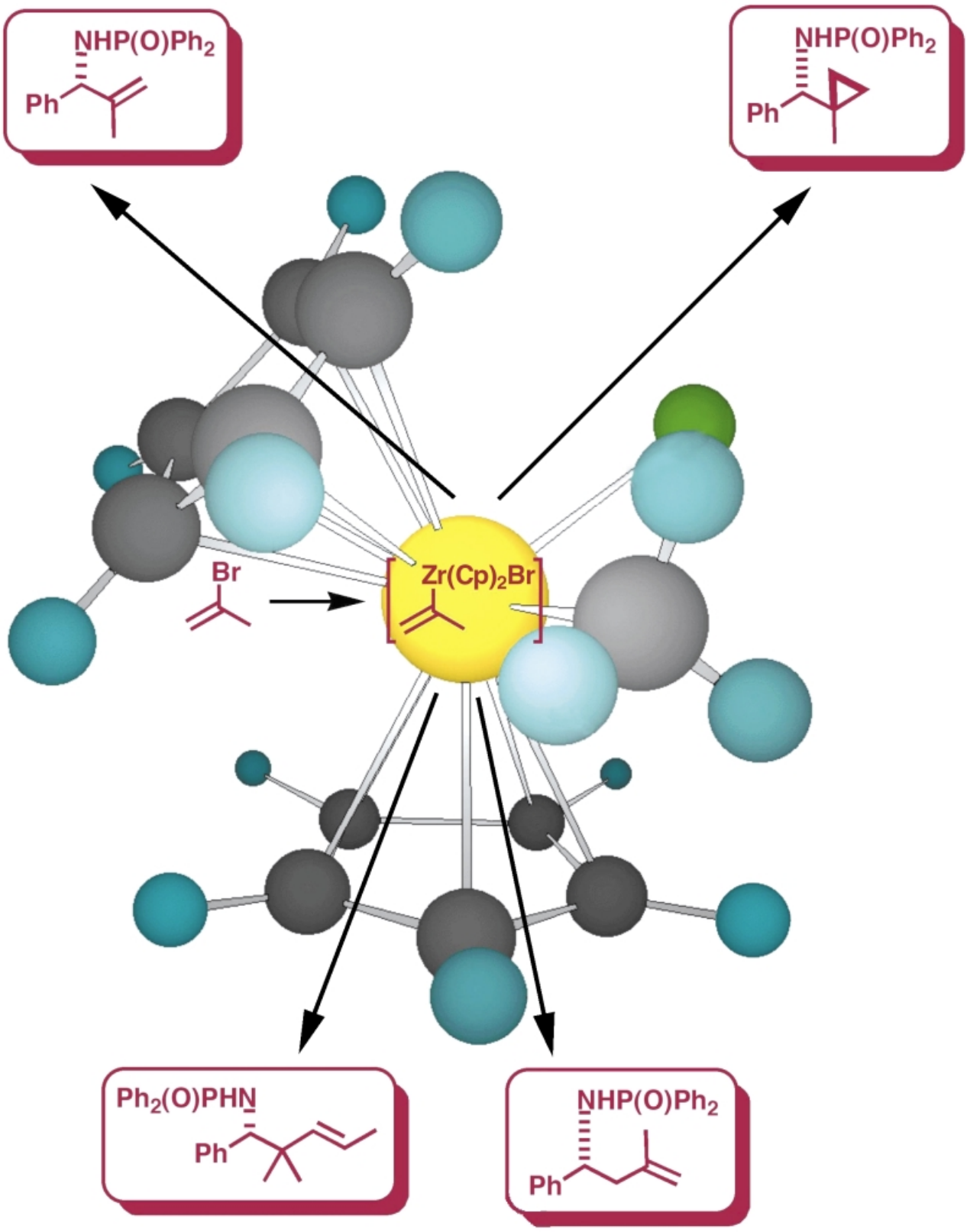
In combination with zinc, zirconocenes display unique reactivity. The bimetallic reagent provides diverse products from simple starting materials.



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Novel Applications of Alkenyl Zirconocenes

Peter Wipf* and Christopher Kendall[a]

Abstract: Alkenyl zirconocene complexes are readily obtained by diverse processes including hydrozirconation, carbozirconation, and cyclozirconation of alkynes, transmetalations, and bond insertions. In combination with other metals, novel reaction manifolds can emerge and provide access to useful synthetic building blocks. Both catalytic asymmetric processes and highly diastereoselective multicomponent transformations that involve the formation of three or more new carbon–carbon bonds are feasible. This Concept paper summarizes the current state of the art and opportunities for future reaction discovery in this field of research, with particular emphasis on synergistic effects of bimetallic combinations of zirconocenes and zinc.

Keywords: cyclopropane · imines · metallocenes · zinc · zirconium

Introduction

Bis(cyclopentadienyl)zirconium(IV) complexes were discovered almost 50 years ago, but their applications in synthetic organic and polymer chemistry continue to expand at a rapid pace.[1] Bis(cyclopentadienyl)zirconium dihalides, that is, zirconocene dihalides, are used as starting materials for the preparation of many organozirconocene catalysts and stoichiometric reagents and are readily prepared from zirconium tetrahalides.[2] An impressively large and versatile collection of secondary zirconocene derivatives can subsequently be obtained by processes such as hydrozirconation, carbozirconation, cyclozirconation, transmetalations, and bond insertions.[1] These multiple synthetic strategies form the foundation of the innovation and diversity in the preparative use of zirconocenes. While these Group IV organometallics are generally categorized as hard Lewis acids, specific electronic properties, steric shielding of the zirconium atom, and air and moisture stability strongly depend on substituent effects. Therefore, a broad reactivity range and impressive substrate selectivity can be accomplished for transformations involving zirconocene derivatives.

This Concept paper focuses on the background and recent innovations of the in situ transmetalation of σ-bonded alkenyl zirconocenes to zinc(II)dialkyls. Similar to the ascendance of zirconium complexes in main stream synthesis and polymer chemistry, organozincs have become increasingly valuable tools for chemo- and stereoselective C,C-bond formations over the past two decades.[3] The combination of these two metals provides powerful new opportunities for synthetic method development and will continue to fertilize the field of organometallic chemistry.

Zinc as a "shuttle" for facilitating Zr–Pd ligand exchange: Pioneering investigations by Negishi and co-workers in 1978 established that zinc dichloride accelerated the Pd^0-catalyzed heterocoupling of alkenyl zirconocenes with alkenyl, aryl, and alkynyl halides.[4] It is likely that transmetalation from the bulky zirconocene to the sterically much more accessible zinc dichloride and subsequent transmetalation from zinc to the palladium complex is faster than a direct Zr/Pd exchange reaction. This process is an attractive alternative to Suzuki–Miyaura cross couplings. Panek and co-workers have recently further optimized the experimental protocol and applied it toward the synthesis of the Adda amino acid side chain of the microcystin family of natural products.[5] Noteworthy recent demonstrations of the versatility of the Zr→Zn→Pd transmetalation cascade in complex molecule synthesis include the total syntheses of reveromycin B,[6] (−)-motuporin,[7] FR901464,[8] eunicenone A,[9] and pitiamide A.[10] The sensitive chlorodiene segment **3** of pitiamide A was obtained in high yield and on a large scale from alkyne **1** and vinyl iodide **2** by this methodology (Scheme 1).

Stereoselective carbonyl additions of alkenyl zinc reagents obtained from alkenyl zirconocenes: While both organozirconocenes and organozincs are generally unreactive toward aldehydes and ketones in the absence of additives, the combination of an alkenyl zirconocene and a dialkyl zinc leads to a rapid 1,2-addition even at low temperatures. The process is likely to involve a Zr→Zn transmetalation followed by a zirconocene-accelerated addition of the mixed alkyl–alkenyl zinc reagent to the carbonyl group (Scheme 2).[11] Allylic alcohol products are isolated in high yields, and the

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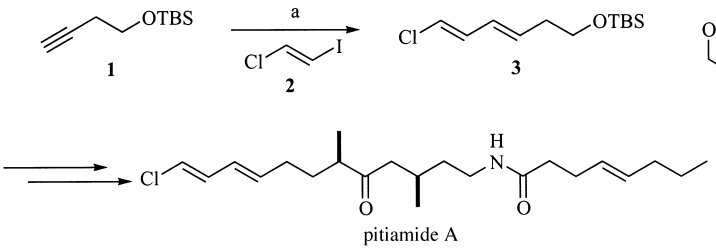
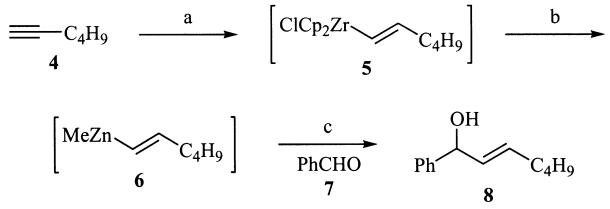
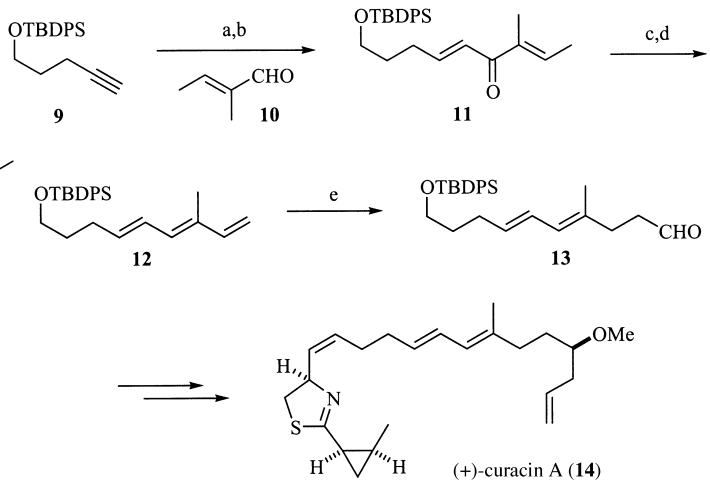


Scheme 1. Use of zirconocene–zinc–palladium triad for the preparation of the chlorodiene segment of the marine natural product pitiamide A. a) 1. $[(Cp)_2ZrHCl]$, THF; 2. $ZnCl_2$; 3. **2**, 8 mol% $[Pd(PPh_3)_4]$ (85%).



Scheme 2. Preparation of allylic alcohols from alkynes and aldehydes. a) $[(Cp)_2ZrHCl]$, CH_2Cl_2, RT; b) Me_2Zn, $-65\,^{\circ}C$; c) **7**, $0\,^{\circ}C$ (93%).



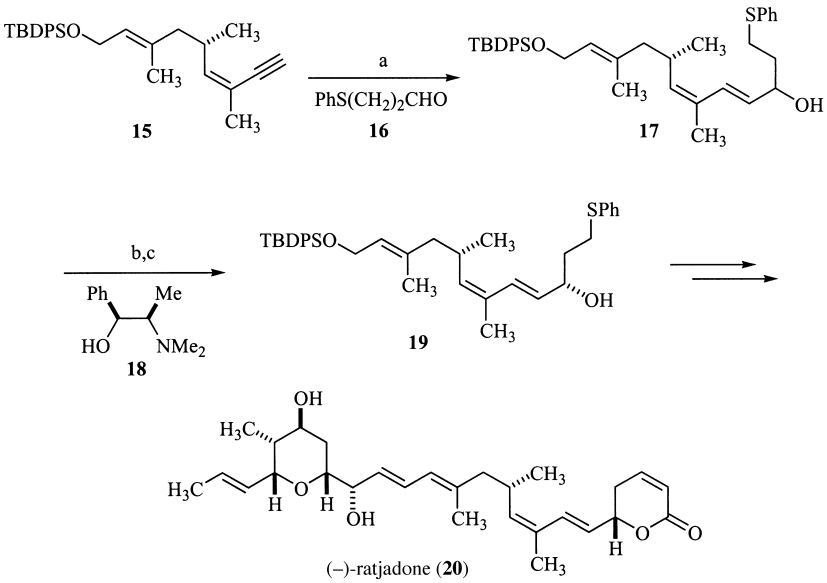
Scheme 3. Use of two zirconocene-mediated transformations in the total synthesis of the marine natural product curacin A. a) 1. $[(Cp)_2ZrHCl]$, CH_2Cl_2; 2. Et_2Zn; 3. **10** (94%); b) MnO_2, hexanes (90%); c) 1. KHMDS, THF; 2. Tf_2NPh; d) $[(Bu)_3SnH]$, $[Pd_2(dba)_3]$, LiCl, PPh_3, THF (71% from **11**); e) 1. $[(Cp)_2ZrHCl]$, THF; 2. BuNC; 3. 3N HCl (54%).

reaction can be performed catalytically in R_2Zn.[12] This same transformation is achieved if $ZnBr_2$[13] or MeLi[14] is substituted for Me_2Zn, though in the latter case a different mechanism is invoked.

The Zr–Zn transmetalation, aldehyde addition methodology has been successfully applied toward the synthesis of natural products. We have found that elimination of the newly formed allylic alcohol moiety is a convenient method for the preparation of *all*-(*E*)-polyenes, and we have used this methodology in the total syntheses of curacin A (**14**, Scheme 3),[15] asukamycin,[16] and nisamycin.[17] The synthesis of the curacin A precursor **13** began with the transmetalation of the alkenyl zirconocene to zinc and addition to aldehyde **10**, followed immediately by oxidation to form ketone **11**. Regiospecific enolization of **11** with KHMDS (potassium bis(trimethylsilyl)amide) at $-78\,^{\circ}C$ and trapping with Tf_2NPh gave a triflate that was reduced with $[(Bu)_3SnH]$ under Pd catalysis to afford triene **12**. Hydrozirconation of the terminal double bond was sluggish, but homologation was achieved by treating the bishomoallylic zirconocene intermediate with *n*-butyl isocyanate followed by acid hydrolysis. Thus, aldehyde **13** was prepared in 32% overall yield from the protected alcohol **9**.

Williams and co-workers prepared the dihydropyranone segment of (−)-ratjadone (**20**) via allylic alcohol **17**, which in turn was prepared from alkyne **15** (Scheme 4).[18] After treatment of the advanced intermediate **15** with $[(Cp)_2ZrHCl]$ in CH_2Cl_2, transmetalation to Me_2Zn, and in the same pot, reaction with aldehyde **16** afforded alcohol **17** in 92% yield. The configuration of the newly formed stereogenic center was set by oxidation of **17** followed by stereoselective reduction of the resulting ketone.

Recently, Jacobsen and co-workers have demonstrated a diastereoselective ketone addition variant of the Zr→Zn transmetalation methodology as part of their total synthesis of fostriecin (**26**, Scheme 5).[19] Their synthetic strategy required a diastereoselective addition of an alkenylorganometallic to ketone **22**, which was obtained from racemic **22** by hydrolytic kinetic resolution. A model study of alkenylzinc addition to **22** was promising as allylic tertiary alcohol **23** was formed in 75%



Scheme 4. Conversion of alkyne **15** to the ratjadone segment **19** utilizes a zirconocene–zinc transmetalation. a) 1. $[(Cp)_2ZrHCl]$, CH_2Cl_2; 2. Me_2Zn; 3. **16** (92%); b) DMP, $NaHCO_3$ (84%); c) $LiAlH_4$, PhNHEt, **18**, Et_2O (98%).

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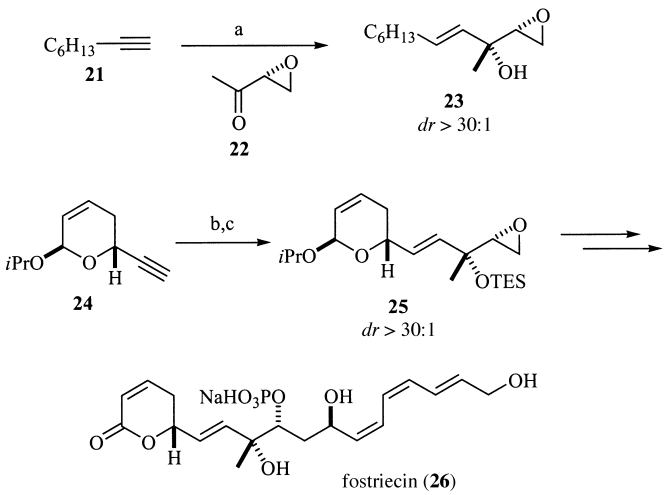
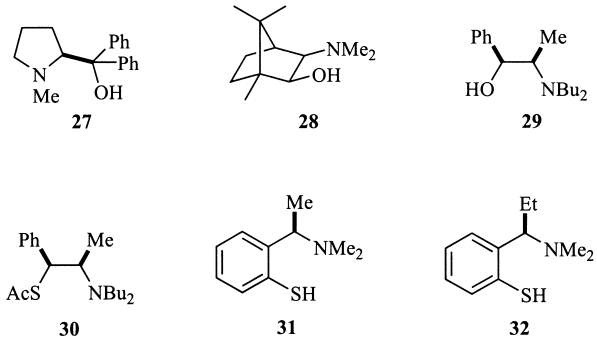


Scheme 5. Chelation controlled stereoselective addition of the alkenyl zinc reagent derived from alkyne **21** to epoxyketone **22**. a) 1. $[(Cp)_2ZrHCl]$, CH_2Cl_2; 2. Me_2Zn; 3. **22** (75%); b) 1. $[(Cp)_2ZrHCl]$, CH_2Cl_2; 2. Me_2Zn; 3. **22**; c) TES-Cl, imidazole, DMF (45% from **24**).

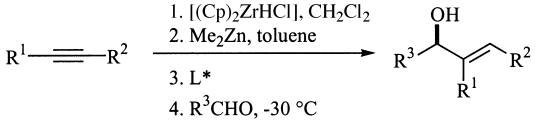
yield with >30:1 diastereoselectivity. Subjecting alkyne **24** to the same conditions, followed by protection of the alcohol, afforded **25** in 45% yield and also with >30:1 diastereoselectivity.

The asymmetric addition of organozinc reagents to aldehydes is one of the most thoroughly studied and successful catalytic enantioselective processes.[3f] While chiral ligand selection is much more delicate for the Zr–Zn system due to the fast background addition reaction mediated by the achiral zirconocene that is present in stoichiometric amounts in the reaction mixture, chiral allylic alcohols can be obtained in >97% *ee* when amino thiols are used as chiral inducers. In our initial communication, we reported that performing the reaction at −20 °C in the presence of 8 mol% of ligand **27** (Scheme 6) afforded allylic alcohol **8** with only 38% *ee*.[11] The enantiomeric excess was subsequently improved to 81% by allowing the reaction mixture to slowly warm from −78 to −30 °C after addition of the ligand but prior to addition of the aldehyde (Table 1, entry 1).[20] A reduced catalyst loading of 2 mol% lowered the *ee* to 19% (entry 2). Other commonly employed amino alcohols **28** and **29** were tested, but neither gave any asymmetric induction. Using a thioacetate anologue of **29** afforded **8** with an *ee* of 70% (entry 5), and thiophenol **31** led to an *ee* of 89% (entry 6). We prepared **32** in the hope of improving enantioselectivity even further and were rewarded with an excellent *ee* of 95% (entry 7). Once again however, lowering the catalyst loading to 2 mol% reduced the *ee* (entry 8). Most other substituted benzaldehydes with the exception of the very electron-rich *para*-anisaldehyde also gave high enantiomeric excesses when subjected to the same reaction conditions (entries 9–12). Slightly lower yields and *ee*s were observed with aliphatic aldehydes (entries 13 and 14), and the bulky alkyne **39** also was slightly less effective than 1-hexyne (entry 15). However, silyl ester functionalized



Scheme 6. Chiral ligands used for an asymmetric variant of the in situ alkenyl zirconocene/zinc transmetalation, aldehyde addition process.

Table 1. Effects of chiral ligands, substrate structure, and catalyst loading on the yield and enantiomeric excess of the asymmetric addition of alkenyl zirconocenes to aldehydes in the presence of 1 equiv of Me_2Zn.



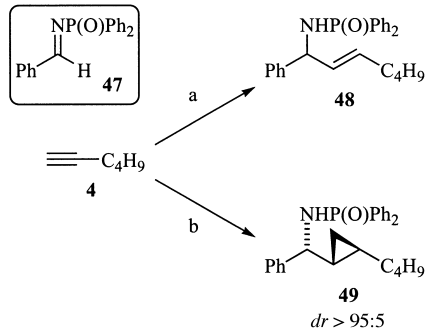
	L* [mol%]	Alkyne	R^1	R^2	Aldehyde	R^3	Yield [%]	*ee* [%]
1	**27** (10)	**4**	H	C_4H_9	**7**	Ph	88	81
2	**27** (2)	**4**	H	C_4H_9	**7**	Ph	99	19
3	**28** (10)	**4**	H	C_4H_9	**7**	Ph	77	3
4	**29** (10)	**4**	H	C_4H_9	**7**	Ph	85	1
5	**30** (10)	**4**	H	C_4H_9	**7**	Ph	80	70
6	**31** (10)	**4**	H	C_4H_9	**7**	Ph	76	89
7	**32** (10)	**4**	H	C_4H_9	**7**	Ph	80	95
8	**32** (2)	**4**	H	C_4H_9	**7**	Ph	88	78
9	**32** (10)	**4**	H	C_4H_9	**33**	(*p*-Cl)C_6H_4	83	97
10	**32** (10)	**4**	H	C_4H_9	**34**	(*p*-CF_3)C_6H_4	71	93
11	**32** (10)	**4**	H	C_4H_9	**35**	(*p*-MeO)C_6H_4	75	63
12	**32** (10)	**4**	H	C_4H_9	**36**	(*m*-MeO)C_6H_4	79	99
13	**32** (10)	**4**	H	C_4H_9	**37**	*c*-C_6H_{11}	63	74
14	**32** (10)	**4**	H	C_4H_9	**38**	$Ph(CH_2)_2$	71	64
15	**32** (10)	**39**	H	$C(CH_3)_3$	**7**	Ph	73	83
16	**32** (10)	**40**	H	$(CH_2)_2CO_2TIPS$	**7**	Ph	67	92
17	**32** (10)	**41**	C_2H_5	C_2H_5	**7**	Ph	66	99

alkyne **40** and internal alkyne **41** each afforded allylic alcohols with very high *ee*s (entries 16 and 17).

Danishefsky and co-workers used this asymmetric transformation at a late stage in their total synthesis of (+)-halichlorine (**46**, Scheme 7).[21] They planned to homologate the advanced intermediate **42** by a Horner–Wadsworth–Emmons chain extension of the corresponding aldehyde; however the substrate proved to be too sensitive. Their alternative was to prepare alkyne **43** and use ligand *ent*-**27** for an asymmetric addition to aldehyde **44**, which proceeded in 67% yield and gave a 4:1 mixture of diastereomers. In the absence of any chiral ligand the *dr* was 1:1. Completion of the total synthesis required only protection of the allylic alcohol, selective deprotection of the primary alcohol, macrolactonization, and deprotection of the allylic alcohol.

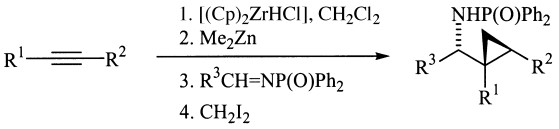
Imine additions of alkenyl zinc reagents obtained from alkenyl zirconocenes - new reaction discovery: As expected, the Zr→Zn transmetalation, in situ carbonyl addition process can be extended to C=N electrophiles such as imines and nitrones.[22, 23] Our initial motivation to explore the addition of alkenyl zirconocenes to imines was the development of a more straightforward synthetic access to chiral ligands of type **32**. While the addition to phosphonoyl imines **47** provides indeed allylic amines **48** in THF as a solvent, we discovered that in the presence of CH_2X_2, where X = Cl, Br, or I, a novel three-component condensation provides amino cyclopropanes (Scheme 8). *trans*-Amino cyclopropane **49**, for example, was formed in >20:1 *dr* in CH_2Cl_2. Toluene or other apolar solvents in the presence of 4–10 equiv of CH_2Cl_2, CH_2Br_2, or CH_2I_2 also lead to cyclopropane formation of the transiently formed allylic amine intermediate.

The scope of this new reaction is illustrated in Table 2. Functional groups tolerated on the alkyne segment include silyl ethers, silyl esters, carbamates, and sulfonamides (entries 3–5). Electron-donating (entry 9) and -withdrawing (entries 6–8) substituents on the benzaldimine did not greatly affect the reaction. Both the internal alkyne **41** (entry 2) and an alkynylimine substrate (entry 10) are converted to amino cyclopropanes, though the isolated yields in these two cases are not as high.

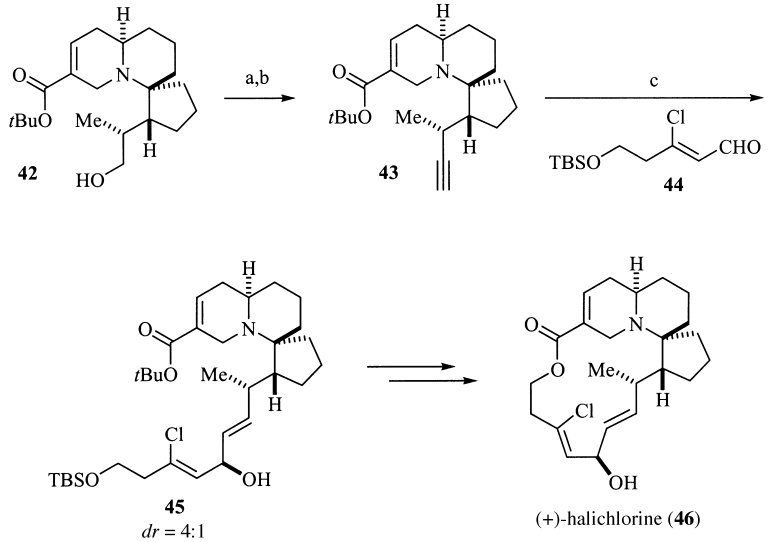


Scheme 8. Solvent dependent formation of allylic amines versus cyclopropyl amines. a) 1. [(Cp)$_2$ZrHCl], THF; 2. Me_2Zn; 3. **47**, 40 °C (65%); b) 1. [(Cp)$_2$ZrHCl], CH_2Cl_2; 2. Me_2Zn, 3. **47**, reflux (58%).

Table 2. Reaction scope of the one-pot conversion of alkynes to amino cyclopropanes by consecutive hydrozirconation, Zr→Zn transmetalation, aldimine addition, and cyclopropanation.



	Alkyne	R^1	R^2	Aldimine	R^3	Yield [%]
1	**4**	H	C_4H_9	**47**	Ph	74
2	**41**	C_2H_5	C_2H_5	**47**	Ph	46
3	**50**	H	$(CH_2)_2OBDPS$	**47**	Ph	68
4	**51**	H	$(CH_2)_3CO_2TIPS$	**47**	Ph	73
5	**52**	H	$(CH_2)_2N(Ts)CO_2Et$	**47**	Ph	45
6	**4**	H	C_4H_9	**53**	$(p\text{-}MeO_2C)C_6H_4$	69
7	**50**	H	$(CH_2)_2OBDPS$	**53**	$(p\text{-}MeO_2C)C_6H_4$	84
8	**4**	H	C_4H_9	**54**	$(p\text{-}Cl)C_6H_4$	65
9	**4**	H	C_4H_9	**55**	$(m\text{-}MeO)C_6H_4$	51
10	**4**	H	C_4H_9	**56**	PhC≡C	44



Scheme 7. Asymmetric addition of the alkenyl organometallic derived from alkyne **43** to aldehyde **44** en route to the natural product (+)-halichlorine. a) TPAP, NMO, MeCN; b) $N_2CHP(O)(OMe)_2$, KO*t*Bu, THF (57% from **42**); c) 1. [(Cp)$_2$ZrHCl], CH_2Cl_2; 2. Me_2Zn, heptane, 3. 10 mol% *ent*-**27**; 4. **44**, −30 °C (67%).

While a Simmons–Smith-type reaction mechanism involving zinc carbenoid attack on the intermediate allylic phosphinoyl amide could readily account for the formation of the observed products, cyclopropanation of the alkenyl zinc intermediate followed by imine addition of the resulting cyclopropylzinc was also a theoretically feasible pathway. A related reaction sequence was reported by Oshima et al.[24] When combined with the Zr–Zn transmetalation, a one-pot conversion of alkynes to *trans*-disubstituted cyclopropanes could be developed (Scheme 9). However, we were able to exclude the possibility that such a mechanism was operative for the formation of

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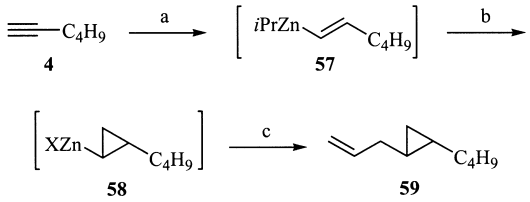
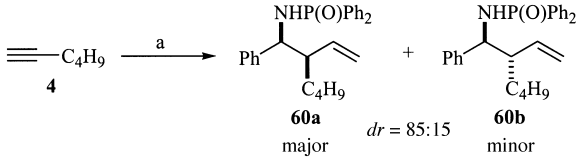


Scheme 9. Conversion of alkynes to *trans*-disubstituted cyclopropanes. a) 1. $[(Cp)_2ZrHCl]$, CH_2Cl_2; 2. $[(i\text{Pr})ZnCl]$; b) Et_2Zn, CH_2I_2, Et_2O; c) $CH_2{=}CHCH_2Br$, $CuCN \cdot 2\,LiCl$, THF (69%).

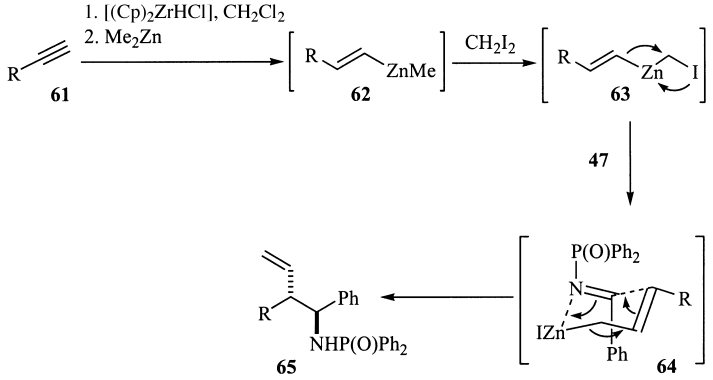
amino cyclopropanes, since allylic imines were formed prior and slowly converted to amino cyclopropanes in the reaction mixture, and since reagents of type **58** proved to be unreactive toward phosphinoyl imine **47**.[25]

A deceptively simple control experiment revealed yet another fascinating chapter in Zr/Zn chemistry. When we changed the order of addition of reagents in the three-component amino cyclopropane synthesis and added CH_2I_2 to the reaction mixture prior to aldimine **47**, homoallylic amide **60** was instead formed in high yield and in an 85:15 ratio of diastereomers favoring the *syn*-isomer **60a** (Scheme 10).[26]



Scheme 10. Diastereoselective formation of homoallylic amines from alkyne **4**. a) 1. $[(Cp)_2ZrHCl]$, CH_2Cl_2; 2. Me_2Zn, 3. CH_2I_2; 4. **47** (71%).

A broad range of terminal and internal alkynes undergo this process and lead to synthetically useful homoallyl derivatives in moderate to excellent diastereoselectivities. While this mechanistic hypothesis needs to be supported by further experimental evidence, we envision a process that involves a [1,2] shift of the alkenylzinc intermediate **63** and formation of the major diasteromeric product **65** via the Zimmermann–Traxler transition state **64** (Scheme 11).



Scheme 11. Consecutive hydrozirconation–transmetalation–chain extension–imine allylation mechanism proposed for homoallylic amine formation.

Conclusion

Both the three-component amino cyclopropane formation and the preparation of homoallylic amines from alkynes and phosphinoylimines are crucially dependent on the presence of both zirconocene and zinc derivatives in the reaction mixture. No other metal combination that we have investigated thus far, including B→Zn and Zr→Al transmetalation cascades, provides analogous products. As pointed out by Negishi in the discussion of bimetallic catalytic systems containing Ti, Zr, Ni, and Pd, the synthetic capability of single metallic elements can, at least theoretically, be vastly increased by the simultaneous use of two or more metals.[27] Zirconocene and zinc appear in fact to be a bimetallic combination that displays unique reactivity characteristics that are not shared by either of the parent compounds. The wealth of synthetically useful and truly novel applications that have already resulted from the synergistic interaction of zirconium and zinc in combination with the multifaceted chemistry of zirconocene derivatives bodes indeed well for future discoveries along this line of research.

Acknowledgements

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