m/z* (rel. intensity) 485 (M^+, 70), 432 (15), 378 (8), 282 (100), 267 (42); HRMS (EI) calc for $C_{28}H_{39}NO_4S$ 485.2600, found 485.2606.



377b

***N*-(Bicyclo[1.1.0]but-1-yl(3-(trifluoromethyl)phenyl)methyl)-2,4,6-triisopropylbenzene-sulfonamide (377b).** A solution of 2,2-dibromo-1-(chloromethyl)cyclopropane **119** (0.85 g, 3.4 mmol) in dry Et_2O (5.0 mL) was cooled to -78 ^oC, treated with a solution of MeLi (1.1 mL, 3.4 mmol, c = 3.0 M in diethoxymethane) and after 1 h at this temperature with a solution of *t*-BuLi (2.3 mL, 3.4 mmol, c = 1.5 M in pentane). The reaction mixture was stirred at -78 ^oC for 1 h, a solution of imine **376b** (0.50 g, 1.1 mmol) in THF (7.0 mL) was added, the mixture was stirred for 3 min at -78 ^oC, quenched at this temperature with sat. NH_4Cl, warmed to rt, and extracted (3x) with EtOAc. The organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOA, 4:1) afforded **377b** (0.33 g, 59%) as a colorless oil: IR (ATR) 3265, 2925, 1599, 1449, 1327, 1161, 1150, 1128 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45-7.42 (m, 1 H), 7.35-7.31 (m, 3 H), 7.11 (s, 2 H), 5.07 (d, *J* = 5.2 Hz, 1 H), 4.89 (d, *J* = 5.2 Hz, 1 H), 4.01 (septet, *J* = 6.7 Hz, 2 H) 2.89 (septet, *J* = 6.9 Hz, 1 H), 1.59 (dd, *J* = 6.3, 2.9 Hz, 1 H), 1.37 (s, 1 H), 1.23 (app. t, *J* = 7.4 Hz, 13 H), 1.15 (d, *J* = 6.7 Hz, 6 H), 0.71 (s, 1 H), 0.59 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.94, 149.72, 140.60, 133.38, 130.79, 130.40, 128.75, 125.58, 124.47, 124.42, 124.37, 123.65, 121.97, 57.73, 34.10, 32.96, 31.33, 29.90, 29.76, 24.75, 24.64, 23.52, 23.46, 14.23, 2.01; MS (EI) *m/z* (rel. intensity) 493 (M^+,

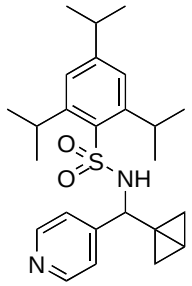
9), 474 (10), 450 (7), 386 (10), 282 (99), 267 (95), 251 (72), 226 (100), 187 (95), 175 (83); HRMS (EI) calc for $C_{27}H_{34}NOF_3S$ 493.2263, found 493.2239.



377c

***N*-(Bicyclo[1.1.0]but-1-yl(furan-2-yl)methyl)-2,4,6-triisopropylbenzenesulfonamide (377c).** A solution 2,2-dibromo-1-(chloromethyl)cyclopropane **119** (0.62 g, 2.5 mmol) in dry Et_2O (5.0 mL) was cooled to -78 ^oC, treated with a solution of MeLi (1.7 mL, 2.5 mmol, c = 1.5 M in Et_2O) and after 1 h at this temperature, with a solution of *t*-BuLi (1.5 mL, 2.5 mmol, c = 1.7 M in pentane). The reaction mixture was stirred at -78 ^oC for 1 h, a solution of imine **376c** (0.30 g, 0.83 mmol) in THF (5.0 mL) was added, the mixture quenched at this temperature with sat. NH_4Cl, warmed to rt, and extracted (3x) with EtOAc. The organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/ EtOA, 4:1) afforded **377c** (0.27 g, 78%) as a colorless oil: IR (neat) 3286, 2959, 1600, 1563, 1462, 1425, 1384, 1362, 1325, 1151, 1103 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.15 (dd, *J* = 1.7, 0.8 Hz, 1 H), 7.11 (s, 2 H), 6.16 (dd, *J* = 3.2, 1.9 Hz, 1 H), 6.01 (d, *J* = 2.0 Hz, 1 H), 4.98, 4.92 (AB, *J* = 7.8 Hz, 2 H), 4.09 (septet, *J* = 6.8 Hz, 2 H), 2.8 (septet, *J* = 6.9 Hz, 1 H), 1.45 (s, 3 H), 1.25 (d, *J* = 6.7, 6 H), 1.24 (d, *J* = 6.9 Hz, 6 H), 1.23 (d, *J* = 6.7 Hz, 6 H); 0.58 (s, 1 H), 0.55 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.6, 152.3, 149.8, 141.9, 133.7, 123.5 (2), 110.1 (2), 107.0, 52.0, 34.2, 32.6, 32.0, 29.9, 29.8, 29.7, 24.8, 23.7, 23.6, 12.8, 2.1; MS (EI) *m/z* (rel. intensity)

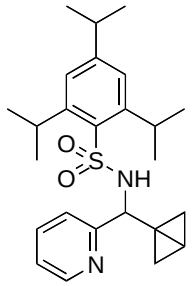
415 (M^+, 100), 362 (21), 282 (86), 267 (95), 251 (34); HRMS (EI) calc for $C_{24}H_{33}NO_3S$ 415.2181, found 415.2192.



377d

***N*-(Bicyclo[1.1.0]but-1-yl(pyridin-4-yl)methyl)-2,4,6-triisopropylbenzenesulfonamide (377d).** A solution of 2,2-dibromo-1-(chloromethyl)cyclopropane **119** (1.0 g, 4.0 mmol) in Et_2O (8.0 mL) was cooled to -78 ^oC, treated with MeLi (2.7 mL, 4.0 mmol, c = 1.5 M in Et_2O) and stirred at -78 ^oC for 1 h. *t*-BuLi (2.7 mL, 4.0 mmol, c = 1.5 M in pentane) was added, the mixture was stirred for 1 h followed by a solution of **376d** (0.50 g, 1.3 mmol). The mixture was quenched with sat. NH_4Cl, warmed up to rt, extracted with EtOAc and the organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:1 to 1:4) afforded **377d** (0.31 g, 54%) as an off-white solid: Mp. 168.2 ^oC (decomp., benzene/hexane); IR (neat) 3036, 2959, 2930, 2969, 1601, 1462, 1420, 1383, 1363, 1323, 1153, 1102 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, *J* = 5.4 Hz, 2 H), 7.12 (s, 2 H), 7.03 (d, *J* = 5.8 Hz, 2 H), 5.05 (d, *J* = 5.5 Hz, 1 H), 4.79 (d, *J* = 5.5 Hz, 1 H), 4.01 (septet, *J* = 6.8 Hz, 2 H), 2.90 (septet, *J* = 7.0 Hz, 1 H), 1.51 (dd, *J* = 6.3, 2.9 Hz, 1 H), 1.36 (s, 1 H), 1.27-1.23 (m, 13 H), 1.18 (d, *J* = 6.7 Hz, 6 H), 0.69 (s, 1 H), 0.58 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1, 149.9, 149.7, 148.5, 133.4, 123.7, 121.9, 57.0, 34.1, 33.0, 32.3, 29.8, 24.9, 24.7, 23.6, 13.8, 2.3;

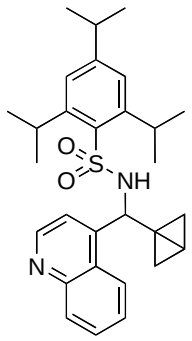
MS (EI) *m/z* (rel. intensity) 426 (M^+, 6), 267 (16), 187 (50), 159 (58), 143 (100), 117 (71); HRMS (EI) calc for $C_{25}H_{34}N_2O_2S$ 426.2341, found 426.2338.



377e

***N*-(Bicyclo[1.1.0]but-1-yl(pyridin-2-yl)methyl)-2,4,6-triisopropylbenzenesulfonamide (377e).** A solution of 2,2-dibromo-1-(chloromethyl)cyclopropane **119** (1.0 g, 4.0 mmol) in Et_2O (8.0 mL) was cooled to -78 ^oC, treated with MeLi (2.7 mL, 4.0 mmol, c = 1.5 M in Et_2O) and stirred at -78 ^oC for 1 h. *t*-BuLi (2.7 mL, 4.0 mmol, c = 1.5 M in pentane) was added, the mixture was stirred for 1 h followed by a solution of **376e** (0.50 g, 1.3 mmol). The mixture was quenched with sat. NH_4Cl, warmed up to rt, extracted with EtOAc and the organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (Hex/EtOAc, 4:1) afforded **377e** (0.21 g, 37%) as a colorless oil: IR (neat) 3286, 2959, 2930, 2870, 1596, 1465, 1437, 1329, 1164, 1102 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.43 (dd, *J* = 4.7, 1.1 Hz, 1 H), 7.58 (dd, *J* = 7.7, 1.7 Hz, 1 H), 7.15-7.09 (m, 5 H), 6.47 (d, *J* = 6.6 Hz, 1 H), 4.96 (d, *J* = 6.7 Hz, 1 H), 4.17 (septet, *J* = 6.7 Hz, 2 H), 2.86 (septet, *J* = 6.9 Hz, 1 H), 1.47-1.44 (m, 2 H), 1.37 (dd, *J* = 5.9, 3.2 Hz, 1 H), 1.26 (d, *J* = 6.6 Hz, 6 H), 1.22 (d, *J* = 6.8 Hz, 12 H), 0.55 (s, 1 H), 0.44 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 152.4, 149.9, 148.6, 136.5, 133.8, 123.4, 122.5, 121.8, 56.7, 34.1, 32.2, 32.0, 29.9, 24.9, 24.8, 23.6, 14.7, 1.8; MS (EI) *m/z* (rel. intensity)

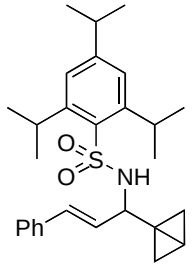
426 (M^+, 2), 187 (16), 159 (60), 144 (100), 131 (44); HRMS (EI) calc for $C_{25}H_{34}N_2O_2S$ 426.2341, found 426.2337.



377f

***N*-(Bicyclo[1.1.0]but-1-yl(quinolin-4-yl)methyl)-2,4,6-triisopropylbenzenesulfonamide (377f).** A solution of 2,2-dibromo-1-(chloromethyl)cyclopropane **119** (0.88 g, 3.6 mmol) in dry Et_2O (5.0 mL) was cooled to -78 ^oC, treated with a solution of MeLi (1.2 mL, 3.5 mmol, c = 3.0 M in diethoxymethane) and after 1 h at this temperature with a solution of *t*-BuLi (2.4 mL, 3.5 mmol, c = 1.5 M in pentane). The reaction mixture was stirred at -78 ^oC for 1 h, a solution of imine **376f** (0.50 g, 1.18 mmol) in THF (5.0 mL) was added, the mixture was stirred for 3 min at -78 ^oC, quenched at this temperature with sat. NH_4Cl, warmed to rt, and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **377f** (0.34 g, 60%) as a colorless oil: IR (ATR) 3138, 2959, 1593, 1510, 1459, 1312, 1148 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.67 (d, *J* = 4.5 Hz, 1 H), 8.09 (d, *J* = 8.4 Hz, 1 H), 7.84 (d, *J* = 8.4 Hz, 1 H), 7.66 (td, *J* = 7.1, 0.8 Hz, 1 H), 7.47 (td, *J* = 0.7, 8.1 Hz, 1 H), 7.33 (d, *J* = 4.5 Hz, 1 H), 7.07 (s, 2 H), 5.76, 5.73 (AB, *J* = 5.7 Hz, 2 H), 4.01 (septet, *J* = 6.7 Hz, 2 H), 2.86 (septet, *J* = 6.9 Hz, 1 H), 1.59 (dd, *J* = 6.2, 2.6 Hz, 1 H), 1.27-1.22 (m, 7 H), 1.17 (d, *J* = 6.6 Hz, 6 H), 1.04 (d, *J* = 6.7

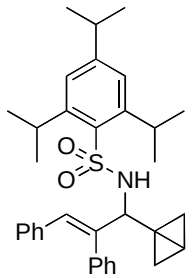
Hz, 6 H), 0.69 (s, 1 H), 0.52 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 150.0, 149.7, 148.4, 144.7, 133.4, 130.3, 129.2, 128.1, 126.7, 125.7, 123.7, 123.6, 122.5, 119.3, 53.0, 48.6, 34.1, 33.1, 31.1, 30.0, 29.9, 24.9, 24.7, 24.6, 23.6, 14.3, 3.7; MS (ESI) *m/z* (rel. intensity) 477 ([M+Na]$^+$, 100), 439 (10); HRMS (ESI) calc for $C_{29}H_{37}N_2O_2S$ (M+Na) 477.2576, found 477.2566.



377g

(*E*)-*N*-(1-(Bicyclo[1.1.0]but-1-yl)-3-phenylallyl)-2,4,6-triisopropylbenzenesulfonamide (377g). A solution of 1,1-dibromo-2-(chloromethyl)cyclopropane**119** (0.75 g, 3.0 mmol) in dry Et_2O (5.0 mL) was cooled to -78 ^oC, treated with a solution of MeLi (2.0 mL, 3.0 mmol, c = 1.5 M in Et_2O) and after 1 h at this temperature with a solution of *t*-BuLi (1.8 mL, 3.0 mmol, c = 1.7 M in pentane). The reaction mixture was stirred at -78 ^oC for 1 h, a solution of imine **376f** (0.40 g, 1.0 mmol) in THF (5.0 mL) was added, the mixture was stirred for 3 min at -78 ^oC, quenched at this temperature with sat. NH_4Cl, warmed to rt, and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **377f** (0.26 g, 57%) as a colorless oil: IR (neat) 3286, 3028, 2959, 2869, 1600, 1461, 1424, 1319, 1256, 1150, 1102 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.19 (m, 3 H), 7.12-7.08 (m, 4 H), 6.40 (d, *J* = 15.8 Hz, 1 H), 5.80 (d, *J* = 15.9, 6.8 Hz, 1 H), 4.72 (d, *J* = 6.4 Hz, 1 H), 4.46 (t, *J* = 6.6 Hz, 1 H), 4.15 (septet, *J* = 6.8 Hz, 2 H), 2.89 (septet, *J* = 6.9 Hz, 1 H), 1.57 (dd, *J* = 6.4, 3.0 Hz, 1 H), 1.49 (dd, *J* = 6.2, 2.8 Hz, 1 H),

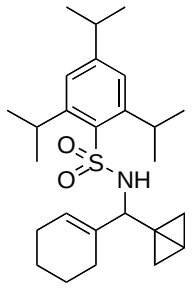
1.29 (d, *J* = 6.8 Hz, 6 H), 1.23 (d, *J* = 6.8 Hz, 9 H), 1.22 (d, *J* = 6.9 Hz, 3 H), 0.60 (s, 1 H), 0.58 (s, 1 H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 152.6, 149.7, 136.0, 134.2, 132.1, 128.4, 127.8, 126.7, 126.4, 123.6, 56.1, 34.1, 33.1, 31.0, 29.8, 29.7, 25.0, 24.6, 23.6, 23.6, 23.5, 12.9, 1.4; MS (EI) *m/z* (rel intensity) 451 (M+, 14), 267 (14), 184 (100), 143 (46); HRMS (EI) calc for $C_{28}H_{37}NO_2S$ 451.2545, found 451.2541.



377h

***N*-(1-(Bicyclo[1.1.0]but-1-yl)-2,3-diphenylallyl)-2,4,6-triisopropylbenzenesulfonamide (377h).** A solution of 1,1-dibromo-2-(chloromethyl)cyclopropane **119** (0.77 g, 3.2 mmol) in dry Et_2O (10 mL) was cooled to -78 °C, treated with a solution of MeLi (1.1 mL, 3.2 mmol, c = 3.0 M in diethoxymethane) and after 1 h at this temperature, with a solution of *t*-BuLi (2.1 mL, 3.2 mmol, c = 1.5 M in pentane). The reaction mixture was stirred at -78 °C for 1 h and a solution of imine **376h** (0.50 g, 1.1 mmol) in THF (5.0 mL) was added. The mixture was quenched at this temperature with sat. NH_4Cl, warmed to rt, and extracted (3x) with EtOAc. The combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **377h** (0.31 g, 55%) as a colorless oil: IR (ATR) 3353, 2958, 2922, 1599, 1428, 1333, 1150 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (s, 2 H), 7.29-7.25 (m, 2 H), 7.15-7.12 (m, 2 H), 7.11-7.10 (m, 1 H), 7.07-7.03 (m, 3 H), 6.83-6.77 (m, 2 H), 6.51 (s, 1 H), 4.78, 4.73 (AB, *J* = 6.9 Hz, 2 H), 4.18 (septet, *J* = 6.7 Hz, 2 H), 2.87 (septet,

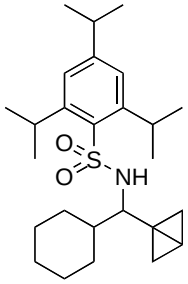
J = 6.9 Hz, 1 H), 1.64 (dd, *J* = 6.3, 2.8 Hz, 1 H), 1.33-1.32 (m, 1 H), 1.30 (d, *J* = 6.8 Hz, 6 H), 1.26 (d, *J* = 6.8 Hz, 6 H), 1.23 (app. dd, *J* = 6.9, 1.9 Hz, 6 H), 1.20-1.19 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 149.7, 140.4, 138.4, 136.0, 134.0, 129.1, 129.0, 128.6 (2), 128.3, 127.8, 127.6, 126.8, 123.6, 60.1, 34.1, 31.8, 31.4, 29.9, 25.0, 24.8, 23.6, 23.5, 13.4, 2.5; MS (EI) *m/z* (rel. intensity) 527 (M^+, 10), 484 (5), 436 (3), 348 (6), 260 (100), 244 (35), 219 (66); HRMS (EI) calc for $C_{34}H_{41}NO_2S$ 527.2858, found 527.2857.



377i

***N*-(Bicyclo[1.1.0]but-1-yl(cyclohexenyl)methyl)-2,4,6-triisopropylbenzenesulfonamide (377i).** A solution of 2,2-dibromo-1-(chloromethyl)cyclopropane **119** (0.20 g, 0.80 mmol) in Et_2O (10 mL) was cooled to -78 ^oC, treated with MeLi (0.27 mL, 0.80 mmol, c = 3.0 M in diethoxymethane) and stirred at -78 ^oC for 1 h. *t*-BuLi (0.53 mL, 0.80 mmol, c = 1.5 M in pentane) was added, the mixture was stirred for 1 h followed by a solution of **376i** (0.10 g, 0.27 mmol). The mixture was quenched with sat. NH_4Cl, warmed up to rt, extracted with EtOAc and the organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 9:1) afforded **377i** (0.11 g, 45%) as a colorless oil: IR (ATR) 3278, 2953, 2924, 2866, 1599, 1459, 1424, 1312, 1150 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (s, 2 H), 5.54 (s, 1 H), 4.51 (d, *J* = 7.0 Hz, 1 H), 4.14-4.08 (m, 3 H), 2.92 (septet, *J* = 7.0 Hz, 1 H), 1.93-1.92 (m, 2 H), 1.87-1.80 (m, 2 H), 1.55-1.41 (m, 4 H), 1.29 (d, *J* = 6.8 Hz, 12 H),

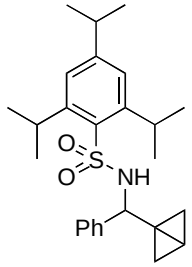
1.27 (d, J = 7.0 Hz, 6 H), 0.59 (s, 1 H), 0.52 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5, 149.8, 136.5, 134.0, 124.6, 123.5, 58.9, 34.1, 32.3, 31.2, 29.9, 25.7, 24.9 (2), 23.6, 22.4, 22.1, 12.8, 1.8; MS (EI) *m/z* (rel. intensity) 429 (M^+, 1), 267 (7), 175 (8), 162 (100), 146 (4), 121 (21), 91 (29); HRMS (EI) calc for $C_{26}H_{39}NO_2S$ 429.2702, found 429.2693.



377j

***N*-(bicyclo[1.1.0]butan-1-yl(cyclohexyl)methyl)-2,4,6-triisopropylbenzenesulfonamide (377j).** A solution of 2,2-dibromo-1-chloromethylcyclopropane **119** (0.99 g, 4.0 mmol) in dry Et_2O (5.0 mL) was cooled to -78 ^oC, treated with a solution of MeLi (2.6 mL, 4.0 mmol, c = 1.5 M in Et_2O) and after 1 h at -78 ^oC, a solution of *t*-BuLi (2.6 mL, 4.0 mmol, c = 1.5 M in pentane) was added. The reaction mixture was stirred at this temperature for 1 h, a solution of amide **376j** (0.50 g, 1.3 mmol) in THF (4.0 mL) was added. The mixture was quenched with sat. NH_4Cl, warmed up to rt, diluted with water, extracted with EtOAc and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **377j** (0.30 g, 52%) as a colorless oil: IR (neat) 3265, 2958, 2927, 2856, 1601, 1425, 1319, 1154 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (s, 2 H), 4.36 (d, J = 8.8 Hz, 1 H), 4.05 (septet, J = 6.7 Hz, 2 H), 3.55 (dd, J = 8.7, 5.4 Hz, 1 H), 2.90 (septet, J = 6.9 Hz, 1 H), 1.72-1.70 (m, 3 H), 1.64 (br s, 2 H), 1.47 (d, J = 6.3, 2.8 Hz, 1 H), 1.38 (dd, J = 6.3, 2.9 Hz, 1 H), 1.28 (d, J = 6.8 Hz, 6 H), 1.27 (d, J = 6.9 Hz, 6 H), 1.25 (d, J = 7.0 Hz, 6 H), 1.14-1.11

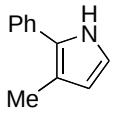
(m, 4 H), 1.08-1.05 (m, 2 H), 0.62 (s, 1 H), 0.36 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5, 149.5, 134.5, 123.6, 57.8, 44.2, 34.1, 33.9, 29.9, 29.7, 29.0, 26.3, 26.0 (2), 24.9, 23.6, 23.6, 11.7; MS (EI) *m/z* (rel. intensity) 431 (M^+, 3), 348 (50), 267 (66), 233 (7), 203 (21), 175 (27), 83 (86), 55 (100); HRMS (EI) calc for $C_{26}H_{41}NO_2S$ 431.2858, found 431.2850.



377k

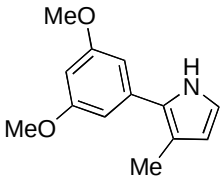
***N*-(Bicyclo[1.1.0]butan-1-yl(phenyl)methyl)-2,4,6-triisopropylbenzenesulfonamide (377k).** A solution of 2,2-dibromo-1-chloromethylcyclopropane **119** (0.60 g, 2.4 mmol) in dry Et_2O (5.0 mL) was cooled to -78 ^oC, treated with MeLi (1.6 mL, 2.4 mmol, c = 1.5 M in Et_2O) and after 1 h at -78 ^oC, a solution of *t*-BuLi (1.6 mL, 2.4 mmol, c = 1.5 M in pentane) was added. The reaction mixture was stirred at this temperature for 1 h, a solution of imine **88c** (0.30 g, 1.2 mmol) in THF (5.0 mL) was added. The mixture was quenched with sat. NH_4Cl, warmed up to rt, diluted with water, extracted with EtOAc and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **377k** (0.18 g, 52%) as a colorless oil which solidified upon standing: Mp. 105.0-107.4 ^oC (EtOAc/hexane); IR (KBr) 3255, 3036, 2959, 2929, 2869, 1600, 1563, 1455, 1423, 1383, 1363, 1346, 1314, 1158, 1151 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (t, *J* = 3.1 Hz, 3 H), 7.11 (s, 2 H), 7.07 (t, *J* = 3.6 Hz, 2 H), 4.89 (d, *J* = 5.9 Hz, 1 H), 4.78 (d, *J* = 5.9 Hz, 1 H), 4.06 (septet, *J* = 6.7 Hz, 2 H), 2.90 (septet, *J* = 6.9 Hz, 1 H), 1.58 (dd, *J* = 6.2, 2.8 Hz, 1 H),

1.32 (s, 1 H), 1.29-1.24 (m, 7 H), 1.20 (app. t, J = 6.4 Hz, 12 H), 0.65 (s, 1 H), 0.57 (s, 1 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 152.7, 149.8, 139.7, 133.7, 128.3, 127.6, 126.9, 123.5, 58.0, 34.1, 32.6, 31.7, 29.8, 24.8, 23.6, 14.2, 1.7; MS (ESI) *m/z* (rel. intensity) 395 ($[M+Na]^+$, 79), 262 (33); HRMS (ESI) calc for $C_{21}H_{28}N_2O_2NaS$ (M+Na) 395.1769, found 395.1765.



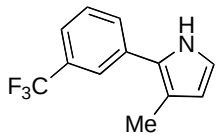
378

3-Methyl-2-phenyl-1*H*-pyrrole (378). A solution of **377k** (0.093 g, 0.22 mmol), dppe (0.0087 g, 0.022 mmol) in dry THF (3.6 mL) was treated with a solution of $[Rh(CO)_2Cl]_2$ (0.0042 g, 0.011 mmol) in THF (0.42 mL). The reaction mixture was stirred at rt for 20 min, placed in an oil bath (80 ^{o}C) and stirred at this temperature for 12 min. The mixture was cooled to rt, diluted with Et_2O, washed with sat. $NaHCO_3$, water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **378** (0.031 g, 90%) as a colorless oil: IR (neat) 3396, 3057, 2925, 2869, 1603, 1497, 1476, 1451, 1107 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46-7.41 (m, 3 H), 7.28-7.25 (m, 2 H), 6.81 (t, J = 2.7 Hz, 1 H), 6.19 (t, J = 2.6, 1 H), 2.32 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.7, 128.7, 128.3, 126.3, 126.0, 117.3, 116.1, 112.2, 12.5; MS (EI) *m/z* (rel. intensity) 157 (92, M^+), 156 (100), 128 (12), 104 (6), 77 (15); HRMS (EI) calc for $C_{11}H_{11}N$ 157.0891, found 157.0891.



379a

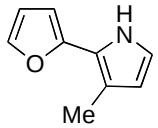
2-(3,5-Dimethoxyphenyl)-3-methyl-1*H*-pyrrole (377a). A solution of amide **377a** (0.061 g, 0.12 mmol) in dry THF (1.5 mL) was treated with a solution of dppe (0.0050 g, 12 mmol) in THF (0.50 mL) followed by a solution of $[Rh(CO)_2Cl]_2$ (0.0024 g, 6.6 mmol) in THF (0.48 mL). The reaction mixture was stirred at rt for 10 min, placed in an oil bath (80 ^oC) and stirred under gentle reflux for 15 min. After cooling to rt, the mixture was quenched with sat. NH_4Cl, diluted with water, extracted with EtOAc and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **379a** (0.021 g, 77%) as a colorless oil: IR (ATR) 3417, 2920, 2862, 1612, 1554, 1472, 1435, 1397, 1381 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (br s, 1 H), 6.77 (t, *J* = 2.7 Hz, 1 H), 6.58 (d, *J* = 2.3 Hz, 2 H), 6.39 (t, *J* = 2.3 H, 1 H), 6.616 (t, *J* = 2.6 Hz, 1 H), 3.84 (s, 6 H), 2.30 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 135.5, 128.10, 117.3, 116.4, 112.2, 104.6, 98.0, 55.3, 12.5; MS (EI) *m/z* (rel. intensity) 217 (M^+, 100), 201 (14), 117 (14), 84 (65); HRMS (EI) calc for $C_{13}H_{15}NO_2$ 217.1103, found 217.1109.



379b

3-Methyl-2-(3-(trifluoromethyl)phenyl)-1*H*-pyrrole (379b). A solution of **377b** (0.074 g, 0.15 mmol) in THF (2.1 mL) was treated with a solution of dppe (0.0060 g, 0.015 mmol) followed by a solution of $[Rh(CO)_2Cl]_2$ (0.0029 g, 0.0075 mmol) in THF (0.29 mL). The reaction mixture was stirred at rt for 10 min, placed in an oil bath (80 ^oC) and stirred under mild reflux for 30 min. After cooling to rt, the mixture was quenched with sat. NH_4Cl, extracted (3 x) with EtOAc and the combined organic layers were washed with sat. $NaHCO_3$, water, brine, dried (Na_2SO_4), and

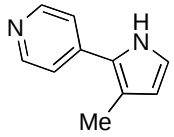
concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 9:1 + 1% Et_3N followed by hexanes/CH_2Cl_2, 2:1) afforded **379b** (0.020 g, 59%) as a colorless oil: IR (ATR) 3479, 3382, 2940, 1613, 1476, 1421, 1325, 1280, 1162, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (br s, 1 H), 7.66 (br s, 1 H), 7.62-7.59 (m, 1 H), 7.55-7.48 (m, 2 H), 6.83 (t, *J* = 2.8 Hz, 1 H), 6.20 (t, *J* = 2.7 Hz, 1 H), 2.31 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.34, 131.72, 131.29, 130.87, 130.44, 129.53, 129.26, 129.15, 126.80, 125.92, 122.76, 122.71, 122.66, 122.61, 122.47, 122.42, 122.37, 122.32, 118.71, 118.17, 117.31, 112.52, 76.57, 12.43; MS (EI) *m/z* (rel. intensity) 224 (M^+, 90), 204 (9), 177 (8) 154 (12), 84 (100); HRMS (EI) calc for $C_{12}H_{10}NF_3$ 225.0765, found 225.0760.



379c

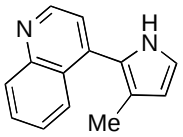
2-(Furan-2-yl)-3-methyl-1*H*-pyrrole (379c). A solution of amide **377c** (69 mg, 0.17 mmol) in dry THF (2.3 mL) under N_2 was treated with a solution of dppe (6.6 mg, 0.017 mmol)in THF (0.66 mL) followed by a solution of $[Rh(CO)_2Cl]_2$ (3.2 mg, 0.083 mmol) in THF (0.32 mL). The reaction mixture was stirred at rt for 10 min, placed in an oil bath (80 ^oC) and stirred under gentle reflux for 12 min. After cooling to rt, the mixture was quenched with sat. $NaHCO_3$, diluted with water, extracted (3x) with EtOAc and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1 followed by CH_2Cl_2:hexanes, 1:2) afforded unstable **379c** (15 mg, 61%) as a colorless oil: IR (ATR) 3386, 2928, 1590, 1478, 1416, 1234, 102, 1152 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.76 (br s, 1 H), 7.37 (dd, *J* = 1.8, 0.6 Hz, 1 H), 6.73 (t, *J* = 2.7 Hz, 1 H), 6.47

(dd, J = 3.4, 1.9 Hz, 1 H), 6.29 (d, J = 3.4 Hz, 1 H), 6.11 (t, J = 2.7 Hz, 1 H), 2.26 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 139.8, 120.6, 117.1, 116.2, 111.6, 111.5, 102.6, 12.3; MS (EI) *m/z* (rel. intensity) 147 (M^+, 11), 118 (9), 91 (15), 86 (62), 84 (100); HRMS (EI) calc for C_9H_9NO 147.0684, found 147.0680.



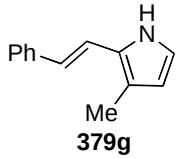
379d

4-(3-Methyl-1*H*-pyrrol-2-yl)pyridine (379d). A solution of amide **377d** (0.22 g, 0.51 mmol) in THF (7.9 mL) was treated with a solution of dppe (20 mg, 0.051 mmol) in THF (2.0 mL) followed by a solution of $[Rh(CO)_2Cl]_2$ (9.9 mg, 0.025 mmol) in THF (0.99 mL). The reaction mixture was stirred at rt for 10 min, placed in an oil bath (80 °C) and stirred at this temperature for 10 min. After cooling to rt, the mixture was quenched with sat. NH_4Cl, extracted (3x) with EtOAc and the combined organic layers were washed with water, sat. $NaHCO_3$, water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (EtOAc/MeOH, 10:1) afforded **379d** (0.062 g, 77%) as a colorless oil, which solidified upon standing: IR (ATR) 3222, 1599, 1569, 1500 1413 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (d, J = 5.7 Hz, 2 H), 8.44 (br s, 1 H), 7.32 (d, J = 6.1 Hz, 2 H), 6.88 (t, J = 2.7 Hz, 1 H), 6.20 (t, J = 2.5 Hz, 1 H), 2.37 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 140.5, 125.1, 120.0, 119.5 (2), 113.4, 13.2; MS (EI) *m/z* (rel. intensity) 158 (M^+, 100), 130 (22), 91 (35), 69 (64); HRMS (EI) calc for $C_{10}H_{10}N_2$ 158.0844, found 158.0841.



379f

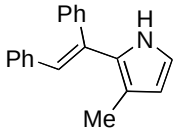
4-(3-Methyl-1*H*-pyrrol-2-yl)quinoline (379f). A solution of **377f** (0.052 g, 0.11 mmol) in THF (1.5 mL) was treated with a solution of dppe (0.0043 g, 0.011 mmol) in THF (0.43 mL) followed by a solution of $[Rh(CO)_2Cl]_2$ (0.0021 g, 0.0054 mmol) in THF (0.21 ml). The reaction mixture was stirred at rt for 10 min, placed in an oil bath (80 ^oC) and stirred under reflux for 20 min. After cooling to rt, the mixture was quenched with sat. NH_4Cl, extracted with EtOAc and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:4 + 1 % Et_3N) afforded **379f** (0.018 g, 79%) as a light-yellow oil which solidified upon standing: IR (ATR) 3129, 1583, 1508, 1422, 1131 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.89-8.83 (m, 1 H), 8.58 (br s, 1 H), 8.11 (d, *J* = 8.4 Hz, 1 H), 7.95 (dd, *J* = 8.4, 0.6 Hz, 1 H), 7.70 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1 H), 7.51 (ddd, *J* = 8.1, 7.2, 0.9 Hz, 1 H), 7.34-7.25 (m, 1 H), 6.98 (t, *J* = 2.7 Hz, 1 H), 6.29 (t, *J* = 2.7 Hz, 1 H), 2.13 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 148.8, 139.8, 129.7, 126.9, 126.5, 126.2, 124.7, 121.4, 119.3, 119.1, 111.7, 12.0; MS (EI) *m/z* (rel. intensity) 208 (M^+, 25), 137 (7), 123 (8), 111 (12), 97 (19), 86 (69), 84 (100), 69 (47); HRMS (EI) calc for $C_{14}H_{12}N$ 208.1000, found 208.0997.



379g

(*E*)-3-Methyl-2-styryl-1*H*-pyrrole (379g). To a solution of **377g** (0.030 g, 0.067 mmol) in THF (0.81 mL) a solution of dppe (0.0027 g, 0.0067 mmol) in THF (0.27 mL) was added followed by

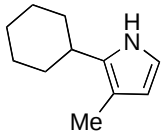
a solution of $[Rh(CO)_2Cl]_2$ (0.0013 g, 0.0034 mmol) in THF (0.26 mL). The reaction mixture was stirred at rt for 15 min, placed in an oil bath (80 ^oC) and stirred under reflux for 12 min. After cooling to rt, the mixture was quenched with sat. $NaHCO_3$, diluted with water, extracted with EtOAc and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **379g** (0.0095 g, 77%) as a light gray, amorphous solid: Mp. 109-112 ^oC (Et_2O); IR (neat) 3431, 3372, 2922, 1630, 1595, 1551, 1403, 1303, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (br s, 1 H), 7.46 (d, *J* = 7.4 Hz, 2 H), 7.35 (t, *J* = 7.9 Hz, 2 H), 7.27-7.18 (m, 1 H), 7.05 (d, *J* = 16.5 Hz, 1 H), 6.76 (t, *J* = 2.6 Hz, 1 H), 6.54 (d, *J* =16.5 Hz, 1 H), 6.10 (t, *J* = 2.5 Hz, 1 H), 2.23 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 128.6, 126.9, 126.7, 125.7, 121.7, 119.7, 118.5, 117.5, 111.6, 11.3; MS (EI) *m/z* (rel. intensity) 183 (M^+, 100), 167 (30), 128 (9), 128 (9), 115 (13); HRMS (EI) calc for $C_{13}H_{13}N$ 183.1048, found 183.1051.



379h

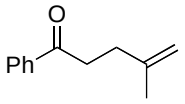
(*E*)-2-(1,2-Diphenylvinyl)-3-methyl-1*H*-pyrrole (379h). A solution of **377h** (63 mg, 0.12 mmol) in THF (1.4 mL) was treated with a solution of dppe (4.7 mg, 0.012 mmol) in THF (0.47 mL) followed by a solution of $[Rh(CO)_2Cl]_2$ (2.3 mg, 0.0059 mmol) in THF (0.46 mL). The reaction mixture was stirred at rt for 10 min, placed in an oil bath (80 ^oC) and stirred at gentle reflux for 12 min. After cooling to rt, the mixture was quenched with sat. NH_4Cl, diluted with water, extracted (3x) with EtOAc and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hex-

anes/EtOAc, 4:1) afforded **379h** (26 mg, 84%) as a light-brown oil: IR (neat) 3429, 2925, 1596, 1445, 1403, 1250, 1100 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) d 7.74 (br s, 1 H), 7.40-7.36 (m, 3 H), 7.33-7.29 (m, 2 H), 7.15-7.08 (m, 3 H), 7.01 (d, *J* = 7.1 Hz, 2 H), 6.76 (s, 1 H), 6.68 (t, *J* = 2.7 Hz, 1 H), 6.15 (t, *J* = 2.7 Hz), 2.18 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) d 139.1, 137.4, 134.5, 130.2, 129.8, 129.2, 128.8, 127.9, 127.8, 126.1, 125.3, 118.2, 117.0, 112.4, 13.4; MS (EI) *m/z* (rel. intensity) 259 (M^+, 100), 244 (19), 215 (7), 180 (12), 168 (54); HRMS (EI) calc for $C_{19}H_{17}N$ 259.1361, found 259.1372.



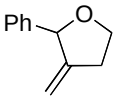
379i

2-Cyclohexyl-3-methyl-1*H*-pyrrole (379i). A solution of **377j** (0.061 g, 0.14 mmol) in PhMe (1.9 mL) was treated with a solution of dppe (0.0056 g, 0.014 mmol) in PhMe (0.56 mL) followed by a solution of $[Rh(CO)_2Cl]_2$ (0.0027 g, 0.0071 mmol) in PhMe (0.071 mL). The reaction mixture was stirred at rt for 10 min, placed in an oil bath (120 ^oC) and stirred at this temperature for 20 min. After cooling to rt, the mixture was quenched with sat. NH_4Cl, extracted (3x) with EtOAc and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 9:1 then CH_2Cl_2/hexanes, 1:2) afforded **379i** (0.0097 g, 42%) as a colorless oil: IR (ATR) 3390, 2918, 2848, 1446, 1396 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (br s, 1 H), 6.59 (t, *J* = 2.6 Hz, 1 H), 6.00 (t, *J* = 2.6 Hz, 1 H), 2.70-2.62 (m, 1 H), 2.07 (s, 3 H), 1.92-1.82 (m, 3 H), 1.78-1.73 (m, 1 H), 1.47-1.17 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.1, 114.4, 112.5, 110.1, 35.5, 33.0, 26.8, 26.2, 10.9; HRMS (ESI) calc for $C_{11}H_{17}NNa$ (M+Na) 186.1259, found 186.1271.



384a

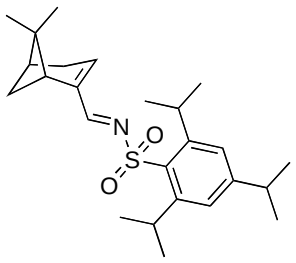
4-Methyl-1-phenylpent-4-en-1-one (384a). A solution of $[Rh(CO)_2Cl]_2$ (2.2 mg, 5.7 μmol) in PhMe (0.22 mL) was added to the solution of dppe (4.6 mg, 11 μmol) in PhMe (1.9 mL). After 10 min at rt, a solution of **124b** (20 mg, 0.11 mmol) in PhMe (0.20 mL) was added and the reaction mixture was placed in an oil bath (110 ^oC) and stirred at this temperature for 8 h. After cooling to rt, the solvent was removed in vacuo and the mixture was purified by chromatography on SiO_2 (Hexanes/EtOAc, 9:1) to afford crude **384a** (6.8 mg, 34%) as a clear, colorless oil: ^1H NMR (600 MHz, $CDCl_3$) δ (characteristic signals) 4.80 (s, 1 H), 4.75 (s, 1 H), 3.15 (t, J = 7.7 Hz, 1 H), 2.48 (t, J = 7.2 Hz, 1 H), 1.82 (s, 3 H).



384b

3-Methylene-2-phenyltetrahydrofuran (384b). A solution of alcohol **124a** (0.10 g, 0.62 mmol) and dppe (0.025 g, 0.062 mmol) in degassed THF (11 mL) was treated with a solution of $[Rh(CO)_2Cl]_2$ (0.012 g, 0.031 mmol) in THF (1.2 mL). The reaction mixture was stirred at rt for 10 min, placed in an oil bath (80 ^oC) and stirred at this temp. for 45 min. The mixture was cooled to rt, quenched with sat. NH_4Cl, extracted (3x) with Et_2O and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (Hexanes/Et_2O, 20:1 to 10:1) afforded **384b** (0.061 g, 61%) as a colorless oil: IR (ATR) 3075, 2848, 1662, 1452, 1046 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.47 (dd, *J* = 7.5, 0.5 Hz, 1 H),

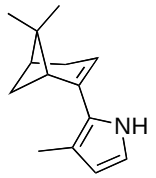
7.31-7.27 (m, 3 H), 7.22 (t, J = 7.5 Hz, 1 H), 5.23 (s, 1 H), 4.98 (d, J = 2.1 Hz, 1 H), 4.80 (d, J = 2.2 Hz, 1 H), 4.02 (ddd, J = 12.5, 8.3, 4.2 Hz, 1 H), 3.74 (q, J = 8.4 Hz, 1 H), 2.50-2.43 (m, 1 H), 2.38-2.33 (m, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 152.2, 142.4, 128.5, 127.8, 127.3, 106.8, 83.2, 67.2, 33.2; MS (EI) *m/z* (rel. intensity) 160 (M^+, 40), 128 (32), 105 (69), 93 (100); HRMS (EI) calc for $C_{11}H_{12}O$ 160.0888, found 160.0892.



386

***N*-(((1*R*,4*R*)-7,7-Dimethylbicyclo[2.2.1]hept-2-en-2-yl)methylene)-2,4,6-triisopropylbenzenesulfonamide (386).** A solution of (-)-myrtenal (0.53 g, 3.5 mmol), 2,4,6-triisopropylbenzenesulfonamide (1.0 g, 3.5 mmol) and freshly distilled DIPEA (1.8 mL, 11 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 ^oC and a solution of $TiCl_4$ (0.24 mL, 2.2 mmol) in CH_2Cl_2 (5.0 mL) was added over 20 min. The reaction mixture was stirred at 0 ^oC for 2 h, poured into dry Et_2O (50 mL), filtered through a pad of SiO_2, washed with Et_2O, and concentrated. Crystallization from boiling hexane afforded **386** (0.86 g, 59%) as a white solid: Mp. 158.7-159.7 ^oC (hexane); $[\alpha]_D$ +21.8 (c 1.0, $CHCl_3$); IR (ATR) 2950, 2932, 1610, 1558, 1310, 1150 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (s, 1 H), 7.18 (s, 2 H), 6.73-6.71 (m, 1 H), 4.23 (septet, J = 6.9 Hz, 2 H), 3.01 (td, J = 5.7, 1.2 Hz, 1 H), 2.91 (septet, J = 6.4 Hz, 1 H), 2.60-2.56 (m, 2 H), 2.49 (td, J = 9.3, 5.7 Hz, 1 H), 2.19-2.18 (m, 1 H), 1.33 (s, 3 H), 1.28-1.24 (m, 18 H), 1.08 (d, J = 9.3 Hz, 1 H), 0.75 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 153.3, 150.9, 149.3, 147.6, 131.4,

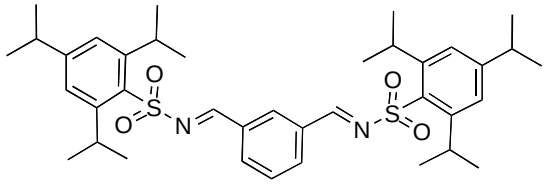
123.7, 40.3, 39.8, 37.6, 34.2, 33.7, 31.1, 29.7, 25.6, 24.7, 23.6, 21.0; MS (EI) *m/z* (rel. intensity) 415 (M^+, 45), 372 (65), 346 (83), 336 (100), 292 (40), 267 (60), 230 (90), 203 (67), 187 (65), 148 (85); HRMS (EI) calc for $C_{25}H_{37}NO_2S$ 415.2545, found 415.2540.



387

2-((1*R*,4*R*)-7,7-Dimethylbicyclo[2.2.1]hept-2-en-2-yl)-3-methyl-1*H*-pyrrole (387). A solution of **119** (0.15 g, 0.60 mmol) in dry Et_2O (1.0 mL) was cooled to -78 ^oC, treated with a solution of MeLi (0.20 mL, 0.60 mmol, c = 3.0 M in diethoxymethane) and after 1 h, with a solution of *t*-BuLi (0.38 mL, 0.60 mmol, c = 1.6 M in pentane). The reaction mixture was stirred for 1 h, a solution of imine **386** (0.084 g, 0.20 mmol) in THF (1.0 mL) was added, the mixture was stirred for 10 min, quenchd with sat. NH_4Cl, warmed up to rt, extracted (3x) with EtOAc and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. The crude oil was transferred into an oven dried microwave tube and concentrated. This mixture was dissolved in THF (2.8 mL), treated with a solution of dppe (0.0080 g, 0.020 mmol) in THF (0.80 mL) and a solution of $[Rh(CO)_2Cl]_2$ (0.0039 g, 0.010 mmol) in THF (0.39 mL). The reaction mixture was stirred at rt for 15 min, placed in an oil bath and stirred under mild reflux for 30 min. The mixture was cooled to rt, poured into sat. $NaHCO_3$, extracted (3x) with EtOAc and the organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (Hexanes/EtOAc, 9:1) afforded **387** (0.017 g, 42%) as a purple, unstable oil: $[\alpha]_D$ +1.8 (c 1.0, MeOH); IR (ATR) 3392, 2915, 2827, 1700, 1463 cm^{-1}; ^1H NMR (300

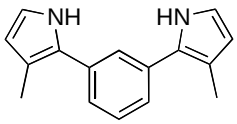
MHz, $CDCl_3$) δ 6.89 (br s, 1 H), 6.28 (d, *J* = 2.7 Hz, 1 H), 6.16 (t, *J* = 2.6 Hz, 1 H), 5.39 (t, *J* = 3.0 Hz, 1 H), 2.40 (d, *J* = 5.9 Hz, 1 H), 2.33 (td, *J* = 6.2, 3.1 Hz, 2 H), 2.24 (s, 3 H), 2.07-2.04 (m, 1 H), 1.39-1.32 (m, 2 H), 1.26 (s, 3 H), 0.93 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 140.8, 117.2, 115.9, 115.5, 112.2, 45.2, 41.1, 38.1, 32.0, 31.9, 26.5, 21.3, 13.4; MS (EI) *m/z* (rel. intensity) 201 (23), 187 (29), 172 (50), 105 (73), 91 (100); HRMS (EI) calc for $C_{14}H_{19}N$ 201.1518, found 201.1513.



388

(*N*,*N*'*E*,*N*,*N*'*E*)-*N*,*N*'-(1,3-Phenylenebis(methan-1-yl-1-ylidene))bis(2,4,6-triisopropylbenzenesulfonamide) (388). A solution of 2,4,6-triisopropylbenzenesulfonamide (2.1 g, 7.5 mmol), isophtalaldehyde (0.50 g, 3.7 mmol), and freshly distilled DIPEA (3.9 mL, 22 mmol) in dry CH_2Cl_2 (35 mL) was cooled to 0 ^oC, and a solution of $TiCl_4$ (0.50 mL, 4.7 mmol) in CH_2Cl_2 (5 mL) was added over ca. 20 min. The reaction mixture was stirred at 0 ^oC for 2 h, warmed up to rt and stirred for 3 h. The mixture was poured into dry Et_2O, filtered through a pad of SiO_2, washed with EtOAc and the solvent was removed in vacuo to afford ligh-yellow oil. The crude product was purified by crystallization from CH_2Cl_2/hexane to afford **388** (2.3 g, 92%) as a white solid: Mp. 255.6-257.3 ^oC (CH_2Cl_2/hexane); IR (KBr) 2960, 2868, 1614, 1588, 1461, 1316, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.05 (s, 2 H), 8.42 (s, 1 H), 8.18 (dd, *J* = 7.7, 0.8 Hz, 2 H), 7.66 (t, *J* = 7.7 Hz, 2 H), 7.22 (s, 4 H), 4.30 (septet, *J* = 6.7 Hz, 4 H), 2.93 (septet, *J* = 6.9 Hz, 2 H), 1.29 (d, *J* = 6.7 Hz, 12 H), 1.27 (d, *J* = 6.7 Hz, 24 H); ^{13}C NMR (75 MHz, CDCl3)

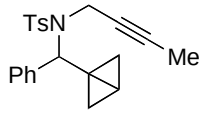
δ 166.9, 154.1, 151.3, 135.8, 133.7, 133.2, 130.2, 130.1, 124.0, 34.3, 29.8, 24.7, 23.5; MS (EI) *m/z* (rel. intensity) 665 (M^+, 1), 422 (99), 394 (100), 381 (60), 320 (56), 303 (44), 284 (54), 256 (37), 187 (47); HRMS (ESI) calc for $C_{38}H_{52}N_2O_4NaS_2$ (M+Na) 687.3266, found 687.3275.



389

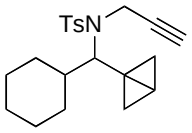
1,3-bis(3-Methyl-1*H*-pyrrol-2-yl)benzene (389). A solution of **128a** (0.10 g, 0.29 mmol) in dry THF (2.2 mL) was cooled to -78 °C, treated with a solution of *n*-BuLi (0.17 mL, 0.24 mmol, c = 1.4 M in hexane) and stirred at this temperature for 1 h. Solid imine **388** (0.065 g, 0.097 mmol) was added, followed by THF (1.0 mL). The mixture was warmed up to rt, stirred for 30 min and quenched with sat. NH_4Cl. The mixture was extracted with EtOAc (3x5 mL), the combined organic layers were washed with water, brine, dried (Na_2SO_4), and concetrated. The crude mixture was filtered through a pad of SiO_2 (Hexanes/Et_2O 100:1 to 4:1) in order to remove all tin residues, dissolved in THF (0.5 mL), followed by a solution of dppe (3.9 mg, 0.0097 mmol) in THF (0.39 mL) was a solution of $[Rh(CO)_2Cl]_2$ (1.9 mg, 0.0048 mmol) in THF (0.38 mL). The reaction mixture was stirred at rt for 15 min, placed in an oil bath and refluxed for min 30 min. After cooling to rt, the mixture was quenched with sat. NH_4Cl, extracted (3x) with EtOAc and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **389** (0.012 g, 52%) as a colorless oil which solidified upon standing: Mp. 136.7-138.0 °C (CH_2Cl_2); IR (neat) 3362, 2921, 1591, 1478, 1108 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 8.23 (br s, 2 H), 7.45 (t, *J* = 1.6 Hz, 1 H), 7.41 (t, *J* = 7.9 Hz, 1 H), 7.26 (dd, *J* = 7.7, 1.8 Hz, 2 H), 6.74 (t, *J* = 2.7 Hz, 2 H), 6.11 (t, *J* = 2.7

Hz, 2 H), 2.27 (s, 6 H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 134.7, 129.7, 128.4, 124.6, 124.2, 118.0, 116.8, 112.8, 13.0 MS (EI) *m/z* (rel. intensity) 236 (M^+, 67), 167 (34), 149 (100); HRMS (EI) calc for $C_{16}H_{16}N_2$ 236.1313, found 236.1321.



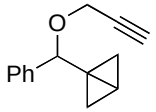
390a

***N*-(Bicyclo[1.1.0]but-1-yl(phenyl)methyl)-*N*-(but-2-ynyl)-4-methylbenzenesulfonamide (390a).** A solution of amide **341e** (0.50 g, 1.6 mmol), Bu_4NHSO_4 (0.023 g, 0.094 mmol) and propargyl bromide (0.30 mL, 1.8 mmol, 80% in PhMe) in PhMe (20 mL) was treated with 50% aq NaOH (10 mL) and stirred at rt for 20 min. The mixture was diluted with water, extracted (3x) wit Et_2O and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 6:1) afforded **390b** (0.47 g, 81%) as a colorless oil: IR (ATR) 3027, 2918, 1597, 1448, 1333, 1155 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2 H), 7.29-7.27 (m, 3 H), 7.25-7.22 (m, 3 H), 5.30 (s, 1 H), 4.28 (dq, *J* = 18.1, 2.3 Hz, 1 H), 4.21 (dq, *J* = 18.1, 2.3 Hz, 1 H), 2.42 (s, 3 H), 1.67 (t, *J* = 2.3 Hz, 3 H), 1.56 (dd, *J* = 6.3, 2.8 Hz, 1 H), 1.43 (s, 1 H), 1.29 (dd, *J* = 6.3, 2.8 Hz, 1 H), 0.67 (s, 1 H), 0.62 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 138.5, 128.9, 128.1, 127.6, 127.5, 127.3, 79.9, 75.0, 62.5, 35.8, 34.3, 31.9, 21.4, 12.0, 3.6, 3.3; MS (EI) *m/z* (rel. intensity) 365 (M^+, 12), 312 (14), 288 (8), 260 (17), 210 (25), 167 (66), 128 (77), 105 (73), 91 (100); HRMS (EI) calc for $C_{22}H_{23}NO_2S$ 365.1450, found 365.1467.



390b

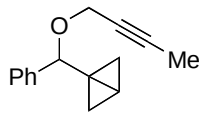
***N*-(Bicyclo[1.1.0]but-1-yl(cyclohexyl)methyl)-4-methyl-*N*-(prop-2-ynyl)benzenesulfonamide (390b).** A solution of amide **341e** (0.30 g, 0.94 mmol), Bu_4NHSO_4 (0.023 g, 0.094 mmol) and propargyl bromide (0.30 mL, 1.8 mmol, 80% in PhMe) in PhMe (10 mL) was treated with 50% aq NaOH (10 mL) and stirred at rt for 20 min. The mixture was diluted with water, extracted (3x) wit Et_2O and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 6:1) afforded **390b** (0.85 g, 90%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2 H), 7.23 (d, *J* = 8.1 Hz, 2 H), 4.21 (dd, *J* = 18.4, 2.5 Hz, 1 H), 4.03 (dd, *J* = 18.3, 2.5 Hz, 1 H), 3.87 (d, *J* = 10.2 Hz, 1 H), 2.39 (s, 3 H), 2.11 (t, *J* = 2.5 Hz, 1 H), 1.92-1.89 (m, 1 H), 1.73-1.71 (m, 1 H), 1.68-1.65 (m, 2 H), 1.64-1.56 (m, 1 H), 1.58-1.56 (m, 2 H), 1.50-1.46 (m, 1 H), 1.19-1.11 (m, 3 H), 1.06-0.95 (m, 1 H), 0.91-0.84 (m, 2 H), 0.39 (s, 1 H), 0.07 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0, 138.0, 129.1, 127.6, 79.7, 71.6, 62.9, 39.8, 33.3, 30.9, 30.8, 30.4, 30.2, 26.1 (2), 25.8, 21.4, 10.7, 5.2; MS (EI) *m/z* (rel. intensity) 357 (M^+, 100), 354 (20), 348 (15), 342 (13), 330 (85), 316 (84); HRMS (EI) calc for $C_{21}H_{27}NO_2S$ 357.1763, found 357.1760.



390c

1-(Phenyl(prop-2-ynyloxy)methyl)bicyclo[1.1.0]butane (390c). Alcohol **124a** (0.60 g, 3.7 mmol), propargyl bromide (2.0 mL, 19 mmol, 80% in PhMe), and Bu_4NHSO_4 (0.12 g, 0.37

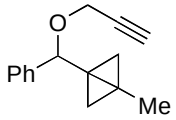
mmol) were dissolved in PhMe (5.0 mL), treated with 50% aq NaOH (5.0 mL) and vigorously stirred at this temperature for 1 h. The mixture was diluted with water, extracted (3 x 5 mL) with Et_2O and the combinded organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Kugelrohr distillation (temperature of oven 120 ^oC, 1 mmHg) afforded **390c** (0.70 g, 95%) as a clear, colorless: IR (ATR) 3291, 2930, 1490, 1452, 1062 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.20 (d, *J* = 7.2 Hz, 2 H), 7.12 (t, *J* = 7.6 Hz, 2 H), 7.06 (d, *J* = 7.4 Hz, 1 H), 4.90 (s, 1 H), 4.08 (dd, *J* = 15.8, 2.4 Hz, 1 H), 3.92 (dd, *J* = 15.8, 2.3 Hz, 1 H), 2.02 (t, *J* = 2.3 Hz, 1 H), 1.56 (dd, *J* = 6.2, 2.8 Hz, 1 H), 1.38 (dd, *J* = 6.2, 2.9 Hz, 1 H), 1.23 (s, 1 H), 0.75 (s, 1 H), 0.59 (s, 1 H); MS (EI) *m/z* (rel. intensity) 198 (M^+, 26), 195 (57), 165 (48), 145 (100), 141 (70); HRMS (EI) calc for $C_{14}H_{14}O$ 198.1045, found 198.1037.



390d

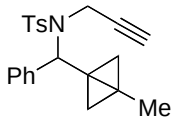
1-((But-2-ynyloxy)(phenyl)methyl)bicyclo[1.1.0]butane (390d). A solution of **124a** (0.50 g, 3.12 mmol), 1-bromo-2-butyne (0.89 mL, 9.4 mmol) and Bu_4NHSO_4 (0.053 g, 0.16 mmol) in PhMe (10 mL) was treated with 50 % aq NaOH (10 mL), vigorously stirred at rt for 30 min, diluted with water, extracted (3x) with Et_2O. The organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by Kugelrohr dist. (120-130 ^oC oven temperature 1 mmHg) afforded **390d** (0.63 g, 95%) as a colorless oil: IR (ATR) 2920, 1490, 1452, 1135, 1079, 1098 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.28 (d, *J* = 7.4 Hz, 2 H), 7.13 (d, *J* = 7.7 Hz, 2 H), 7.07 (t, *J* = 7.2 Hz, 1 H), 4.99 (s, 1 H), 4.21 (dd, *J* = 15.2, 2.1 Hz, 1 H), 4.07 (dd, *J* = 15.3, 2.1 Hz, 1 H), 1.60 (dd, *J* = 6.2, 2.8 Hz, 1 H), 1.48 (s, 3 H), 1.46 (dd, *J* = 6.1, 2.9 Hz, 1 H), 1.28

(s, 1 H), 0.77 (s, 1 H), 0.63 (s, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 140.4, 128.4, 127.8, 127.3, 81.9, 79.5, 76.3, 56.4, 33.7, 31.5, 14.1, 3.3, 1.1; MS (EI) *m/z* (rel. intensity) 212 (M^+, 4), 211 (15), 197 (19), 181 (26), 171 (31), 167 (100), 159 (67), 141 (96); HRMS (EI) calc for $C_{14}H_{13}O$ [M-CH_3] 197.0966, found 197.0961.



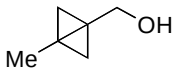
391a

1-Methyl-3-(phenyl(prop-2-ynyloxy)methyl)bicyclo[1.1.0]butane (391a). A solution of **124b** (0.84 g, 4.8 mmol) in PhMe (10 mL) was treated with Bu_4NHSO_4 (0.17 g, 0.48 mmol), propargyl bromide (1.1 mL, 9.6 mmol, 80% in PhMe) and 50% aq NaOH (10 mL). The reaction mixture was stirred at rt for 1 h, diluted with water, extracted (3 x 10 mL) with Et_2O. The combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purfication by Kugelrohr distillation (120-130 ^oC, oven temperature 1 mmHg) afforded **391a** (0.70 g, 68%) as a colorless oil: IR (ATR) 3295, 2920, 1452, 1375 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.7.23 (m, 2 H), 7.16-7.02 (m, 3 H), 4.87 (s, 1 H), 4.04 (dd, *J* = 15.8, 2.4 Hz, 1 H), 3.85 (dd, *J* = 15.8, 2.4 Hz, 1 H), 2.06 (t, *J* = 2.4 Hz, 1 H), 1.41 (d, *J* = 6.5 Hz, 1 H), 1.32 (s, 3 H), 1.13 (d, *J* = 6.5 Hz, 1 H), 0.69 (s, 1 H), 0.56 (s, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 140.5, 128.5, 127.9, 127.7, 80.6, 89.6, 74.3, 55.3, 33.9, 32.9, 16.0, 11.3, 10.9; MS (EI) *m/z* (rel. intensity) 212 (M^+, 40), 210 (92), 203 (47), 197 (44), 189 (100); HRMS (EI) calc for $C_{15}H_{16}O$ 212.1201, found 212.1192.



391b

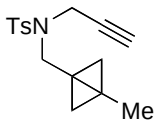
4-Methyl-*N*-((3-methylbicyclo[1.1.0]but-1-yl)(phenyl)methyl)-*N*-(3-phenylprop-2-ynyl)benzenesulfonamide (392a). A solution of amide **123b** (0.36 g, 1.1 mmol), propargyl bromide (0.50 mL), 3.3 mmol) and Bu_4NHSO_4 (0.019 g, 0.055 mmol) in PhMe (5.0 mL) was treated with 50% aq NaOH (5.0 mL), vigorously stirred for 40 min, diluted with water, and extracted (3 x 20 mL) with Et_2O. The combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc 4:1) afforded **391b** (0.36 g, 90%) as a colorless oil: IR (ATR) 3285, 2918, 1597, 1451, 1332, 1155, 1090 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.3 Hz, 2 H), 7.27-7.20 (m, 5 H), 7.15 (d, *J* = 8.1 Hz, 2 H), 5.25 (s, 1 H), 4.46, 4.39, 2.17 (ABX, *J* = 18.4, 2.5 Hz, 3 H), 2.38 (s, 3 H), 1.32 (s, 3 H), 1.23 (s, *J* = 6.7 Hz, 1 H), 1.03 (d, *J* = 6.6 Hz, 1 H), 0.62 (s, 1 H), 0.58 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 138.6, 137.7, 128.9, 128.0, 127.8, 127.4, 80.1, 71.9, 62.7, 35.9, 35.3, 33.0, 21.4, 13.9, 13.4, 10.9; MS (EI) *m/z* (rel. intensity) 366 (M^+, 1), 310 (6), 298 (21), 288 (14), 194 (42), 167 (57), 155 (58), 142 (56), 129 (62), 115 (67), 91 (100); HRMS (ESI) calc for $C_{22}H_{23}NO_2NaS$ (M+Na) 388.1347, found 388.1324.



393

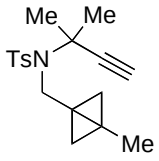
(3-Methylbicyclo[1.1.0]but-1-yl)methanol (393). A solution of methyl ester **125b** (1.2 g, 9.5 mmol) in dry Et_2O (10 mL) was cooled to -78 ^oC, treated with LAH (9.5 mL, 9.5 mmol, c = 1.0 M in Et_2O) and stirred at -78 ^oC for 1 h, warmed up to 0 ^oC and quenched with a minimal amount

of water. The mixture was dried ($MgSO_4$), filtered, and concentrated *in vacuo* (water bath <10 ^oC). The crude oil was purified by Kugelrohr distillation (water aspirator, 60-100 ^oC oven temperature) to afford **393** (0.49 g, 52%) as a colorless oil: IR (ATR) 3369, 3002, 2918, 1420, 1375, 1088, 998 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 3.59 (d, *J* = 5.7 Hz, 2 H), 1.30 (s, 3 H), 1.20 (s, 2 H), 0.77 (t, *J* = 5.8 Hz, 1 H), 0.69 (s, 2 H); ^{13}C NMR (75 MHz, C_6D_6) δ 61.6, 34.7, 12.4, 11.3, 5.6; MS (EI) *m/z* (rel. intensity) 98 (M^+, 100), 92 (91), 91 (47); HRMS (EI) calc for $C_6H_{10}O$ 98.0732, found 98.0728.



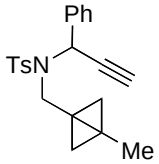
394a

4-Methyl-*N*-((3-methylbicyclo[1.1.0]but-1-yl)methyl)-*N*-(prop-2-ynyl)benzenesulfonamide (394a). A solution of **393** (0.15 g, 1.5 mmol), amide **392a** (0.32 g, 1.5 mmol) and Ph_3P (0.40 g, 1.5 mmol) in dry THF (15 mL) was cooled to 0 ^oC, treated with DIAD (0.30 mL, 1.5 mmol) over 5 min and stirred at 0 ^oC for 2 h 10 min. The solvent was removed in vacuo and the product was purified by chromatography on SiO_2 (hexanes/EtOAc, 9:1 to 4:1) to afford **394a** (0.18 g, 41%) as a colorless oil: IR (ATR) 3276, 2952, 1448, 1323, 1157 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.79 (d, *J* = 8.3 Hz, 2 H), 6.87 (d, *J* = 8.0 Hz, 2 H), 4.23 (d, *J* = 2.5 Hz, 2 H), 3.64 (s, 2 H), 1.96 (s, 3 H), 1.67 (t, *J* = 2.5 Hz, 1 H), 1.17 (s, 3 H), 1.12 (s, 2 H), 0.55 (s, 2 H); ^{13}C NMR (74 MHz, C_6D_6) δ 143.0, 137.4, 129.5, 128.3, 77.4, 73.7, 47.3, 36.4, 36.1, 21.2, 10.7, 6.7, 8.4; HRMS (ES) calc for $C_{16}H_{19}NO_2NaS$ (M+Na) 312.1034, found 312.1048.



394b

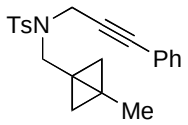
4-Methyl-*N*-((3-methylbicyclo[1.1.0]but-1-yl)methyl)-*N*-(2-methylbut-3-yn-2-yl)benzenesulfonamide (394b). A solution of alcohol **393** (0.17 g, 1.7 mmol), amide **392b** (0.36 g, 1.7 mmol) and Ph_3P (0.40 g, 1.7 mmol) in dry THF (15 mL) was cooled to 0 ^oC, treated with DIAD (0.30 mL, 1.7 mmol) over 5 min and stirred at 0 ^oC for 2 h 10 min. The solvent was removed in vacuo and the product was purified by chromatography on SiO_2 (hexanes/EtOAc, 9:1 to 4:1) to afford **394b** (0.21 g, 43%) as a colorless oil: IR (ATR) 3261, 2952, 1360, 1318, 1305, 1146 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.84 (d, J = 8.4 Hz, 2 H), 6.80 (d, J = 8.0 Hz, 2 H), 4.07 (s, 2 H), 1.96 (s, 1 H); 1.93 (s, 2 H), 1.75 (s, 6 H), 1.49 (s, 2 H), 1.34 (s, 2 H), 0.85 (s, 2 H); ^{13}C NMR (125 MHz, C_6D_6) δ 142.3, 142.2, 129.4, 127.2, 87.1, 72.3, 56.1, 48.7, 37.4, 30.7, 21.1, 13.4, 11.6, 11.0; MS (EI) *m/z* (rel. intensity) 317 (M^+, 2), 302 (86), 212 (41), 198 (22), 184 (40), 155 (100), 91 (70); HRMS (EI) calc for $C_{18}H_{23}NO_2S$ 317.1450, found 317.1440.



394c

4-Methyl-*N*-((3-methylbicyclo[1.1.0]but-1-yl)methyl)-*N*-(1-phenylprop-2-ynyl)benzenesulfonamide (394c). A solution of alcohol **393** (0.21 g, 4.0 mmol), amide **392c**[490] (0.30 g, 1.1 mmol), and Ph_3P (0.41 g, 1.6 mmol) in dry THF (10 mL) was cooled to 0 ^oC, treated with DIAD (0.31 mL, 1.6 mmol) and stirred at this temperature for 1 h. The solvent was re-

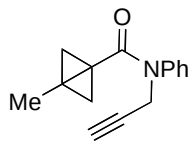
moved in vacuo and the crude oil was purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to afford **394c** (0.10 g, 26%) as a colorless oil: IR (ATR) 3060, 2918, 1597, 1492, 1449, 1332, 1159, 1088 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.5 Hz, 2 H), 7.65 (d, *J* = 7.4 Hz, 2 H), 7.25-7.31 (m, 4 H), 7.26 (t, *J* = 7.5 Hz, 1 H), 6.21 (s, 1 H), 4.52, 4.44 (AB, *J* = 14.7 Hz, 2 H), 2.34 (s, 3 H), 2.41 (d, *J* = 2.4 Hz, 1 H), 1.28 (s, 3 H), 1.07 (d, *J* = 6.5 Hz, 1 H), 0.77 (d, *J* = 6.5 Hz, 1 H), 0.16 (s, 1 H), -0.02 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.1, 136.9, 136.4, 129.3, 128.0, 127.8, 127.7, 127.6, 78.4, 76.3, 52.4, 46.4, 37.2, 36.9, 21.5, 12.5, 10.8, 9.9; MS (EI) *m/z* (rel. intensity) 365 (M^+, 1), 310 (17), 260 (24), 210 (53), 194 (24), 155 (59), 115 (100), 91 (92); HRMS (ESI) calc for $C_{22}H_{23}NO_2NaS$ (M+Na) 388.1347, found 388.1320.



394d

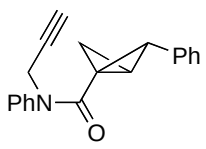
4-Methyl-*N*-((3-methylbicyclo[1.1.0]but-1-yl)methyl)-*N*-(3-phenylprop-2-ynyl)benzenesulfonamide (394d). A solution of alcohol **393** (0.068 g, 0.70 mmol), amide **392d**[491] (0.20 g, 0.70 mmol) and Ph_3P (0.18 g, 0.70 mmol) in dry THF (8.0 mL) was cooled to 0 ^oC, treated with DIAD (0.14 mL, 0.70 mmol) over 5 min and stirred at 0 ^oC for 2 h. The solvent was removed *in vacuo* and the product was purified by chromatography on SiO_2 (hexanes/EtOAc, 9:1 to 4:) to afford **394d** (0.090 g, 35%) as a colorless oil: IR (ATR) 2922, 1593, 1487, 1346, 1321, 1159 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.77 (d, *J* = 8.2 Hz, 2 H), 7.33-7.28 (m, 2 H), 7.27-7.24 (m, 3 H), 7.06 (dd, *J* = 8.2, 1.4 Hz, 2 H), 4.49 (s, 2 H), 3.65 (s, 2 H), 2.31 (s, 3 H), 1.48 (s, 3 H), 1.33 (s, 2 H), 0.70 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 143.3, 136.0, 131.4, 129.4, 128.3, 128.1, 127.8, 122.3, 85.4, 82.1, 47.6, 37.1, 36.1, 21.4, 11.1, 9.7, 8.1; MS (EI) *m/z*

(rel. intensity) 365 (M^+, 7), 194 (35), 167 (67), 115 (100), 91 (62); HRMS (EI) calc for $C_{22}H_{23}NO_2S$ 365.1450, found 365.1458.



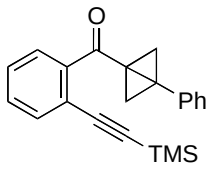
395a

3-Methyl-*N*-phenyl-*N*-(prop-2-ynyl)bicyclo[1.1.0]butane-1-carboxamide (395a). A solution of **126** (0.20 g, 1.07 mmol) was dissolved in DMF (10 mL), cooled to 0 ^oC and NaH (0.040 g, 1.6 mmol, 95%) was added in one portion followed by propargyl bromide (0.46 mL, 4.3 mmol, 80 % in PhMe). The reaction mixture was stirred at 0 ^oC for 5 h, quenched with sat. NH_4Cl, diluted with water and extracted (3 x 10 mL) with EtOAc. The combined organic layers were washed with water (3 x 20 mL), brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 9:1 to 4:1) afforded **395a** (0.22 g, 91%) as a clear, colorless oil: IR (ATR) 3290, 2946, 1628, 1593, 1493, 1379, 1206 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39-7.30 (m, 3 H), 7.28-7.18 (m, 2 H), 4.51 (d, J = 2.5 Hz, 2 H), 2.17 (t, J = 2.4 Hz, 1 H), 1.68 (s, 2 H), 1.49 (s, 3 H), 0.89 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ, 170.7, 143.5, 129.02, 127.3, 126.7, 79.7, 71.5, 40.0, 39.0, 28.6, 13.1, 12.1; MS (EI) *m/z* (rel. intensity) 225 (M^+, 39), 210 (12), 196 (15), 184 (19), 170 (100), 142 (59), 130 (27), 91 (45), 77 (49); HRMS (EI) calc for $C_{15}H_{15}NO$ 225.1154, found 225.1165.



395b

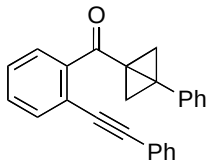
(1*S,2*S**,3*R**)-*N*,2-Diphenyl-*N*-(prop-2-ynyl)bicyclo[1.1.0]butane-1-carboxamide (395b).** A solution of **152d** (0.028 g, 0.11 mmol) in dry DMF (2.0 mL) was cooled to 0 ^{o}C, treated with NaH (0.0056 g, 0.22 mmol) and propargyl bromide (0.067 mL, 0.45 mmol, 80% in PhMe). The mixture was stirred at 0 ^{o}C for 2.5 h, quenched with sat. NH_4Cl, diluted with water and extracted (3 x 5 mL) with EtOAc. The combined organic layers were washed with water (3x), brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on neutral alumina (hexanes/EtOAc, 2:1) afforded **395b** (0.030 g, 94%) as a clear, colorless oil: ^{1}H NMR (300 MHz, C_6D_6) δ 7.25 (s, 2 H), 7.12-7.02 (m, 3 H), 6.90 (t, *J* = 6.1 Hz, 3 H), 6.76-6.71 (m, 4 H), 4.50 (dd, *J* = 17.2, 2.4 Hz, 1 H), 4.31 (d, *J* = 17.0 Hz, 1 H), 2.42 (d, *J* = 3.5 Hz, 1 H), 2.39-2.37 (m, 1 H), 1.89 (t, *J* = 2.5 Hz, 1 H), 1.61 (s, 1 H), 0.87 (s, 1 H), ^{13}C NMR (75 MHz, C_6D_6) δ 167.9, 142.4, 136.5, 128.2, 127.4, 126.9 (2), 126.5, 125.9, 79.7, 71.8, 51.7, 38.4, 32.7, 18.3, 17.6; MS (EI) *m/z* (rel. intensity) 287 (M^+, 14), 258 (12), 196 (12), 181 (21), 158 (51), 129 (100), 117 (90), 77 (62); HRMS (EI) calc for $C_{20}H_{17}NO$ 287.1310, found 287.1304.



397a

(3-Phenylbicyclo[1.1.0]but-1-yl)(2-((trimethylsilyl)ethynyl)phenyl)methanone (397a). A solution of **121a** (1.0 g, 2.7 mmol) in dry Et_2O (2.0 mL) was cooled to -78 ^{o}C, treated with a solution of MeLi (1.8 mL, 2.7 mmol, c = 1.5 M) and stirred for 1 h. After warming up to rt, the mixture was quenched with sat. NH_4Cl, extracted (3 x 10 mL) with Et_2O and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. The crude oil was dried

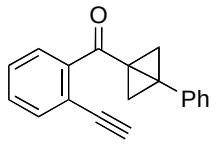
on high vacuum, dissolved in Et_2O (2.0 mL), cooled to -78 ^oC, and treated with *t*-BuLi (1.8 mL, 2.7 mL, c = 1.5 M in pentane). After 1 h at -78 ^oC, a solution of amide **151** (0.14 g, 0.54 mmol) in THF (2.0 mL) was added in one portion. After stirring for 5 min, sat. NH_4Cl was added and the mixture was allowed to warm to rt, extracted with Et_2O (3 x 5 mL), and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (pentane/EtOAc, 8:1) afforded **397a** (0.15 g, 82%) as a light yellow oil: IR (neat) 3056, 2955, 2156, 1632, 1474, 1399, 1341, 1246 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.7 Hz, 1 H), 7.30-7.29 (m, 1 H), 7.25-7.22 (m, 3 H), 7.12-7.06 (m, 3 H), 6.44 (d, *J* = 7.7 Hz, 1 H), 3.04 (d, *J* = 0.9 Hz, 2 H), 1.87 (d, *J* = 0.9 Hz, 2 H), 0.24 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.4, 141.9, 132.7, 132.3, 129.9, 128.3, 127.2, 126.4, 125.7, 124.9, 122.0, 102.7, 99.9, 41.7, 37.7, 34.4, -0.2; MS (EI) *m/z* (rel. intensity) 257 (7), 227 (10), 159 (17), 57 (100); HRMS (EI) calc for $C_{22}H_{22}OSi$ 330.1440, found 330.1438.



397b

(3-Phenylbicyclo[1.1.0]but-1-yl)(2-(phenylethynyl)phenyl)methanone (397b). A solution of **121a**(1.0 g, 2.7 mmol) in Et_2O (10 mL) was cooled to -78 ^oC, treated with MeLi (0.90 mL, 2.7 mmol, c = 3.0 M in diethoxymethane) and after 1 h, the reaction mixture was quenched with sat. NH_4Cl, warmed to rt, extracted (3 x) with Et_2O and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. The crude oil was dried on high vacuum for 10 min, dissolved in dry Et_2O (10 mL) and treated with a solution of *t*-BuLi (1.8 mL, 2.7 mmol, c = 1.5 M in pentane) and after 1 h, a solution of **151** (0.24 g, 0.90 mmol) in THF (5.0 mL) was

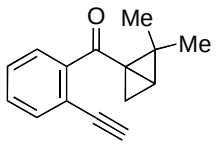
added in one portion. The reaction mixture was stirred at -78 ^{o}C for 10 min, quenched at this temperature with sat. NH_4Cl, warmed up to rt, diluted with water and extracted (3x) with Et_2O. The organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 6:1) afforded **397b** (0.25 g, 83%) as a colorless oil: IR (ATR) 3056, 1628, 1491, 1397, 1344 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 7.8, 0.6 Hz, 1 H), 7.52-7.60 (m, 2 H), 7.39-7.36 (m, 4 H), 7.28-7.23 (m, 3 H), 7.22-7.16 (m, 3 H), 6.69 (dd, *J* = 7.9, 1.0 Hz, 1 H), 3.15 (t, *J* = 1.3 Hz, 2 H), 1.98 (t, *J* = 1.4 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.1, 141.2, 132.6, 132.0, 131.5, 130.0, 128.4, 128.3, 128.2, 127.9, 127.2, 126.9, 125.9, 125.7, 123.0, 121.9, 94.2, 87.5, 41.3, 37.5, 34.1.



398

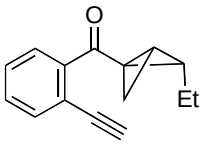
(2-Ethynylphenyl)(3-phenylbicyclo[1.1.0]but-1-yl)methanone (398). A solution of **397a** (0.10 g, 0.31 mmol) in dry THF (3.1 mL) was cooled to 0 ^{o}C, treated with a solution of TBAF (0.32 mL, 0.32 mmol, 1.0 M in THF) and stirred for 15 min. After quenching with sat. NH_4Cl, the mixture was warmed up to rt, diluted with water, extracted (3 x 5 mL) with Et_2O and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **398** (0.067g, 84%) as a light yellow oil: IR (neat) 2925, 2854, 2359, 1715, 1635, 1478, 1446, 1347 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.8 Hz, 1 H), 7.3-7.32 (m, 1 H), 7.28-7.27 (m, 2 H), 7.21-7.16 (m, 2 H), 6.68 (dd, *J* = 8.0, 1.0 Hz, 1 H), 3.13 (s, 1 H), 3.07 (s, 2 H), 1.93 (s, 2 H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 197.9, 141.9, 133.1, 132.6, 129.9, 128.4, 128.3, 127.3, 126.9, 125.8, 124.9, 120.5, 81.7,

81.0, 41.5, 37.5, 36.8, 34.2; MS (EI) *m/z* (rel. intensity) 258 (M^+, 44), 229 (66), 215 (47), 202 (15), 181 (17), 152 (13), 129 (79), 101 (100); HRMS (EI) calc for $C_{19}H_{14}O$ 258.1045, found 258.1033.



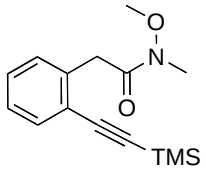
399a

(2,2-Dimethylbicyclo[1.1.0]but-1-yl)(2-ethynylphenyl)methanone (399a). A solution of **152a** (0.038 g, 0.13 mmol) in THF (2.5 mL) was cooled to 0 ^oC, treated with TBAF (0.15 mL, 0.15 mmol, c = 1.0 M in THF) and stirred at 0 ^oC for 5 min. The reaction mixture was quenched with sat. NH_4Cl, diluted with water, extracted with EtOAc and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 6:1) afforded **399a** (0.024 g, 83%) as a light-yellow oil: IR (neat) 2959, 2924, 2856, 1711, 1646, 1468, 1444, 1370, 1232 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55-7.51 (m, 1 H), 7.48-7.42 (m, 1 H), 7.44-7.35 (m, 2 H), 3.22 (s, 1 H), 2.64 (dd, *J* = 4.1, 2.8 Hz, 1 H), 2.43 (t, *J* = 3.7 Hz, 1 H), 1.99 (dd, *J* = 3.3, 3.1 Hz, 1 H), 1.06 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 143.9, 133.6, 129.7, 128.4, 127.6, 119.7, 52.8, 36.6, 35.7, 28.2, 23.1, 15.1; MS (EI) *m/z* (rel. intensity) 209 ($[M-1]^+$, 4), 195 (14), 149 (100), 129 (34), 121 (12), 101 (16); HRMS (EI) calc for $C_{14}H_{12}O$ (M-14) 196.0889, found 196.0891.



399b

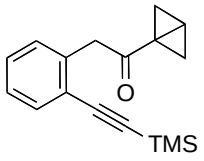
((1*R,2*R**,3*S**)-2-Ethylbicyclo[1.1.0]but-1-yl)(2-ethynylphenyl)methanone (399b).** A solution of **152f** (0.12 g, 0.42 mmol) in dry THF (2.1 mL) was cooled to 0 ^{o}C, treated with TBAF (0.46 mL, 0.46 mmol, 1.0 M in THF), and stirred at 0 ^{o}C for 10 min. The mixture was quenched with sat. NH_4Cl, diluted with water, and extracted with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 9:1) afforded **399b** (0.065 g, 74%) as a light-yellow oil: IR (neat) 3249, 3061, 2963, 2932, 2106, 1649, 1483, 1465, 1426, 1343, 1209, 1118 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 7.35 (dd, *J* = 7.3, 1.4 Hz, 1 H), 7.23 (dd, *J* = 1.3, 7.2 Hz, 1 H), 6.87-6.82 (m, 2 H), 2.93 (app. septet, *J* = 3.7 Hz, 1 H), 2.80 (s, 1 H), 2.53 (dd, *J* = 6.7, 3.8 Hz, 1 H), 1.99 (q, *J* = 3.7 Hz, 1 H), 1.79 (t, *J* = 2.9 Hz, 1 H), 1.20 (dqd, *J* = 14.3, 7.3, 7.0 Hz, 1 H), 1.07 (dqd, *J* = 14.5, 7.4, 7.1 Hz, 1 H), 0.75 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (150 MHz, C_6D_6) δ 199.9, 143.1, 129.5, 128.3 (2), 127.9, 120.6, 82.0, 81.9, 54.7, 36.4, 28.1, 25.5, 16.6, 13.3.



400b

***N*-Methoxy-*N*-methyl-2-(2-((trimethylsilyl)ethynyl)phenyl)acetamide (400b).** A solution of 2-(2-iodophenyl)-*N*-methoxy-*N*-methylacetamide **400a**[492] (4.1 g, 13 mmol), $Pd(PPh_3)_4$ (0.77 g, 0.67 mmol), CuI (0.25 g, 1.3 mmol) in freshly distilled *i*-Pr_2NH (100 mL) was cooled to 0 ^{o}C, degassed and TMSCCH (2.3 mL, 16 mmol) was added in one portion. The reaction mixture was stirred at 0 ^{o}C for 4 h, quenched with sat. NH_4Cl, extracted (3 x 20 mL) with Et_2O and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. The crude

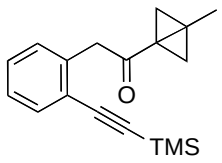
oil was purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to afford **400a** (2.8 g, 75%) as a colorless oil: IR (ATR) 2956, 2153, 1664, 1483, 1407, 1377, 1247, 1172 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.4 Hz, 1 H), 7.32-7.25 (m, 2 H), 7.22-7.16 (m, 1 H), 3.99 (s, 2 H), 3.67 (s, 3 H), 3.21 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 137.1, 132.3, 129.3, 128.5, 126.4, 123.1, 103.4, 98.1, 61.1, 37.5, 32.2, -0.1; MS (ESI) *m/z* (rel. intensity) 298 ($[M+Na]^+$, 100); HRMS (ESI) calc for $C_{15}H_{21}NO_2NaSi$ (M+Na) 298.1239, found 298.1266.



401a

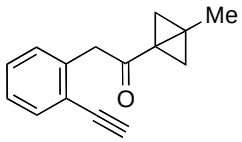
1-(Bicyclo[1.1.0]but-1-yl)-2-(2-((trimethylsilyl)ethynyl)phenyl)ethanone(401a). A solution of **119** (5.0 g, 20 mmol) in dry Et_2O (20 mL) was cooled to -78 ^oC, treated with a solution of MeLi (13 mL, 20 mmol, c = 1.6 M in Et_2O) and allowed to warm up to -50 ^oC over 1 h. The mixture was cooled to -78 ^oC, treated with *t*-BuLi (13 mL, 20 mmol, c = 1.5 M in pentane) and after 1 h, a solution of **400b** (1.1 g, 4.0 mmol) in THF (20 mL) was added in one portion. The mixture was stirred for 3 min, quenched with sat. NH_4Cl, warmed up to rt, diluted with water, and extracted with Et_2O. The combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc 4:1) afforded **401a** (0.33 g, 31%) as a colorless oil: IR (neat) 3060, 2959, 2900, 2154, 1672, 1485, 1447, 1397, 1250, 1107 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.5 Hz, 1 H), 7.33-7.28 (m, 2 H), 7.25-7.17 (m, 1 H), 3.97 (s, 2 H), 2.56 (dd, *J* = 2.5, 1.1 Hz, 2 H), 2.20 (app. quintet, *J* = 3.2 Hz, 1 H), 1.24 (dd, *J* = 2.9, 1.1 Hz, 2 H), 0.28 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.4, 136.9, 132.6, 129.8,

128.7, 126.8, 122.9, 103.6, 98.4, 44.0, 36.1, 20.6, 18.7, -0.0; MS (EI) *m/z* (rel. intensity) 268 (M^+, 8), 253 (6), 240 (7), 179 (9), 157 (8), 145 (6), 105 (7), 81 (65); HRMS (EI) calc for $C_{17}H_{20}OSi$ 268.1283, found 268.1279.



401b

1-(3-Methylbicyclo[1.1.0]but-1-yl)-2-(2-((trimethylsilyl)ethynyl)phenyl)ethanone (401b). A solution of 1,1-dibromo-2-(chloromethyl)-2-methylcyclopropane **122** (5.0 g, 19 mmol) in Et_2O (10 mL) was cooled to -78 ^oC, treated with MeLi (13 mL, 19 mmol, c = 1.5 M in Et_2O) and after 1 h, a solution of *t*-BuLi (12 mL, 19 mmol, c = 1.5 M in pentane) was added. After additional 1 h at -78 ^oC, a solution of **400b** (1.0 g, 3.8 mmol) in THF (10 mL) was added. The reaction mixture was quenched with sat. NH_4Cl, warmed up to rt, extracted with Et_2O, and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **401b** (0.38 g, 35%) as a colorless oil: IR (neat) 2957, 2154, 1725, 1660, 1520, 1484, 1449, 1412, 1376, 1330, 1250, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.5 Hz, 1 H), 7.28-7.24 (m, 2 H), 7.21-7.13 (m, 1 H), 3.90 (s, 2 H), 2.39 (s, 2 H), 1.45 (s, 3 H), 1.26 (s, 2 H), 0.26 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 136.4, 132.5, 129.7, 128.6, 126.6, 122.9, 103.8, 98.3, 45.1, 39.0, 34.0, 23.1, 12.7, -0.1; MS (EI) *m/z* (rel. intensity) 282 (M^+, 6), 267 (10), 254 (8), 239 (7), 192 (10), 157 (11), 128 (10), 73 (58), 67 (100); HRMS (EI) calc for $C_{18}H_{22}OSi$ 282.1440, found 282.1440.

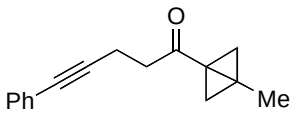


402b

2-(2-Ethynylphenyl)-1-(3-methylbicyclo[1.1.0]but-1-yl)ethanone (402b). A solution of **401b** (0.12 g, 0.43 mmol) in THF (4.2 mL) was cooled to 0 ^{o}C, treated with TBAF (0.47 mL, 0.47 mmol, c = 1.0 M in THF) and stirred at 0 ^{o}C for 5 min. The mixture was quenched with sat. NH_4Cl, diluted with water, extracted with Et_2O and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexenes/EtOAc, 4:1) afforded **402b** (86 mg, 96%) as a light yellow oil that solidified upon standing: IR (neat) 3285, 2951, 1715, 1663, 1485, 1413, 1377 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.5 Hz, 1 H), 7.35-7.20 (m, 3 H), 3.93 (s, 2 H), 3.27 (s, 1 H), 2.38 (s, 2 H), 1.51 (s, 3 H), 1.30 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.1, 136.8, 132.8, 129.9, 128.9, 126.7, 122.1, 82.4, 81.1, 45.3, 38.9, 34.0, 23.0, 12.8; MS (EI) *m/z* (rel. intensity) 209 (M^+, 4), 195 (14), 182 (100), 167 (72), 115 (55), 95 (25), 67 (56); HRMS (EI) calc for $C_{15}H_{14}O$ 210.1045, found 210.1037.

***N*-Methoxy-*N*-methyl-5-phenylpent-4-ynamide (400c).** 4-Pentynoic acid (2.0 g, 20 mmol) in CH_2Cl_2 was treated with EDCI (4.1 g, 21 mmol), HNMe(OMe)·HCl (2.1 g, 21 mmol) and Et_3N (5.0 mL, 36 mmol) in CH_2Cl_2 (50 mL) at rt. The mixture was stirred at rt for 3 h, quenched with sat. NH_4Cl, extracted (3x) with CH_2Cl_2 and the organic layers were washed with water, brine, dried (MgSO4), and concentrated. The crude oil was dissolved in THF (10 mL) and added to a degassed solution of PhI (3.7 g, 18 mmol), CuI (0.34 g, 1.8 mmol) and $Pd(PPh_3)_4$ (0.33 g, 0.89 mmol) in *i*-Pr_2NH (100 mL) at 0 ^{o}C. The mixture was stirred at 0 ^{o}C for 1 h, quenched with sat.

NH_4Cl, extracted (3x) with EtOAc and the combined organic layers were washed with water, brine, dried (MgSO4), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 1:1) afforded **400c** (3.4 g, 82%) as a colorless oil: IR (ATR) 2933, 1657, 1489, 1439, 1418, 1383, 1336, 1103, 991 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2 H), 7.17-7.12 (m, 3 H), 3.53 (s, 3 H), 3.05 (s, 3 H), 2.63 (br s, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 131.0, 127.7, 127.2, 123.2, 88.6, 80.4, 60.7, 31.6, 30.8, 14.4.



401c

1-(3-Methylbicyclo[1.1.0]but-1-yl)-5-phenylpent-4-yn-1-one (401c). A solution of **119** (0.91 g, 3.5 mmol) in Et_2O (10 mL) was cooled to -78 ^oC, treated with MeLi (2.3 mL, 3.5 mmol, 1.5 M in Et_2O). After 1 h, a solution of *t*-BuLi (2.3 mL, 3.5 mmol, c = 1.5 M in pentane) was added and the reaction mixture was stirred at -78 ^oC for 1 h. A solution of **400c** (0.30 g, 1.4 mol) in THF (5.0 mL) was added and the reaction mixture was warmed up to rt, quenched with sat. NH_4Cl and extracted (3 x 10 mL) with Et_2O. The combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1 then hexanes/CH_2Cl_2, 1:1) afforded **401c** (0.15 g, 49%) as a clear, colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.35 (m, 2 H), 7.27-7.24 (m, 3 H), 2.74-2.62 (m, 4 H), 2.34 (s, 2 H), 1.56 (s, 3 H), 1.31 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ, 203.1, 131.4, 128.1, 127.6, 123.6, 89.0, 80.7, 39.2, 38.6, 32.9, 22.5, 14.0, 12.6.

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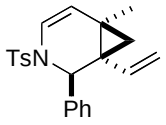
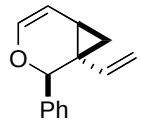


403a

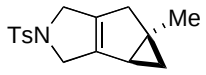
(1*S,2*R**,6*R**)-6-Methyl-2-phenyl-3-tosyl-1-vinyl-3-azabicyclo[4.1.0]hept-4-ene (403a).** A solution of **390a** (0.030g, 0.081 mmol) and $PtCl_2$ (0.0021 g, 0.0081 mmol) were suspended in degassed PhMe (1.6 mL) and placed in an oil bath (110-120 ^oC). The reaction mixture was stirred at this temperature for 1 h and 10 min, cooled to rt, filtered through a pad of silica (washed with Et_2O), and concentrated. Purification by preparative TLC (hexanes/EtOAc, 4:1) afforded **403a** (0.0061 g, 21%) as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.3 Hz, 2 H), 7.38-7.36 (m, 3 H), 7.27-7.23 (m, 4 H), 6.15 (dd, *J* = 7.8, 0.9 Hz, 1 H), 5.57 (d, *J* = 7.8 Hz, 1 H), 5.53 (dd, *J* = 17.1, 10.5 Hz, 1 H), 5.12 (s, 1 H), 5.03 (dd, *J* = 10.5, 1.5 Hz, 1 H), 5.02 (d, *J* = 17.1, 1.5 Hz, 1 H), 2.42 (s, 3 H), 1.20 (s, 3 H), 0.86 (d, *J* = 4.6 Hz, 1 H), 0.50 (d, *J* = 4.6 Hz, 1 H).



403c

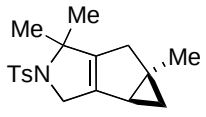
(1*S,2*R**,6*R**)-2-Phenyl-1-vinyl-3-oxabicyclo[4.1.0]hept-4-ene (403c).** A solution of ether **390c** (0.050 g, 0.25 mmol) and $PtCl_2$ (0.0034 g, 0.013 mmol) in PhMe (5.0 mL) was stirred at 60 ^oC (oil bath) for 20 h. The solvent was removed in vacuo and the crude mixture was purified by chromatography on SiO_2 (hexanes/EtOAc, 20:1 and hexanes/CH_2Cl_2, 7:1) to afford **403c** (0.031 g, 61%) as a colorless oil: IR (ATR) 3064, 1636, 1454, 1226 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.39-7.35 (m, 2 H), 7.20-.716 (m, 2 H), 7.12-7.06 (m, 1 H), 6.28 (d, *J* = 5.5 Hz, 1 H), 5.63 (dd, *J*

= 10.7, 17.2 Hz, 1 H), 5.25 (t, *J* = 5.5 Hz, 1 H), 4.71 (dd, *J* = 1.2, 11.8 Hz, 1 H), 4.66 (dd, *J* = 17.1, 1.2 Hz, 1 H), 4.60 (s, 1 H), 1.52 (t, *J* = 3.2 Hz, 1 H), 1.16-1.06 (m, 2 H); ^{13}C NMR (150 MHz, C_6D_6) 142.5, 140.5, 138.6, 128.3, 128.2, 128.1, 113.4, 106.7, 76.4, 36.3, 18.7, 18.2; MS (EI) *m/z* (rel. intensity) 198 (M^+, 20), 180 (17), 167 (20), 141 (20), 91 (55), 69 (74), 57 (100); HRMS (EI) calc for $C_{14}H_{14}O$ 198.1045, found 198.1040.



409a

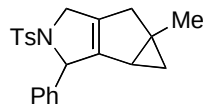
4-Methyl-8-[(4-methylphenyl)sulfonyl]-8-azatricyclo[4.3.0.0^{2,4}]non-1(6)-ene (409a). A solution of **394a** (19 mg, 0.066 mmol) and $PtCl_2$ (0.9 mg, 0.0033 mmol) in PhMe (1.3 mL) was stirred at 50 ^{o}C (oil bath) for 1 h 55 min. The solvent was removed *in vacuo* and purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **409a** (16 mg, 84%) as a colorless oil: IR (ATR) 2973, 1625, 1338, 1161 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.2 Hz, 2 H), 7.30 (d, *J* = 8.1 Hz, 2 H), 3.99-3.94 (m, 3 H), 3.83-3.76 (m, 1 H), 2.41 (s, 3 H), 2.27 (d, *J* = 17.1 Hz, 1 H), 2.16 (d, *J* = 16.1 Hz, 1 H), 1.33-1.29 (m, 1 H), 1.26 (s, 3 H), 0.75 (dd, *J* = 7.2, 4.1 Hz, 1 H), 0.19 (t, *J* = 3.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 143.2, 137.2, 134.8, 129.7, 127.3, 52.0, 51.7, 37.4, 28.4, 24.9, 23.8, 21.7, 21.5.



409b

4,7,7-Trimethyl-8-[(4-methylphenyl)sulfonyl]-8-azatricyclo[4.3.0.0^{2,4}]non-1(6)-ene (409b). A solution of amide **394b** (18 mg, 0.056 mmol) and $PtCl_2$ (0.7 mg, 0.0028 mmol) in PhMe (1.1

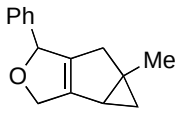
mL) was stirred at 50 °C (oil bath) for 3 h 15 min. The solvent was removed *in vacuo* and purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded crude **409b**, which was repurified by preparative-TLC (hexanes/THF, 4:1) to afford 409b (3.0 mg, 17%) as a colorless oil: IR (ATR) 2924, 1484, 1334, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 8.3, 17. Hz, 2 H), 7.28 (dd, *J* = 8.0, 1.9 Hz, 2 H), 3.95 (dd, *J* = 12.6, 1.3 Hz, 1 H), 3.80 (d, *J* = 12.6 Hz, 1 H), 2.42 (s, 3 H), 2.32 (d, *J* = 18.5 Hz, 1 H), 2.24 (dd, *J* = 17.4, 0.9 Hz, 1 H), 1.57 (s, 3 H), 1.53 (s, 3 H), 1.31 (s, 3 H), 0.81 (dd, *J* = 7.2, 4.1 Hz, 1 H), 0.26 (t, *J* = 3.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 142.6, 138.4, 132.0, 129.3, 127.3, 69.4, 51.6, 37.5, 27.1, 27.0, 26.5, 24.1, 23.8, 21.7, 21.5; MS (EI) *m/z* (rel. intensity) 317 (M^+, 11), 302 (100), 274 (5), 146 (77), 105 (72), 91 (98); HRMS (EI) calc for $C_{18}H_{23}NO_2S$ 317.1450, found 317.1452.



409c

4-Methyl-8-[(4-methylphenyl)sulfonyl]-9-phenyl-8-azatricyclo[4.3.0.0^{2,4}]non-1(6)-ene (409c). A solution of **394c** (0.019 g, 0.053 mmol) and $PtCl_2$ (0.00070 g, 0.0027 mmol) in PhMe (1.1 mL) was stirred under N_2 at 50 °C (oil bath) for 1 h. After cooling to rt, the mixture was filtered through a pad of SiO_2, washed with EtOAc, and concentrated. ^1H NMR spectrum of the crude mixture showed 72:28 ratio of diastereomers. Purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **409c** (0.013 g, 64%) as a colorless oil, mixture of diastereomers. Pure compounds were prepared by separation using Supercritical Fluid Chromtography (Cyano Column 250x10 mm, 8.00 mL/min, 10% methanol) with R_t = 6.48 min (major diastereomer) and 6.86 min (minor diastereomer). Major diastereomer: IR (ATR) 2952, 1718, 1597, 1339, 1159

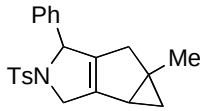
cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.2 Hz, 2 H), 7.18 (d, *J* = 8.0 Hz, 2 H), 5.38 (app. dd, *J* = 5.1, 2.5 Hz, 1 H), 4.15 (dd, *J* = 13.4, 4.3 Hz, 1 H), 4.01 (d, *J* = 13.4, Hz, 1 H), 2.40 (s, 3 H), 2.31 (br s, 2 H), 1.25 (s, 3 H), 1.12-1.11 (m, 1 H), 0.74 (dd, *J* = 7.2, 4.1 Hz, 1 H), 0.18 (t, *J* = 3.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.2, 142.8, 139.9, 136.0, 129.3, 128.3, 127.3, 127.4, 124.1, 52.2, 37.5, 28.5, 24.3, 21.7, 21.5, -0.0; MS (ESI) *m/z* (rel. intensity) 388 ($[M+Na]^+$, 100), 386 ($[M+H]^+$, 2); HRMS (ESI) calc for $C_{22}H_{23}NO_2NaS$ (M+Na) 388.1347, found 388.1309.



409d

4-Methyl-7-phenyl-8-oxatricyclo[4.3.0.0^{2,4}]non-1(6)-ene (409d). A solution of ether **391a** (0.10 g, 0.47 mmol) and $PtCl_2$ (0.0063 g, 0.024 mmol) in PhMe (9.4 mL) was placed in an oil bath (50 ^oC), stirred at this temp for 1 h 20 min, cooled to rt and the solvent was removed in vacuo. ^1H NMR of the crude reaction mixture showed 56:44 ratio of diastereomers. Purification by chromatography on SiO_2 (hexanes/EtOAc, 20:1 to 10:1) afforded **409d** (0.052 g, 52%) as a colorless oil (53:47 mixture of diastereomers): IR (ATR) 2885, 2835, 2491, 1452, 1006 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55-7.49 (m, 1 H), 7.39-7.24 (m, 8 H), 7.19-7.10 (m, 1 H), 5.61 (s, 1 H), 5.43 (d, *J* = 4.1 Hz, 1 H), 4.77-4.69 (m, 2 H), 4.65-4.57 (m, 1 H), 2.32 (app. t, *J* = 18.2 Hz, 2 H), 2.09 (app. t, *J* = 17.1 Hz, 2 H), 1.48-1.46 (m, 2 H), 1.36 (s, 3 H), 1.35 (s, 3 H), 0.90-0.85 (m, 3 H), 0.45-0.35 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 148.1, 143.3, 142.8, 142.1, 141.4, 129.3, 129.2, 128.5, 128.4 (2), 128.3, 127.6 (6), 126.9, 126.4, 126.2, 123.5, 84.1, 84.0, 74.2, 71.7, 71.0, 36.1, 35.9, 33.0, 29.9, 29.3, 28.9, 27.9, 25.5, 24.2, 24.1 (2), 23.8; MS (EI) *m/z*

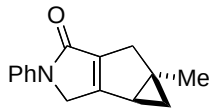
(rel. intensity) 212 (M^+, 9), 197 (4), 165 (7), 141 (25), 105 (100); HRMS (EI) calc for $C_{15}H_{16}O$ 212.1201, found 212.1198.



409e

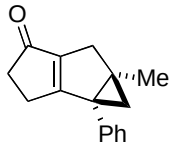
4-Methyl-8-[(4-methylphenyl)sulfonyl]-7-phenyl-8-azatricyclo[4.3.0.0^{2,4}]non-1(6)-ene (409e). A solution of **391b** (0.084 g, 0.23 mmol) and $PtCl_2$ (3.0 mg, 0.011 mmol) in PhMe (4.6 mL) under N_2 was stirred at 50 ^oC for 1 h. The solvent was removed *in vacuo* and purification by chromatography on SiO_2 (hexanes/EtOAc, 4:1) afforded **409e** (0.060 g, 71%) as a mixture of diastereomers, colorless oil. Analytical samples were prepared by separation using SFC (Chiralpak-IC 250x10 mm, 10 mL/min, 30% MeOH) R_t = 5.95, 7.33 min (minor diastereomer), R_t = 6.34, 7.68 min (major diastereomer). Major diastereomer: IR (ATR) 2918, 1597, 1344, 1161 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.1 Hz, 2 H), 7.23 (d, *J* = 6.3 Hz, 3 H), 7.17 (d, *J* = 7.9 Hz, 2 H), 7.08 (dd, *J* = 7.3, 1.5 Hz, 2 H), 5.33 (s, 1 H), 4.24 (d, *J* = 13.4 Hz, 1 H), 4.20-4.16 (m, 1 H), 2.39 (s, 3 H), 2.13 (d, *J* = 17.1 Hz, 1 H), 1.95 (d, *J* = 17.0 Hz, 1 H), 1.40 (dd, *J* = 6.2, 3.7 Hz, 1 H), 1.25 (s, 3 H), 0.79 (dd, *J* = 7.0, 4.3 Hz, 1 H), 0.27 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 142.8, 142.0, 140.5, 136.1, 129.4, 128.4, 127.5, 127.1, 127.0, 52.2, 36.3, 27.4, 24.8, 23.2, 21.6, 21.5; HRMS (ESI) calc for $C_{22}H_{23}NO_2NaS$ (M+Na) 388.1347, found 388.1346. Minor diastereomer: IR (ATR) 2918, 1597, 1342, 1162, 1096 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.1 Hz, 2 H), 7.28-7.26 (m, 3 H), 7.22 (d, *J* = 6.4 Hz, 2 H), 7.18 (d, *J* = 7.18 Hz, 2 H), 5.17 (s, 1 H), 4.24-4.21 (m, 2 H), 2.40 (s, 3 H), 2.19 (d, *J* = 17.0 Hz, 1 H), 1.90 (d, *J* = 17.1

Hz, 1 H), 1.43 (dd, *J* = 6.9, 3.6 Hz, 1 H), 1.25 (s, 3 H), 0.81 (dd, *J* = 6.9, 4.1 Hz, 1 H), 0.19 (s, 1 H); HRMS (ESI) calc for $C_{22}H_{23}NO_2NaS$ (M+Na) 388.1347, found 388.1334.



417a

(*2R*,4R)-4-Methyl-8-phenyl-8-azatricyclo[4.3.0.0^{2,4}]non-1(6)-en-7-one (417a).** A solution of **395a** (0.020 g, 0.91 mmol) and $PtCl_2$ (0.0012 g, 0.0091 mol) in PhMe (1.8 mL) was stirred under microwave heating at 150 ^oC for 20 min. The solvent was removed and the mixture was purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to afford **417a** (0.012 g, 59%) as a light yellow oil that solidified upon standing: IR (ATR) 2922, 2851, 1685, 1599, 1500, 1366, 1308 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.1 Hz, 2 H), 7.35 (t, *J* = 7.7 Hz, 2 H), 7.08 (d, *J* = 7.4 Hz, 1 H), 4.37, 4.33, 0.51 (AB_2X, *J* = 18.5, 2.3 Hz, 3 H); 2.71 (dq, *J* = 17.1, 2.3 Hz, 1 H), 2.55 (dt, *J* = 17.1, 2.5 Hz, 1 H), 1.76-1.72 (m, 1 H), 1.42 (s, 3 H), 1.13 (dd, *J* = 7.8, 4.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 165.8, 140.2, 139.5, 128.9, 123.3, 118.4, 49.8, 35.3, 30.5, 26.3, 25.0, 21.5; MS (EI) *m/z* (rel. intensity) 225 (M^+, 55), 210 (10), 196 (12), 182 (12), 119 (15), 105 (23), 84 (100); HRMS (EI) calc for $C_{15}H_{15}NO$ 225.1153, found 225.1164.



417b

(*2R*,4R)-4-Methyl-2-phenyltricyclo[4.3.0.0^{2,4}]non-1(6)-en-7-one (417b).** A suspension of **401c** (0.013 g, 0.058 mmol) and $PtCl_2$ (0.0015 g, 5.8 μmol) in PhMe (2.2 mL) was heated under

microwave irradiation (120 ^{o}C) for 15 min. The mixture was cooled to rt, filtered through a pad of SiO_2, washed with Et_2O, and concentrated. The product was purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to afford **417b** (0.0079 g, 61%) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.26 (m, 3 H), 7.21-7.18 (m, 2 H), 2.75-2.65 (m, 3 H), 2.51-2.42 (m, 3 H), 1.70 (d, *J* = 4.5 Hz, 1 H), 1.11 (s, 3 H), 0.93 (d, *J* = 4.5 Hz, 1 H).

APPENDIX A

X-RAY DATA FOR 120B

Table 35. Crystal data and structure refinement for **120b**.

Identification code	mac1025	
Empirical formula	$C_{18}H_{19}NO_2S$	
Formula weight	313.4	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/m	
Unit cell dimensions	a = 9.7926(8) Å	α= 90°.
	b = 9.5431(8) Å	β= 119.063(2)°.
	c = 9.9070(8) Å	γ = 90°.
Volume	809.25(12) $Å^3$	
Z	2	
Density (calculated)	1.286 Mg/m^3	
Absorption coefficient	0.206 mm^{-1}	

F(000)	332
Crystal size	0.34 x 0.06 x 0.06 mm^3
Theta range for data collection	2.35 to 26.00°.
Index ranges	-12<=h<=12, -11<=k<=11, -12<=l<=12
Reflections collected	7100
Independent reflections	1691 [R(int) = 0.0546]
Completeness to theta = 26.00°	100.00%
Absorption correction	Sadabs (multi-scan)
Max. and min. transmission	0.9877 and 0.9331
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1691 / 0 / 159
Goodness-of-fit on F^2	1.202
Final R indices [I>2sigma(I)]	R1 = 0.0641, wR2 = 0.1585
R indices (all data)	R1 = 0.0946, wR2 = 0.1708
Largest diff. peak and hole	0.523 and -0.207 $e \cdot Å^{-3}$

Table 36. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2x10^3$) for **120b**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S	4318(1)	2500	4216(1)	53(1)
O	4549(3)	3759(2)	3629(4)	88(1)
N	5493(5)	1870(5)	5999(6)	43(1)
C(1)	-2235(8)	2500	3344(13)	101(2)
C(2)	-582(5)	2500	3598(5)	58(1)

C(3)	187(4)	3727(4)	3696(4)	64(1)
C(4)	1669(4)	3750(3)	3883(4)	55(1)
C(5)	2413(4)	2500	3963(4)	41(1)
C(6)	5786(5)	2500	7279(6)	88(2)
C(7)	4675(4)	2500	7905(5)	55(1)
C(8)	4190(6)	1279(5)	8239(5)	89(1)
C(9)	3269(6)	1271(6)	8934(6)	102(2)
C(10)	2814(6)	2500	9278(7)	95(2)
C(11)	7454(5)	2500	8504(6)	71(1)
C(12)	8547(5)	1346(7)	9220(7)	104(2)
C(13)	8888(6)	2500	8402(8)	95(2)

Table 37. Bond lengths [Å] and angles [°] for **120b**.

S-O#1	1.400(2)	C(3)-C(4)	1.370(4)
S-O	1.400(2)	C(3)-H(3)	0.87(3)
S-N#1	1.682(5)	C(4)-C(5)	1.380(4)
S-N	1.682(5)	C(4)-H(4)	0.93(3)
S-C(5)	1.758(4)	C(5)-C(4)#1	1.380(4)
N-N#1	1.202(10)	C(6)-N#1	1.303(6)
N-C(6)	1.303(6)	C(6)-C(11)	1.488(6)
N-H(1N)	0.88(4)	C(6)-C(7)	1.492(7)
C(1)-C(2)	1.512(7)	C(6)-H(6A)	0.9597
C(1)-H(1B)	0.95(7)	C(7)-C(8)#1	1.358(5)
C(1)-H(1A)	0.89(5)	C(7)-C(8)	1.358(5)
C(2)-C(3)#1	1.370(4)	C(8)-C(9)	1.375(6)
C(2)-C(3)	1.370(4)	C(8)-H(8)	0.94(4)

C(9)-C(10)	1.356(5)	S-N-H(1N)	118(2)
C(9)-H(9)	0.98(5)	C(2)-C(1)-H(1B)	108(4)
C(10)-C(9)#1	1.356(6)	C(2)-C(1)-H(1A)	112(4)
C(10)-H(10)	0.83(7)	H(1B)-C(1)-H(1A)	104(4)
C(11)-C(13)	1.456(7)	C(3)#1-C(2)-C(3)	117.4(4)
C(11)-C(12)	1.457(6)	C(3)#1-C(2)-C(1)	121.3(2)
C(11)-C(12)#1	1.457(6)	C(3)-C(2)-C(1)	121.3(2)
C(12)-C(13)	1.498(7)	C(4)-C(3)-C(2)	122.2(3)
C(12)-H(12A)	1.04(5)	C(4)-C(3)-H(3)	117(2)
C(12)-H(12B)	1.18(6)	C(2)-C(3)-H(3)	120(2)
C(13)-C(12)#1	1.498(7)	C(3)-C(4)-C(5)	119.3(3)
C(13)-H(13)	0.90(5)	C(3)-C(4)-H(4)	121.2(18)
O#1-S-O	118.2(2)	C(5)-C(4)-H(4)	119.4(18)
O#1-S-N#1	125.2(2)	C(4)#1-C(5)-C(4)	119.7(4)
O-S-N#1	87.9(2)	C(4)#1-C(5)-S	120.16(18)
O#1-S-N	87.9(2)	C(4)-C(5)-S	120.16(19)
O-S-N	125.2(2)	N-C(6)-N#1	54.9(5)
N#1-S-N	41.9(3)	N-C(6)-C(11)	115.4(4)
O#1-S-C(5)	108.37(12)	N#1-C(6)-C(11)	115.4(4)
O-S-C(5)	108.37(12)	N-C(6)-C(7)	123.0(4)
N#1-S-C(5)	106.64(19)	N#1-C(6)-C(7)	123.0(4)
N-S-C(5)	106.64(19)	C(11)-C(6)-C(7)	113.2(4)
N#1-N-C(6)	62.5(3)	N-C(6)-H(6A)	99.9
N#1-N-S	69.06(17)	N#1-C(6)-H(6A)	45.0
C(6)-N-S	124.9(4)	C(11)-C(6)-H(6A)	99.5
N#1-N-H(1N)	169(2)	C(7)-C(6)-H(6A)	99.6
C(6)-N-H(1N)	107(2)	C(8)#1-C(7)-C(8)	118.2(5)

C(8)#1-C(7)-C(6)	120.9(3)	C(12)#1-C(11)-C(6)	130.7(3)
C(8)-C(7)-C(6)	120.9(3)	C(11)-C(12)-C(13)	59.0(4)
C(7)-C(8)-C(9)	121.2(4)	C(11)-C(12)-H(12A)	124(3)
C(7)-C(8)-H(8)	120(3)	C(13)-C(12)-H(12A)	124(3)
C(9)-C(8)-H(8)	118(3)	C(11)-C(12)-H(12B)	121(3)
C(10)-C(9)-C(8)	119.8(5)	C(13)-C(12)-H(12B)	118(3)
C(10)-C(9)-H(9)	117(3)	H(12A)-C(12)-H(12B)	106(4)
C(8)-C(9)-H(9)	122(3)	C(11)-C(13)-C(12)	59.1(3)
C(9)-C(10)-C(9)#1	119.7(6)	C(11)-C(13)-C(12)#1	59.1(3)
C(9)-C(10)-H(10)	120.1(4)	C(12)-C(13)-C(12)#1	94.6(6)
C(9)#1-C(10)-H(10)	120.1(4)	C(11)-C(13)-H(13)	117(3)
C(13)-C(11)-C(12)	61.9(3)	C(12)-C(13)-H(13)	129.0(11)
C(13)-C(11)-C(12)#1	61.9(3)	C(12)#1-C(13)-H(13)	129.0(11)
C(12)-C(11)-C(12)#1	98.2(5)	S-O#1	1.400(2)
C(13)-C(11)-C(6)	131.1(5)		
C(12)-C(11)-C(6)	130.7(3)		

Symmetry transformations used to generate equivalent atoms: #1 x,-y+1/2,z

Table 38. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **120b**.

The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S	37(1)	77(1)	50(1)	0	24(1)	0
O	92(2)	46(1)	170(3)	-21(2)	99(2)	-19(1)
N	32(2)	34(2)	62(3)	2(2)	23(2)	5(2)
C(1)	50(3)	134(7)	127(7)	0	50(4)	0
C(2)	41(2)	81(3)	58(3)	0	29(2)	0
C(3)	54(2)	65(2)	74(2)	-5(2)	32(2)	15(2)

C(4)	49(2)	48(2)	71(2)	-9(2)	30(2)	-5(2)
C(5)	35(2)	51(2)	37(2)	0	16(2)	0
C(6)	38(3)	167(6)	53(3)	0	17(2)	0
C(7)	30(2)	83(3)	43(2)	0	10(2)	0
C(8)	92(3)	87(3)	107(3)	-17(3)	64(3)	-15(3)
C(9)	105(4)	117(4)	114(4)	14(3)	77(3)	-37(3)
C(10)	43(3)	177(8)	71(4)	0	33(3)	0
C(11)	32(2)	106(4)	69(3)	0	19(2)	0
C(12)	53(2)	156(5)	97(4)	4(4)	32(2)	15(3)
C(13)	39(3)	163(7)	77(4)	0	24(3)	0

Table 39. Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2x10^3$) for **120b**.

	x	y	z	U(eq)
H(1N)	5450(40)	960(50)	6150(40)	3(9)
H(1B)	-2930(90)	2500	2260(90)	120(30)
H(1A)	-2460(70)	1700(50)	3670(60)	140(20)
H(3)	-210(40)	4520(30)	3740(30)	59(9)
H(4)	2200(30)	4590(30)	4010(30)	53(8)
H(6A)	5688	3459	6952	30
H(8)	4600(50)	420(50)	8130(50)	125(17)
H(9)	3060(60)	420(50)	9350(60)	150(20)
H(10)	2300(80)	2500	9740(70)	110(20)
H(12A)	9180(60)	1180(50)	10400(60)	129(17)
H(12B)	8270(70)	220(70)	8660(60)	180(30)
H(13)	8790(60)	2500	7450(60)	68(15)

APPENDIX B

X-RAY DATA FOR AMIDE 123C

Table 40. Crystal data and structure refinement for **123c**.

Identification code	mw0130s	
Empirical formula	$C_{19}H_{21}NO_2S$	
Formula weight	327.43	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 10.3036(9) Å	α= 90°.
	b = 7.2736(7) Å	β= 91.619(2)°.
	c = 22.952(2) Å	γ = 90°.
Volume	1719.5(3) $Å^3$	
Z	4	
Density (calculated)	1.265 Mg/m^3	
Absorption coefficient	0.197 mm^{-1}	

F(000)	696
Crystal size	0.21 x 0.21 x 0.29 mm^3
Theta range for data collection	1.78 to 32.50°.
Index ranges	-15<=h<=15, -10<=k<=10, -34<=l<=34
Reflections collected	21826
Independent reflections	6080 [R(int) = 0.0371]
Completeness to theta = 32.50°	98.00%
Absorption correction	Sadabs
Refinement method	Full-matrix least-squares on F_2
Data / restraints / parameters	6080 / 0 / 304
Goodness-of-fit on F_2	0.808
Final R indices [I>2sigma(I)]	R1 = 0.0638, wR2 = 0.1680
R indices (all data)	R1 = 0.0816, wR2 = 0.1855
Largest diff. peak and hole	0.808 and -0.377 $e \cdot Å^{-3}$

Table 41. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2x10^3$) for **123c**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S	7936(1)	10150(1)	232(1)	22(1)
N	8856(2)	9619(2)	786(1)	25(1)
O(1)	8743(1)	11119(2)	-166(1)	28(1)
C(1)	6122(2)	7774(2)	-225(1)	27(1)
O(2)	6803(1)	11047(2)	444(1)	30(1)
C(2)	5740(2)	6187(3)	-520(1)	30(1)

C(3)	6652(2)	4902(2)	-692(1)	29(1)
C(4)	7958(2)	5231(2)	-559(1)	28(1)
C(5)	8357(2)	6811(2)	-272(1)	26(1)
C(6)	7431(2)	8089(2)	-107(1)	22(1)
C(7)	6237(3)	3201(3)	-1022(1)	40(1)
C(8)	8287(2)	8651(2)	1289(1)	26(1)
C(9)	8241(3)	9950(3)	1800(1)	42(1)
C(10)	9004(2)	6900(3)	1408(1)	30(1)
C(11)	8645(3)	4985(3)	1231(1)	44(1)
C(12)	8704(2)	5472(3)	1868(1)	36(1)
C(13)	9992(2)	6443(4)	1878(1)	43(1)
C(14)	6449(2)	4730(3)	2168(1)	36(1)
C(15)	5477(3)	4787(3)	2570(1)	41(1)
C(16)	5714(2)	5553(3)	3117(1)	40(1)
C(17)	6924(2)	6247(3)	3253(1)	40(1)
C(18)	7897(2)	6202(3)	2853(1)	37(1)
C(19)	7676(2)	5462(3)	2296(1)	31(1)

Table 42. Bond lengths [Å] and angles [°] for **123c**.

S-O(2)	1.4345(13)	C(1)-C(2)	1.390(3)
S-O(1)	1.4378(13)	C(1)-H(1)	0.96(2)
S-N	1.6098(15)	C(2)-C(3)	1.390(3)
S-C(6)	1.7618(17)	C(2)-H(2)	0.99(3)
N-C(8)	1.488(2)	C(3)-C(4)	1.392(3)
N-H(1N)	0.82(3)	C(3)-C(7)	1.507(3)
C(1)-C(6)	1.386(2)	C(4)-C(5)	1.382(3)

C(4)-H(4)	0.94(3)	C(14)-H(14)	0.95(3)
C(5)-C(6)	1.392(2)	C(15)-C(16)	1.389(3)
C(5)-H(5)	0.93(3)	C(15)-H(15)	0.94(4)
C(7)-H(7A)	0.90(7)	C(16)-C(17)	1.373(4)
C(7)-H(7B)	1.03(6)	C(16)-H(16)	1.02(3)
C(7)-H(7C)	0.94(6)	C(17)-C(18)	1.378(3)
C(7)-H(7D)	0.96(6)	C(17)-H(17)	0.97(3)
C(7)-H(7E)	1.17(5)	C(18)-C(19)	1.399(3)
C(7)-H(7F)	1.05(7)	C(18)-H(18)	0.96(3)
C(8)-C(10)	1.494(3)	O(2)-S-O(1)	118.91(8)
C(8)-C(9)	1.508(3)	O(2)-S-N	107.98(8)
C(8)-H(8)	1.00(2)	O(1)-S-N	106.36(8)
C(9)-H(9A)	0.99(4)	O(2)-S-C(6)	107.66(8)
C(9)-H(9B)	1.03(3)	O(1)-S-C(6)	107.73(8)
C(9)-H(9C)	0.97(3)	N-S-C(6)	107.76(8)
C(10)-C(11)	1.494(3)	C(8)-N-S	119.32(12)
C(10)-C(13)	1.500(3)	C(8)-N-H(1N)	122(2)
C(10)-C(12)	1.518(3)	S-N-H(1N)	111(2)
C(11)-C(12)	1.503(3)	C(6)-C(1)-C(2)	119.53(16)
C(11)-H(11A)	0.96(3)	C(6)-C(1)-H(1)	122.6(15)
C(11)-H(11B)	0.95(3)	C(2)-C(1)-H(1)	117.8(15)
C(12)-C(19)	1.466(3)	C(1)-C(2)-C(3)	120.78(17)
C(12)-C(13)	1.503(3)	C(1)-C(2)-H(2)	118.6(16)
C(13)-H(13B)	1.00(3)	C(3)-C(2)-H(2)	120.6(16)
C(13)-H(13A)	1.00(3)	C(4)-C(3)-C(2)	118.69(17)
C(14)-C(15)	1.381(3)	C(4)-C(3)-C(7)	120.65(19)
C(14)-C(19)	1.394(3)	C(2)-C(3)-C(7)	120.66(19)

C(5)-C(4)-C(3)	121.30(17)	H(7C)-C(7)-H(7F)	52(4)
C(5)-C(4)-H(4)	118.8(16)	H(7D)-C(7)-H(7F)	117(5)
C(3)-C(4)-H(4)	119.9(16)	H(7E)-C(7)-H(7F)	102(4)
C(4)-C(5)-C(6)	119.21(16)	N-C(8)-C(10)	109.97(14)
C(4)-C(5)-H(5)	122.0(16)	N-C(8)-C(9)	109.24(16)
C(6)-C(5)-H(5)	118.7(16)	C(10)-C(8)-C(9)	114.74(17)
C(1)-C(6)-C(5)	120.48(16)	N-C(8)-H(8)	109.6(14)
C(1)-C(6)-S	120.04(13)	C(10)-C(8)-H(8)	106.4(14)
C(5)-C(6)-S	119.45(13)	C(9)-C(8)-H(8)	106.7(14)
C(3)-C(7)-H(7A)	111(4)	C(8)-C(9)-H(9A)	107.3(19)
C(3)-C(7)-H(7B)	108(3)	C(8)-C(9)-H(9B)	112.4(17)
H(7A)-C(7)-H(7B)	111(5)	H(9A)-C(9)-H(9B)	106(3)
C(3)-C(7)-H(7C)	113(3)	C(8)-C(9)-H(9C)	110.4(19)
H(7A)-C(7)-H(7C)	107(5)	H(9A)-C(9)-H(9C)	111(3)
H(7B)-C(7)-H(7C)	106(5)	H(9B)-C(9)-H(9C)	110(2)
C(3)-C(7)-H(7D)	112(3)	C(11)-C(10)-C(8)	128.91(19)
H(7A)-C(7)-H(7D)	62(4)	C(11)-C(10)-C(13)	98.43(19)
H(7B)-C(7)-H(7D)	52(4)	C(8)-C(10)-C(13)	129.98(18)
H(7C)-C(7)-H(7D)	134(5)	C(11)-C(10)-C(12)	59.84(14)
C(3)-C(7)-H(7E)	107(2)	C(8)-C(10)-C(12)	126.95(16)
H(7A)-C(7)-H(7E)	141(5)	C(13)-C(10)-C(12)	59.72(15)
H(7B)-C(7)-H(7E)	61(4)	C(10)-C(11)-C(12)	60.89(14)
H(7C)-C(7)-H(7E)	50(4)	C(10)-C(11)-H(11A)	115.5(16)
H(7D)-C(7)-H(7E)	109(4)	C(12)-C(11)-H(11A)	117.8(17)
C(3)-C(7)-H(7F)	110(3)	C(10)-C(11)-H(11B)	119.1(19)
H(7A)-C(7)-H(7F)	60(5)	C(12)-C(11)-H(11B)	117.5(18)
H(7B)-C(7)-H(7F)	141(5)	H(11A)-C(11)-H(11B)	115(2)

C(19)-C(12)-C(11)	129.9(2)	C(14)-C(15)-H(15)	123(2)
C(19)-C(12)-C(13)	130.2(2)	C(16)-C(15)-H(15)	117(2)
C(11)-C(12)-C(13)	97.91(19)	C(17)-C(16)-C(15)	119.2(2)
C(19)-C(12)-C(10)	129.37(18)	C(17)-C(16)-H(16)	122.6(15)
C(11)-C(12)-C(10)	59.27(13)	C(15)-C(16)-H(16)	118.2(16)
C(13)-C(12)-C(10)	59.53(14)	C(16)-C(17)-C(18)	120.9(2)
C(10)-C(13)-C(12)	60.74(14)	C(16)-C(17)-H(17)	118.7(17)
C(10)-C(13)-H(13B)	117.3(18)	C(18)-C(17)-H(17)	120.4(18)
C(12)-C(13)-H(13B)	116.7(19)	C(17)-C(18)-C(19)	120.9(2)
C(10)-C(13)-H(13A)	116.7(16)	C(17)-C(18)-H(18)	119.4(16)
C(12)-C(13)-H(13A)	117.8(15)	C(19)-C(18)-H(18)	119.5(16)
H(13B)-C(13)-H(13A)	116(2)	C(14)-C(19)-C(18)	117.54(19)
C(15)-C(14)-C(19)	121.2(2)	C(14)-C(19)-C(12)	121.90(19)
C(15)-C(14)-H(14)	118.6(16)	C(18)-C(19)-C(12)	120.6(2)
C(19)-C(14)-H(14)	120.1(16)		
C(14)-C(15)-C(16)	120.2(2)		

Symmetry transformations used to generate equivalent atoms:

Table 43. Anisotropic displacement parameters ($Å^2x10^3$) for **123c**.

The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S	20(1)	19(1)	27(1)	1(1)	0(1)	3(1)
N	21(1)	27(1)	26(1)	2(1)	-1(1)	1(1)
O(1)	26(1)	23(1)	34(1)	8(1)	1(1)	1(1)
C(1)	22(1)	26(1)	33(1)	-1(1)	1(1)	2(1)
O(2)	24(1)	29(1)	39(1)	-7(1)	0(1)	7(1)
C(2)	26(1)	29(1)	35(1)	1(1)	-2(1)	-4(1)

C(3)	38(1)	22(1)	27(1)	3(1)	-3(1)	0(1)
C(4)	33(1)	22(1)	31(1)	-1(1)	1(1)	5(1)
C(5)	24(1)	25(1)	30(1)	-1(1)	0(1)	5(1)
C(6)	23(1)	21(1)	23(1)	2(1)	1(1)	3(1)
C(7)	52(1)	26(1)	40(1)	-5(1)	-9(1)	-3(1)
C(8)	27(1)	26(1)	25(1)	1(1)	3(1)	0(1)
C(9)	58(1)	33(1)	34(1)	-7(1)	11(1)	0(1)
C(10)	36(1)	27(1)	26(1)	1(1)	5(1)	2(1)
C(11)	69(2)	28(1)	36(1)	-5(1)	20(1)	1(1)
C(12)	47(1)	28(1)	32(1)	5(1)	9(1)	5(1)
C(13)	36(1)	53(1)	40(1)	15(1)	3(1)	11(1)
C(14)	49(1)	27(1)	33(1)	-3(1)	2(1)	-2(1)
C(15)	46(1)	31(1)	47(1)	2(1)	6(1)	-3(1)
C(16)	49(1)	31(1)	39(1)	7(1)	13(1)	7(1)
C(17)	57(1)	37(1)	26(1)	3(1)	5(1)	8(1)
C(18)	44(1)	38(1)	29(1)	0(1)	0(1)	2(1)
C(19)	43(1)	23(1)	26(1)	4(1)	5(1)	5(1)

Table 44. Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2x10^3$) for **123c**.

	x	y	z	U(eq)
H(1N)	9600(30)	9420(40)	686(13)	50(8)
H(1)	5460(20)	8640(30)	-125(10)	34(6)
H(2)	4800(30)	5970(40)	-592(11)	41(7)
H(4)	8590(30)	4370(40)	-670(11)	36(6)
H(5)	9230(20)	7080(40)	-202(11)	35(6)

H(7A)	5380(70)	2970(100)	-980(30)	53(17)
H(7B)	6460(60)	3370(80)	-1450(20)	43(14)
H(7C)	6680(60)	2140(80)	-900(30)	36(13)
H(7D)	5660(60)	3490(80)	-1350(30)	37(13)
H(7E)	7180(50)	2530(70)	-1200(20)	28(11)
H(7F)	5930(70)	2200(90)	-730(30)	53(17)
H(8)	7360(20)	8300(30)	1190(10)	32(6)
H(9A)	9150(40)	10270(50)	1911(15)	60(9)
H(9B)	7850(30)	9350(40)	2160(13)	47(7)
H(9C)	7750(30)	11050(50)	1695(14)	63(9)
H(11A)	7810(30)	4850(40)	1046(13)	40(7)
H(11B)	9300(30)	4190(40)	1091(13)	52(8)
H(13B)	10760(30)	5700(50)	1764(13)	59(9)
H(13A)	10150(30)	7400(40)	2187(12)	43(7)
H(14)	6260(30)	4200(40)	1795(12)	42(7)
H(15)	4650(30)	4270(50)	2500(15)	69(10)
H(16)	4970(30)	5570(40)	3404(12)	41(7)
H(17)	7080(30)	6810(40)	3634(13)	52(8)
H(18)	8710(30)	6770(40)	2947(12)	42(7)

APPENDIX C

X-RAY DATA FOR 125C

Table 45. Crystal data and structure refinement for **125c**.

Identification code	mac508s	
Empirical formula	$C_{12}H_{12}O_2$	
Formula weight	188.22	
Temperature	295(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 5.922(5) Å	α= 104.425(17)°.
	b = 7.858(7) Å	β= 91.455(17)°.
	c = 11.339(10) Å	γ = 103.568(16)°.
Volume	494.8(7) $Å^3$	
Z	2	
Density (calculated)	1.263 Mg/m^3	
Absorption coefficient	0.085 mm^{-1}	

F(000)	200
Crystal size	0.38 x 0.24 x 0.10 mm^3
Theta range for data collection	1.86 to 27.49°.
Index ranges	-7<=h<=7, -10<=k<=10, -14<=l<=14
Reflections collected	3880
Independent reflections	2045 [R(int) = 0.0178]
Completeness to theta = 27.49∞	90.00%
Absorption correction	None
Max. and min. transmission	0.9915 and 0.9684
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2045 / 0 / 164
Goodness-of-fit on F^2	1.178
Final R indices [I>2sigma(I)]	R1 = 0.0482, wR2 = 0.1337
R indices (all data)	R1 = 0.0772, wR2 = 0.1669
Extinction coefficient	0.067(16)
Largest diff. peak and hole	0.188 and -0.179 e· $Å^{-3}$

Table 46. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2x10^3$) for **125c**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	4442(2)	6299(2)	6976(1)	56(1)
C(1)	7369(3)	6875(2)	5710(2)	48(1)
O(2)	7506(2)	5126(2)	7102(1)	68(1)
C(2)	6644(4)	8363(3)	5314(2)	57(1)

C(3)	8917(3)	8837(2)	6046(2)	47(1)
C(4)	9833(4)	7273(2)	5390(2)	56(1)
C(5)	6494(3)	5997(2)	6648(1)	46(1)
C(6)	3402(4)	5448(3)	7890(2)	69(1)
C(7)	9632(3)	10056(2)	7271(2)	46(1)
C(8)	8374(4)	11317(2)	7782(2)	57(1)
C(9)	9026(4)	12446(3)	8945(2)	67(1)
C(10)	10900(4)	12351(3)	9622(2)	70(1)
C(11)	12191(4)	11137(3)	9122(2)	69(1)
C(12)	11568(3)	10004(3)	7955(2)	57(1)

Table 47. Bond lengths [Å] and angles [°] for **125c**.

O(1)-C(5)	1.337(2)	C(6)-H(6A)	0.96
O(1)-C(6)	1.444(2)	C(6)-H(6B)	0.96
C(1)-C(5)	1.450(2)	C(6)-H(6C)	0.96
C(1)-C(4)	1.492(3)	C(7)-C(12)	1.382(3)
C(1)-C(2)	1.497(2)	C(7)-C(8)	1.398(2)
C(1)-C(3)	1.545(3)	C(8)-C(9)	1.380(3)
O(2)-C(5)	1.2018(19)	C(8)-H(8)	0.96(2)
C(2)-C(3)	1.481(3)	C(9)-C(10)	1.361(3)
C(2)-H(2B)	0.950(17)	C(9)-H(9)	0.97(2)
C(2)-H(2A)	0.99(2)	C(10)-C(11)	1.382(3)
C(3)-C(7)	1.464(3)	C(10)-H(10)	0.95(3)
C(3)-C(4)	1.495(3)	C(11)-C(12)	1.383(3)
C(4)-H(4A)	0.986(19)	C(11)-H(11)	0.96(2)
C(4)-H(4B)	0.961(19)	C(12)-H(12)	0.947(19)

C(5)-O(1)-C(6)	116.35(14)
C(5)-C(1)-C(4)	126.03(15)
C(5)-C(1)-C(2)	129.20(16)
C(4)-C(1)-C(2)	98.07(15)
C(5)-C(1)-C(3)	121.22(15)
C(4)-C(1)-C(3)	58.95(11)
C(2)-C(1)-C(3)	58.23(13)
C(3)-C(2)-C(1)	62.52(12)
C(3)-C(2)-H(2B)	115.7(11)
C(1)-C(2)-H(2B)	116.3(10)
C(3)-C(2)-H(2A)	121.9(12)
C(1)-C(2)-H(2A)	118.9(11)
H(2B)-C(2)-H(2A)	112.8(15)
C(7)-C(3)-C(2)	128.77(16)
C(7)-C(3)-C(4)	129.35(16)
C(2)-C(3)-C(4)	98.65(17)
C(7)-C(3)-C(1)	127.37(13)
C(2)-C(3)-C(1)	59.25(12)
C(4)-C(3)-C(1)	58.76(13)
C(1)-C(4)-C(3)	62.29(12)
C(1)-C(4)-H(4A)	116.0(11)
C(3)-C(4)-H(4A)	118.4(10)
C(1)-C(4)-H(4B)	116.5(12)
C(3)-C(4)-H(4B)	118.8(11)
H(4A)-C(4)-H(4B)	114.7(16)
O(2)-C(5)-O(1)	123.44(16)
O(2)-C(5)-C(1)	124.36(17)
O(1)-C(5)-C(1)	112.18(14)
O(1)-C(6)-H(6A)	109.5
O(1)-C(6)-H(6B)	109.5
H(6A)-C(6)-H(6B)	109.5
O(1)-C(6)-H(6C)	109.5
H(6A)-C(6)-H(6C)	109.5
H(6B)-C(6)-H(6C)	109.5
C(12)-C(7)-C(8)	117.93(19)
C(12)-C(7)-C(3)	121.32(16)
C(8)-C(7)-C(3)	120.75(17)
C(9)-C(8)-C(7)	120.8(2)
C(9)-C(8)-H(8)	117.8(12)
C(7)-C(8)-H(8)	121.3(12)
C(10)-C(9)-C(8)	120.8(2)
C(10)-C(9)-H(9)	121.9(14)
C(8)-C(9)-H(9)	117.4(14)
C(9)-C(10)-C(11)	119.3(2)
C(9)-C(10)-H(10)	121.2(15)
C(11)-C(10)-H(10)	119.4(15)
C(10)-C(11)-C(12)	120.7(2)
C(10)-C(11)-H(11)	123.9(13)
C(12)-C(11)-H(11)	115.4(13)
C(7)-C(12)-C(11)	120.61(19)
C(7)-C(12)-H(12)	118.8(13)
C(11)-C(12)-H(12)	120.6(13)

Symmetry transformations used to generate equivalent atoms:

Table 48. Anisotropic displacement parameters ($Å^2x10^3$) for **125c**.

The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	50(1)	64(1)	63(1)	27(1)	14(1)	20(1)
C(1)	52(1)	44(1)	47(1)	12(1)	6(1)	12(1)
O(2)	68(1)	74(1)	81(1)	40(1)	16(1)	33(1)
C(2)	64(1)	58(1)	54(1)	24(1)	6(1)	18(1)
C(3)	49(1)	43(1)	50(1)	16(1)	10(1)	10(1)
C(4)	60(1)	54(1)	53(1)	13(1)	16(1)	15(1)
C(5)	48(1)	41(1)	48(1)	11(1)	4(1)	13(1)
C(6)	63(1)	83(1)	68(1)	33(1)	22(1)	16(1)
C(7)	49(1)	40(1)	52(1)	18(1)	13(1)	9(1)
C(8)	60(1)	49(1)	65(1)	16(1)	12(1)	17(1)
C(9)	77(2)	53(1)	69(2)	9(1)	23(1)	19(1)
C(10)	89(2)	55(1)	56(1)	9(1)	13(1)	4(1)
C(11)	73(2)	63(1)	67(2)	17(1)	-5(1)	10(1)
C(12)	59(1)	50(1)	62(1)	13(1)	6(1)	17(1)

Table 49. Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2x10^3$) for **125c**.

	x	y	z	U(eq)
H(2B)	5430(30)	8800(20)	5725(16)	56(5)
H(2A)	6540(30)	8310(30)	4433(19)	69(6)
H(4A)	10050(30)	7110(20)	4514(18)	64(5)
H(4B)	10920(30)	6870(20)	5831(17)	64(5)
H(6A)	1941	5750	8056	104

H(6B)	4431	5872	8627	104
H(6C)	3141	4156	7595	104
H(8)	7070(40)	11470(30)	7324(19)	79(6)
H(9)	8110(40)	13320(30)	9250(20)	89(7)
H(10)	11400(40)	13160(30)	10410(20)	91(7)
H(11)	13600(40)	11050(30)	9520(20)	83(7)
H(12)	12480(40)	9200(30)	7604(17)	72(6)

APPENDIX D

X-RAY DATA FOR 126

Table 50. Crystal data and structure refinement for **126**.

Identification code	mac731	
Empirical formula	$C_{12}H_{13}NO$	
Formula weight	187.23	
Temperature	203(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 12.225(6) Å	α= 90°.
	b = 18.951(10) Å	β= 90.085(12)°.
	c = 9.132(5) Å	γ = 90°.
Volume	2115.7(18) $Å^3$	
Z	8	
Density (calculated)	1.176 Mg/m^3	
Absorption coefficient	0.075 mm^{-1}	
F(000)	800	
Crystal size	0.15 x 0.04 x 0.04 mm^3	

Theta range for data collection	1.67 to 24.00∞.
Index ranges	-13<=h<=13, -21<=k<=21, -10<=l<=10
Reflections collected	15084
Independent reflections	3323 [R(int) = 0.1512]
Completeness to theta = 24.00°	100.0 %
Absorption correction	None
Max. and min. transmission	0.9970 and 0.9888
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3323 / 0 / 244
Goodness-of-fit on F^2	3.807
Final R indices [I>2sigma(I)]	R1 = 0.3513, wR2 = 0.6525
R indices (all data)	R1 = 0.4213, wR2 = 0.6647
Extinction coefficient	0.10(3)
Largest diff. peak and hole	1.104 and -0.748 e·Å^{-3}

Table 51. Atomic coordinates (x10^4) and equivalent isotropic displacement parameters (Å^{2}x10^3) for **126**.

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	2073(12)	7446(8)	2324(17)	53(5)
O(1')	-2476(16)	6953(9)	-2171(16)	106(7)
N(1')	-2900(13)	7559(10)	-4312(17)	75(6)
C(1')	-4430(20)	7824(14)	-2620(30)	87(8)
O(1)	2541(11)	8070(7)	240(16)	67(4)
C(1)	1260(20)	6314(14)	2230(20)	87(8)
C(2')	-5114(16)	8384(16)	-2050(30)	76(8)
C(2)	491(15)	5816(13)	1670(30)	67(7)

C(3')	-5080(30)	9091(19)	-2500(30)	112(13)
C(3)	-220(30)	5974(13)	570(30)	110(12)
C(4')	-4570(30)	9158(13)	-3530(40)	106(10)
C(4)	-40(20)	6650(14)	120(20)	86(9)
C(5')	-3680(18)	8683(10)	-4190(30)	70(7)
C(5)	516(16)	7191(12)	600(20)	57(6)
C(6')	-3760(20)	8044(12)	-3640(20)	76(8)
C(6)	1256(19)	7014(11)	1680(20)	69(7)
C(7')	-2391(14)	7048(10)	-3560(20)	47(5)
C(7)	2688(19)	7962(11)	1680(20)	68(7)
C(8')	-1640(30)	6596(12)	-4400(30)	134(13)
C(8)	3660(50)	8363(16)	2440(30)	220(30)
C(9')	-1680(20)	6360(17)	-6010(20)	118(12)
C(9)	3350(20)	8540(15)	4080(30)	111(10)
C(10')	-1890(30)	5880(20)	-4770(40)	160(17)
C(10)	3162(17)	9159(15)	2950(30)	79(8)
C(11')	-870(20)	6048(13)	-3830(30)	97(9)
C(11)	4130(30)	8983(16)	1890(30)	171(19)
C(12')	-2810(30)	5463(17)	-4190(40)	150(13)
C(12)	2200(20)	9423(15)	2830(30)	114(10)

Table 52. Bond lengths [Å] and angles [°] for **126**.

N(1)-C(7)	1.37(2)	N(1')-C(7')	1.34(2)
N(1)-C(6)	1.42(2)	N(1')-C(6')	1.53(3)
N(1)-H(1A)	0.8700	N(1')-H(1'A)	0.8700
O(1')-C(7')	1.29(2)	C(1')-C(6')	1.31(3)

C(1')-C(2')	1.45(3)	C(8)-C(11)	1.40(4)
C(1')-H(1'B)	0.9400	C(8)-C(9)	1.58(4)
O(1)-C(7)	1.35(2)	C(8)-C(10)	1.69(4)
C(1)-C(6)	1.42(3)	C(9')-C(10')	1.48(5)
C(1)-C(2)	1.42(3)	C(9')-H(9'A)	0.9800
C(1)-H(1B)	0.9400	C(9')-H(9'B)	0.9800
C(2')-C(3')	1.40(3)	C(9)-C(10)	1.58(4)
C(2')-H(2'A)	0.9400	C(9)-H(9A)	0.9800
C(2)-C(3)	1.36(3)	C(9)-H(9B)	0.9800
C(2)-H(2)	0.9400	C(10')-C(12')	1.47(4)
C(3')-C(4')	1.14(3)	C(10')-C(11')	1.55(4)
C(3')-H(3'A)	0.9400	C(10)-C(12)	1.28(3)
C(3)-C(4)	1.36(3)	C(10)-C(11)	1.56(4)
C(3)-H(3A)	0.9400	C(11')-H(11A)	0.9800
C(4')-C(5')	1.54(3)	C(11')-H(11B)	0.9800
C(4')-H(4'A)	0.9400	C(11)-H(11C)	0.9800
C(4)-C(5)	1.30(3)	C(11)-H(11D)	0.9800
C(4)-H(4A)	0.9400	C(12')-H(12A)	0.9700
C(5')-C(6')	1.31(3)	C(12')-H(12B)	0.9700
C(5')-H(5'A)	0.9400	C(12')-H(12C)	0.9700
C(5)-C(6)	1.38(3)	C(12)-H(12D)	0.9700
C(5)-H(5A)	0.9400	C(12)-H(12E)	0.9700
C(7')-C(8')	1.47(3)	C(12)-H(12F)	0.9700
C(7)-C(8)	1.57(5)	C(7)-N(1)-C(6)	128.6(18)
C(8')-C(10')	1.44(4)	C(7)-N(1)-H(1A)	115.7
C(8')-C(11')	1.49(3)	C(6)-N(1)-H(1A)	115.7
C(8')-C(9')	1.54(3)	C(7')-N(1')-C(6')	123.6(16)

C(7')-N(1')-H(1'A)	118.2	C(6')-C(5')-H(5'A)	125.2
C(6')-N(1')-H(1'A)	118.2	C(4')-C(5')-H(5'A)	125.2
C(6')-C(1')-C(2')	112(2)	C(4)-C(5)-C(6)	113(2)
C(6')-C(1')-H(1'B)	123.8	C(4)-C(5)-H(5A)	123.7
C(2')-C(1')-H(1'B)	123.8	C(6)-C(5)-H(5A)	123.7
C(6)-C(1)-C(2)	119.4(19)	C(1')-C(6')-C(5')	128(3)
C(6)-C(1)-H(1B)	120.3	C(1')-C(6')-N(1')	122(2)
C(2)-C(1)-H(1B)	120.3	C(5')-C(6')-N(1')	111(2)
C(3')-C(2')-C(1')	126(2)	C(5)-C(6)-N(1)	128(2)
C(3')-C(2')-H(2'A)	117.2	C(5)-C(6)-C(1)	118.8(19)
C(1')-C(2')-H(2'A)	117.1	N(1)-C(6)-C(1)	113(2)
C(3)-C(2)-C(1)	123(2)	O(1')-C(7')-N(1')	124.5(17)
C(3)-C(2)-H(2)	118.7	O(1')-C(7')-C(8')	119(2)
C(1)-C(2)-H(2)	118.7	N(1')-C(7')-C(8')	116.7(19)
C(4')-C(3')-C(2')	111(3)	O(1)-C(7)-N(1)	117(2)
C(4')-C(3')-H(3'A)	124.4	O(1)-C(7)-C(8)	117(2)
C(2')-C(3')-H(3'A)	124.4	N(1)-C(7)-C(8)	125(2)
C(2)-C(3)-C(4)	109(3)	C(10')-C(8')-C(7')	123(3)
C(2)-C(3)-H(3A)	125.6	C(10')-C(8')-C(11')	64(2)
C(4)-C(3)-H(3A)	125.6	C(7')-C(8')-C(11')	128(2)
C(3')-C(4')-C(5')	130(3)	C(10')-C(8')-C(9')	60(2)
C(3')-C(4')-H(4'A)	114.8	C(7')-C(8')-C(9')	130(3)
C(5')-C(4')-H(4'A)	114.8	C(11')-C(8')-C(9')	98.6(19)
C(5)-C(4)-C(3)	136(2)	C(11)-C(8)-C(7)	124(3)
C(5)-C(4)-H(4A)	111.8	C(11)-C(8)-C(9)	105(2)
C(3)-C(4)-H(4A)	111.8	C(7)-C(8)-C(9)	110(4)
C(6')-C(5')-C(4')	110(2)	C(11)-C(8)-C(10)	60(2)

C(7)-C(8)-C(10)	106(4)
C(9)-C(8)-C(10)	57.7(18)
C(10')-C(9')-C(8')	56.7(16)
C(10')-C(9')-H(9'A)	118.1
C(8')-C(9')-H(9'A)	118.1
C(10')-C(9')-H(9'B)	118.1
C(8')-C(9')-H(9'B)	118.1
H(9'A)-C(9')-H(9'B)	115.3
C(8)-C(9)-C(10)	64.6(19)
C(8)-C(9)-H(9A)	117.3
C(10)-C(9)-H(9A)	117.3
C(8)-C(9)-H(9B)	117.3
C(10)-C(9)-H(9B)	117.3
H(9A)-C(9)-H(9B)	114.3
C(8')-C(10')-C(12')	126(3)
C(8')-C(10')-C(9')	64(3)
C(12')-C(10')-C(9')	137(4)
C(8')-C(10')-C(11')	59.9(19)
C(12')-C(10')-C(11')	122(4)
C(9')-C(10')-C(11')	99(3)
C(12)-C(10)-C(11)	137(3)
C(12)-C(10)-C(9)	118(2)
C(11)-C(10)-C(9)	98(2)
C(12)-C(10)-C(8)	131(3)
C(11)-C(10)-C(8)	51(2)
C(9)-C(10)-C(8)	57.7(17)
C(8')-C(11')-C(10')	56(2)
C(8')-C(11')-H(11A)	118.1
C(10')-C(11')-H(11A)	118.1
C(8')-C(11')-H(11B)	118.1
C(10')-C(11')-H(11B)	118.1
H(11A)-C(11')-H(11B)	115.3
C(8)-C(11)-C(10)	69(3)
C(8)-C(11)-H(11C)	116.7
C(10)-C(11)-H(11C)	116.7
C(8)-C(11)-H(11D)	116.7
C(10)-C(11)-H(11D)	116.7
H(11C)-C(11)-H(11D)	113.7
C(10')-C(12')-H(12A)	109.5
C(10')-C(12')-H(12B)	109.5
H(12A)-C(12')-H(12B)	109.5
C(10')-C(12')-H(12C)	109.5
H(12A)-C(12')-H(12C)	109.5
H(12B)-C(12')-H(12C)	109.5
C(10)-C(12)-H(12D)	109.5
C(10)-C(12)-H(12E)	109.5
H(12D)-C(12)-H(12E)	109.5
C(10)-C(12)-H(12F)	109.5
H(12D)-C(12)-H(12F)	109.5
H(12E)-C(12)-H(12F)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 53. Anisotropic displacement parameters ($Å^2x10^3$) for **126**.

The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	58(11)	59(11)	40(10)	10(8)	2(8)	-15(9)
O(1')	186(18)	109(14)	24(9)	16(8)	-10(9)	-30(12)
N(1')	63(12)	128(17)	35(10)	19(10)	4(8)	61(12)
C(1')	110(20)	100(20)	59(17)	1(15)	-42(15)	-39(18)
O(1)	73(10)	70(10)	59(10)	10(8)	-6(7)	1(7)
C(1)	91(19)	120(20)	46(14)	-7(14)	-52(13)	14(17)
C(2')	36(12)	120(20)	70(17)	-54(17)	32(11)	10(14)
C(2)	33(13)	100(20)	63(15)	33(14)	-3(11)	-30(12)
C(3')	150(30)	140(30)	53(18)	17(18)	55(18)	70(20)
C(3)	200(30)	44(16)	90(20)	-14(15)	100(20)	3(18)
C(4')	140(30)	67(18)	110(30)	-9(17)	-20(20)	65(18)
C(4)	130(20)	68(17)	56(16)	-52(14)	-33(14)	19(16)
C(5')	82(17)	35(13)	93(18)	10(12)	-13(13)	6(12)
C(5)	53(13)	80(17)	38(12)	-1(11)	-5(10)	56(13)
C(6')	140(20)	58(16)	35(13)	7(12)	-7(14)	-19(15)
C(6)	102(19)	36(13)	68(16)	-1(12)	15(14)	-40(13)
C(7')	39(12)	49(13)	55(14)	-12(11)	16(10)	6(10)
C(7)	94(18)	58(15)	52(15)	-6(13)	24(13)	-1(13)
C(8')	290(40)	43(15)	70(18)	-10(14)	30(20)	90(20)
C(8)	550(80)	60(20)	60(20)	-30(16)	-40(30)	-60(40)
C(9')	80(18)	260(40)	15(12)	-11(17)	2(12)	20(20)
C(9)	100(20)	140(30)	90(20)	-60(20)	4(16)	-25(18)
C(10')	110(30)	250(40)	120(30)	-140(30)	60(20)	-30(30)

C(10)	31(13)	140(20)	66(17)	0(17)	-4(11)	9(14)
C(11')	120(20)	100(20)	72(18)	-4(15)	-8(16)	66(18)
C(11)	300(50)	140(30)	80(20)	0(20)	0(30)	-190(30)

Table 54. Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2x10^3$) for **126**.

	x	y	z	U(eq)
H(1A)	2199	7372	3249	63
H(1'A)	-2730	7618	-5229	90
H(1'B)	-4463	7354	-2286	104
H(1B)	1765	6180	2956	104
H(2'A)	-5623	8262	-1324	91
H(2)	475	5361	2083	81
H(3'A)	-5437	9462	-2004	135
H(3A)	-750	5667	187	132
H(4'A)	-4726	9569	-4070	127
H(4A)	-401	6751	-759	103
H(5'A)	-3154	8829	-4876	84
H(5A)	421	7652	240	68
H(9'A)	-2305	6510	-6610	142
H(9'B)	-987	6312	-6541	142
H(9A)	3946	8593	4785	134
H(9B)	2692	8311	4481	134
H(11A)	-889	5936	-2782	116
H(11B)	-147	6009	-4290	116
H(11C)	4008	9081	846	206
H(11D)	4865	9101	2231	206

H(12A)	-2573	5192	-3349	225
H(12B)	-3078	5144	-4944	225
H(12C)	-3398	5779	-3901	225
H(12D)	2198	9774	2060	170
H(12E)	2000	9643	3752	170

APPENDIX E

X-RAY DATA FOR 242

Table 55. Crystal data and structure refinement for **242**.

Identification code	ms0801t	
Empirical formula	$C_{32}H_{30}NO_3P$	
Formula weight	507.54	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 6.2389(5) Å	α= 81.753(3)°.
	b = 12.0936(12) Å	β= 89.201(2)°.
	c = 18.4126(16) Å	γ = 75.262(2)°.
Volume	1329.3(2) $Å^3$	
Z	2	
Density (calculated)	1.268 Mg/m^3	
Absorption coefficient	0.137 mm^{-1}	
F(000)	536	
Crystal size	25.00 x 0.29 x 0.24 mm^3	

Theta range for data collection	1.76 to 25.00°.
Index ranges	-7<=h<=7, -14<=k<=14, -21<=l<=21
Reflections collected	10812
Independent reflections	4699 [R(int) = 0.0319]
Completeness to theta = 25.00°	100.0 %
Absorption correction	Sadabs
Max. and min. transmission	0.9677 and 0.1304
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4699 / 0 / 334
Goodness-of-fit on F^2	1.203
Final R indices [I>2sigma(I)]	R1 = 0.0664, wR2 = 0.1558
R indices (all data)	R1 = 0.0865, wR2 = 0.1635
Largest diff. peak and hole	0.301 and -0.266 e·Å^{-3}

Table 56. Atomic coordinates (x10^4) and equivalent isotropic displacement parameters (Å^{2}x10^3) for **242**.

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
P(1)	3657(1)	6258(1)	2857(1)	39(1)
N(1)	1320(3)	7119(2)	2482(1)	37(1)
O(1)	5745(3)	6362(2)	2502(1)	58(1)
C(1)	1113(4)	8393(2)	2375(1)	40(1)
C(2)	420(4)	8778(2)	1548(1)	43(1)
O(2)	2641(4)	8974(2)	485(1)	81(1)
C(3)	-968(5)	7934(2)	1417(1)	42(1)
O(3)	2290(4)	10612(2)	1656(1)	75(1)
C(4)	315(5)	6799(2)	1845(2)	43(1)

C(5)	-1466(6)	7846(3)	623(2)	62(1)
C(6)	2501(5)	8544(3)	1097(2)	51(1)
C(7)	-892(5)	10031(2)	1340(2)	51(1)
C(8)	382(6)	10904(3)	1425(2)	54(1)
C(9)	446(8)	12962(3)	1278(2)	76(1)
C(10)	-570(11)	14128(4)	1088(2)	98(2)
C(11)	-2708(12)	14484(4)	847(3)	105(2)
C(12)	-3872(8)	13699(3)	770(2)	89(1)
C(13)	-2919(7)	12532(3)	952(2)	71(1)
C(14)	-737(6)	12151(3)	1215(2)	56(1)
C(15)	-2367(5)	8712(3)	3137(2)	53(1)
C(16)	-3633(6)	9222(3)	3674(2)	67(1)
C(17)	-2967(8)	10036(3)	4006(2)	84(1)
C(18)	-1078(8)	10337(3)	3796(2)	82(1)
C(19)	198(6)	9825(3)	3253(2)	58(1)
C(20)	-418(5)	9001(2)	2918(2)	42(1)
C(21)	5030(5)	3972(3)	2688(2)	51(1)
C(22)	4884(7)	2851(3)	2755(2)	67(1)
C(23)	3017(7)	2553(3)	3019(2)	68(1)
C(24)	1259(6)	3385(3)	3213(2)	62(1)
C(25)	1391(5)	4516(3)	3149(2)	53(1)
C(26)	3279(4)	4823(2)	2892(1)	40(1)
C(27)	5729(5)	6317(3)	4143(2)	63(1)
C(28)	5879(7)	6441(4)	4870(2)	78(1)
C(29)	4014(8)	6797(3)	5251(2)	77(1)
C(30)	1967(7)	6993(3)	4918(2)	71(1)
C(31)	1811(5)	6843(3)	4195(2)	54(1)

C(32)	3699(5)	6512(2)	3796(2)	42(1)

Table 57. Bond lengths [Å] and angles [°] for **242**.

P(1)-O(1)	1.476(2)	C(6)-H(6A)	0.9300
P(1)-N(1)	1.654(2)	C(7)-C(8)	1.500(4)
P(1)-C(32)	1.799(3)	C(7)-H(7A)	0.9700
P(1)-C(26)	1.802(3)	C(7)-H(7B)	0.9700
N(1)-C(4)	1.481(3)	C(8)-C(14)	1.488(4)
N(1)-C(1)	1.497(3)	C(9)-C(14)	1.387(5)
C(1)-C(20)	1.510(4)	C(9)-C(10)	1.387(6)
C(1)-C(2)	1.560(4)	C(9)-H(9A)	0.9300
C(1)-H(1B)	0.9800	C(10)-C(11)	1.353(7)
C(2)-C(6)	1.518(4)	C(10)-H(10A)	0.9300
C(2)-C(7)	1.525(4)	C(11)-C(12)	1.357(7)
C(2)-C(3)	1.541(4)	C(11)-H(11A)	0.9300
O(2)-C(6)	1.184(3)	C(12)-C(13)	1.379(5)
C(3)-C(4)	1.514(4)	C(12)-H(12A)	0.9300
C(3)-C(5)	1.523(4)	C(13)-C(14)	1.392(5)
C(3)-H(3A)	0.9800	C(13)-H(13A)	0.9300
O(3)-C(8)	1.217(4)	C(15)-C(16)	1.374(4)
C(4)-H(4A)	0.9700	C(15)-C(20)	1.387(4)
C(4)-H(4B)	0.9700	C(15)-H(15A)	0.9300
C(5)-H(5A)	0.9600	C(16)-C(17)	1.379(6)
C(5)-H(5B)	0.9600	C(16)-H(16A)	0.9300
C(5)-H(5C)	0.9600	C(17)-C(18)	1.355(6)

C(17)-H(17A)	0.9300	O(1)-P(1)-N(1)	117.50(12)
C(18)-C(19)	1.386(5)	O(1)-P(1)-C(32)	110.35(13)
C(18)-H(18A)	0.9300	N(1)-P(1)-C(32)	106.12(12)
C(19)-C(20)	1.378(4)	O(1)-P(1)-C(26)	111.67(13)
C(19)-H(19A)	0.9300	N(1)-P(1)-C(26)	104.43(11)
C(21)-C(22)	1.369(5)	C(32)-P(1)-C(26)	105.97(12)
C(21)-C(26)	1.386(4)	C(4)-N(1)-C(1)	110.05(19)
C(21)-H(21A)	0.9300	C(4)-N(1)-P(1)	119.11(17)
C(22)-C(23)	1.368(5)	C(1)-N(1)-P(1)	117.58(16)
C(22)-H(22A)	0.9300	N(1)-C(1)-C(20)	112.4(2)
C(23)-C(24)	1.369(5)	N(1)-C(1)-C(2)	103.45(19)
C(23)-H(23A)	0.9300	C(20)-C(1)-C(2)	116.2(2)
C(24)-C(25)	1.379(4)	N(1)-C(1)-H(1B)	108.2
C(24)-H(24A)	0.9300	C(20)-C(1)-H(1B)	108.2
C(25)-C(26)	1.381(4)	C(2)-C(1)-H(1B)	108.2
C(25)-H(25A)	0.9300	C(6)-C(2)-C(7)	109.6(2)
C(27)-C(28)	1.376(5)	C(6)-C(2)-C(3)	109.3(2)
C(27)-C(32)	1.377(4)	C(7)-C(2)-C(3)	111.4(2)
C(27)-H(27A)	0.9300	C(6)-C(2)-C(1)	108.2(2)
C(28)-C(29)	1.356(5)	C(7)-C(2)-C(1)	115.9(2)
C(28)-H(28A)	0.9300	C(3)-C(2)-C(1)	102.1(2)
C(29)-C(30)	1.374(5)	C(4)-C(3)-C(5)	113.3(2)
C(29)-H(29A)	0.9300	C(4)-C(3)-C(2)	103.2(2)
C(30)-C(31)	1.378(4)	C(5)-C(3)-C(2)	117.1(2)
C(30)-H(30A)	0.9300	C(4)-C(3)-H(3A)	107.6
C(31)-C(32)	1.382(4)	C(5)-C(3)-H(3A)	107.6
C(31)-H(31A)	0.9300	C(2)-C(3)-H(3A)	107.6

N(1)-C(4)-C(3)	105.2(2)	C(11)-C(10)-C(9)	120.7(4)
N(1)-C(4)-H(4A)	110.7	C(11)-C(10)-H(10A)	119.6
C(3)-C(4)-H(4A)	110.7	C(9)-C(10)-H(10A)	119.6
N(1)-C(4)-H(4B)	110.7	C(10)-C(11)-C(12)	120.2(4)
C(3)-C(4)-H(4B)	110.7	C(10)-C(11)-H(11A)	119.9
H(4A)-C(4)-H(4B)	108.8	C(12)-C(11)-H(11A)	119.9
C(3)-C(5)-H(5A)	109.5	C(11)-C(12)-C(13)	120.8(5)
C(3)-C(5)-H(5B)	109.5	C(11)-C(12)-H(12A)	119.6
H(5A)-C(5)-H(5B)	109.5	C(13)-C(12)-H(12A)	119.6
C(3)-C(5)-H(5C)	109.5	C(12)-C(13)-C(14)	119.8(4)
H(5A)-C(5)-H(5C)	109.5	C(12)-C(13)-H(13A)	120.1
H(5B)-C(5)-H(5C)	109.5	C(14)-C(13)-H(13A)	120.1
O(2)-C(6)-C(2)	125.0(3)	C(9)-C(14)-C(13)	118.8(3)
O(2)-C(6)-H(6A)	117.5	C(9)-C(14)-C(8)	118.8(3)
C(2)-C(6)-H(6A)	117.5	C(13)-C(14)-C(8)	122.4(3)
C(8)-C(7)-C(2)	114.5(3)	C(16)-C(15)-C(20)	121.2(3)
C(8)-C(7)-H(7A)	108.6	C(16)-C(15)-H(15A)	119.4
C(2)-C(7)-H(7A)	108.6	C(20)-C(15)-H(15A)	119.4
C(8)-C(7)-H(7B)	108.6	C(15)-C(16)-C(17)	119.9(4)
C(2)-C(7)-H(7B)	108.6	C(15)-C(16)-H(16A)	120.1
H(7A)-C(7)-H(7B)	107.6	C(17)-C(16)-H(16A)	120.1
O(3)-C(8)-C(14)	120.1(3)	C(18)-C(17)-C(16)	119.8(4)
O(3)-C(8)-C(7)	121.4(3)	C(18)-C(17)-H(17A)	120.1
C(14)-C(8)-C(7)	118.5(3)	C(16)-C(17)-H(17A)	120.1
C(14)-C(9)-C(10)	119.7(4)	C(17)-C(18)-C(19)	120.3(4)
C(14)-C(9)-H(9A)	120.2	C(17)-C(18)-H(18A)	119.8
C(10)-C(9)-H(9A)	120.2	C(19)-C(18)-H(18A)	119.8

C(20)-C(19)-C(18)	121.0(3)	C(25)-C(26)-P(1)	123.4(2)
C(20)-C(19)-H(19A)	119.5	C(21)-C(26)-P(1)	117.9(2)
C(18)-C(19)-H(19A)	119.5	C(28)-C(27)-C(32)	120.9(3)
C(19)-C(20)-C(15)	117.8(3)	C(28)-C(27)-H(27A)	119.5
C(19)-C(20)-C(1)	119.3(3)	C(32)-C(27)-H(27A)	119.5
C(15)-C(20)-C(1)	122.8(3)	C(29)-C(28)-C(27)	120.2(3)
C(22)-C(21)-C(26)	120.2(3)	C(29)-C(28)-H(28A)	119.9
C(22)-C(21)-H(21A)	119.9	C(27)-C(28)-H(28A)	119.9
C(26)-C(21)-H(21A)	119.9	C(28)-C(29)-C(30)	120.0(3)
C(23)-C(22)-C(21)	120.9(3)	C(28)-C(29)-H(29A)	120.0
C(23)-C(22)-H(22A)	119.6	C(30)-C(29)-H(29A)	120.0
C(21)-C(22)-H(22A)	119.6	C(29)-C(30)-C(31)	119.9(4)
C(22)-C(23)-C(24)	119.8(3)	C(29)-C(30)-H(30A)	120.0
C(22)-C(23)-H(23A)	120.1	C(31)-C(30)-H(30A)	120.0
C(24)-C(23)-H(23A)	120.1	C(30)-C(31)-C(32)	120.6(3)
C(23)-C(24)-C(25)	119.8(3)	C(30)-C(31)-H(31A)	119.7
C(23)-C(24)-H(24A)	120.1	C(32)-C(31)-H(31A)	119.7
C(25)-C(24)-H(24A)	120.1	C(27)-C(32)-C(31)	118.3(3)
C(24)-C(25)-C(26)	120.8(3)	C(27)-C(32)-P(1)	118.0(2)
C(24)-C(25)-H(25A)	119.6	C(31)-C(32)-P(1)	123.6(2)
C(26)-C(25)-H(25A)	119.6		
C(25)-C(26)-C(21)	118.5(3)		

Symmetry transformations used to generate equivalent atoms:

Table 58. Anisotropic displacement parameters ($Å^2x10^3$) for **242**.

The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}

P(1)	37(1)	40(1)	41(1)	-3(1)	3(1)	-12(1)
N(1)	46(1)	34(1)	35(1)	-4(1)	0(1)	-15(1)
O(1)	45(1)	64(1)	65(1)	-6(1)	10(1)	-17(1)
C(1)	42(2)	37(2)	43(2)	-1(1)	-3(1)	-16(1)
C(2)	45(2)	44(2)	38(2)	3(1)	-3(1)	-15(1)
O(2)	78(2)	109(2)	49(2)	13(1)	10(1)	-26(2)
C(3)	44(2)	48(2)	37(2)	-5(1)	-2(1)	-15(1)
O(3)	79(2)	63(2)	86(2)	12(1)	-24(1)	-33(1)
C(4)	49(2)	45(2)	39(2)	-10(1)	-1(1)	-19(1)
C(5)	72(2)	73(2)	46(2)	-9(2)	-11(2)	-23(2)
C(6)	52(2)	59(2)	45(2)	0(1)	-1(1)	-22(2)
C(7)	61(2)	47(2)	42(2)	4(1)	-9(1)	-14(2)
C(8)	72(2)	51(2)	40(2)	6(1)	-5(2)	-24(2)
C(9)	125(3)	58(2)	53(2)	-6(2)	-9(2)	-38(2)
C(10)	165(5)	54(3)	82(3)	-11(2)	-1(3)	-42(3)
C(11)	173(6)	47(2)	84(3)	-7(2)	7(3)	-11(3)
C(12)	111(3)	56(3)	83(3)	5(2)	0(2)	1(2)
C(13)	92(3)	50(2)	62(2)	1(2)	0(2)	-10(2)
C(14)	87(3)	50(2)	31(2)	-1(1)	2(2)	-21(2)
C(15)	53(2)	56(2)	47(2)	-3(1)	1(1)	-10(2)
C(16)	59(2)	70(2)	62(2)	-5(2)	13(2)	1(2)
C(17)	103(3)	64(3)	70(3)	-14(2)	26(2)	6(2)
C(18)	128(4)	50(2)	68(2)	-26(2)	6(2)	-14(2)
C(19)	74(2)	42(2)	58(2)	-7(1)	0(2)	-15(2)
C(20)	50(2)	35(2)	37(2)	1(1)	-6(1)	-5(1)
C(21)	57(2)	51(2)	42(2)	-6(1)	2(1)	-5(2)
C(22)	86(3)	43(2)	59(2)	-14(2)	-2(2)	10(2)
C(23)	105(3)	40(2)	57(2)	-1(2)	-18(2)	-18(2)
C(24)	75(2)	57(2)	57(2)	5(2)	-8(2)	-31(2)
C(25)	53(2)	43(2)	64(2)	-8(1)	4(2)	-12(2)
C(26)	42(2)	39(2)	36(2)	-3(1)	-2(1)	-6(1)
C(27)	54(2)	72(2)	67(2)	-6(2)	-9(2)	-22(2)
C(28)	76(3)	103(3)	62(2)	-7(2)	-25(2)	-37(2)
C(29)	115(3)	78(3)	43(2)	-4(2)	-18(2)	-37(2)

C(30)	88(3)	74(2)	45(2)	-5(2)	3(2)	-12(2)
C(31)	56(2)	59(2)	42(2)	-4(1)	-3(1)	-7(2)
C(32)	49(2)	35(2)	40(2)	-1(1)	-5(1)	-11(1)

Table 59. Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2x10^3$) for **242**.

	x	y	z	U(eq)
H(1B)	2587	8514	2445	48
H(3A)	-2389	8173	1657	51
H(4A)	-667	6311	2007	51
H(4B)	1454	6390	1547	51
H(5A)	-2353	7306	611	94
H(5B)	-101	7586	378	94
H(5C)	-2258	8591	379	94
H(6A)	3761	8023	1319	62
H(7A)	-1403	10142	833	61
H(7B)	-2191	10174	1643	61
H(9A)	1913	12725	1446	91
H(10A)	226	14672	1128	117
H(11A)	-3382	15270	734	126
H(12A)	-5329	13951	593	107
H(13A)	-3733	12001	899	85
H(15A)	-2825	8163	2916	64
H(16A)	-4936	9019	3813	81
H(17A)	-3813	10377	4373	100
H(18A)	-636	10890	4017	98
H(19A)	1488	10041	3113	69

H(21A)	6308	4163	2505	62
H(22A)	6070	2286	2618	80
H(23A)	2942	1788	3067	82
H(24A)	-20	3188	3388	74
H(25A)	193	5079	3281	64
H(27A)	7018	6098	3882	76
H(28A)	7262	6280	5101	94
H(29A)	4122	6909	5737	92
H(30A)	688	7227	5181	86
H(31A)	423	6965	3974	65

APPENDIX F

X-RAY DATA FOR 244A

Table 60. Crystal data and structure refinement for **244a**.

Identification code	mw330	
Empirical formula	$C_{30}H_3$ NOP	
Formula weight	453.54	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 9.9264(9) Å	α= 90°.
	b = 23.063(2) Å	β= 110.959(2)°.
	c = 11.6053(11) Å	γ = 90°.
Volume	2481.0(4) $Å^3$	
Z	4	
Density (calculated)	1.214 Mg/m^3	
Absorption coefficient	0.133 mm^{-1}	
F(000)	968	
Crystal size	0.35 x 0.24 x 0.24 mm^3	

Theta range for data collection	1.77 to 32.59°.
Index ranges	-14<=h<=14, -34<=k<=34, -17<=l<=17
Reflections collected	32025
Independent reflections	8793 [R(int) = 0.0710]
Completeness to theta = 32.59°	97.3 %
Absorption correction	None
Max. and min. transmission	0.9687 and 0.9548
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8793 / 0 / 426
Goodness-of-fit on F^2	1.015
Final R indices [I>2sigma(I)]	R1 = 0.0638, wR2 = 0.1374
R indices (all data)	R1 = 0.1166, wR2 = 0.1617
Largest diff. peak and hole	0.610 and -0.256 e.$Å^{-3}$

Table 61. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2x10^3$) for **244a**.

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
P	9505(1)	1995(1)	3114(1)	20(1)
O	8899(1)	1952(1)	1748(1)	26(1)
N	8267(2)	1902(1)	3746(1)	21(1)
C(1)	8572(2)	1671(1)	5006(2)	24(1)
C(2)	7326(2)	1267(1)	4869(2)	23(1)
C(3)	6428(2)	1228(1)	3509(2)	22(1)
C(4)	6795(2)	684(1)	2837(2)	24(1)
C(5)	5225(2)	517(1)	2524(2)	25(1)
C(6)	4926(2)	968(1)	3117(2)	25(1)
C(7)	6725(2)	1809(1)	2976(2)	20(1)
C(8)	5748(2)	2333(1)	2971(2)	23(1)
C(9)	4261(2)	2238(1)	1969(2)	31(1)

C(10)	6406(2)	2877(1)	2634(2)	28(1)
C(11)	5563(2)	2432(1)	4212(2)	29(1)
C(12)	5066(2)	-382(1)	1314(2)	32(1)
C(13)	4281(3)	-834(1)	599(2)	35(1)
C(14)	2808(3)	-878(1)	340(2)	38(1)
C(15)	2134(3)	-467(1)	815(2)	40(1)
C(16)	2916(2)	-14(1)	1535(2)	34(1)
C(17)	4398(2)	33(1)	1794(2)	27(1)
C(18)	12135(2)	1572(1)	4808(2)	29(1)
C(19)	13084(2)	1127(1)	5386(2)	35(1)
C(20)	12780(2)	565(1)	4972(2)	36(1)
C(21)	11544(2)	442(1)	3980(2)	37(1)
C(22)	10592(2)	882(1)	3399(2)	33(1)
C(23)	10870(2)	1453(1)	3820(2)	24(1)
C(24)	11200(2)	2918(1)	2977(2)	28(1)
C(25)	11902(2)	3445(1)	3329(2)	33(1)
C(26)	11811(2)	3738(1)	4346(2)	33(1)

Table 62. Bond lengths [Å] and angles [°] for **244a**.

P-O	1.4845(13)	C(2)-C(3)	1.512(2)
P-N	1.6544(15)	C(3)-C(6)	1.518(2)
P-C(29)	1.8045(17)	C(3)-C(7)	1.548(2)
P-C(23)	1.8098(18)	C(3)-C(4)	1.588(2)
N-C(1)	1.482(2)	C(4)-C(5)	1.518(2)
N-C(7)	1.486(2)	C(4)-H(4B)	1.00(2)
C(1)-C(2)	1.511(2)	C(4)-H(4A])	1.01(2)
C(1)-H(1B)	0.99(2)	C(5)-C(6)	1.338(3)
C(1)-H(1A)	0.99(2)	C(5)-C(17)	1.464(2)
C(2)-C(30)	1.324(3)	C(6)-H(6')	0.96(2)

C(7)-C(8)	1.548(2)	C(18)-H(18)	0.96(2)
C(7)-H(7)	0.932(18)	C(19)-C(20)	1.379(3)
C(8)-C(10)	1.529(3)	C(19)-H(19)	0.99(2)
C(8)-C(11)	1.533(3)	C(20)-C(21)	1.379(3)
C(8)-C(9)	1.533(3)	C(20)-H(20)	0.96(2)
C(9)-H(9C)	0.99(2)	C(21)-C(22)	1.387(3)
C(9)-H(9A)	0.96(3)	C(21)-H(21)	0.91(2)
C(9)-H(9B)	0.95(2)	C(22)-C(23)	1.396(3)
C(10)-H(10A)	1.00(2)	C(22)-H(22)	0.98(2)
C(10)-H(10B)	1.02(2)	C(24)-C(25)	1.389(3)
C(10)-H(10C)	0.99(2)	C(24)-C(29)	1.396(2)
C(11)-H(11B)	0.98(2)	C(24)-H(24)	0.94(2)
C(11)-H(11C)	0.97(2)	C(25)-C(26)	1.391(3)
C(11)-H(11A)	1.00(2)	C(25)-H(25)	0.98(2)
C(12)-C(13)	1.386(3)	C(26)-C(27)	1.387(3)
C(12)-C(17)	1.389(3)	C(26)-H(26)	0.99(2)
C(12)-H(12)	0.94(2)	C(27)-C(28)	1.388(3)
C(13)-C(14)	1.386(3)	C(27)-H(27)	0.89(2)
C(13)-H(13)	0.90(2)	C(28)-C(29)	1.392(2)
C(14)-C(15)	1.384(3)	C(28)-H(28)	0.937(19)
C(14)-H(14)	0.96(2)	C(30)-H(30A)	0.98(2)
C(15)-C(16)	1.388(3)	C(30)-H(30B)	0.96(2)
C(15)-H(15)	0.94(2)	O-P-N	112.54(7)
C(16)-C(17)	1.396(3)	O-P-C(29)	111.89(8)
C(16)-H(16)	0.97(2)	N-P-C(29)	108.57(8)
C(18)-C(23)	1.391(2)	O-P-C(23)	112.94(8)
C(18)-C(19)	1.392(3)	N-P-C(23)	105.37(8)

C(29)-P-C(23)	105.03(8)	C(17)-C(5)-C(4)	130.26(16)
C(1)-N-C(7)	110.15(13)	C(5)-C(6)-C(3)	94.95(15)
C(1)-N-P	124.14(12)	C(5)-C(6)-H(6')	133.5(12)
C(7)-N-P	121.39(11)	C(3)-C(6)-H(6')	131.5(12)
N-C(1)-C(2)	104.28(13)	N-C(7)-C(3)	100.78(13)
N-C(1)-H(1B)	109.9(12)	N-C(7)-C(8)	113.50(14)
C(2)-C(1)-H(1B)	111.6(12)	C(3)-C(7)-C(8)	117.94(14)
N-C(1)-H(1A)	109.2(13)	N-C(7)-H(7)	107.9(11)
C(2)-C(1)-H(1A)	110.1(13)	C(3)-C(7)-H(7)	109.0(11)
H(1B)-C(1)-H(1A)	111.5(18)	C(8)-C(7)-H(7)	107.3(11)
C(30)-C(2)-C(1)	125.23(17)	C(10)-C(8)-C(11)	108.93(15)
C(30)-C(2)-C(3)	127.21(17)	C(10)-C(8)-C(9)	107.85(15)
C(1)-C(2)-C(3)	107.56(14)	C(11)-C(8)-C(9)	109.12(16)
C(2)-C(3)-C(6)	119.09(14)	C(10)-C(8)-C(7)	108.48(15)
C(2)-C(3)-C(7)	103.86(13)	C(11)-C(8)-C(7)	113.46(14)
C(6)-C(3)-C(7)	121.91(14)	C(9)-C(8)-C(7)	108.85(15)
C(2)-C(3)-C(4)	114.04(14)	C(8)-C(9)-H(9C)	109.7(12)
C(6)-C(3)-C(4)	85.09(13)	C(8)-C(9)-H(9A)	110.0(15)
C(7)-C(3)-C(4)	112.19(14)	H(9C)-C(9)-H(9A)	111.6(18)
C(5)-C(4)-C(3)	85.44(13)	C(8)-C(9)-H(9B)	111.1(14)
C(5)-C(4)-H(4B)	118.0(11)	H(9C)-C(9)-H(9B)	106.0(17)
C(3)-C(4)-H(4B)	113.2(12)	H(9A)-C(9)-H(9B)	108(2)
C(5)-C(4)-H(4A])	117.1(12)	C(8)-C(10)-H(10A)	112.5(13)
C(3)-C(4)-H(4A])	113.8(12)	C(8)-C(10)-H(10B)	106.9(13)
H(4B)-C(4)-H(4A])	107.9(16)	H(10A)-C(10)-H(10B)	111.4(18)
C(6)-C(5)-C(17)	135.23(17)	C(8)-C(10)-H(10C)	112.7(13)
C(6)-C(5)-C(4)	94.50(14)	H(10A)-C(10)-H(10C)	103.1(18)

H(10B)-C(10)-H(10C)	110.2(18)	C(19)-C(18)-H(18)	120.8(12)
C(8)-C(11)-H(11B)	112.2(13)	C(20)-C(19)-C(18)	119.97(19)
C(8)-C(11)-H(11C)	111.4(13)	C(20)-C(19)-H(19)	120.8(14)
H(11B)-C(11)-H(11C)	108.6(18)	C(18)-C(19)-H(19)	119.3(14)
C(8)-C(11)-H(11A)	108.1(13)	C(21)-C(20)-C(19)	120.18(19)
H(11B)-C(11)-H(11A)	106.8(18)	C(21)-C(20)-H(20)	120.9(14)
H(11C)-C(11)-H(11A)	109.6(18)	C(19)-C(20)-H(20)	118.8(14)
C(13)-C(12)-C(17)	120.8(2)	C(20)-C(21)-C(22)	120.2(2)
C(13)-C(12)-H(12)	120.2(14)	C(20)-C(21)-H(21)	118.5(15)
C(17)-C(12)-H(12)	118.7(14)	C(22)-C(21)-H(21)	121.2(15)
C(12)-C(13)-C(14)	120.5(2)	C(21)-C(22)-C(23)	120.34(19)
C(12)-C(13)-H(13)	117.0(15)	C(21)-C(22)-H(22)	122.2(13)
C(14)-C(13)-H(13)	122.4(15)	C(23)-C(22)-H(22)	117.5(13)
C(15)-C(14)-C(13)	119.10(19)	C(18)-C(23)-C(22)	118.82(17)
C(15)-C(14)-H(14)	121.9(14)	C(18)-C(23)-P	123.03(14)
C(13)-C(14)-H(14)	119.0(14)	C(22)-C(23)-P	118.03(14)
C(14)-C(15)-C(16)	120.6(2)	C(25)-C(24)-C(29)	120.65(18)
C(14)-C(15)-H(15)	121.3(15)	C(25)-C(24)-H(24)	118.9(12)
C(16)-C(15)-H(15)	118.1(15)	C(29)-C(24)-H(24)	120.4(12)
C(15)-C(16)-C(17)	120.5(2)	C(24)-C(25)-C(26)	119.79(19)
C(15)-C(16)-H(16)	120.9(13)	C(24)-C(25)-H(25)	120.1(13)
C(17)-C(16)-H(16)	118.7(13)	C(26)-C(25)-H(25)	120.1(13)
C(12)-C(17)-C(16)	118.49(17)	C(27)-C(26)-C(25)	120.04(18)
C(12)-C(17)-C(5)	120.62(17)	C(27)-C(26)-H(26)	117.2(13)
C(16)-C(17)-C(5)	120.87(17)	C(25)-C(26)-H(26)	122.7(13)
C(23)-C(18)-C(19)	120.44(19)	C(26)-C(27)-C(28)	119.97(18)
C(23)-C(18)-H(18)	118.7(12)	C(26)-C(27)-H(27)	119.4(13)

C(28)-C(27)-H(27)	120.7(13)
C(27)-C(28)-C(29)	120.67(17)
C(27)-C(28)-H(28)	119.3(12)
C(29)-C(28)-H(28)	119.9(12)
C(28)-C(29)-C(24)	118.89(16)
C(28)-C(29)-P	122.93(13)
C(24)-C(29)-P	118.18(13)
C(2)-C(30)-H(30A)	121.2(13)
C(2)-C(30)-H(30B)	123.2(13)
H(30A)-C(30)-H(30B)	115.6(19)

Symmetry transformations used to generate equivalent atoms:

Table 63. Anisotropic displacement parameters ($Å^2x10^3$) for **244a**.

The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
P	21(1)	21(1)	18(1)	-2(1)	7(1)	-2(1)
O	28(1)	31(1)	20(1)	-3(1)	9(1)	-5(1)
N	20(1)	25(1)	15(1)	1(1)	4(1)	-2(1)
C(1)	25(1)	30(1)	16(1)	2(1)	6(1)	-1(1)
C(2)	27(1)	20(1)	22(1)	1(1)	9(1)	3(1)
C(3)	23(1)	21(1)	21(1)	-2(1)	9(1)	-3(1)
C(4)	26(1)	23(1)	24(1)	-4(1)	10(1)	-2(1)
C(5)	27(1)	23(1)	25(1)	-1(1)	9(1)	-4(1)
C(6)	25(1)	25(1)	26(1)	0(1)	11(1)	-4(1)
C(7)	20(1)	23(1)	16(1)	-1(1)	5(1)	-2(1)
C(8)	24(1)	24(1)	21(1)	1(1)	7(1)	0(1)
C(9)	25(1)	35(1)	29(1)	4(1)	4(1)	3(1)
C(10)	34(1)	24(1)	26(1)	2(1)	8(1)	1(1)
C(11)	35(1)	28(1)	26(1)	3(1)	15(1)	7(1)
C(12)	39(1)	25(1)	31(1)	-2(1)	10(1)	-2(1)

C(13)	49(1)	22(1)	30(1)	-3(1)	10(1)	-2(1)
C(14)	55(1)	27(1)	25(1)	-1(1)	5(1)	-14(1)
C(15)	39(1)	41(1)	35(1)	-2(1)	6(1)	-16(1)
C(16)	37(1)	32(1)	33(1)	-3(1)	12(1)	-10(1)
C(17)	35(1)	21(1)	22(1)	1(1)	8(1)	-6(1)
C(18)	29(1)	28(1)	28(1)	-3(1)	8(1)	2(1)
C(19)	30(1)	41(1)	31(1)	4(1)	7(1)	6(1)
C(20)	35(1)	34(1)	44(1)	13(1)	20(1)	11(1)
C(21)	38(1)	23(1)	53(1)	-1(1)	19(1)	1(1)
C(22)	27(1)	26(1)	43(1)	-4(1)	11(1)	-2(1)
C(23)	23(1)	24(1)	25(1)	0(1)	10(1)	0(1)
C(24)	29(1)	29(1)	26(1)	-1(1)	12(1)	-3(1)
C(25)	33(1)	33(1)	37(1)	-1(1)	16(1)	-10(1)
C(26)	34(1)	23(1)	40(1)	-2(1)	11(1)	-6(1)
C(27)	28(1)	25(1)	27(1)	-6(1)	6(1)	0(1)
C(28)	25(1)	24(1)	24(1)	0(1)	9(1)	0(1)
C(29)	20(1)	20(1)	21(1)	2(1)	6(1)	0(1)
C(30)	38(1)	27(1)	28(1)	4(1)	14(1)	2(1)

Table 64. Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2x10^3$) for **244a**.

	x	y	z	U(eq)
H(1B)	8610(20)	1993(9)	5580(20)	30(6)
H(1A)	9490(20)	1452(10)	5270(20)	37(6)
H(4B)	7120(20)	792(9)	2145(19)	27(5)
H(4A])	7550(20)	416(9)	3411(19)	29(5)
H(6')	4080(20)	1092(9)	3255(18)	27(5)

H(7)	6666(18)	1750(8)	2165(17)	14(4)
H(9C)	3630(20)	2577(9)	1938(18)	25(5)
H(9A)	4360(30)	2172(10)	1190(20)	46(7)
H(9B)	3790(20)	1912(10)	2160(20)	40(6)
H(10A)	7370(30)	2976(10)	3270(20)	41(6)
H(10B)	5680(20)	3206(11)	2530(20)	45(7)
H(10C)	6620(20)	2829(10)	1870(20)	37(6)
H(11B)	5160(20)	2092(10)	4480(20)	34(6)
H(11C)	6470(20)	2529(10)	4850(20)	39(6)
H(11A)	4860(20)	2757(10)	4110(20)	39(6)
H(12)	6040(20)	-329(10)	1410(20)	38(6)
H(13)	4760(20)	-1086(11)	300(20)	43(7)
H(14)	2280(30)	-1182(11)	-190(20)	47(7)
H(15)	1130(30)	-475(10)	630(20)	47(7)
H(16)	2450(20)	274(10)	1870(20)	42(6)
H(18)	12340(20)	1965(9)	5080(19)	27(5)
H(19)	13980(30)	1222(10)	6080(20)	49(7)
H(20)	13410(20)	258(10)	5420(20)	41(6)
H(21)	11340(30)	63(11)	3750(20)	47(7)
H(22)	9710(20)	809(10)	2700(20)	36(6)
H(24)	11250(20)	2728(9)	2274(19)	26(5)
H(25)	12470(20)	3608(9)	2870(20)	37(6)
H(26)	12270(20)	4120(10)	4620(20)	37(6)
H(27)	10970(20)	3694(9)	5658(19)	28(5)
H(28)	9720(20)	2837(8)	5059(17)	18(5)
H(30A)	7730(20)	1058(9)	6650(20)	35(6)

APPENDIX G

X-RAY DATA FOR 245

Table 65. Crystal data and structure refinement for **245**.

Identification code	mww313	
Empirical formula	$C_{26}H_{23}ClN$	
Formula weight	384.90	
Temperature	203(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 10.173(2) Å	α= 90°.
	b = 9.3952(18) Å	β= 93.989(4)°.
	c = 10.685(2) Å	γ = 90°.
Volume	1018.8(3) $Å^3$	
Z	2	
Density (calculated)	1.255 Mg/m^3	
Absorption coefficient	0.198 mm^{-1}	
F(000)	406	
Crystal size	? x ? x ? mm^3	

Theta range for data collection	1.91 to 27.50°.
Index ranges	-13<=h<=13, -12<=k<=12, -13<=l<=13
Reflections collected	9978
Independent reflections	4652 [R(int) = 0.0392]
Completeness to theta = 27.50°	100.0 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4652 / 1 / 258
Goodness-of-fit on F^2	0.937
Final R indices [I>2sigma(I)]	R1 = 0.0475, wR2 = 0.1143
R indices (all data)	R1 = 0.0593, wR2 = 0.1214
Absolute structure parameter	0.29(6)
Largest diff. peak and hole	0.360 and -0.339 $e \cdot Å^{-3}$

Table 66. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2x10^3$) for **245**.

U(eq) is defined as one third of the trace of the orthogonalized U^{ij}tensor.

	x	y	z	U(eq)
Cl	-8773(1)	-1476(1)	-5859(1)	32(1)
N	-9589(2)	-3619(2)	-3928(2)	29(1)
C(1)	-10814(2)	-4480(2)	-1268(2)	26(1)
C(2)	-10836(2)	-3832(2)	-160(2)	27(1)
C(3)	-9829(2)	-2714(2)	-455(2)	28(1)
C(4)	-9754(2)	-3505(2)	-1732(2)	26(1)
C(5)	-8470(2)	-4256(3)	-1983(2)	29(1)
C(6)	-8306(2)	-4201(3)	-3380(2)	32(1)
C(7)	-10049(2)	-2631(2)	-2938(2)	28(1)

C(8)	-12490(2)	-5100(3)	1034(2)	33(1)
C(9)	-13115(3)	-5328(3)	2120(3)	38(1)
C(10)	-12766(3)	-4525(3)	3187(2)	41(1)
C(11)	-11795(3)	-3493(3)	3144(2)	36(1)
C(12)	-11166(2)	-3260(3)	2057(2)	30(1)
C(13)	-11507(2)	-4067(3)	984(2)	27(1)
C(14)	-7679(3)	-4900(3)	-1116(2)	33(1)
C(15)	-6059(3)	-6646(3)	-280(3)	45(1)
C(16)	-4952(3)	-7500(3)	-368(4)	58(1)
C(17)	-4221(3)	-7409(4)	-1389(4)	58(1)
C(18)	-4564(3)	-6455(4)	-2332(3)	57(1)
C(19)	-5688(3)	-5608(3)	-2258(3)	47(1)
C(20)	-6460(3)	-5710(3)	-1244(3)	37(1)
C(21)	-11597(3)	-601(3)	-3301(3)	38(1)
C(22)	-12822(3)	-29(3)	-3614(3)	50(1)
C(23)	-13875(3)	-924(4)	-3888(3)	57(1)
C(24)	-13719(3)	-2380(4)	-3831(3)	48(1)
C(25)	-12483(3)	-2953(3)	-3501(3)	36(1)
C(26)	-11414(3)	-2070(3)	-3250(2)	29(1)

Table 67. Bond lengths [Å] and angles [°] for **245**.

N-C(6)	1.496(3)	C(1)-H(1)	1.01(3)
N-C(7)	1.506(3)	C(2)-C(13)	1.458(3)
N-H(0A)	0.87	C(2)-C(3)	1.516(3)
C(1)-C(2)	1.333(3)	C(3)-C(4)	1.561(3)
C(1)-C(4)	1.524(3)	C(3)-H(3A)	0.98

C(3)-H(3B)	0.98	C(17)-C(18)	1.375(5)
C(4)-C(5)	1.524(3)	C(17)-H(17A)	0.94
C(4)-C(7)	1.540(3)	C(18)-C(19)	1.399(4)
C(5)-C(14)	1.330(4)	C(18)-H(18A)	0.94
C(5)-C(6)	1.514(3)	C(19)-C(20)	1.385(4)
C(6)-H(6A)	0.98	C(19)-H(19A)	0.94
C(6)-H(6B)	0.98	C(21)-C(22)	1.377(4)
C(7)-C(26)	1.500(3)	C(21)-C(26)	1.393(3)
C(7)-H(7A)	0.99	C(21)-H(21A)	0.94
C(8)-C(9)	1.378(4)	C(22)-C(23)	1.378(5)
C(8)-C(13)	1.397(4)	C(22)-H(22A)	0.94
C(8)-H(8A)	0.94	C(23)-C(24)	1.378(5)
C(9)-C(10)	1.393(4)	C(23)-H(23A)	0.94
C(9)-H(9A)	0.94	C(24)-C(25)	1.391(4)
C(10)-C(11)	1.387(4)	C(24)-H(24A)	0.94
C(10)-H(10A)	0.94	C(25)-C(26)	1.380(4)
C(11)-C(12)	1.381(4)	C(25)-H(25A)	0.94
C(11)-H(11A)	0.94	C(6)-N-C(7)	104.87(18)
C(12)-C(13)	1.398(3)	C(6)-N-H(0A)	127.6
C(12)-H(12A)	0.94	C(7)-N-H(0A)	127.6
C(14)-C(20)	1.470(4)	C(2)-C(1)-C(4)	94.08(19)
C(14)-H(14A)	0.94	C(2)-C(1)-H(1)	133.4(15)
C(15)-C(16)	1.391(5)	C(4)-C(1)-H(1)	132.2(15)
C(15)-C(20)	1.393(4)	C(1)-C(2)-C(13)	135.5(2)
C(15)-H(15A)	0.94	C(1)-C(2)-C(3)	94.47(18)
C(16)-C(17)	1.365(5)	C(13)-C(2)-C(3)	130.0(2)
C(16)-H(16A)	0.94	C(2)-C(3)-C(4)	85.80(17)

C(2)-C(3)-H(3A)	114.4	C(9)-C(8)-H(8A)	119.6
C(4)-C(3)-H(3A)	114.4	C(13)-C(8)-H(8A)	119.6
C(2)-C(3)-H(3B)	114.4	C(8)-C(9)-C(10)	119.9(3)
C(4)-C(3)-H(3B)	114.4	C(8)-C(9)-H(9A)	120.1
H(3A)-C(3)-H(3B)	111.5	C(10)-C(9)-H(9A)	120.1
C(5)-C(4)-C(1)	114.45(18)	C(11)-C(10)-C(9)	119.6(2)
C(5)-C(4)-C(7)	102.68(19)	C(11)-C(10)-H(10A)	120.2
C(1)-C(4)-C(7)	119.4(2)	C(9)-C(10)-H(10A)	120.2
C(5)-C(4)-C(3)	118.0(2)	C(12)-C(11)-C(10)	120.7(2)
C(1)-C(4)-C(3)	85.56(17)	C(12)-C(11)-H(11A)	119.6
C(7)-C(4)-C(3)	117.30(18)	C(10)-C(11)-H(11A)	119.6
C(14)-C(5)-C(6)	126.8(2)	C(11)-C(12)-C(13)	120.0(2)
C(14)-C(5)-C(4)	124.9(2)	C(11)-C(12)-H(12A)	120
C(6)-C(5)-C(4)	108.2(2)	C(13)-C(12)-H(12A)	120
N-C(6)-C(5)	104.13(19)	C(8)-C(13)-C(12)	118.9(2)
N-C(6)-H(6A)	110.9	C(8)-C(13)-C(2)	121.0(2)
C(5)-C(6)-H(6A)	110.9	C(12)-C(13)-C(2)	120.1(2)
N-C(6)-H(6B)	110.9	C(5)-C(14)-C(20)	130.1(3)
C(5)-C(6)-H(6B)	110.9	C(5)-C(14)-H(14A)	114.9
H(6A)-C(6)-H(6B)	108.9	C(20)-C(14)-H(14A)	114.9
C(26)-C(7)-N	112.9(2)	C(16)-C(15)-C(20)	120.7(3)
C(26)-C(7)-C(4)	119.8(2)	C(16)-C(15)-H(15A)	119.6
N-C(7)-C(4)	101.90(18)	C(20)-C(15)-H(15A)	119.6
C(26)-C(7)-H(7A)	107.2	C(17)-C(16)-C(15)	120.4(3)
N-C(7)-H(7A)	107.2	C(17)-C(16)-H(16A)	119.8
C(4)-C(7)-H(7A)	107.2	C(15)-C(16)-H(16A)	119.8
C(9)-C(8)-C(13)	120.9(2)	C(16)-C(17)-C(18)	120.1(3)

C(16)-C(17)-H(17A)	119.9	C(23)-C(22)-H(22A)	120.3
C(18)-C(17)-H(17A)	119.9	C(21)-C(22)-H(22A)	120.3
C(17)-C(18)-C(19)	119.7(3)	C(24)-C(23)-C(22)	120.8(3)
C(17)-C(18)-H(18A)	120.1	C(24)-C(23)-H(23A)	119.6
C(19)-C(18)-H(18A)	120.1	C(22)-C(23)-H(23A)	119.6
C(20)-C(19)-C(18)	121.0(3)	C(23)-C(24)-C(25)	119.7(3)
C(20)-C(19)-H(19A)	119.5	C(23)-C(24)-H(24A)	120.2
C(18)-C(19)-H(19A)	119.5	C(25)-C(24)-H(24A)	120.2
C(19)-C(20)-C(15)	118.0(3)	C(26)-C(25)-C(24)	120.2(3)
C(19)-C(20)-C(14)	124.4(3)	C(26)-C(25)-H(25A)	119.9
C(15)-C(20)-C(14)	117.6(3)	C(24)-C(25)-H(25A)	119.9
C(22)-C(21)-C(26)	120.8(3)	C(25)-C(26)-C(21)	119.1(3)
C(22)-C(21)-H(21A)	119.6	C(25)-C(26)-C(7)	122.5(2)
C(26)-C(21)-H(21A)	119.6	C(21)-C(26)-C(7)	118.4(2)
C(23)-C(22)-C(21)	119.4(3)		

Symmetry transformations used to generate equivalent atoms:

Table 68. Anisotropic displacement parameters ($Å^2x10^3$) for **245**.

The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl	46(1)	23(1)	29(1)	3(1)	8(1)	-2(1)
N	37(1)	28(1)	22(1)	-1(1)	3(1)	3(1)
C(1)	33(1)	18(1)	27(1)	1(1)	5(1)	0(1)
C(2)	32(1)	22(1)	28(1)	1(1)	4(1)	2(1)
C(3)	39(1)	22(1)	24(1)	-3(1)	5(1)	-3(1)

C(4)	34(1)	21(1)	24(1)	1(1)	4(1)	-2(1)
C(5)	31(1)	24(1)	31(1)	2(1)	6(1)	-4(1)
C(6)	33(1)	32(1)	32(1)	3(1)	6(1)	1(1)
C(7)	37(1)	21(1)	26(1)	0(1)	8(1)	-4(1)
C(8)	35(1)	36(1)	28(1)	-2(1)	3(1)	2(1)
C(9)	34(1)	45(2)	35(1)	1(1)	6(1)	-9(1)
C(10)	39(1)	58(2)	28(1)	0(1)	10(1)	-1(1)
C(11)	40(1)	45(2)	24(1)	-4(1)	4(1)	2(1)
C(12)	35(1)	28(1)	26(1)	0(1)	4(1)	3(1)
C(13)	32(1)	24(1)	25(1)	2(1)	1(1)	3(1)
C(14)	38(1)	27(1)	33(1)	4(1)	1(1)	-4(1)
C(15)	42(1)	39(2)	53(2)	4(1)	-13(1)	-6(1)
C(16)	52(2)	39(2)	78(3)	-3(2)	-27(2)	5(2)
C(17)	44(2)	46(2)	82(3)	-26(2)	-23(2)	12(1)
C(18)	40(1)	66(2)	64(2)	-20(2)	-3(1)	3(2)
C(19)	38(2)	49(2)	52(2)	0(1)	0(1)	6(1)
C(20)	35(1)	30(1)	46(2)	-3(1)	-5(1)	-4(1)
C(21)	53(2)	26(1)	37(2)	1(1)	14(1)	4(1)
C(22)	67(2)	31(2)	55(2)	13(1)	26(2)	20(2)
C(23)	48(2)	63(2)	62(2)	23(2)	25(2)	30(2)
C(24)	40(2)	51(2)	54(2)	8(2)	10(1)	5(1)
C(25)	38(1)	33(1)	38(2)	2(1)	9(1)	6(1)
C(26)	42(1)	25(1)	22(1)	3(1)	9(1)	4(1)
C(4)	34(1)	21(1)	24(1)	1(1)	4(1)	-2(1)

Table 69. Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2x10^3$) for **245**.

	x	y	z	U(eq)
H(0A)	-9982	-3810	-4657	35
H(1)	-11260(20)	-5360(30)	-1640(20)	27(7)
H(3A)	-9013	-2746	88	34
H(3B)	-10181	-1744	-529	34
H(6A)	-7573	-3576	-3566	39
H(6B)	-8143	-5153	-3711	39
H(7A)	-9446	-1803	-2894	33
H(8A)	-12729	-5647	317	39
H(9A)	-13777	-6025	2140	46
H(10A)	-13185	-4681	3931	49
H(11A)	-11563	-2946	3862	43
H(12A)	-10509	-2559	2039	36
H(14A)	-7940	-4824	-292	39
H(15A)	-6541	-6701	437	54
H(16A)	-4706	-8144	279	69
H(17A)	-3483	-8000	-1448	70
H(18A)	-4045	-6371	-3023	68
H(19A)	-5922	-4961	-2906	56
H(21A)	-10875	7	-3118	45
H(22A)	-12939	964	-3642	60
H(23A)	-14710	-537	-4115	68
H(24A)	-14445	-2983	-4015	58
H(25A)	-12376	-3946	-3450	43

APPENDIX H

X-RAY DATA FOR 247I

Table 70. Crystal data and structure refinement for **247i**.

Identification code	mw80406s	
Empirical formula	$C_{32}H_{28}BrNO_2S$	
Formula weight	570.52	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 11.149(3) Å	α= 72.111(6)°.
	b = 13.216(4) Å	β= 79.891(7)°.
	c = 19.913(6) Å	γ = 81.576(7)°.
Volume	2735.4(14) $Å^3$	
Z	4	
Density (calculated)	1.385 Mg/m^3	
Absorption coefficient	1.609 mm^{-1}	
F(000)	1176	
Crystal size	0.26 x 0.09 x 0.09 mm^3	

Theta range for data collection	1.63 to 25.00°.
Index ranges	-13<=h<=13, -15<=k<=15, -23<=l<=23
Reflections collected	21894
Independent reflections	9573 [R(int) = 0.1080]
Completeness to theta = 25.00°	99.5 %
Absorption correction	None
Max. and min. transmission	0.8687 and 0.6798
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9573 / 0 / 668
Goodness-of-fit on F^2	0.860
Final R indices [I>2sigma(I)]	R1 = 0.0874, wR2 = 0.1908
R indices (all data)	R1 = 0.2881, wR2 = 0.2323
Extinction coefficient	0.0005(3)
Largest diff. peak and hole	0.747 and -0.381 e·Å^{-3}

Table 71. Atomic coordinates (x10^4) and equivalent isotropic displacement parameters (Å^{2}x10^3) for **247i**.

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	2572(2)	-44(1)	4545(1)	104(1)
Br(2)	7432(2)	5056(2)	10457(1)	107(1)
S(1)	2520(3)	-2442(3)	7870(2)	48(1)
S(2)	7454(4)	7430(2)	7134(2)	49(1)
O(1)	3655(8)	-3114(5)	7948(4)	54(2)
O(2)	1380(8)	-2877(7)	8122(4)	58(3)
O(3)	6343(8)	8077(6)	7048(4)	60(3)
O(4)	8601(8)	7895(6)	6883(5)	71(3)

N(1)	2534(8)	-1539(7)	8250(5)	38(2)
N(2)	7458(11)	6512(8)	6740(5)	53(3)
C(1)	1376(11)	-781(8)	8300(7)	56(4)
C(2)	1917(10)	63(8)	8517(6)	38(3)
C(3)	1442(12)	1260(9)	8297(7)	50(3)
C(4)	2685(14)	1674(10)	7873(8)	65(4)
C(5)	3062(14)	885(10)	7424(7)	66(4)
C(6)	3212(12)	80(10)	8162(7)	49(3)
C(7)	3649(12)	-1118(8)	8304(5)	42(3)
C(8)	3684(12)	993(8)	8351(5)	40(3)
C(9)	3496(13)	-2297(10)	9598(7)	56(4)
C(10)	3901(16)	-2691(13)	10249(7)	84(5)
C(11)	4893(17)	-2382(18)	10333(10)	116(7)
C(12)	5610(15)	-1747(15)	9818(12)	109(7)
C(13)	5175(16)	-1260(12)	9114(9)	83(5)
C(14)	4097(11)	-1609(10)	9030(7)	49(3)
C(15)	1192(15)	1503(11)	9535(7)	70(4)
C(16)	697(16)	2046(12)	10032(7)	73(5)
C(17)	-162(15)	2901(15)	9854(10)	89(5)
C(18)	-451(17)	3255(15)	9173(13)	115(7)
C(19)	18(14)	2707(9)	8704(9)	78(5)
C(20)	864(13)	1805(10)	8866(6)	52(4)
C(21)	2765(16)	3521(11)	7947(8)	80(5)
C(22)	2576(18)	4593(12)	7663(10)	103(7)
C(23)	2225(18)	5066(10)	7012(10)	103(7)
C(24)	2120(17)	4439(12)	6609(9)	111(7)
C(25)	2360(13)	3321(10)	6838(6)	56(4)

C(26)	2602(13)	2841(10)	7544(6)	55(4)
C(27)	1417(14)	-1584(8)	6648(7)	61(4)
C(28)	1462(14)	-1013(9)	5936(6)	52(4)
C(29)	2609(15)	-801(8)	5544(7)	58(4)
C(30)	3651(13)	-972(15)	5834(9)	107(7)
C(31)	3627(14)	-1479(11)	6564(7)	61(4)
C(32)	2472(13)	-1811(10)	6989(6)	51(4)
C(33)	8557(12)	5789(11)	6699(6)	63(4)
C(34)	8115(12)	4940(10)	6431(7)	55(4)
C(35)	8547(13)	3745(9)	6698(5)	47(3)
C(36)	7313(11)	3309(8)	7139(5)	37(3)
C(37)	6350(14)	3976(10)	6662(8)	68(4)
C(38)	6767(11)	4916(8)	6811(6)	41(3)
C(39)	6296(11)	6080(10)	6727(7)	57(4)
C(40)	6932(11)	4125(9)	7561(5)	41(3)
C(41)	9927(12)	2331(12)	6306(6)	65(4)
C(42)	10461(13)	1811(11)	5787(9)	72(5)
C(43)	10077(15)	2132(13)	5134(8)	76(5)
C(44)	9289(14)	2984(14)	4949(9)	82(5)
C(45)	8793(14)	3560(12)	5429(6)	60(4)
C(46)	9098(11)	3221(10)	6127(7)	51(4)
C(47)	7726(16)	1670(10)	8075(9)	81(5)
C(48)	7905(16)	596(12)	8403(6)	94(6)
C(49)	7788(16)	-65(14)	8005(8)	96(6)
C(50)	7425(17)	362(12)	7348(8)	92(6)
C(51)	7207(17)	1470(11)	7071(8)	87(6)
C(52)	7317(13)	2108(9)	7443(7)	56(4)

C(53)	4816(14)	6273(13)	5862(10)	92(6)
C(54)	4440(20)	6649(16)	5204(11)	124(8)
C(55)	5030(20)	7386(14)	4653(10)	117(8)
C(56)	6072(19)	7686(14)	4810(9)	101(6)
C(57)	6488(15)	7273(13)	5453(7)	81(5)
C(58)	5833(13)	6559(9)	6004(7)	55(4)
C(59)	8507(12)	6545(11)	8310(8)	61(4)
C(60)	8513(17)	6072(12)	9031(10)	88(6)
C(61)	7500(16)	5625(13)	9493(6)	82(5)
C(62)	6413(14)	5975(7)	9176(6)	65(4)
C(63)	6421(14)	6501(10)	8493(7)	57(4)
C(64)	7427(11)	6765(7)	8074(6)	33(3)

Table 72. Bond lengths [Å] and angles [°] for **247i**.

Br(1)-C(29)	1.937(13)	N(2)-C(33)	1.445(16)
Br(2)-C(61)	1.826(12)	N(2)-C(39)	1.497(15)
S(1)-O(2)	1.418(9)	C(1)-C(2)	1.543(15)
S(1)-O(1)	1.438(9)	C(1)-H(1A)	0.99
S(1)-N(1)	1.601(9)	C(1)-H(1B)	0.99
S(1)-C(32)	1.702(12)	C(2)-C(6)	1.492(16)
S(2)-O(3)	1.404(8)	C(2)-C(3)	1.544(15)
S(2)-O(4)	1.442(8)	C(2)-H(2A)	1
S(2)-N(2)	1.634(11)	C(3)-C(20)	1.525(16)
S(2)-C(64)	1.804(11)	C(3)-C(4)	1.569(19)
N(1)-C(7)	1.466(14)	C(3)-H(3A)	1
N(1)-C(1)	1.522(13)	C(4)-C(26)	1.475(17)

C(4)-C(5)	1.540(18)	C(17)-C(18)	1.37(2)
C(4)-C(8)	1.585(17)	C(17)-H(17A)	0.95
C(5)-C(6)	1.546(16)	C(18)-C(19)	1.34(2)
C(5)-H(5A)	0.99	C(18)-H(18A)	0.95
C(5)-H(5B)	0.99	C(19)-C(20)	1.398(17)
C(6)-C(7)	1.540(15)	C(19)-H(19A)	0.95
C(6)-C(8)	1.553(15)	C(21)-C(22)	1.354(19)
C(7)-C(14)	1.530(16)	C(21)-C(26)	1.423(17)
C(7)-H(7A)	1	C(21)-H(21A)	0.95
C(8)-H(8A)	0.99	C(22)-C(23)	1.35(2)
C(8)-H(8B)	0.99	C(22)-H(22A)	0.95
C(9)-C(14)	1.356(17)	C(23)-C(24)	1.35(2)
C(9)-C(10)	1.369(17)	C(23)-H(23A)	0.95
C(9)-H(9A)	0.95	C(24)-C(25)	1.406(18)
C(10)-C(11)	1.29(2)	C(24)-H(24A)	0.95
C(10)-H(10A)	0.95	C(25)-C(26)	1.410(15)
C(11)-C(12)	1.33(2)	C(25)-H(25A)	0.95
C(11)-H(11A)	0.95	C(27)-C(28)	1.383(15)
C(12)-C(13)	1.49(2)	C(27)-C(32)	1.408(16)
C(12)-H(12A)	0.95	C(27)-H(27A)	0.95
C(13)-C(14)	1.401(18)	C(28)-C(29)	1.395(18)
C(13)-H(13A)	0.95	C(28)-H(28A)	0.95
C(15)-C(20)	1.367(17)	C(29)-C(30)	1.347(19)
C(15)-C(16)	1.388(18)	C(30)-C(31)	1.40(2)
C(15)-H(15A)	0.95	C(30)-H(30A)	0.95
C(16)-C(17)	1.37(2)	C(31)-C(32)	1.457(18)
C(16)-H(16A)	0.95	C(31)-H(31A)	0.95

C(33)-C(34)	1.553(17)	C(43)-H(43A)	0.95
C(33)-H(33A)	0.99	C(44)-C(45)	1.392(17)
C(33)-H(33B)	0.99	C(44)-H(44A)	0.95
C(34)-C(35)	1.535(16)	C(45)-C(46)	1.409(17)
C(34)-C(38)	1.560(17)	C(45)-H(45A)	0.95
C(34)-H(34A)	1	C(47)-C(52)	1.344(18)
C(35)-C(46)	1.504(16)	C(47)-C(48)	1.368(19)
C(35)-C(36)	1.579(16)	C(47)-H(47A)	0.95
C(35)-H(35A)	1	C(48)-C(49)	1.379(19)
C(36)-C(52)	1.515(15)	C(48)-H(48A)	0.95
C(36)-C(40)	1.531(14)	C(49)-C(50)	1.36(2)
C(36)-C(37)	1.550(18)	C(49)-H(49A)	0.95
C(37)-C(38)	1.514(16)	C(50)-C(51)	1.397(19)
C(37)-H(37A)	0.99	C(50)-H(50A)	0.95
C(37)-H(37B)	0.99	C(51)-C(52)	1.312(17)
C(38)-C(39)	1.518(16)	C(51)-H(51A)	0.95
C(38)-C(40)	1.560(15)	C(53)-C(58)	1.347(18)
C(39)-C(58)	1.530(16)	C(53)-C(54)	1.37(2)
C(39)-H(39A)	1	C(53)-H(53A)	0.95
C(40)-H(40A)	0.99	C(54)-C(55)	1.36(3)
C(40)-H(40B)	0.99	C(54)-H(54A)	0.95
C(41)-C(46)	1.380(17)	C(55)-C(56)	1.39(2)
C(41)-C(42)	1.413(18)	C(55)-H(55A)	0.95
C(41)-H(41A)	0.95	C(56)-C(57)	1.363(19)
C(42)-C(43)	1.362(19)	C(56)-H(56A)	0.95
C(42)-H(42A)	0.95	C(57)-C(58)	1.383(19)
C(43)-C(44)	1.32(2)	C(57)-H(57A)	0.95

C(59)-C(64)	1.329(17)	C(39)-N(2)-S(2)	121.1(9)
C(59)-C(60)	1.38(2)	N(1)-C(1)-C(2)	98.2(9)
C(59)-H(59A)	0.95	N(1)-C(1)-H(1A)	112.1
C(60)-C(61)	1.40(2)	C(2)-C(1)-H(1A)	112.1
C(60)-H(60A)	0.95	N(1)-C(1)-H(1B)	112.2
C(61)-C(62)	1.415(19)	C(2)-C(1)-H(1B)	112.1
C(62)-C(63)	1.323(15)	H(1A)-C(1)-H(1B)	109.8
C(62)-H(62A)	0.95	C(6)-C(2)-C(3)	102.0(10)
C(63)-C(64)	1.297(17)	C(6)-C(2)-C(1)	105.7(9)
C(63)-H(63A)	0.95	C(3)-C(2)-C(1)	122.6(9)
O(2)-S(1)-O(1)	120.9(5)	C(6)-C(2)-H(2A)	108.5
O(2)-S(1)-N(1)	107.1(5)	C(3)-C(2)-H(2A)	108.6
O(1)-S(1)-N(1)	107.4(5)	C(1)-C(2)-H(2A)	108.6
O(2)-S(1)-C(32)	104.8(6)	C(20)-C(3)-C(2)	120.1(10)
O(1)-S(1)-C(32)	108.9(6)	C(20)-C(3)-C(4)	114.4(10)
N(1)-S(1)-C(32)	107.2(5)	C(2)-C(3)-C(4)	96.3(9)
O(3)-S(2)-O(4)	120.2(6)	C(20)-C(3)-H(3A)	108.4
O(3)-S(2)-N(2)	106.7(6)	C(2)-C(3)-H(3A)	108.4
O(4)-S(2)-N(2)	107.6(6)	C(4)-C(3)-H(3A)	108.4
O(3)-S(2)-C(64)	107.2(6)	C(26)-C(4)-C(5)	122.0(12)
O(4)-S(2)-C(64)	107.3(6)	C(26)-C(4)-C(3)	113.4(11)
N(2)-S(2)-C(64)	107.3(5)	C(5)-C(4)-C(3)	100.3(10)
C(7)-N(1)-C(1)	114.2(8)	C(26)-C(4)-C(8)	125.6(12)
C(7)-N(1)-S(1)	124.1(7)	C(5)-C(4)-C(8)	86.0(9)
C(1)-N(1)-S(1)	117.5(7)	C(3)-C(4)-C(8)	104.2(11)
C(33)-N(2)-C(39)	115.3(9)	C(6)-C(5)-C(4)	82.3(10)
C(33)-N(2)-S(2)	117.8(9)	C(6)-C(5)-H(5A)	114.9

C(4)-C(5)-H(5A)	114.9	C(9)-C(10)-H(10A)	120.7
C(6)-C(5)-H(5B)	114.9	C(10)-C(11)-C(12)	124.7(16)
C(4)-C(5)-H(5B)	114.9	C(10)-C(11)-H(11A)	117.7
H(5A)-C(5)-H(5B)	112	C(12)-C(11)-H(11A)	117.6
C(2)-C(6)-C(5)	101.3(10)	C(11)-C(12)-C(13)	118.1(14)
C(2)-C(6)-C(7)	102.4(10)	C(11)-C(12)-H(12A)	121
C(5)-C(6)-C(7)	125.9(10)	C(13)-C(12)-H(12A)	120.9
C(2)-C(6)-C(8)	103.7(10)	C(14)-C(13)-C(12)	116.1(15)
C(5)-C(6)-C(8)	87.0(9)	C(14)-C(13)-H(13A)	121.9
C(7)-C(6)-C(8)	132.1(10)	C(12)-C(13)-H(13A)	122
N(1)-C(7)-C(14)	113.3(9)	C(9)-C(14)-C(13)	118.5(14)
N(1)-C(7)-C(6)	100.8(9)	C(9)-C(14)-C(7)	125.0(12)
C(14)-C(7)-C(6)	112.7(9)	C(13)-C(14)-C(7)	116.4(13)
N(1)-C(7)-H(7A)	109.9	C(20)-C(15)-C(16)	122.1(14)
C(14)-C(7)-H(7A)	109.9	C(20)-C(15)-H(15A)	119
C(6)-C(7)-H(7A)	109.9	C(16)-C(15)-H(15A)	118.9
C(6)-C(8)-C(4)	80.7(8)	C(17)-C(16)-C(15)	119.3(15)
C(6)-C(8)-H(8A)	115.2	C(17)-C(16)-H(16A)	120.3
C(4)-C(8)-H(8A)	115.2	C(15)-C(16)-H(16A)	120.4
C(6)-C(8)-H(8B)	115.1	C(16)-C(17)-C(18)	119.5(17)
C(4)-C(8)-H(8B)	115.2	C(16)-C(17)-H(17A)	120.3
H(8A)-C(8)-H(8B)	112.2	C(18)-C(17)-H(17A)	120.2
C(14)-C(9)-C(10)	123.5(14)	C(19)-C(18)-C(17)	120.1(18)
C(14)-C(9)-H(9A)	118.2	C(19)-C(18)-H(18A)	119.9
C(10)-C(9)-H(9A)	118.3	C(17)-C(18)-H(18A)	120
C(11)-C(10)-C(9)	118.7(15)	C(18)-C(19)-C(20)	122.5(16)
C(11)-C(10)-H(10A)	120.6	C(18)-C(19)-H(19A)	118.8

C(20)-C(19)-H(19A)	118.7	C(29)-C(28)-H(28A)	121.1
C(15)-C(20)-C(19)	116.2(13)	C(30)-C(29)-C(28)	124.0(13)
C(15)-C(20)-C(3)	123.1(12)	C(30)-C(29)-Br(1)	121.1(13)
C(19)-C(20)-C(3)	120.5(12)	C(28)-C(29)-Br(1)	114.4(10)
C(22)-C(21)-C(26)	119.1(14)	C(29)-C(30)-C(31)	119.3(15)
C(22)-C(21)-H(21A)	120.4	C(29)-C(30)-H(30A)	120.4
C(26)-C(21)-H(21A)	120.5	C(31)-C(30)-H(30A)	120.3
C(21)-C(22)-C(23)	123.6(15)	C(30)-C(31)-C(32)	118.9(13)
C(21)-C(22)-H(22A)	118.2	C(30)-C(31)-H(31A)	120.5
C(23)-C(22)-H(22A)	118.2	C(32)-C(31)-H(31A)	120.5
C(24)-C(23)-C(22)	118.3(13)	C(27)-C(32)-C(31)	118.4(12)
C(24)-C(23)-H(23A)	120.9	C(27)-C(32)-S(1)	125.5(11)
C(22)-C(23)-H(23A)	120.9	C(31)-C(32)-S(1)	116.2(10)
C(23)-C(24)-C(25)	122.6(14)	N(2)-C(33)-C(34)	101.8(10)
C(23)-C(24)-H(24A)	118.7	N(2)-C(33)-H(33A)	111.4
C(25)-C(24)-H(24A)	118.7	C(34)-C(33)-H(33A)	111.4
C(24)-C(25)-C(26)	117.9(13)	N(2)-C(33)-H(33B)	111.5
C(24)-C(25)-H(25A)	121	C(34)-C(33)-H(33B)	111.5
C(26)-C(25)-H(25A)	121.1	H(33A)-C(33)-H(33B)	109.3
C(25)-C(26)-C(21)	117.9(12)	C(35)-C(34)-C(33)	122.3(11)
C(25)-C(26)-C(4)	122.4(11)	C(35)-C(34)-C(38)	99.0(10)
C(21)-C(26)-C(4)	119.7(12)	C(33)-C(34)-C(38)	100.5(10)
C(28)-C(27)-C(32)	121.0(14)	C(35)-C(34)-H(34A)	111.1
C(28)-C(27)-H(27A)	119.5	C(33)-C(34)-H(34A)	111.1
C(32)-C(27)-H(27A)	119.5	C(38)-C(34)-H(34A)	111.2
C(27)-C(28)-C(29)	117.7(12)	C(46)-C(35)-C(34)	115.5(9)
C(27)-C(28)-H(28A)	121.2	C(46)-C(35)-C(36)	114.2(9)

C(34)-C(35)-C(36)	99.9(10)	C(38)-C(39)-H(39A)	111.9
C(46)-C(35)-H(35A)	109	C(36)-C(40)-C(38)	83.2(7)
C(34)-C(35)-H(35A)	108.9	C(36)-C(40)-H(40A)	114.7
C(36)-C(35)-H(35A)	108.9	C(38)-C(40)-H(40A)	114.7
C(52)-C(36)-C(40)	125.9(10)	C(36)-C(40)-H(40B)	114.8
C(52)-C(36)-C(37)	121.2(10)	C(38)-C(40)-H(40B)	114.8
C(40)-C(36)-C(37)	84.9(9)	H(40A)-C(40)-H(40B)	111.9
C(52)-C(36)-C(35)	116.8(11)	C(46)-C(41)-C(42)	119.6(13)
C(40)-C(36)-C(35)	99.3(8)	C(46)-C(41)-H(41A)	120.3
C(37)-C(36)-C(35)	102.2(9)	C(42)-C(41)-H(41A)	120.2
C(38)-C(37)-C(36)	84.2(10)	C(43)-C(42)-C(41)	119.9(14)
C(38)-C(37)-H(37A)	114.7	C(43)-C(42)-H(42A)	120
C(36)-C(37)-H(37A)	114.6	C(41)-C(42)-H(42A)	120.1
C(38)-C(37)-H(37B)	114.6	C(44)-C(43)-C(42)	121.4(13)
C(36)-C(37)-H(37B)	114.6	C(44)-C(43)-H(43A)	119.3
H(37A)-C(37)-H(37B)	111.7	C(42)-C(43)-H(43A)	119.3
C(37)-C(38)-C(39)	136.2(11)	C(43)-C(44)-C(45)	120.6(15)
C(37)-C(38)-C(34)	102.7(10)	C(43)-C(44)-H(44A)	119.8
C(39)-C(38)-C(34)	105.0(9)	C(45)-C(44)-H(44A)	119.7
C(37)-C(38)-C(40)	85.1(8)	C(44)-C(45)-C(46)	120.3(14)
C(39)-C(38)-C(40)	121.0(9)	C(44)-C(45)-H(45A)	119.9
C(34)-C(38)-C(40)	101.6(10)	C(46)-C(45)-H(45A)	119.8
N(2)-C(39)-C(58)	111.7(11)	C(41)-C(46)-C(45)	118.0(12)
N(2)-C(39)-C(38)	99.7(10)	C(41)-C(46)-C(35)	117.8(12)
C(58)-C(39)-C(38)	109.0(10)	C(45)-C(46)-C(35)	124.2(12)
N(2)-C(39)-H(39A)	111.9	C(52)-C(47)-C(48)	124.9(13)
C(58)-C(39)-H(39A)	112	C(52)-C(47)-H(47A)	117.5

C(48)-C(47)-H(47A)	117.5
C(47)-C(48)-C(49)	116.0(14)
C(47)-C(48)-H(48A)	122
C(49)-C(48)-H(48A)	122
C(50)-C(49)-C(48)	119.8(16)
C(50)-C(49)-H(49A)	120
C(48)-C(49)-H(49A)	120.1
C(49)-C(50)-C(51)	119.9(15)
C(49)-C(50)-H(50A)	120.1
C(51)-C(50)-H(50A)	120
C(52)-C(51)-C(50)	120.9(15)
C(52)-C(51)-H(51A)	119.6
C(50)-C(51)-H(51A)	119.6
C(51)-C(52)-C(47)	118.0(13)
C(51)-C(52)-C(36)	124.0(13)
C(47)-C(52)-C(36)	116.4(11)
C(58)-C(53)-C(54)	122.4(17)
C(58)-C(53)-H(53A)	118.8
C(54)-C(53)-H(53A)	118.8
C(55)-C(54)-C(53)	122.7(19)
C(55)-C(54)-H(54A)	118.6
C(53)-C(54)-H(54A)	118.6
C(54)-C(55)-C(56)	114.2(17)
C(54)-C(55)-H(55A)	123
C(56)-C(55)-H(55A)	122.9
C(57)-C(56)-C(55)	123.5(19)
C(57)-C(56)-H(56A)	118.2
C(55)-C(56)-H(56A)	118.3
C(56)-C(57)-C(58)	120.1(16)
C(56)-C(57)-H(57A)	119.9
C(58)-C(57)-H(57A)	120
C(53)-C(58)-C(57)	116.9(14)
C(53)-C(58)-C(39)	122.3(12)
C(57)-C(58)-C(39)	120.7(12)
C(64)-C(59)-C(60)	117.3(14)
C(64)-C(59)-H(59A)	121.3
C(60)-C(59)-H(59A)	121.4
C(59)-C(60)-C(61)	123.3(14)
C(59)-C(60)-H(60A)	118.3
C(61)-C(60)-H(60A)	118.4
C(60)-C(61)-C(62)	111.2(12)
C(60)-C(61)-Br(2)	125.1(12)
C(62)-C(61)-Br(2)	120.7(11)
C(63)-C(62)-C(61)	122.5(14)
C(63)-C(62)-H(62A)	118.8
C(61)-C(62)-H(62A)	118.7
C(64)-C(63)-C(62)	122.0(13)
C(64)-C(63)-H(63A)	119
C(62)-C(63)-H(63A)	119
C(63)-C(64)-C(59)	121.9(12)
C(63)-C(64)-S(2)	122.3(10)
C(59)-C(64)-S(2)	115.8(10)

Symmetry transformations used to generate equivalent atoms:

Table 73. Anisotropic displacement parameters ($Å^2x10^3$) for **247i**.

The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	172(2)	81(1)	51(1)	-11(1)	-29(1)	14(1)
Br(2)	178(2)	82(1)	49(1)	-11(1)	-26(1)	20(1)
S(1)	43(2)	50(2)	55(2)	-13(2)	-21(2)	-3(2)
S(2)	73(3)	29(2)	49(2)	-12(2)	-13(2)	-12(2)
O(1)	54(6)	24(4)	76(6)	-7(4)	9(5)	-16(4)
O(2)	57(6)	72(6)	67(6)	-37(5)	-36(5)	-3(5)
O(3)	75(6)	61(6)	55(5)	-30(4)	-54(5)	40(5)
O(4)	77(7)	42(5)	84(7)	8(5)	9(6)	-49(5)
N(1)	19(5)	52(6)	58(6)	-33(5)	-14(5)	0(5)
N(2)	68(8)	31(6)	54(7)	-4(5)	-5(6)	-8(6)
C(1)	51(8)	25(6)	98(10)	-30(6)	-24(8)	27(6)
C(2)	32(7)	25(6)	51(7)	-6(5)	-8(6)	7(5)
C(3)	43(8)	49(8)	72(9)	-40(7)	-9(7)	1(7)
C(4)	72(10)	43(8)	93(11)	-41(8)	-31(9)	21(8)
C(5)	68(10)	52(8)	59(9)	12(7)	1(8)	-18(8)
C(6)	54(9)	52(8)	58(8)	-26(7)	-36(7)	-2(7)
C(7)	63(9)	32(6)	24(6)	-11(5)	10(6)	6(6)
C(8)	62(9)	35(6)	23(6)	-4(5)	-5(6)	-14(6)
C(9)	57(9)	50(8)	58(9)	-18(7)	9(7)	-10(7)
C(10)	99(14)	103(12)	39(8)	17(7)	-29(9)	-27(11)
C(11)	72(12)	190(20)	73(13)	-12(13)	-39(11)	12(14)
C(12)	61(11)	139(16)	170(20)	-78(15)	-37(12)	-43(11)
C(13)	95(13)	66(10)	94(12)	-17(9)	-57(11)	10(9)

C(14)	23(7)	64(9)	74(10)	-44(8)	-11(7)	13(6)
C(15)	92(12)	52(8)	55(9)	-18(7)	4(9)	16(8)
C(16)	96(13)	78(10)	37(8)	-1(7)	-3(9)	-30(10)
C(17)	62(11)	114(15)	88(13)	-29(11)	-12(10)	10(10)
C(18)	101(15)	94(14)	180(20)	-82(15)	-69(15)	34(12)
C(19)	82(12)	23(6)	139(14)	-35(8)	-35(11)	14(7)
C(20)	76(10)	44(7)	33(7)	-7(6)	-13(7)	1(7)
C(21)	133(16)	54(9)	59(9)	-2(7)	-45(10)	-21(10)
C(22)	163(19)	49(9)	98(13)	-6(9)	-5(13)	-64(11)
C(23)	153(18)	18(7)	106(14)	9(8)	2(13)	11(9)
C(24)	159(18)	48(9)	100(13)	13(9)	-58(13)	48(10)
C(25)	76(10)	63(9)	18(5)	-3(5)	2(6)	-3(7)
C(26)	79(10)	58(8)	30(7)	-23(6)	22(7)	-29(8)
C(27)	88(10)	27(6)	69(9)	8(6)	-59(8)	3(7)
C(28)	79(10)	43(7)	30(6)	15(5)	-39(7)	-8(7)
C(29)	101(12)	13(5)	67(9)	-24(5)	-16(9)	2(6)
C(30)	47(9)	217(19)	105(13)	-132(14)	-7(9)	15(10)
C(31)	60(10)	77(10)	57(9)	-38(7)	0(8)	-13(8)
C(32)	66(9)	59(8)	49(7)	-42(6)	-21(7)	2(7)
C(33)	57(9)	104(11)	31(7)	-8(7)	4(7)	-57(9)
C(34)	62(9)	67(9)	38(7)	-23(7)	4(7)	-9(8)
C(35)	83(10)	37(7)	22(6)	-5(5)	-8(7)	-19(7)
C(36)	57(8)	42(7)	16(5)	-7(5)	9(6)	-35(6)
C(37)	67(10)	59(9)	88(11)	-44(8)	8(9)	-14(8)
C(38)	42(7)	29(6)	44(7)	-10(5)	21(6)	-10(6)
C(39)	41(8)	70(9)	82(10)	-34(8)	-22(7)	-32(7)
C(40)	48(8)	57(8)	30(6)	-33(6)	1(6)	-3(6)
C(41)	48(9)	107(11)	41(7)	-30(7)	-6(7)	10(9)

C(42)	48(9)	51(9)	122(14)	-45(9)	3(10)	8(7)
C(43)	85(12)	100(12)	78(11)	-84(10)	18(10)	-29(11)
C(44)	50(9)	124(14)	94(12)	-80(11)	-1(9)	19(10)
C(45)	78(11)	79(10)	26(7)	-17(7)	-16(7)	-5(8)
C(46)	29(7)	54(8)	84(10)	-42(7)	2(7)	-13(7)
C(47)	120(14)	36(8)	95(12)	-27(8)	-3(11)	-31(9)
C(48)	163(16)	110(12)	25(7)	-17(7)	8(8)	-95(12)
C(49)	119(15)	108(13)	65(11)	-9(9)	-15(10)	-56(11)
C(50)	142(16)	71(11)	73(11)	-47(9)	1(11)	0(11)
C(51)	155(18)	47(9)	69(10)	-30(8)	4(11)	-31(11)
C(52)	78(10)	27(7)	64(9)	-1(6)	-32(8)	-4(7)
C(53)	55(10)	97(13)	132(16)	-24(11)	-30(11)	-39(10)
C(54)	144(18)	123(16)	134(17)	-52(13)	-124(16)	47(14)
C(55)	210(20)	80(12)	76(13)	-17(10)	-72(15)	-24(14)
C(56)	126(17)	110(14)	82(12)	-62(11)	-19(12)	15(12)
C(57)	92(12)	113(13)	52(9)	-23(9)	-52(9)	-2(11)
C(58)	73(10)	35(7)	46(8)	8(6)	-11(7)	-10(7)
C(59)	45(8)	86(10)	82(10)	-69(9)	4(7)	-17(7)
C(60)	103(14)	75(11)	117(15)	-61(11)	-47(13)	4(10)
C(61)	88(11)	140(14)	14(6)	-22(7)	-24(7)	21(10)
C(62)	99(12)	15(5)	50(8)	31(5)	-3(8)	-6(6)
C(63)	79(11)	49(8)	48(8)	-23(6)	-36(8)	31(8)
C(64)	33(7)	8(5)	45(7)	8(4)	8(6)	-7(5)

Table 74. Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2x10^3$) for **247i**.

	x	y	z	U(eq)
H(1A)	724	-1126	8669	68
H(1B)	1060	-479	7837	68
H(2A)	1917	-183	9044	46
H(3A)	850	1376	7951	60
H(5A)	2401	765	7193	79
H(5B)	3833	1011	7091	79
H(7A)	4313	-1229	7917	51
H(8A)	4542	1131	8150	48
H(8B)	3503	969	8861	48
H(9A)	2755	-2517	9543	67
H(10A)	3459	-3183	10630	101
H(11A)	5130	-2624	10797	140
H(12A)	6378	-1610	9898	131
H(13A)	5602	-743	8742	99
H(15A)	1777	903	9664	84
H(16A)	951	1827	10490	87
H(17A)	-554	3246	10200	107
H(18A)	-983	3890	9032	138
H(19A)	-236	2940	8245	94
H(21A)	3003	3227	8408	96
H(22A)	2696	5038	7936	123
H(23A)	2057	5820	6844	124
H(24A)	1874	4766	6152	133
H(25A)	2359	2902	6527	67
H(27A)	665	-1827	6912	73
H(28A)	735	-772	5721	62

H(30A)	4395	-751	5546	128
H(31A)	4351	-1604	6779	73
H(33A)	8835	5467	7172	75
H(33B)	9227	6155	6358	75
H(34A)	8146	5180	5902	66
H(35A)	9155	3645	7032	56
H(37A)	6537	3973	6157	81
H(37B)	5492	3838	6861	81
H(39A)	5653	6167	7129	68
H(40A)	7593	4265	7784	50
H(40B)	6165	4004	7898	50
H(41A)	10138	2070	6775	78
H(42A)	11087	1239	5893	87
H(43A)	10383	1735	4805	91
H(44A)	9058	3205	4485	99
H(45A)	8248	4185	5286	72
H(47A)	7905	2141	8313	97
H(48A)	8097	323	8876	113
H(49A)	7960	-817	8189	115
H(50A)	7321	-92	7078	111
H(51A)	6976	1764	6608	105
H(53A)	4341	5792	6232	110
H(54A)	3745	6385	5127	148
H(55A)	4753	7671	4201	140
H(56A)	6516	8205	4450	121
H(57A)	7228	7477	5523	98
H(59A)	9243	6707	7995	73
H(60A)	9241	6049	9224	106

H(62A)	5649	5826	9465	78
H(63A)	5667	6692	8304	68

APPENDIX I

X-RAY DATA FOR 345

Table 75. Crystal data and strcture refinement for **345**.

Identification code	mw718s	
Empirical formula	$C_{20}H_{21}NO_3S$	
Formula weight	355.44	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 5.6829(5) Å	α= 90°.
	b = 18.5447(17) Å	β= 96.860(2)°.
	c = 16.8844(16) Å	γ = 90°.
Volume	1766.7(3) $Å^3$	
Z	4	
Density (calculated)	1.336 Mg/m^3	
Absorption coefficient	0.202 mm^{-1}	
F(000)	752	
Crystal size	0.28 x 0.25 x 0.18 mm^3	

Theta range for data collection	1.64 to 32.50°.
Index ranges	-8<=h<=8, -27<=k<=28, -25<=l<=25
Reflections collected	22665
Independent reflections	6232 [R(int) = 0.0256]
Completeness to theta = 32.50°	97.4 %
Absorption correction	None
Max. and min. transmission	0.9645 and 0.9456
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6232 / 0 / 226
Goodness-of-fit on F^2	1.346
Final R indices [I>2sigma(I)]	R1 = 0.0487, wR2 = 0.1397
R indices (all data)	R1 = 0.0581, wR2 = 0.1484
Largest diff. peak and hole	0.631 and -0.322 e·Å^{-3}

Table 76. Atomic coordinates (x10^4) and equivalent isotropic displacement parameters (Å^{2}x10^3) for **345**.

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	1190(1)	10285(1)	6966(1)	26(1)
O(1)	-1365(2)	8135(1)	6475(1)	35(1)
O(2)	1396(2)	10748(1)	6298(1)	37(1)
O(3)	-1084(2)	10134(1)	7208(1)	40(1)
N(1)	2402(2)	9522(1)	6774(1)	23(1)
C(1)	1725(2)	8853(1)	7157(1)	23(1)
C(2)	709(2)	8308(1)	6517(1)	24(1)
C(3)	2317(2)	8029(1)	5936(1)	26(1)
C(4)	2130(2)	8555(1)	5237(1)	28(1)
C(5)	4315(3)	8779(1)	4884(1)	34(1)

C(6)	3093(2)	9306(1)	5379(1)	27(1)
C(7)	4197(2)	9497(1)	6209(1)	23(1)
C(8)	4849(2)	11094(1)	7686(1)	29(1)
C(9)	6280(2)	11361(1)	8344(1)	36(1)
C(10)	5810(2)	11202(1)	9116(1)	40(1)
C(11)	3871(3)	10779(1)	9214(1)	42(1)
C(12)	2400(2)	10509(1)	8565(1)	34(1)
C(13)	2918(2)	10665(1)	7800(1)	24(1)
C(14)	7393(3)	11501(1)	9822(1)	62(1)
C(15)	5649(2)	8930(1)	8061(1)	26(1)
C(16)	7422(2)	8613(1)	8582(1)	31(1)
C(17)	7332(3)	7885(1)	8762(1)	38(1)
C(18)	5442(3)	7477(1)	8426(1)	42(1)
C(19)	3654(2)	7793(1)	7911(1)	35(1)
C(20)	3740(2)	8522(1)	7717(1)	24(1)

Table 77. Bond lengths [Å] and angles [°] for **345**.

S(1)-O(3)	1.4285(10)	C(2)-C(3)	1.5099(16)
S(1)-O(2)	1.4343(10)	C(3)-C(4)	1.5245(16)
S(1)-N(1)	1.6222(9)	C(3)-H(3A)	0.99
S(1)-C(13)	1.7639(11)	C(3)-H(3B)	0.99
O(1)-C(2)	1.2147(13)	C(4)-C(5)	1.4989(18)
N(1)-C(1)	1.4713(14)	C(4)-C(6)	1.5050(16)
N(1)-C(7)	1.4786(14)	C(4)-H(4A)	1
C(1)-C(20)	1.5254(15)	C(5)-C(6)	1.5077(17)
C(1)-C(2)	1.5412(15)	C(5)-H(5A)	0.99
C(1)-H(1A)	1	C(5)-H(5B)	0.99

C(6)-C(7)	1.5063(15)	C(19)-H(19A)	0.95
C(6)-H(6A)	1	O(3)-S(1)-O(2)	120.25(6)
C(7)-H(7A)	0.99	O(3)-S(1)-N(1)	107.86(5)
C(7)-H(7B)	0.99	O(2)-S(1)-N(1)	106.69(5)
C(8)-C(9)	1.3873(17)	O(3)-S(1)-C(13)	106.68(6)
C(8)-C(13)	1.3876(17)	O(2)-S(1)-C(13)	107.36(6)
C(8)-H(8A)	0.95	N(1)-S(1)-C(13)	107.41(5)
C(9)-C(10)	1.393(2)	C(1)-N(1)-C(7)	119.55(8)
C(9)-H(9A)	0.95	C(1)-N(1)-S(1)	120.46(7)
C(10)-C(11)	1.378(2)	C(7)-N(1)-S(1)	119.99(7)
C(10)-C(14)	1.5113(19)	N(1)-C(1)-C(20)	113.34(8)
C(11)-C(12)	1.3891(19)	N(1)-C(1)-C(2)	109.97(9)
C(11)-H(11A)	0.95	C(20)-C(1)-C(2)	111.16(9)
C(12)-C(13)	1.3894(17)	N(1)-C(1)-H(1A)	107.4
C(12)-H(12A)	0.95	C(20)-C(1)-H(1A)	107.4
C(14)-H(14A)	0.98	C(2)-C(1)-H(1A)	107.4
C(14)-H(14B)	0.98	O(1)-C(2)-C(3)	122.05(10)
C(14)-H(14C)	0.98	O(1)-C(2)-C(1)	119.55(10)
C(15)-C(16)	1.3865(16)	C(3)-C(2)-C(1)	118.34(9)
C(15)-C(20)	1.3908(15)	C(2)-C(3)-C(4)	107.03(9)
C(15)-H(15A)	0.95	C(2)-C(3)-H(3A)	110.3
C(16)-C(17)	1.3872(18)	C(4)-C(3)-H(3A)	110.3
C(16)-H(16A)	0.95	C(2)-C(3)-H(3B)	110.3
C(17)-C(18)	1.379(2)	C(4)-C(3)-H(3B)	110.3
C(17)-H(17A)	0.95	H(3A)-C(3)-H(3B)	108.6
C(18)-C(19)	1.3859(18)	C(5)-C(4)-C(6)	60.25(8)
C(18)-H(18A)	0.95	C(5)-C(4)-C(3)	120.03(11)
C(19)-C(20)	1.3936(16)	C(6)-C(4)-C(3)	118.54(9)

C(5)-C(4)-H(4A)	115.6	C(11)-C(10)-C(14)	121.58(15)
C(6)-C(4)-H(4A)	115.6	C(9)-C(10)-C(14)	119.84(16)
C(3)-C(4)-H(4A)	115.6	C(10)-C(11)-C(12)	121.66(13)
C(4)-C(5)-C(6)	60.07(8)	C(10)-C(11)-H(11A)	119.2
C(4)-C(5)-H(5A)	117.8	C(12)-C(11)-H(11A)	119.2
C(6)-C(5)-H(5A)	117.8	C(11)-C(12)-C(13)	118.94(13)
C(4)-C(5)-H(5B)	117.8	C(11)-C(12)-H(12A)	120.5
C(6)-C(5)-H(5B)	117.8	C(13)-C(12)-H(12A)	120.5
H(5A)-C(5)-H(5B)	114.9	C(8)-C(13)-C(12)	120.44(11)
C(4)-C(6)-C(7)	117.96(9)	C(8)-C(13)-S(1)	119.56(9)
C(4)-C(6)-C(5)	59.67(8)	C(12)-C(13)-S(1)	119.94(9)
C(7)-C(6)-C(5)	119.94(11)	C(10)-C(14)-H(14A)	109.5
C(4)-C(6)-H(6A)	115.9	C(10)-C(14)-H(14B)	109.5
C(7)-C(6)-H(6A)	115.9	H(14A)-C(14)-H(14B)	109.5
C(5)-C(6)-H(6A)	115.9	C(10)-C(14)-H(14C)	109.5
N(1)-C(7)-C(6)	111.37(9)	H(14A)-C(14)-H(14C)	109.5
N(1)-C(7)-H(7A)	109.4	H(14B)-C(14)-H(14C)	109.5
C(6)-C(7)-H(7A)	109.4	C(16)-C(15)-C(20)	120.37(11)
N(1)-C(7)-H(7B)	109.4	C(16)-C(15)-H(15A)	119.8
C(6)-C(7)-H(7B)	109.4	C(20)-C(15)-H(15A)	119.8
H(7A)-C(7)-H(7B)	108	C(15)-C(16)-C(17)	120.57(11)
C(9)-C(8)-C(13)	119.46(12)	C(15)-C(16)-H(16A)	119.7
C(9)-C(8)-H(8A)	120.3	C(17)-C(16)-H(16A)	119.7
C(13)-C(8)-H(8A)	120.3	C(18)-C(17)-C(16)	119.42(12)
C(8)-C(9)-C(10)	120.91(13)	C(18)-C(17)-H(17A)	120.3
C(8)-C(9)-H(9A)	119.5	C(16)-C(17)-H(17A)	120.3
C(10)-C(9)-H(9A)	119.5	C(17)-C(18)-C(19)	120.21(12)
C(11)-C(10)-C(9)	118.57(12)	C(17)-C(18)-H(18A)	119.9

C(19)-C(18)-H(18A)	119.9	C(15)-C(20)-C(19)	118.54(11)
C(18)-C(19)-C(20)	120.88(12)	C(15)-C(20)-C(1)	121.99(10)
C(18)-C(19)-H(19A)	119.6	C(19)-C(20)-C(1)	119.45(10)
C(20)-C(19)-H(19A)	119.6	Symmetry transformations used to generate equivalent atoms:	

Table 78. Anisotropic displacement parameters ($Å^2x10^3$) for **345**.

The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	25(1)	23(1)	28(1)	-5(1)	-5(1)	5(1)
O(1)	24(1)	38(1)	42(1)	-3(1)	-1(1)	-7(1)
O(2)	53(1)	26(1)	29(1)	1(1)	-10(1)	10(1)
O(3)	22(1)	39(1)	58(1)	-16(1)	1(1)	3(1)
N(1)	25(1)	20(1)	23(1)	-2(1)	2(1)	1(1)
C(1)	22(1)	24(1)	23(1)	-1(1)	1(1)	-2(1)
C(2)	23(1)	22(1)	25(1)	2(1)	-2(1)	-2(1)
C(3)	29(1)	22(1)	26(1)	-3(1)	0(1)	-3(1)
C(4)	34(1)	28(1)	21(1)	-3(1)	-2(1)	-5(1)
C(5)	44(1)	33(1)	26(1)	-4(1)	10(1)	-4(1)
C(6)	35(1)	24(1)	22(1)	1(1)	1(1)	-1(1)
C(7)	24(1)	22(1)	22(1)	-1(1)	1(1)	-3(1)
C(8)	28(1)	27(1)	30(1)	-6(1)	2(1)	2(1)
C(9)	27(1)	36(1)	44(1)	-14(1)	-2(1)	1(1)
C(10)	36(1)	43(1)	36(1)	-16(1)	-13(1)	15(1)
C(11)	52(1)	48(1)	24(1)	-4(1)	-1(1)	10(1)
C(12)	40(1)	35(1)	28(1)	-3(1)	5(1)	-2(1)
C(13)	26(1)	22(1)	24(1)	-4(1)	-1(1)	4(1)

C(14)	49(1)	82(1)	49(1)	-30(1)	-24(1)	17(1)
C(15)	28(1)	25(1)	23(1)	1(1)	-1(1)	-3(1)
C(16)	32(1)	34(1)	26(1)	3(1)	-5(1)	-3(1)
C(17)	45(1)	36(1)	30(1)	9(1)	-9(1)	2(1)
C(18)	61(1)	26(1)	34(1)	9(1)	-11(1)	-4(1)
C(19)	45(1)	28(1)	28(1)	5(1)	-7(1)	-9(1)
C(20)	27(1)	25(1)	18(1)	1(1)	1(1)	-3(1)

Table 79. Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2x10^3$) for **345.**

	x	y	z	U(eq)
H(1A)	426	8977	7484	27
H(3A)	1816	7541	5748	31
H(3B)	3973	8003	6194	31
H(4A)	655	8516	4852	34
H(5A)	4176	8860	4301	41
H(5B)	5850	8575	5121	41
H(6A)	2177	9699	5077	32
H(7A)	5419	9134	6393	27
H(7B)	4985	9972	6198	27
H(8A)	5189	11204	7162	34
H(9A)	7598	11657	8267	43
H(11A)	3531	10669	9738	50
H(12A)	1061	10223	8643	41
H(14A)	8668	11785	9632	93
H(14B)	8080	11102	10154	93
H(14C)	6459	11809	10138	93

H(15A)	5738	9428	7937	31
H(16A)	8709	8898	8817	37
H(17A)	8562	7669	9114	46
H(18A)	5366	6978	8548	50
H(19A)	2351	7508	7687	41

APPENDIX J

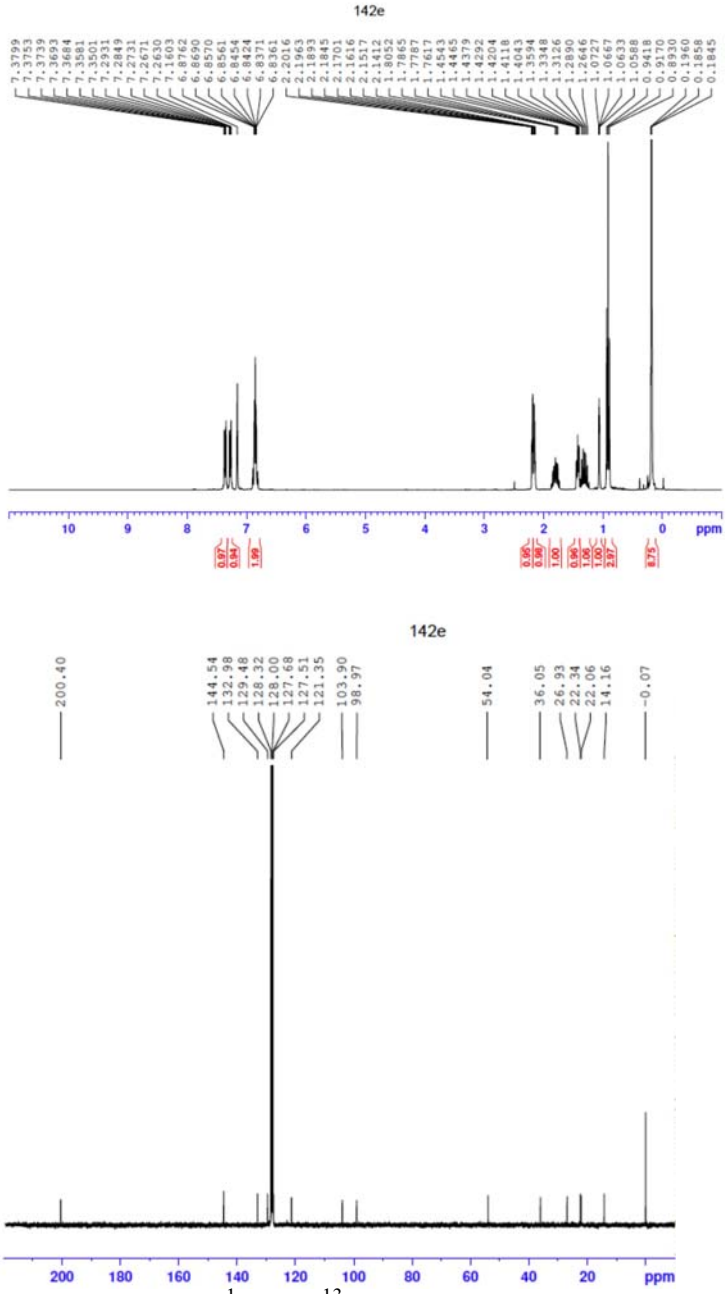


Figure 29. ^{1}H and ^{13}C NMR spectra of **142e**.

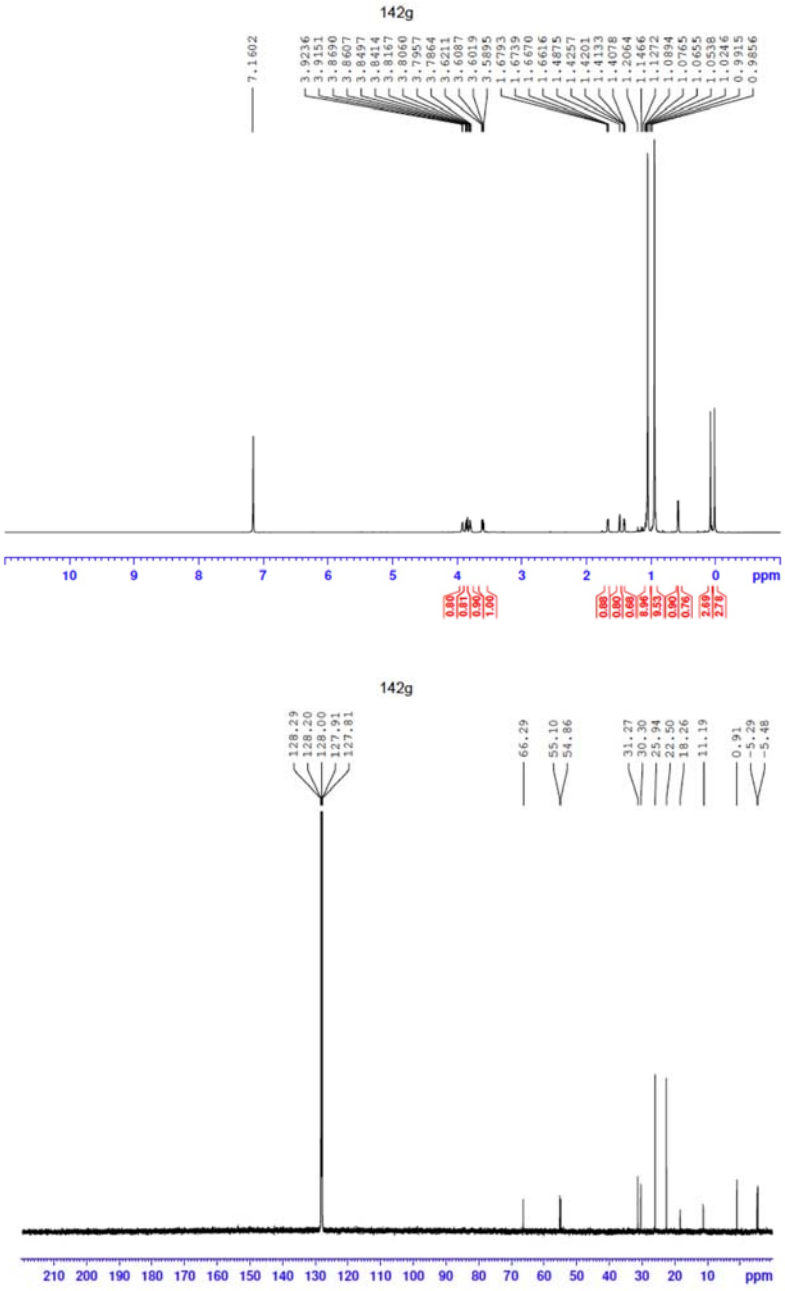


Figure 30. ^{1}H and ^{13}C NMR spectra of **142g**.

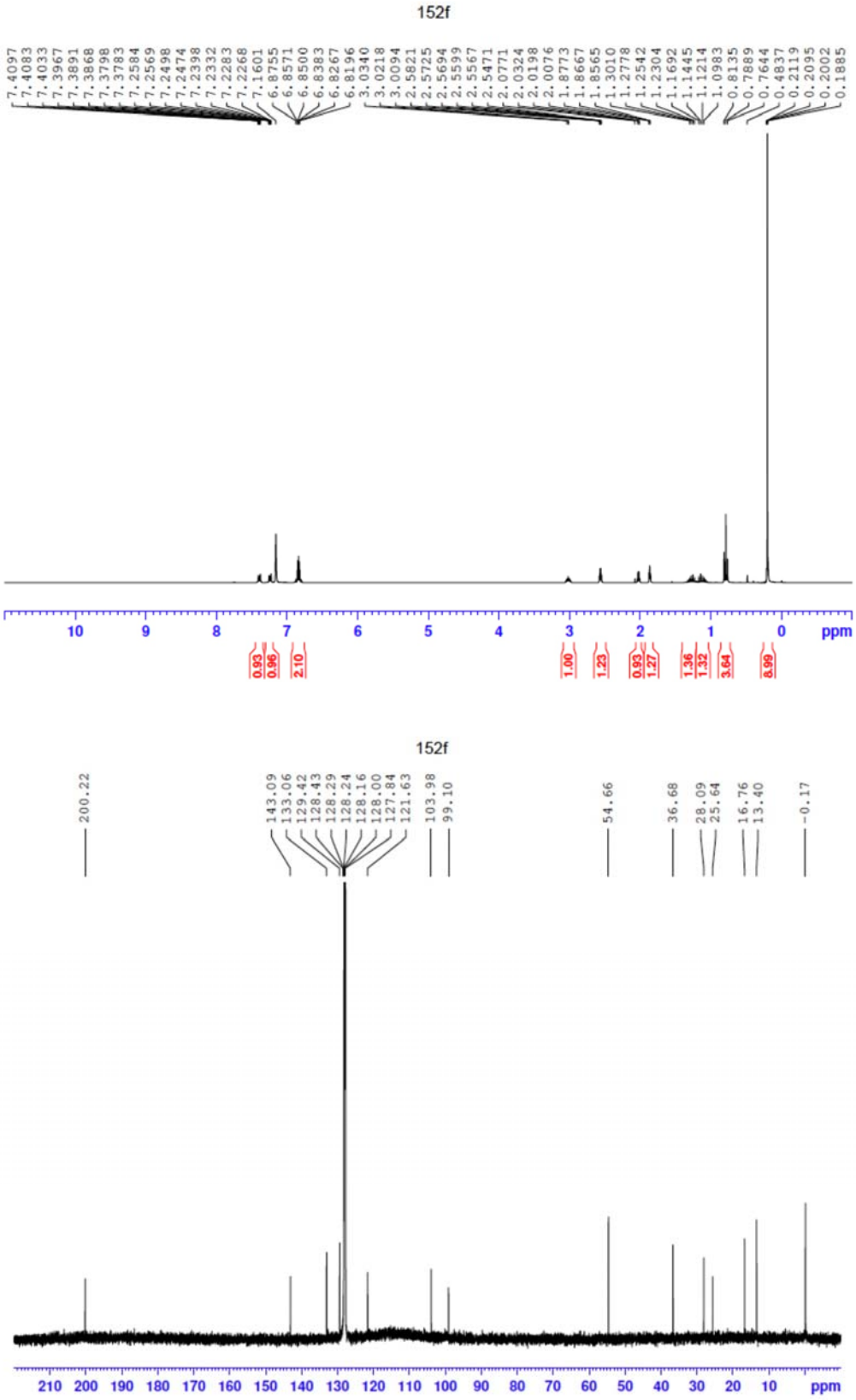


Figure 31. ^{1}H and ^{13}C NMR spectra of **152f**.

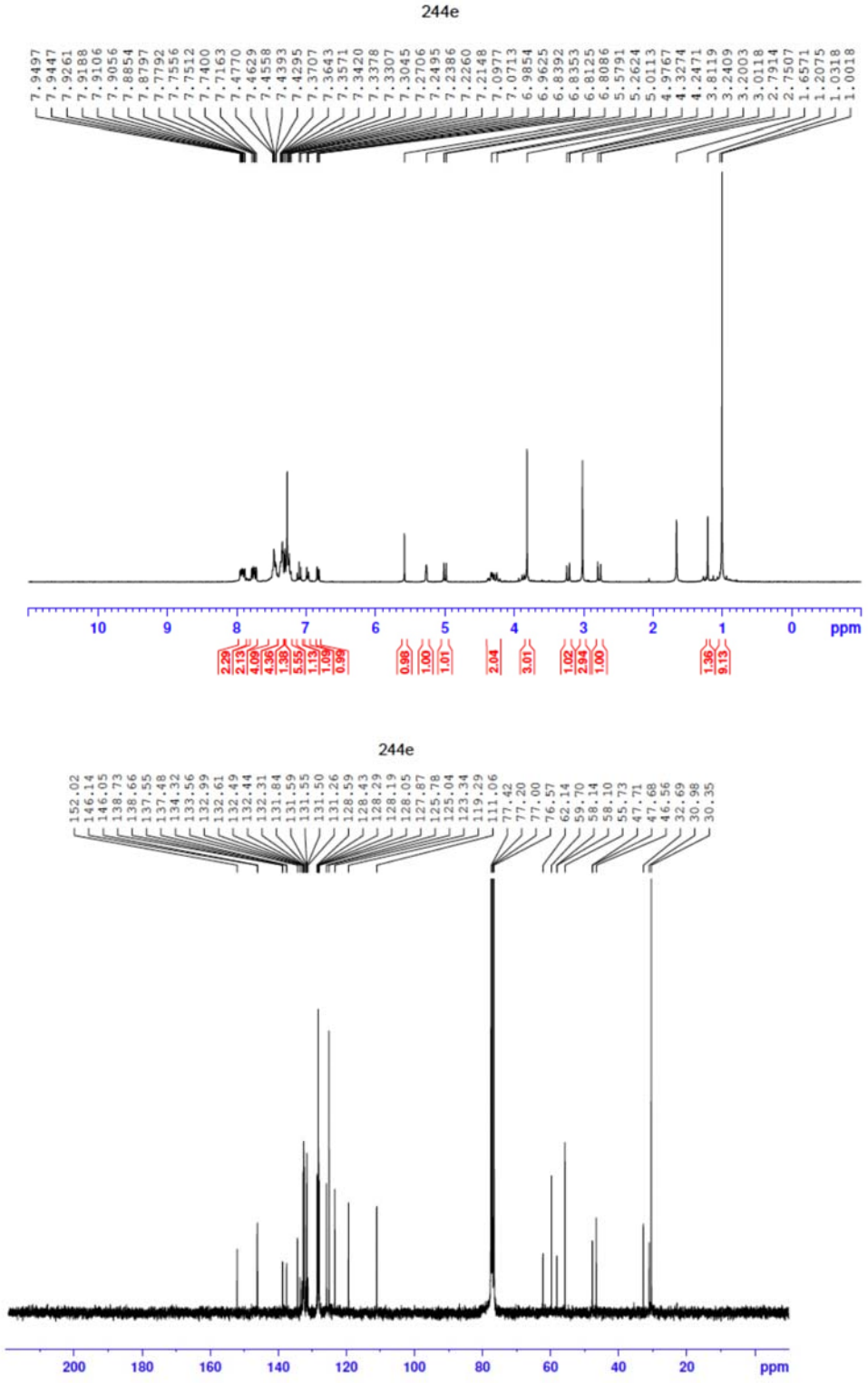


Figure 32. ^{1}H and ^{13}C NMR spectra of **244e**.

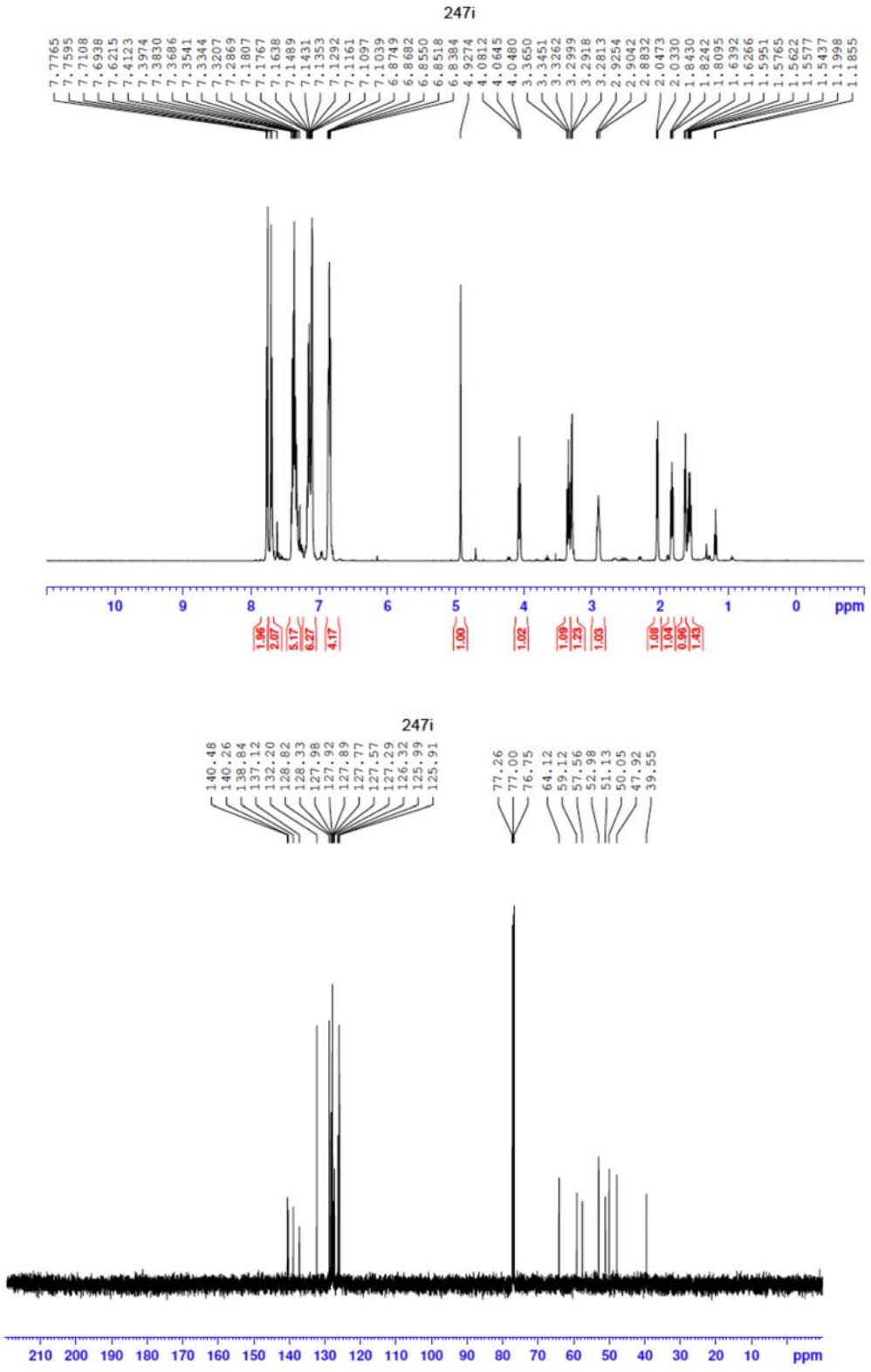


Figure 33. ^{1}H and ^{13}C NMR spectra of **247i**.

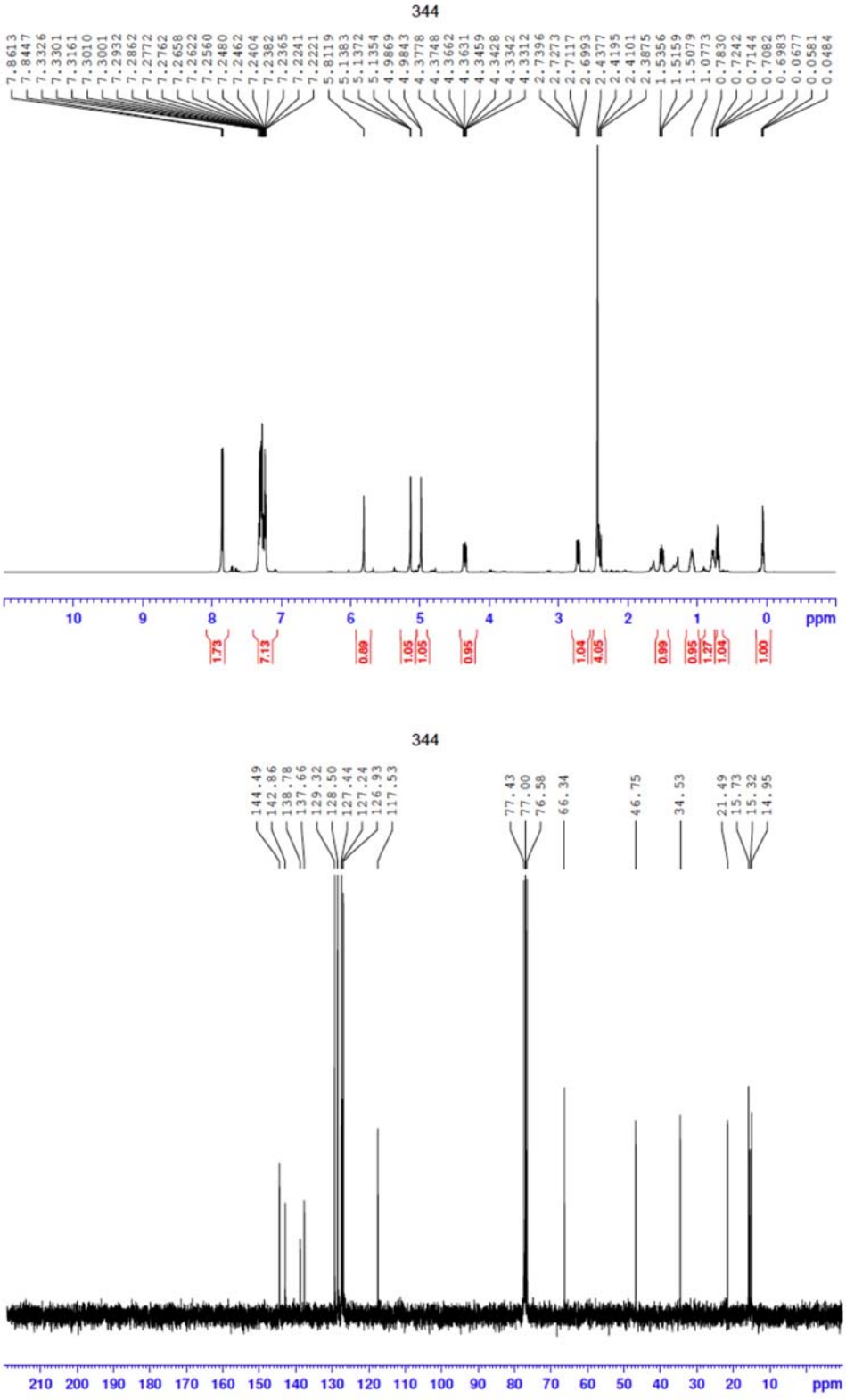


Figure 34. ^{1}H and ^{13}C NMR spectra of **344**.

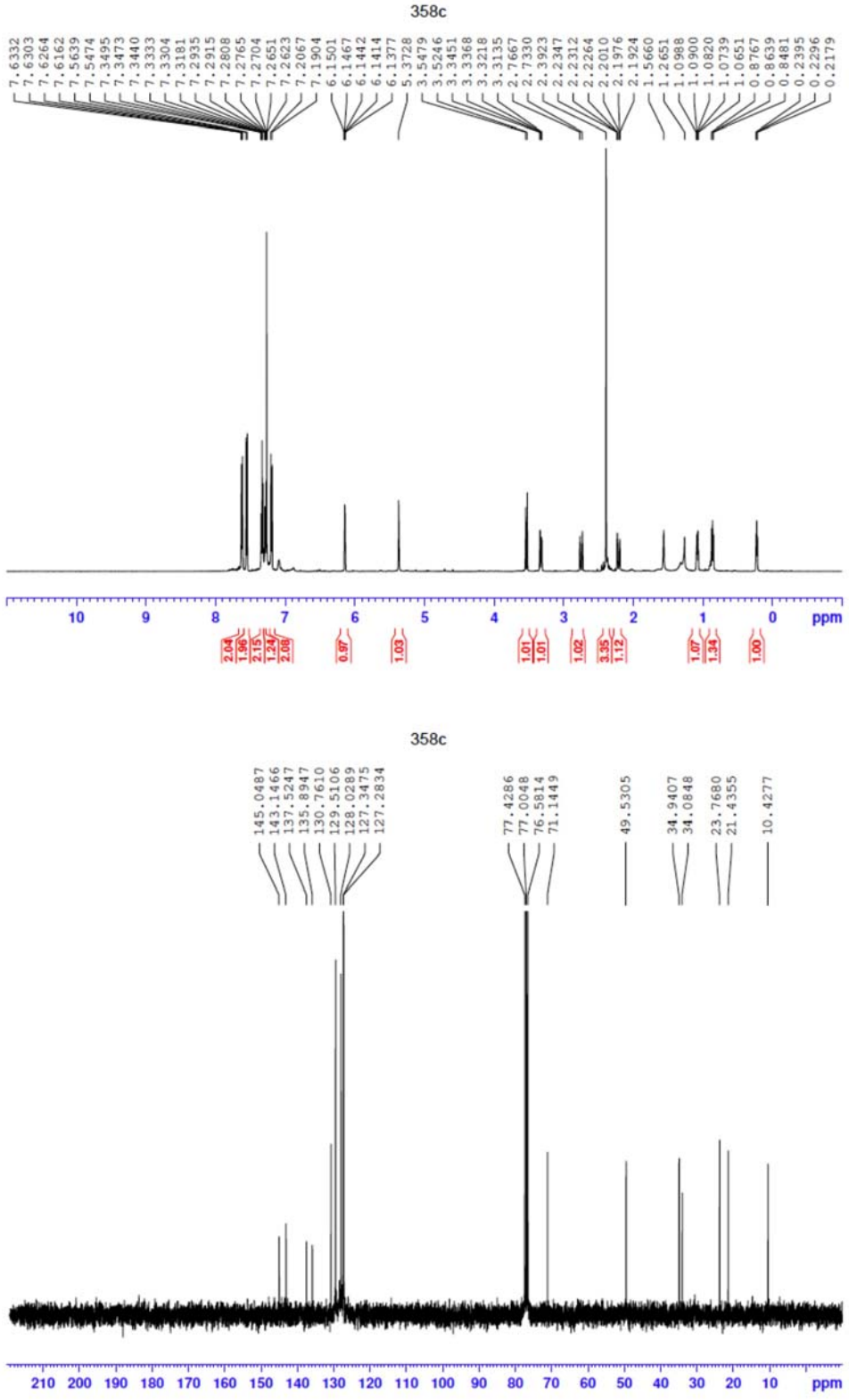


Figure 35. ^{1}H and ^{13}C NMR spectra of **358c**.

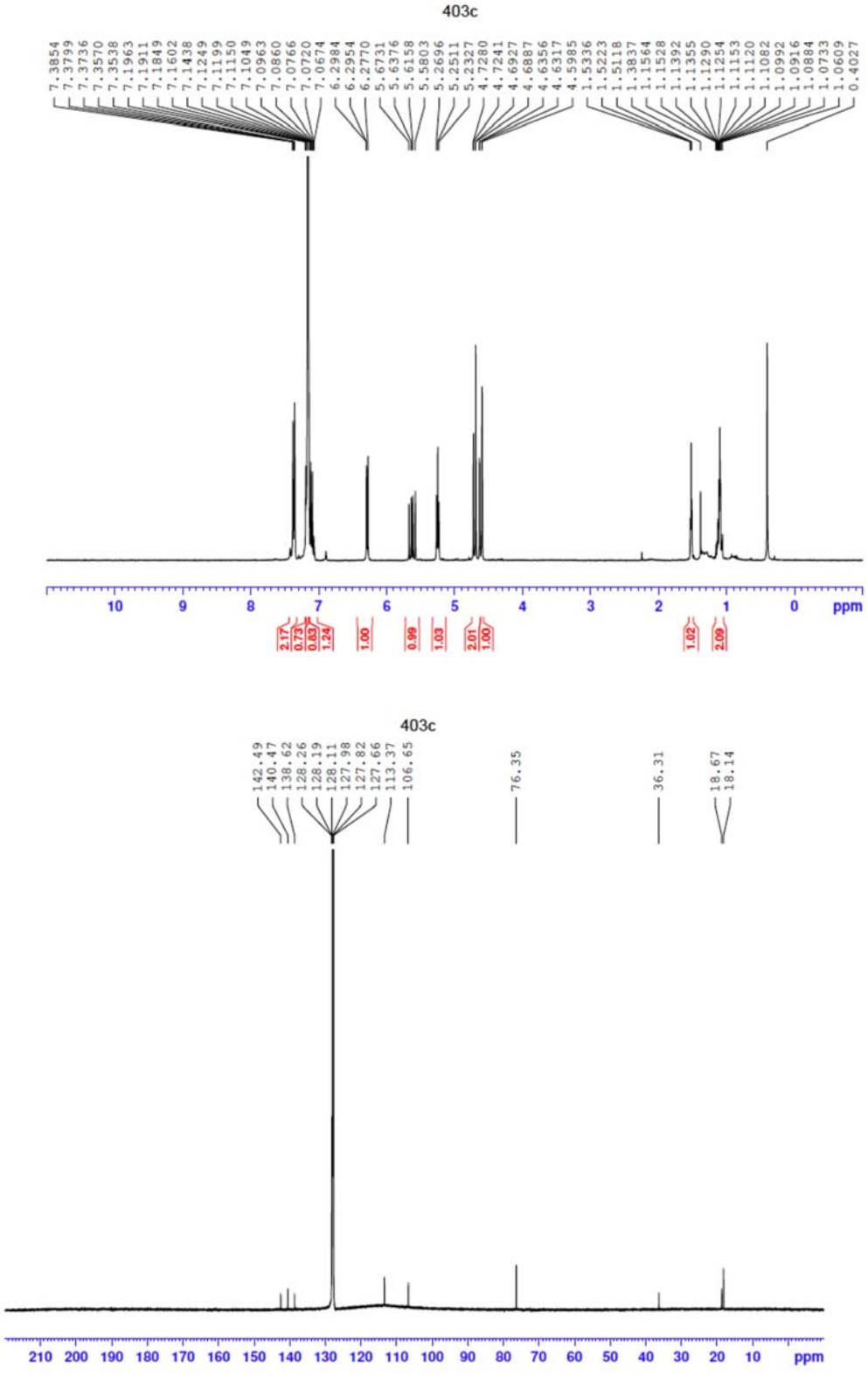


Figure 36. ^{1}H and ^{13}C NMR spectra of **403c**.

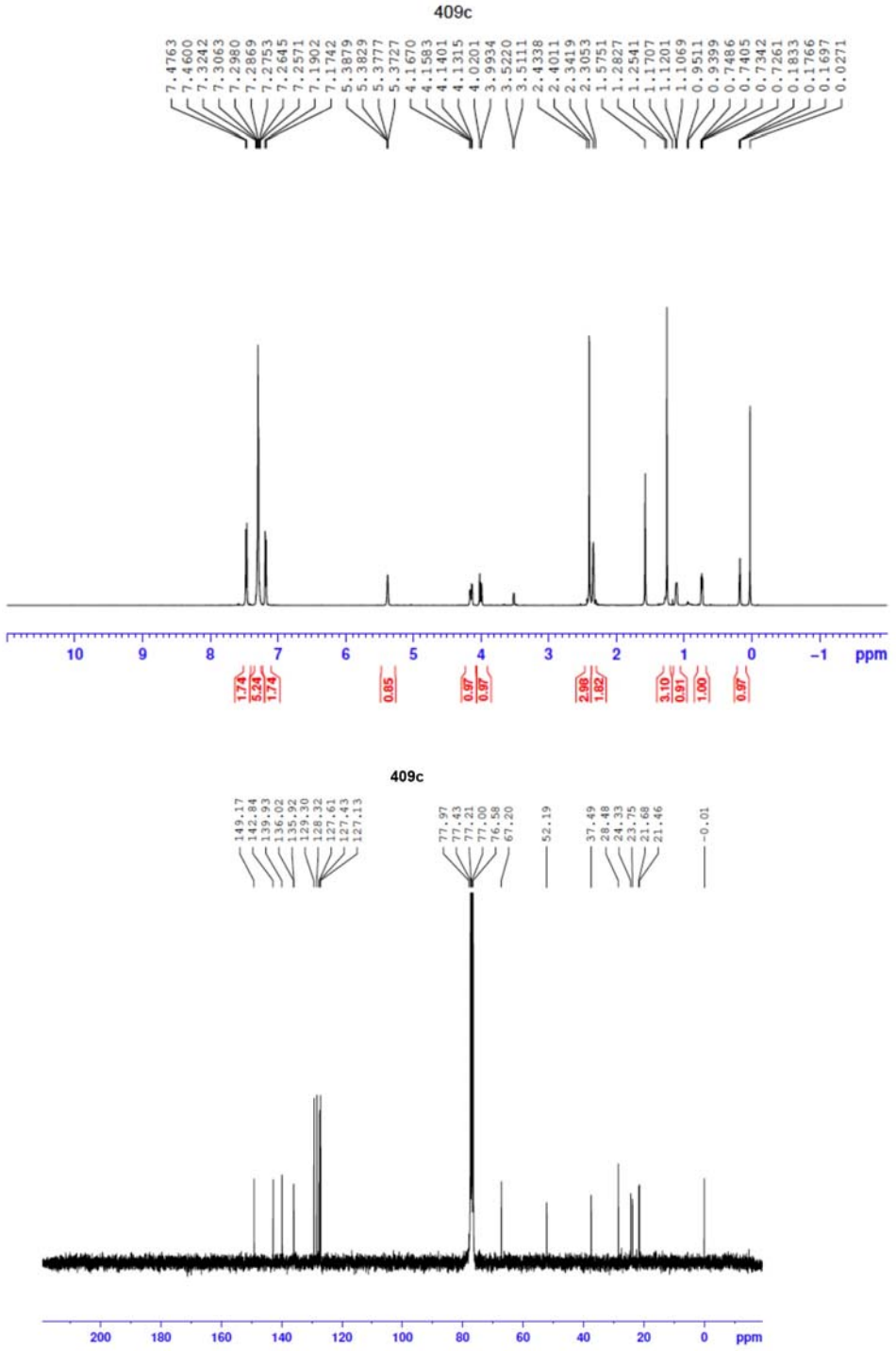


Figure 37. ^{1}H and ^{13}C NMR spectra of **409c**.

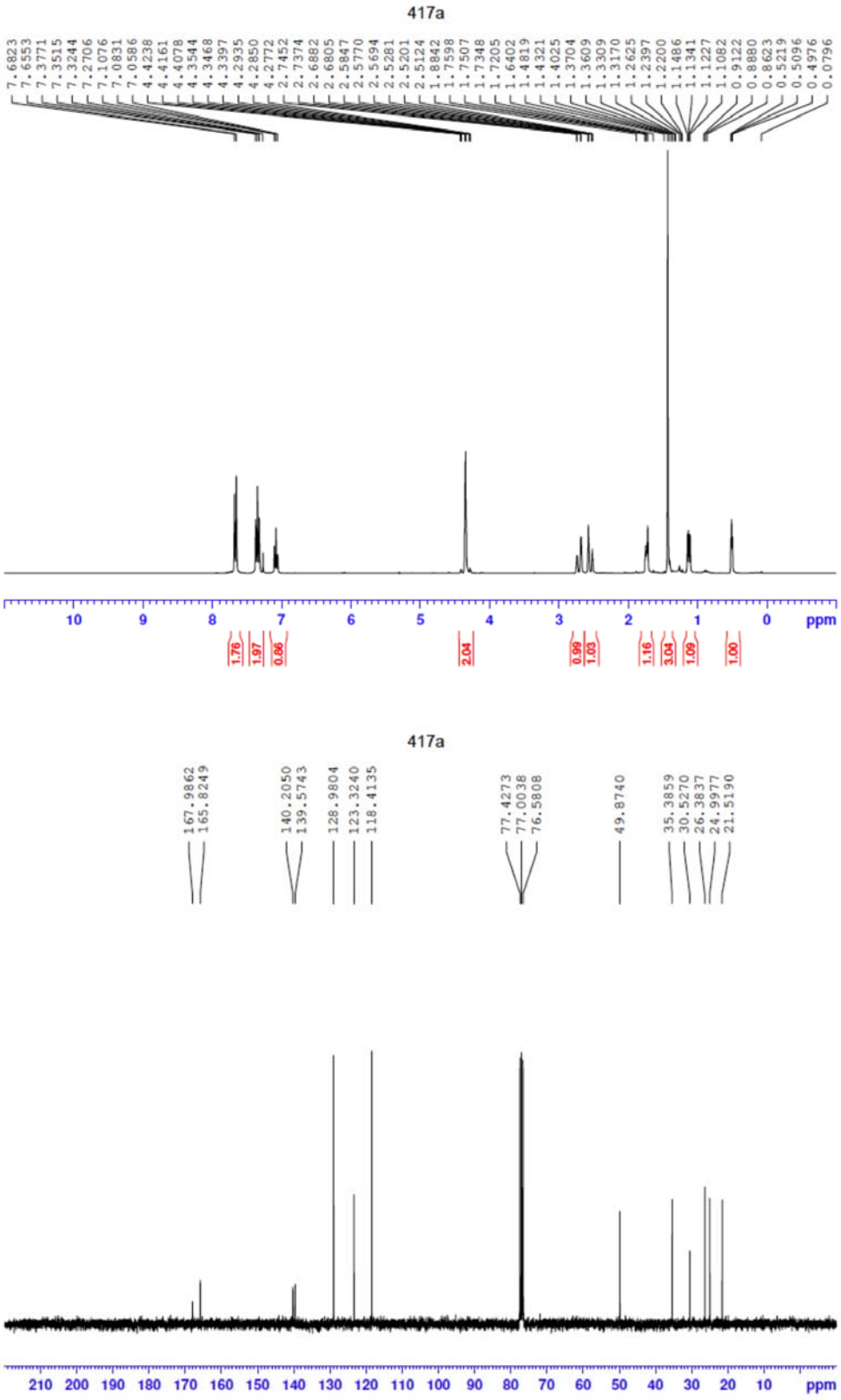


Figure 38. ^{1}H and ^{13}C NMR spectra of **417a**.

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