Studies of Memory of Chirality in Amide Radical Cyclizations

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University of Pittsburgh, 2011

Radical cyclization of amide substrates was performed to establish the Memory of Chirality (MOC). Amides with *N*-*tert*-butyl substituent due to their hindered rotation around *C*-*N* bond gives cyclized product with retention of configuration upon radical reaction condition. Chiral GC analysis and theoretical optical rotation calculation were used to verify the MOC. An unexpected 1,4-phenyl radical migration was also observed during the radical reaction of *N*-benzyl substituted amides.

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PREFACE

Over the past few years, my scientific career has undergone a remarkable journey. I think the time has come to take a moment to acknowledge those who have made my journey meaningful.

Firstly, I'd like to thank my M.S. advisor Dr. Dennis P. Curran for his guidance through my research in past two and half years. The motivated lesson I learned from him will help me to move forward in my career. I also thank my M.Sc. thesis advisor Dr. Krishna P. Kaliappan, who helped me to firm the stepping-stone of my career at Indian Institute of Technology Bombay, India. Both of them made a great impact in my scientific career and helped me to embark for the scientific voyage.

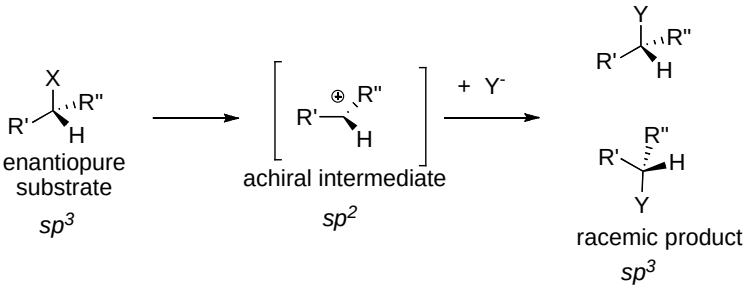
I also want to acknowledge all the Curran group members, past and present, for their supports. I would like to thank Dr. Paul Floreancig and Dr. Craig Wilcox for being on my committee.

At the end, I express my gratitude to my family for allowing me to pursue my dreams. I forever indebted to you for everything you did for me.

1.0 INTRODUCTION

1.1 PRINCIPLES OF RACEMIZATION AND MEMORY OF CHIRALITY

Eliel defines as the macroscopic and statistical process by which one optically active compound (be it optically pure or impure) is irreversibly transformed into the racemic mixture over a period of time.[1] Racemization commonly occurs when an enantiopure sp^3-hybridized stereogenic center undergoes trigonalization during the process of reaction to give a mixture of chiral products (**Scheme 1.1**).



Scheme 1.1 Racemization due to trigonalization

For example, an enantiopure substrate with leaving group X undergoes heterolytic bond cleavage to give achiral cationic intermediate. The sp^2 carbon center in achiral intermediate is attacked by a nucleophile Y^- at both *alpha* and *beta* faces with equal preference to result in racemic products. The stereogenic center in the enantiopure substrate is lost since a planar sp^2 carbon center is created from an sp^3 carbon center. Thus, it is impossible to obtain a nonracemic

product in this type of reaction unless an external chiral environment (chiral electrophiles, chiral ligands, and chiral solvents) is present.

Can the memory of the sole chiral center of a substrate be retained in a process that destroys that center? In the absence of any of external chiral environment, a non-racemic outcome is possible if the reactive intermediate possesses some form of *conformational chirality*.[2,3] Chiral conformations are present in most conformationally mobile compounds, even in the absence of any chiral center. For example, the *gauche* conformers of *n*-butane are chiral enantiomers (**Figure 1.1**) that are present in equal concentration in any sample of this hydrocarbon at any given time. The isomerization time constant for internal rotation of *n*-butane in CCl_4 at room temperature is ~ 40 picoseconds.[4]

Fuji and Kawabata illustrated the concept of conformational chirality by contrasting the chirality present in phenylalanine **1.2a** and phenylpropionic acid **1.2b** (**Figure 1.2**).[5] For phenylalanine **1.2a**, the *S* and *R* enantiomers differ at a stereogenic carbon center and this is known as static, central chirality. However, phenylpropionic acid **1.2b** is normally considered to be achiral because it has no stereogenic center. But closer consideration leads to the realization that on a limited timescale phenylpropionic acid can take either of two chiral, enantiomeric *gauche* conformations (**1.2b**-g^+ or **1.2b**-g^-) along with an achiral *anti* conformation **1.2b**-*a* drawn as in **Figure 1.2b**. The interconversion of these enantiomeric conformers can be achieved by single bond rotation under normal conditions.

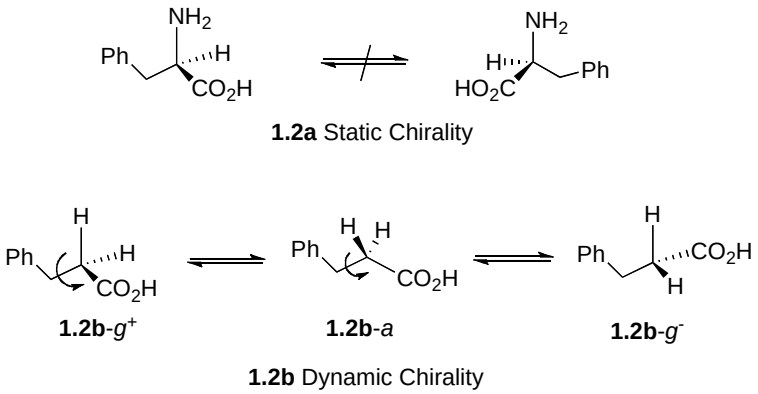


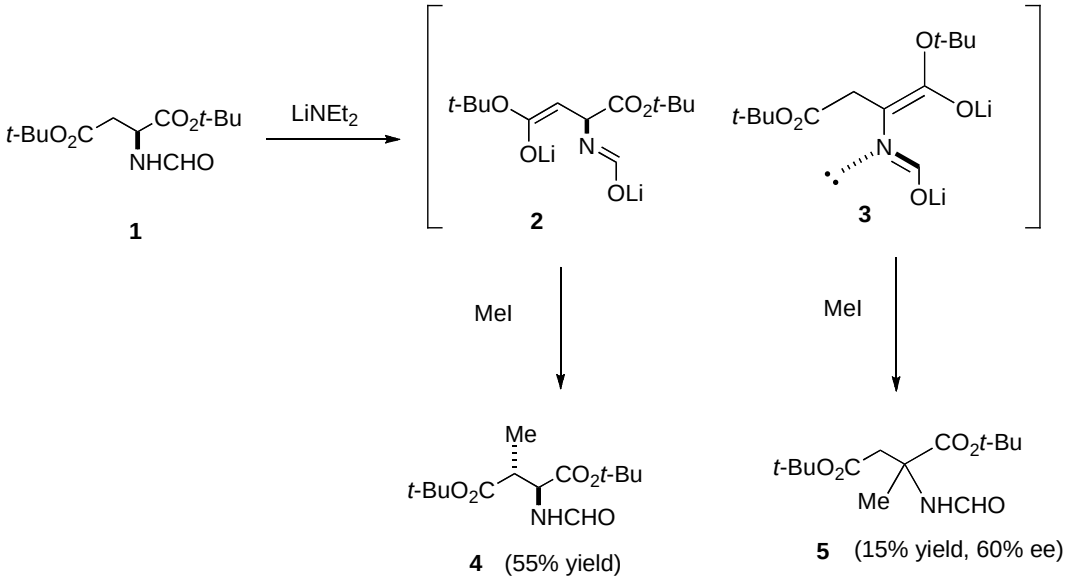
Figure 1.1 Static chirality and dynamic chirality

'Memory of Chirality' occurs when of a chiral starting material results in a chiral product, despite proceeding through a configurationally labile intermediate containing no other permanent chiral features.[6] The term 'Memory of Chirality' was coined in 1991 by Fuji who was the first to successfully design a reaction to exploit this principle.[2] The MOC approach to stereocontrol does not rely upon the influence of a permanent chiral center in the reactive intermediate. Interest has burgeoned in the synthetic possibilities and mechanistic features of this type of reactions.[7,8] .

1.2 EARLY EXAMPLES OF MEMORY OF CHIRALITY

To date, most applications of MOC involve enolate intermediates. Before the term MOC appeared, Seebach and Wasmuth deprotonated *N*-formyl aspartate **1** in presence of 2 equiv of

lithium diethylamide and quenched the reaction with methyl iodide to furnish alkylated product **4** in 55% yield.[3] Unexpectedly α-alkylated product **5** was isolated in 15% yield and with 60% ee.

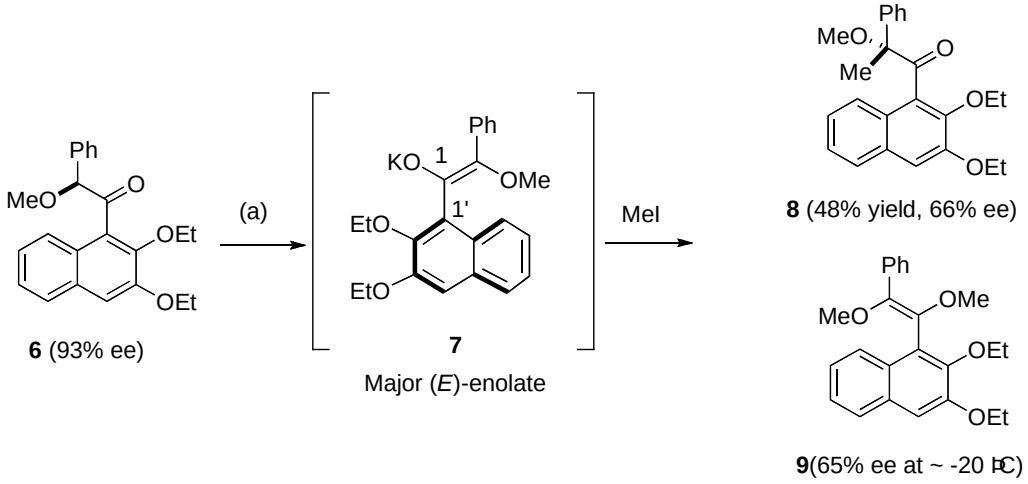


Scheme 1.2 α-Alkylation of aspartic acid ester enolate

Dilithio intermediates **2** and **3** were formed during the course of the reaction. Reactive intermediate **2** possesses a stereogenic center and gave alkylated product **4**. The intermediate **3** that did not possess any chiral center produces **5** in 60% ee. The formation of enantioenriched **5** contradicts the idea of asymmetric induction in enantioselective alkylation. Seebach's proposal was either the achiral **3** forms mixed aggregates with chiral dilithio-derivative **2** or the intermediate **3** possesses axial chirality due to non-co-planar orientation of enolate and imine moieties. This second explanation is today recognized as MOC.

An MOC reaction was first intentionally designed and reported by Fuji. He deprotonated chiral 1-naphthylketone **6** in presence of potassium hydride in 18-crown-6 and THF and then

treated the enolate **7** with methyl iodide to yield alkylated ketone **8** in 48% yield and 60% ee **Scheme 1.3**).



Scheme 1.3 *Reagents and conditions:* (a) KH, 18-crown-6, THF, -78 ˚C to -20 ˚C.

Fuji proposed that central chirality of **6** is transferred to axial chirality about $C_1 - C_{1'}$ bond of enolate intermediate **7**. This in turn is transferred back to central chirality during formation of methyl enol ether **9** in 65% ee. The axial chirality in **7** is responsible for enantioenriched product **8**.

1.3 MODERN DEFINITION OF MEMORY OF CHIRALITY

The modern definition of MOC was offered by Carlier *et. al.* to broaden Fuji's idea: *A 'Memory of chirality' reaction [is] a formal substitution at an* sp^3 *stereogenic center that proceeds stereospecifically, even though the reaction proceeds by trigonalization of that center, and despite the fact that no other permanently chiral elements are present in the system.*

The Eyring equation[10] provides a physical chemical foundation upon which to design MOC methods, provided the racemization is unimolecular process. **Table 1.1** shows that at –78 ˚C, a racemization barrier of 16 kcal/mol would provide a reactive intermediate a half-life of 20 h. This is sufficient time to undergo an intermolecular reaction without significant racemization. Hindered rotation around typical sp^3-sp^3 bond (for example, 1,2-dibromoethane, 2,3-dimethylbutane) has the energy barrier[11] less than 7 kcal/mol whereas, sp^2-sp^2 bond (for example, simple biphenyl or styrene system) rotational barrier[12] measures in excess of 16 kcal/mol. Thus sp^2-sp^2 bond rotation can be considered as one of the important factors to engineer successful intermolecular MOC reactions.

Racemization Barrier $\Delta G^{\ddagger}$ (kcal/mol)	$t_{1/2}$ at – 78 ˚C[a]	$t_{1/2}$ at 25 ˚C[a]
12	2.4 s	3.5×10^{-5} s
14	7 min	1.0×10^{-3} s
16	20 h	3.0×10^{-2} s
18	148 d	0.9 s
20	70 years	26 s

[a] Racemization $t_{1/2} = \ln 2/k_{rac}$, where $k_{rac} = 2*(kT/h)*\exp(-\Delta G^{\ddagger}/RT)$.

Table 1.1. Dependence of $t_{1/2}$ on racemization barrier and temperature

The conditions for MOC are:[9]

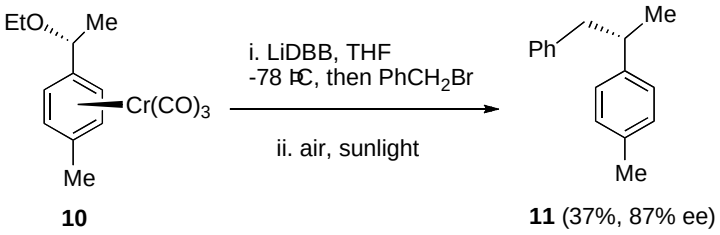
1. The reaction must involve a conformationally chiral intermediate.
2. The conformationlly chiral intermediate must be formed enantioselectively from the centrally chiral precursor.

3. The onward reaction of the conformationlly chiral intermediate must occur enantioselectively.
4. The conformationlly chiral intermediate must not readily racemize on the timescale of onward reaction.

1.4 MEMORY OF CHIRALITY IN RADICAL CHEMISTRY

1.4.1 BENZYLIC SUBSTITUTION INDUCED BY DYNAMIC PLANAR CHIRALTY

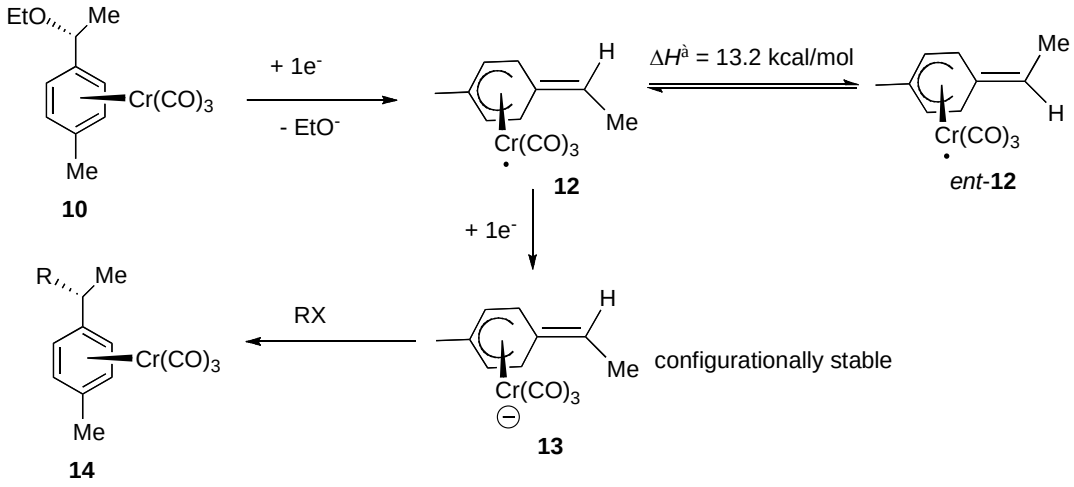
Koning and co-workers successfully developed a convenient method for the stereospecific benzylation of arene-tricarbonylchromium complex **10** by an umpulong reaction (**Scheme 1.4**).[13] Complex **10** was treated with 2 equiv each of LiDBB and benzyl bromide to give benzylated Cr-complex.



10 **11** (37%, 87% ee)

Scheme 1.4 Enantioselective benzylic substitution

Direct oxidative removal of $Cr(CO)_3$ gave **11** in 37% yield and 87% ee. Koning suggested that planar chiral radical intermediate **12** was generated enantioselectively, and then rapidly reduced to form the configurationally stable anion **13** (**Scheme 1.5**).



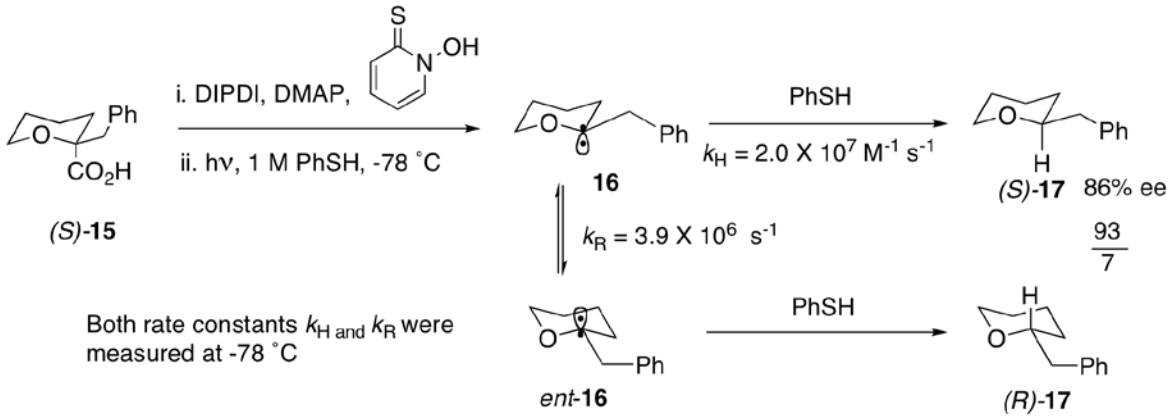
Scheme 1.5 Mechanism of retentive benzylic substitution

In this case, the central chirality of starting material is preserved as transient planar chirality in 17-valence electron complex **12** and 18-valence electron complex **13**. The retention of stereochemistry comes from the way the intermediate is generated and reacts. This phenomenon supports the idea of MOC.

1.4.2 CONFORMATIONAL MEMORY CONTROLLED ENANTIOSELECTIVE RADICAL QUENCHING

Radical reactions are usually very rapid compared to most other types of reactions and they can often be competitive with conformational isomerization. For example the rate constant of first-order ring inversion of a cyclohexane is 10^4 - 10^5 sec^{-1},[14] whereas the rate constant for cyclization of 5-hexenyl radical is in the range of 10^5 – 10^7 sec^{-1}.[15] This clearly suggests that a radical reaction may occur in the timescale of conformational change of a molecule having modest inversion barrier.

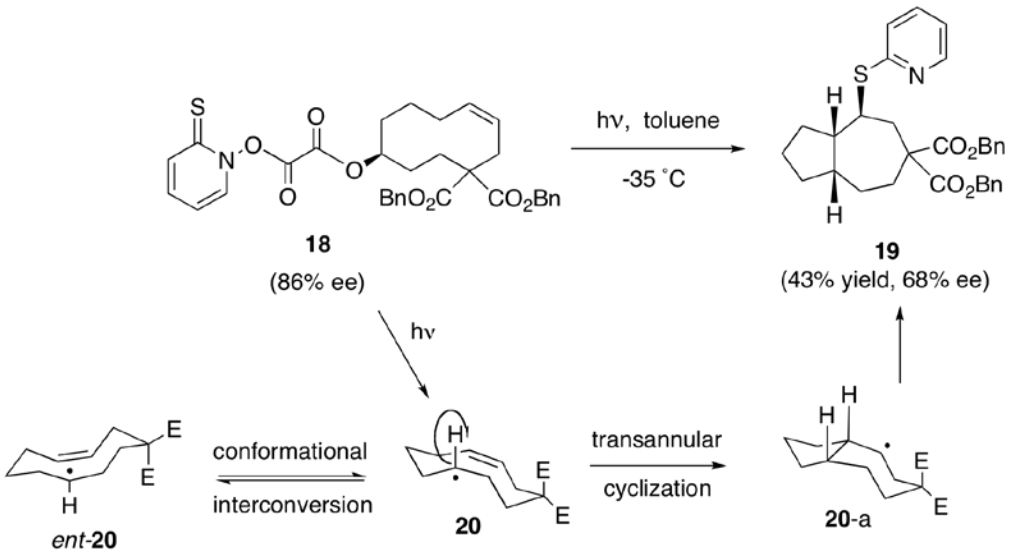
Rychnovsky and co-workers exploited the chair-chair interconversion for MOC with tetrahydropyranyl radicals.[16] Barton deoxygenation of enantiomerically pure carboxylic acid (*S*)-**15** by treatment with *N*-hydroxypyridine-2-thione and 1 M PhSH gave reduced product (*S*)-**17** in 86% ee (**Scheme 1.6**) with retention of configuration.



Scheme 1.6 Radical trapping controlled by slow ring inversion

At -78 ˚C the rate for racemization of **16** that is a first order process, is same as the rate constant k_R (3.9×10^6 s^{-1}). The hydrogen donation of PhSH to **16** is a second order reaction and rate of the reaction = k_H × [PhSH] where k_H = 2.0×10^7 M^{-1} s^{-1}. At [PhSH] greater than 0.1 M, the racemization process of **16** is overwhelmed by hydrogen donation from PhSH. Changing concentration of PhSH from 1 M to 0.1 molar resulted in drop of yield of **17** from 92% to 57% and the enantiomeric excess dropped from 86% to 4%. The formation of enantioenriched **17** shows MOC is operating and here the chiral element is the ring conformation rather than a stereogenic center.

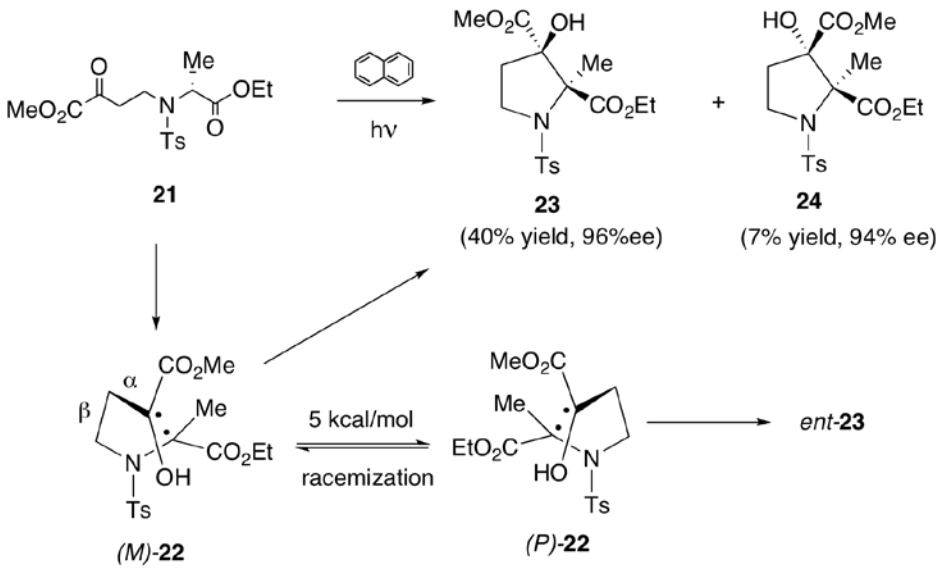
Rychnovsky also used the ring flip strategy in a transannular radical cyclization.[17] Enantiomerically enriched *N*-hydroxypyridine-2-thione mixed oxalate **18** was photolyzed at – 35 ˚C in toluene to obtain bicyclo [5.3.0]decane **19** (**Scheme 1.7**) in 43% yield and 68% ee. A conformationally chiral radical intermediate **20** was formed due to photolysis of compound **18** and the ring inversion of **20** is overwhelmed by the faster transannular cyclization.



Scheme 1.7 MOC in transannular cyclization

1.4.3 MEMORY OF CHIRALITY DUE TO SPIN ISOMERS

Molecules in their excited state are differentiated from each other as singlets (S_1) and triplets (T_1), and these spin-isomers have different reactivity. Giese and co-workers reported Norrish-Yang photocyclization of alanine derivative **21** in presence of naphthalene, a triplet quencher (**Scheme 1.8**).[18] Two diastereomeric products, **23** and **24** were obtained in 40% yield (96% ee) and 7% yield (94% ee) respectively. Singlet diradical intermediate *(M)*-**22** is formed enantiospecifically from **19** with helical chirality and slowly racemizes to *(P)*-**22.** Rapid cyclization of *(M)*-**22** results in major product **23**.



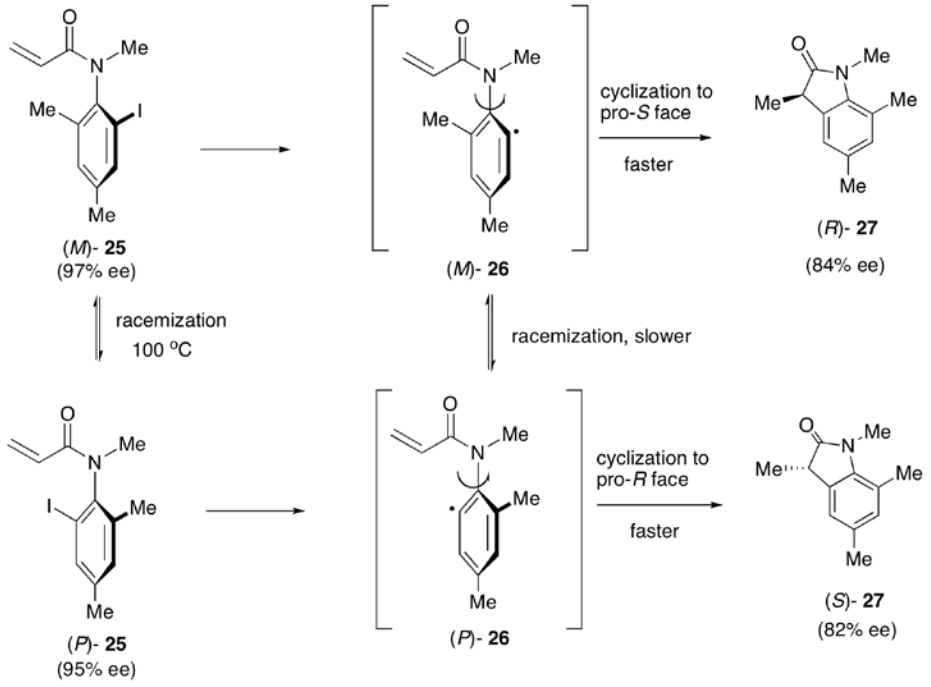
Scheme 1.8 Cyclization of photochemically generated diradicals

The barrier for cyclization (2 kcal/mol) of **22** is lower than the barrier of the rotation (5 kcal/mol) around the β-single bond, which would be the slow step of racemization of **22**. Because of their

long lifetime, triplet isomers are more racemizable than their singlet congeners and hence in absence of any triplet quencher enantiomeric ratio of product **23** is decreased significantly.

1.4.4 MEMORY OF CHIRALITY IN RADICAL CYCLIZATIONS

In 1999, the Curran group first disclosed chirality transfer in intramolecular radical cyclizations of axially chiral anilides.[19] Chirality transfer involves destruction of an original chiral element with reformation of a new chiral element elsewhere. It is a subset of MOC. The (*M*)- and (*P*) – enantiomers of *o*-iodoacrylanilide **25** underwent radical cyclizations under Et_3B/Bu_3SnH initiation condition resulting the final product (*R*)- and (*S*)- **27** with good chirality transfer (**Scheme 1.9**).

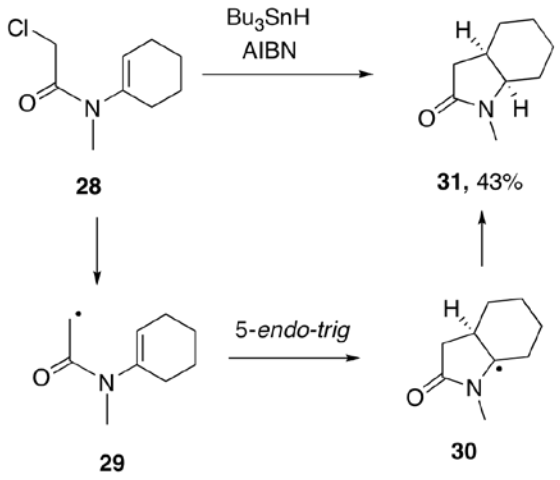


Scheme 1.9 Radical translocation and cyclization of *ortho*-iodoanilides

The barrier for interconversion of the enantiomers of **25** was measured to be 30.8 kcal/mol. The radical **26** formed via deiodination of **25** is more vulnerable to racemization because of the absence of *ortho*-iodo group that might restrict the C-N bond rotation. However, the cyclization occurs at a faster rate to produce oxindoles (*R*)-**27** and (*S*)-**27** in high enantiomeric excess. This reaction is also facially selective with respect to the alkene. The absolute configuration of the product **27** indicates that the alkene twists towards the aryl radical in the transition state for cyclization.[20]

1.5 RADICAL CYCLIZATIONS OF AMIDES

One of the valuable reactions of esters or amides is functionalization of α-carbon by which a carbon-heteroatom bond can directly be replaced by a carbon-carbon bond. This functionalization is possible by radical means via abstraction of a heteroatom from the α-carbon and then trapping of resulting radical. Ishibashi and co-workers reported that α-halo amide **28** in presence of 0.1 equiv AIBN and 1.1 equiv of tin hydride underwent radical cyclization to form lactam **31** in 43% yield (**Scheme 1.10**).[21]

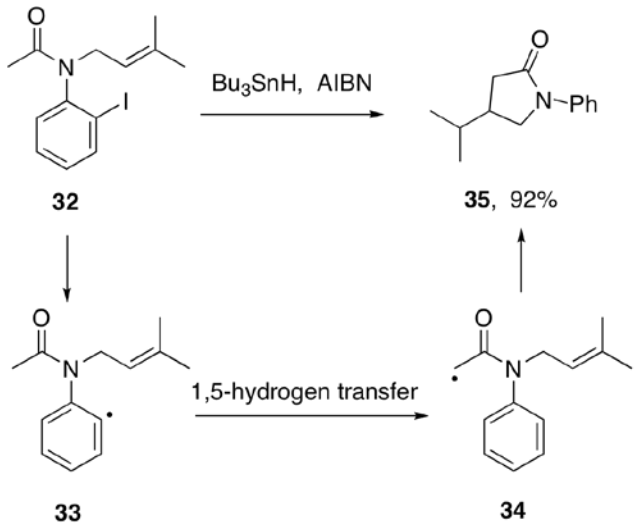


Scheme 1.10 Radical cyclization of amide

Presumably, the radical **29** is formed by radical dehalogenation of **28**, which readily underwent *5-endo-trig* cyclization to give **30**. Hydrogen transfer from tin hydride gave the final product **31**.

α-Carbonyl carbon radicals can also be formed by radical translocation. In radical translocation method a radical is first generated at a remote position and then translocated to the α-carbon center before any C-C bond formation.[22,23] 1,5-Hydrogen transfer is an extensively

used radical translocation process by which a radical can be generated at α-carbon of amide or ester. Curran and coworkers reported that anilide **32**, in presence of AIBN and tin hydride gave lactam **35** in 92% (**Scheme 1.11**).[24]

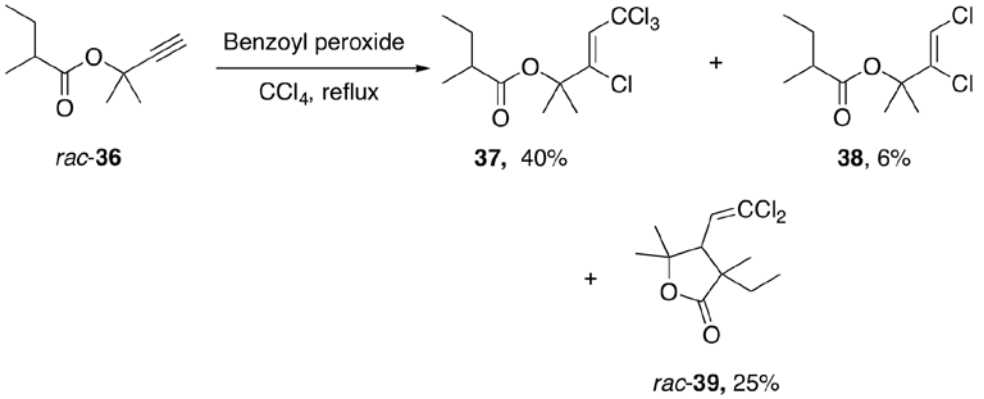


Scheme 1.11 Acyl radical formation by radical translocation process

1,5-Hydrogen transfer occurred from the α-carbon of radical **33** to the *ortho*-position of phenyl ring and acyl radical **34** is generated. Radical **34** rapidly underwent favorable *5-exo-trig* cyclization and tin hydride reduction to give compound **35**.

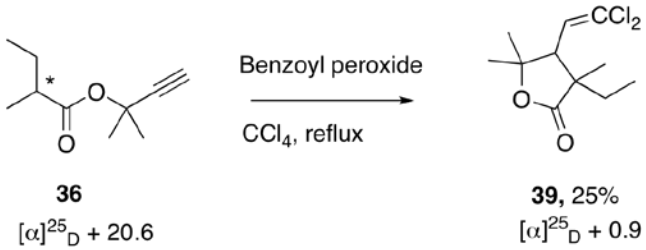
1.6 UNUSUAL OBSERVATIONS OF HEIBA AND DESSAU

In early studies of ester radical cyclization involving radical translocation, Heiba and Dessau subjected propargyl ester *rac*-**36** to benzoyl peroxide initiated addition reaction with carbon tetrachloride at reflux (**Scheme 1.12**). Besides addition products **37** and **38**, they isolated γ-butyrolactone *rac*-**39** in 25% yield.[25,26]



Scheme 1.12 Radical reaction of propargyl ester

Surprisingly when Heiba and Dessau used optically active ester **36**, the optically active lactone **39** was isolated in 20-25% yield (**Scheme 1.13**). The report did not mention the enantiopurities of the starting material **36** or the product **39**, except the optical rotation.



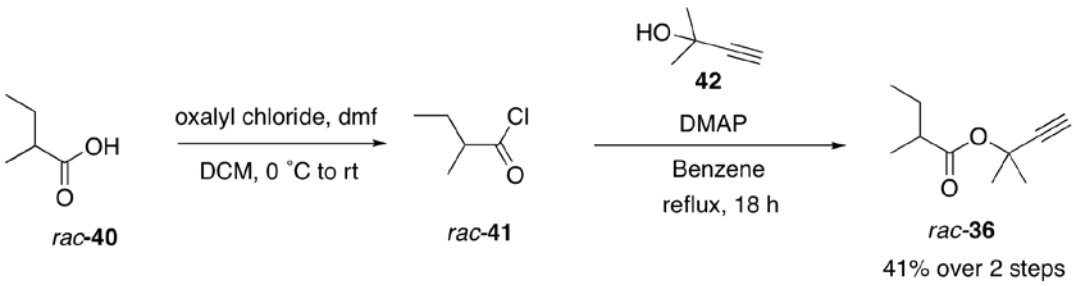
Scheme 1.13 Radical cyclization of enantiopure propargyl ester

The residual optical activity of lactone **39** clearly suggests that the radical cyclization did not occur with complete racemization at α-carbon of ester **36**. This might be a possible example of MOC in ester radical cyclization chemistry.

2.0 RESULTS AND DISCUSSION

2.1 VALIDATION OF PREVIOUS WORK

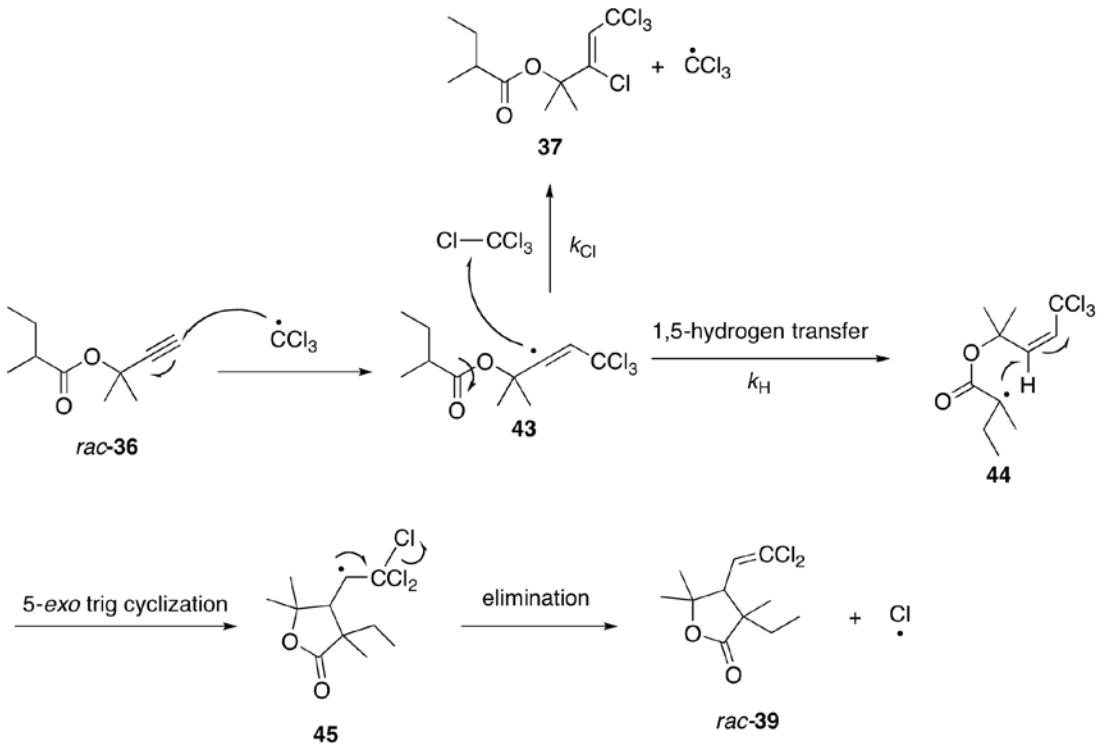
We planned to reproduce the result from Heiba and Dessau's work to ensure that it was reliable. If so, we could try to determine the enantiomeric excess of the product by modern methods. The reactions were first tried with racemic starting materials to optimize the reaction conditions. Ester *rac*-**36** was prepared from commercially available 2-methylbutyric acid *rac*-**40** (**Scheme 2.1**).



Scheme 2.1 Preparation of propargyl ester

Racemic 2-methylbutyric acid was chlorinated by oxalyl chloride in presence of DMF to give acid chloride *rac*-**41**. The coupling reaction between crude acid chloride *rac*-**41** and propargyl alcohol **42** was conducted in refluxing anhydrous benzene in presence of catalytic amount of DMAP. After flash chromatography of crude product, target ester *rac*-**36** was obtained in 41% yield over the two steps.

Following the literature procedure,[26] ester *rac*-**36** was refluxed in carbon tetrachloride with benzoyl peroxide as initiator (**Scheme 1.12**). However, the target product γ-lactone *rac*-**39** was not detected by the crude ^{1}H NMR. Wide ranges of benzoyl peroxide concentrations (0.5, 1, 10, 50, 100 mol percent) were tried, but these reactions also failed to produce the target cyclized product *rac*-**39**.

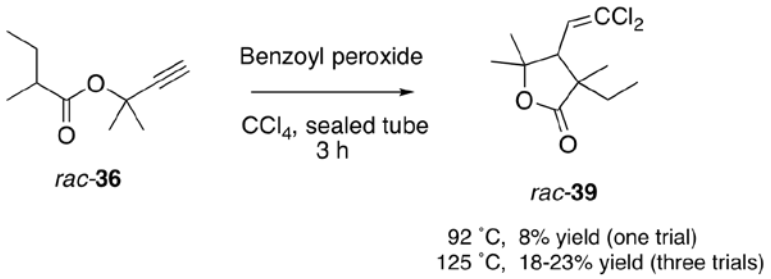


Scheme 2.2 Mechanism for 1,5-hydrogen transfer and radical cyclization of *rac*-**39**

The mechanism of the reaction is outlined here for radical reaction of propargyl ester *rac*-**36** (**Scheme 2.2**). The trichloromethyl radical attacks the triple bond of propargyl ester *rac*-**36** to give vinyl radical **43**. From **43** there are two competing pathways: 1) bimolecular halogen radical addition (k_{Cl}) to give addition product **37,** or 2) intramolecular 1,5-hydrogen abstraction

(k_H) to give tertiary radical **44**. 1,5-Hydrogen transfer is followed by 5-*exo*-*trig* cyclization and then chlorine atom elimination from β-halo radical **45** produces *rac*-**39**.

In the study of similar kind of radical cyclization of 1-heptyne,[25] Heiba and Dessau reported that the yield of cyclized product increases with increasing reaction temperature. Subsequently, various literature precedents[27] have shown the benefits of heating in such reactions. We repeated the radical reaction of ester *rac*-**36** at elevated temperatures (**Scheme 2.3**). The reaction was performed with 5 mol percent of benzoyl peroxide at 92 ˚C and 125 ˚C and the cyclized product *rac*-**39** was obtained in 8% and 23% yield, respectively, after column chromatography.

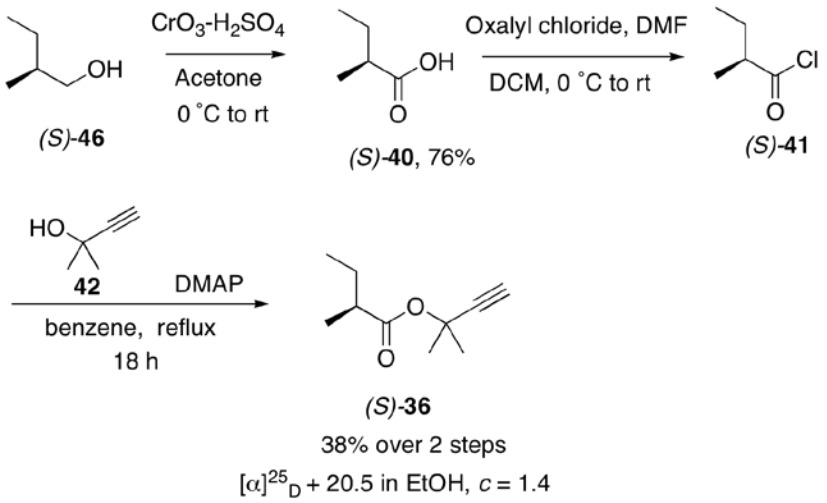


Scheme 2.3 Radical cyclization of propargyl ester

The reaction at 125 ˚C was repeated three times and the yield was obtained in the range of 18-23%. Product *rac*-**39** was quite pure as checked by ^{1}H NMR. However, the GC analysis resulted decomposition of *rac*-**39**. From the ^{1}H NMR spectrum, we found that the ratio of *cis* and *trans* isomers present in lactone *rac*-**39** was 1:1.3. This diastereomeric mixture could not be separated completely by column chromatography.

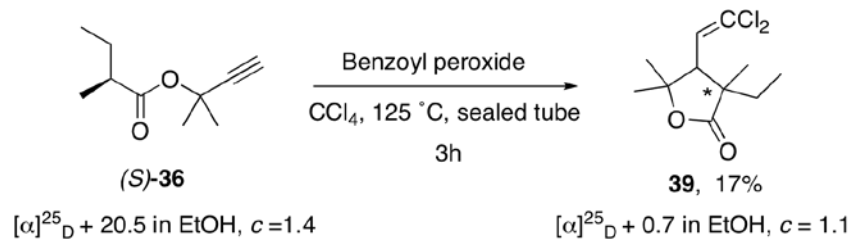
Then we repeated the same protocol for enantiopure substrate. Commercially available *(S)*-2-methyl butanol *(S)*-**46** was oxidized to *(S)*-2-methylbutyric acid *(S)*-**40** by Jones

reagent in 76% yield. Acid *(S)*-**40** was chlorinated with oxalyl chloride and then esterification was performed with propargyl alcohol **42** in presence of DMAP in refluxing anhydrous benzene to afford ester *(S)*-**36** with the overall yield of 38% over two steps (**Scheme 2.4**). The specific rotation ($[\alpha]^{25}_{D}$) of the ester *(S)*-**40** in absolute ethanol at room temperature was +20.5 (*c* = 1.4). This is well accordance with the reported value of +20.6 (*c* = not reported) in absolute ethanol.[26]



Scheme 2.4 Preparation of enantiopure propargyl ester *(S)*-**36**

Using the same protocol as in **Scheme 2.3**, enantiopure ester *(S)*-**36** was heated in a sealed tube with 0.5 mol percent of benzoyl peroxide in carbon tetrachloride at 0.2 M concentration (**Scheme 2.5**) to afford lactone **39** in 17% yield after flash chromatography.



Scheme 2.5 Radical cyclization of enantiopure propargyl ester *(S)*-**36**

From the diastereomeric mixture of *cis* and *trans* isomers of **39,** only a fraction of more polar diastereomer can be separated by column chromatography. The specific rotation ($[\alpha]^{25}_{D}$) measured for lactone **39** in absolute ethanol was +0.7 (*c* = 1.1), again comparable to the reported value of +0.9 (*c* not reported).[26] Product **39** was pure as of ^{1}H NMR spectrum The result shows that the tandem 1,5-hydrogen transfer and 5-*exo*-*trig* radical cyclization do not occur with full racemization. Upon injection of lactone **39** in GC the compound decomposed. We planned to analysis 39 by chiral GC, but now this was not possible.

2.2 PROPOSED MEMORY OF CHIRALITY FOR AMIDES

1,5-Hydrogen transfer and radical cyclization is quite common in esters but it is also known for amides.[24] Accordingly, we decided to adopt the MOC concept for conjugated 1,5-hydrogen transfer and 5-*exo* cyclization reactions for amides. Amides' nitrogens contain two branches that can be used for radical generation. Esters have only one group substituted on oxygen and the major conformer due to (O)C-O bond rotation is not well disposed for 1,5-hydrogen transfer and radical cyclization. For example, in **Fig 2.1** the ester conformer **47**-*syn* is preferred (typical rotation barrier ~ 13 kcal/mol)[28] over **47**-*anti***.** So the minor conformer is in suitable orientation to undergo 1,5-hydrogen transfer and radical cyclization. On contrary, by manipulating R-group of an amide, **48**-*anti* can be made as favored rotamer (typical rotation barrier ~ 16-22 kcal/mol).[28] Now, the major rotamer can easily undergo 1,5-hydrogen transfer and radical cyclization.

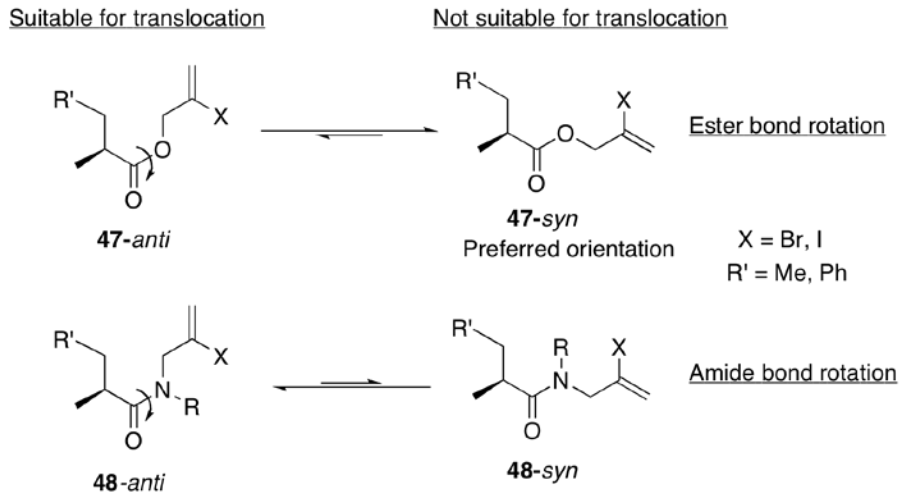
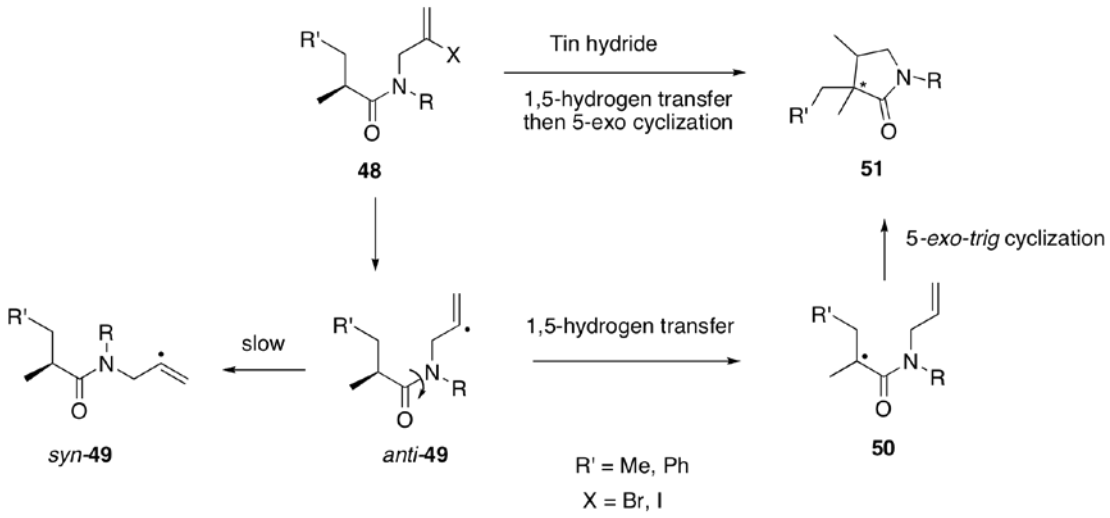


Figure 2.1. Comparison of ester and amide bond rotations from the view point of radical translocation

Also the rotameric preference of spatial disposition of amide may play a vital role to determine MOC in 1,5-hydrogen transfer and 5-*exo* cyclization. A general mechanism for amide radical translocation and cyclization is shown in **Scheme 2.6**.



Scheme 2.6 Mechanism for amide radical translocation/cyclization

Vinyl radical *anti*-**49** is generated from amide **48.** Newcomb's work[29,30] showed that when R= *t*-butyl group, the interconversion between *anti* and *syn*-isomer of **49** is slower than radical cyclization. Abstraction of the hydrogen (1,5-hydrogen transfer) from α-carbonyl carbon is preferred and the radical on tertiary carbon **50** is formed. Successive 5-*exo*-*trig* cyclization will form the five-membered ring, which in presence of tin hydride will be reduced and give lactone **51** as two diastereomers. The observation of an unequal ratio of enantiomers in **51** will signify MOC because the chiral α-carbon undergoes radical formation and attacks at vinylic carbon. The attack at vinylic carbon is equally possible from both faces.

We planned to manipulate the substitution (R-group) on nitrogen in amide **48** to facilitate the 1,5-hydrogen transfer and ring closure in 5-*exo* cyclization. Bulky groups like the *tert*-butyl group gives the advantage over non-bulky groups, as *tert*-butyl group prefers to be in *cis* position to oxygen in amide rotamers (**Figure 2.2**).[31,32] In the preferred rotamer *(Z)*-**52,** vicinity of non-terminal vinylic carbon and α-carbon increases hence better chance of radical translocation and cyclization. In other approach, symmetrical substitution on nitrogen, *i.e*. two $CH_2C(X)=CH_2$ groups could be used to get rid of any rotameric preferences.

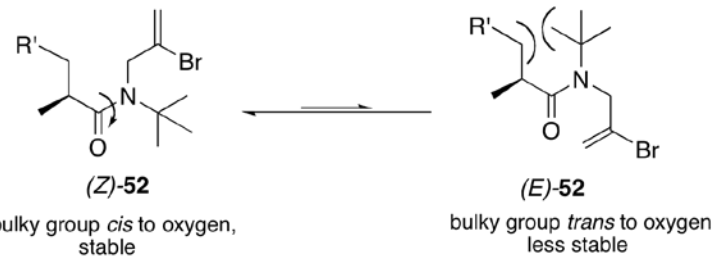
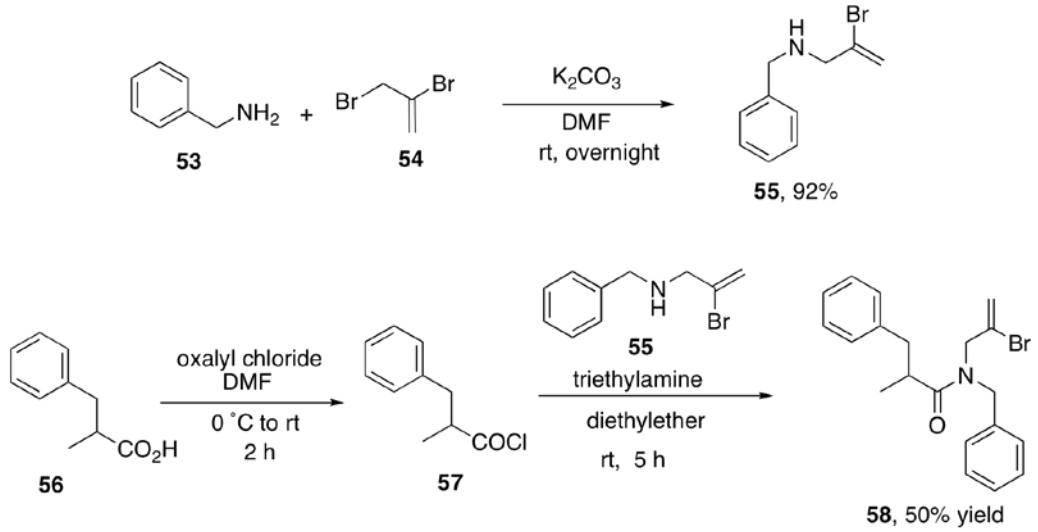


Figure 2.2. Rotameric preference of *tert*-butyl substituted amide

2.3 UNEXPECTED RADICAL PHENYL MIGRATION

We studied *N*-benzyl amide **58** as radical precursor. Since allyl and benzyl groups have a similar size, this should exist as about a 50/50 ratio of amide rotamers. *Sec*-amine **55** was prepared from benzylamine **53** and 2,3-dibromopropene **54** with potassium carbonate in DMF in 92% yield (**Scheme 2.7**). Commercially available acid **56** was stirred with oxalyl chloride and DMF to give acid chloride **57**. Amine **55** was then coupled with acid chloride **57** in presence of 1.1 equiv of triethylamine to furnish the amide **58** in 50% yield over two steps.

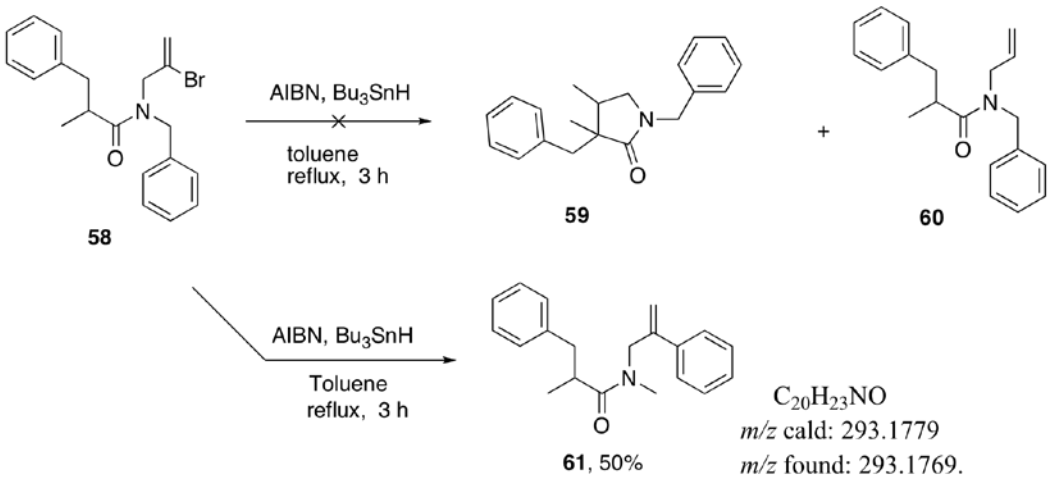


Scheme 2.7 Synthesis of *N*-benzyl amide 58

As expected, **58** coexists with its rotamer in 48:52 (from ^{1}H NMR) ratio at room temperature, though individual rotamers have not been assigned.

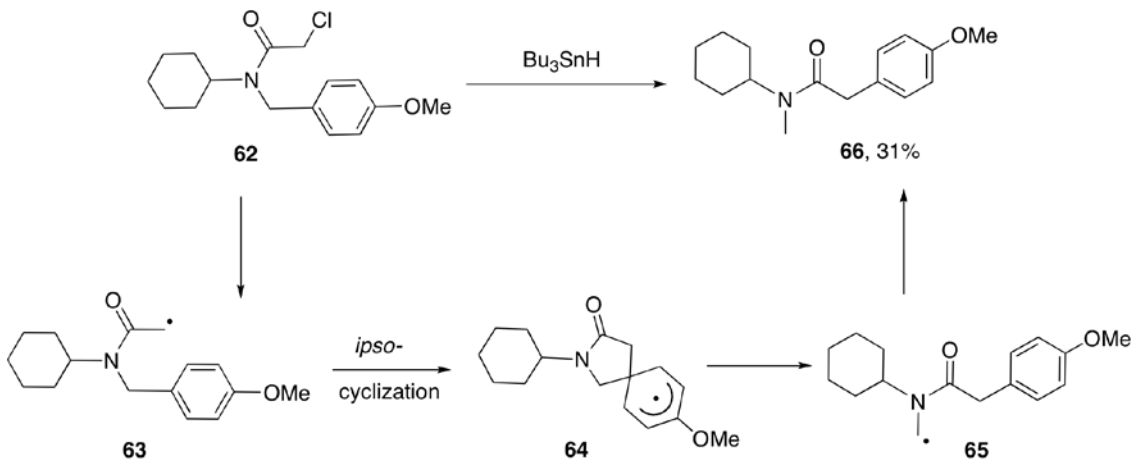
A mixture of 1.1 equiv tin hydride and 10 mol percent AIBN was added via syringe pump to a refluxing solution of amide **58.** The crude ^{1}H NMR spectrum did not show **59** or **60**. Flash chromatography gave a new product **61** in 31% yield (**Scheme 2.8**). The proton NMR

spectrum of **61** showed the presence of *N*-methyl protons as two singlets at 2.72 ppm and 2.93 ppm and two vinylic protons (5.40, 5.33, 4.98, and 4.78 ppm). We propose that product **61** was obtained due to 1,4-phenyl migration.



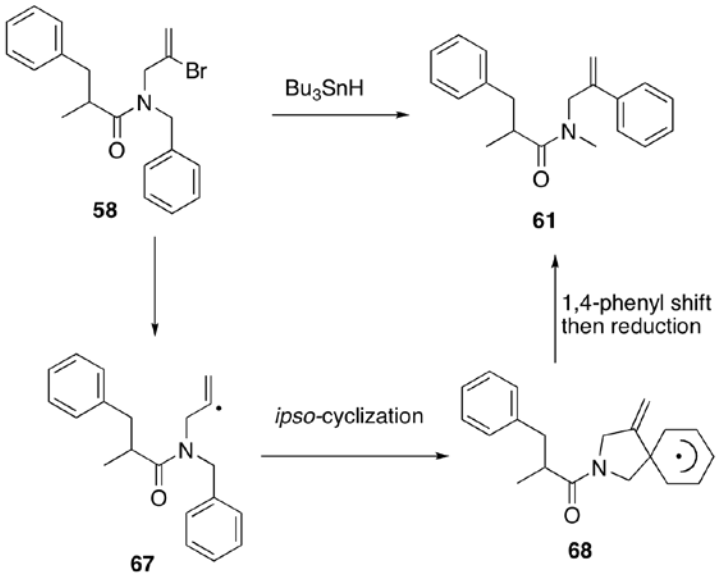
Scheme 2.8 Unexpected product from radical reaction of 58

1,4-Aryl migrations are relatively common reactions.[33,34] Ishibashi and co-workers reported 1,4-phenyl migration while they attempted radical dehalogenation of α-chloroamide **62** (**Scheme 2.9**).[35] Treatment of α-chloroamide **62** with Bu_3SnH gave *N*-methyl amide **66** in 31% yield. Acetyl radical **63** is formed by radical dehalogenation, which then underwent *ipso* cyclization to form migrated radical **65**. Hydrogen donation from Bu_3SnH to **65** yielded *N*-methyl amide **66**.



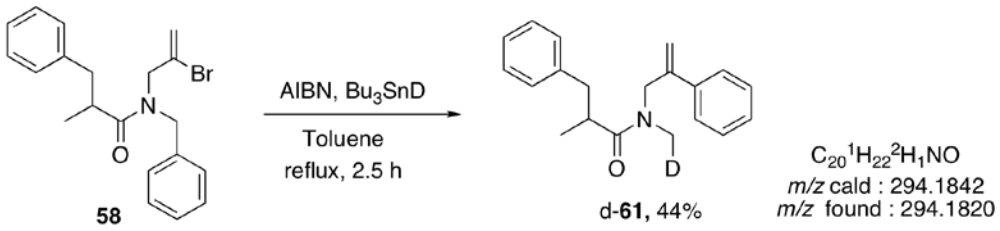
Scheme 2.9 Mechanism for 1,4-phenyl migration of 62

The formation of **61** can be explained by the mechanism outlined in **Scheme 2.10**. The 1,4-phenyl shift by *ipso*-cyclization and fragmentation of **67** occurs before 1,5-hydrogen transfer to give product **61**. *Ipso*-cyclization can occur in both rotamers of **67**; however, here we illustrate it only for *anti*-isomer.



Scheme 2.10 1,4-phenyl migration in *N*-benzyl substituted amide 58

To support the reaction mechanism, we repeated the reaction of **58** with Bu_3SnD, which afforded the product d-**61** having mono-deuterated *N*-methyl group (**Scheme 2.11**). The proton NMR spectrum shows ~ 30% reduction of peak integrals at 2.92 and 2.71 ppm. This result supports the 1,4-phenyl shift mechanism.



Scheme 2.11 Deuterium incorporation in amide 58 during 1,4-phenyl migration

2.4 RACEMIC SUBSTRATE WITH *TERT*-BUTYL SUBSTITUENT ON NITROGEN

Our focus now shifted to *N*-tert-butyl amides **69** and **70** (**Figure 2.3**). Because 1) the removal of benzyl group eliminates the possibility of undesired aryl migration, and 2) the *t*-butyl group on nitrogen favors *Z* rotamer,[30] which disposes to 1,5-hydrogen transfer and cyclization. Though the phenyl group on β-carbon in amide **69** is not necessary for MOC strategy, it was included as a UV-active group to make separation and analysis eaasier.

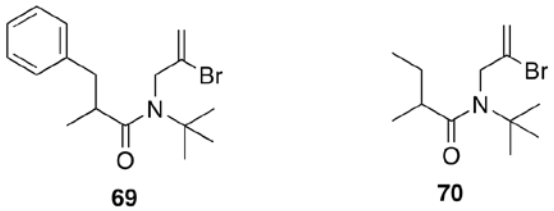
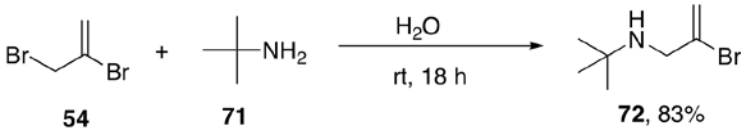


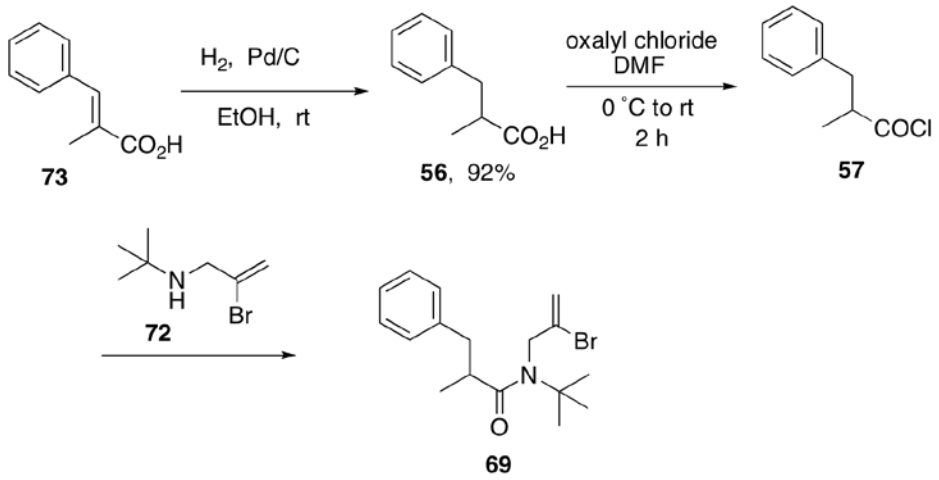
Figure 2.3. *N-tert*-butyl substituted amides

The synthesis of amine **72** needed for both substrates is shown in **Scheme 2.12**. Commercially available 2,3-dibromopropene **54** and *tert*-butylamine **71** were coupled in presence of water to afford *sec*-amine **72** in 83% yield. The crude amine was used without purification for the subsequent acylation.



Scheme 2.12 Preparation of *sec*-amine 72

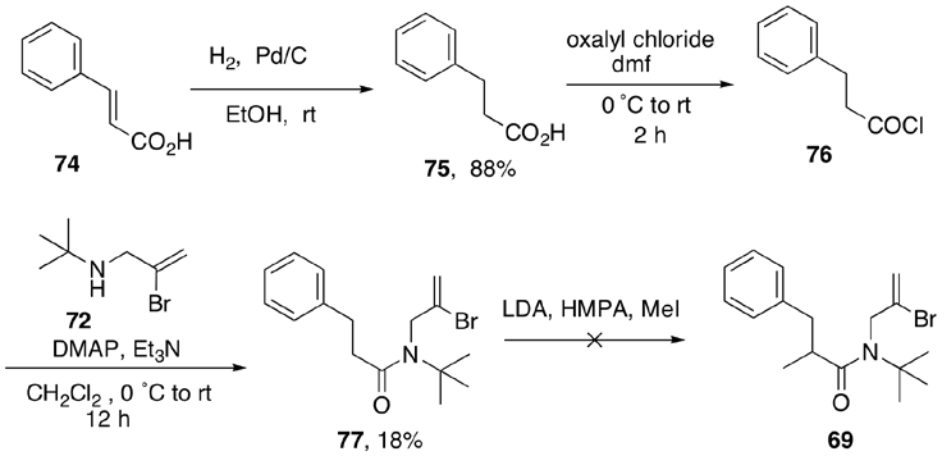
2-Methyl-3-phenylpropanoic acid **56** was prepared from α-methyl cinnamic acid **73** under hydrogen gas in presence 10% Pd/C in 92% yield. Chlorination of **56** with oxalyl chloride and catalytic amount of DMF gave crude acid chloride **57**, which was directly used in acylation (**Scheme 2.13**).



Scheme 2.13 Attempted synthesis of amide 69

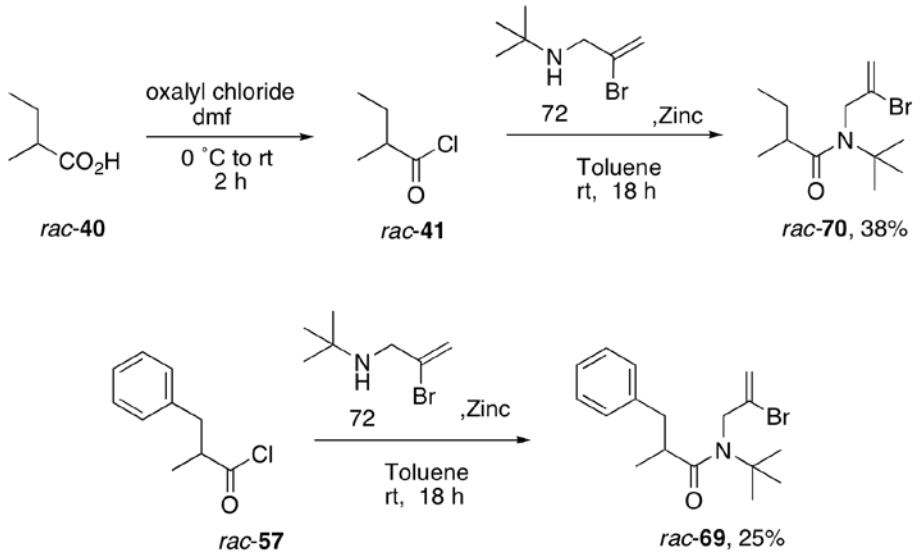
We tried the coupling of acid chloride **57** with amine **72** in presence of triethylamine-DMAP or pyridine, but no desired amide **69** was obtained. Coupling of acid **56** with amine **72** was tried with DCC, DCC-DMAP, and HATU and none of the attempts was fruitful. Evidently, the coupling of an *N*-*t*-butyl amine with an α-branched acid is retarded by steric hindrance.

Accordingly, we pursued the revised route in **Scheme 2.14** in which the acylation was conducted before introducing the α-methyl group. Reduction of **74** with hydrogen and palladium produced 3-phenylpropanoic acid **75** in 88% yield. Conversion to the acid chloride **76** with oxalyl chloride as usual was followed by addition of amine **72** (1.5 equiv), triethylamine and DMAP. The coupled product **77** was isolated in 18% yield after column chromatography. However, α-methylation of **77** with LDA, HMPA and MeI did not produce **69**.



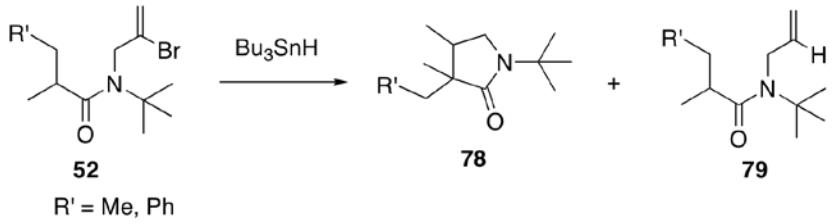
Scheme 2.14 Attempted synthesis of amide 69 from less hindered 74

We thought that the presence of phenyl group on β-carbon might pose a steric hindrance during amide coupling, so we targeted to synthesize amide *rac*-**70**. 2-Methylbutyric acid *rac*-**40** was chlorinated and coupling with amine **72** was tried. Standard amide bond forming reactions such as with triethylamine-DMAP, DCC were tried and neither of them yielded amide *rac*-**70**. Yadav and co-workers reported an unusual amide bond forming reaction between primary amine and acid chloride in the presence of metallic zinc.[36] The reactions were fast and high yielding. We first prepared acid chloride *rac*-**41** by reacting commercially available acid *rac*-**40** with oxalyl chloride and used crude for subsequent reaction. Following Yadav's protocol, acid chloride *rac*-**41** and *sec*-amine **72** were reacted in presence of equimolar amount of zinc in dry toluene for 18 h to produce the target amide *rac*-**70** in 38% yield (**Scheme 2.15**) after purification by flash chromatography. Likewise, amide *rac*-**69** was furnished in 25% yield by coupling amine **72** and acid chloride *rac*-**57** (**Scheme 2.15**).



Scheme 2.15 Synthesis of amide *rac*-69 and *rac*-70

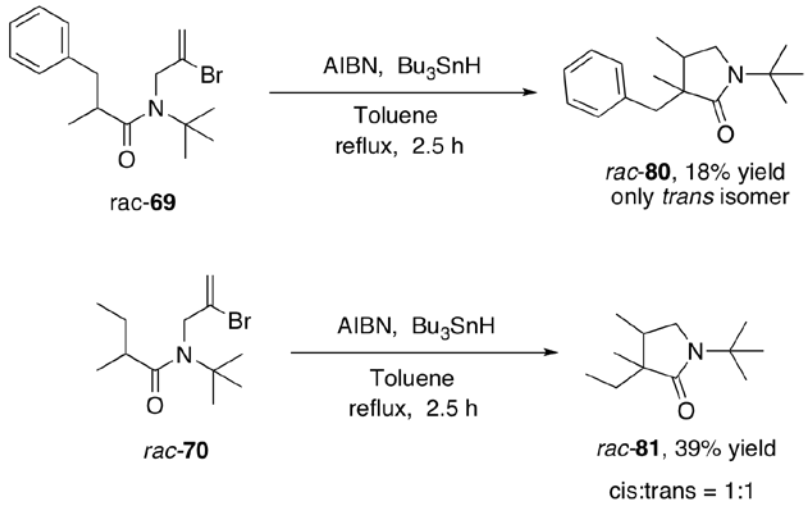
We then set out to study 1,5-hydrogen transfer and 5-*exo* cyclization of **52** in radical pathways. We anticipated γ-lactam **78** as a product along with reduced product **79** (**Scheme 2.16**). Also 5-*exo-trig* cyclization is faster than 6-*endo-trig* cyclization[15] and hence the γ-lactam **78** should be the only cyclized product.



Scheme 2.16 Radical translocation/cyclization of amide 52

A mixture of AIBN and Bu_3SnH was added via syringe pump to a 0.01 M solution of amide *rac*-**69** or *rac*-**70** in refluxing toluene (**Scheme 2.17**). Amide *rac*-**69** produced the lactam *rac*-**80** in only 18% yield. Lactam *rac*-**81** was obtained from amide *rac*-**70** in 39% yield after purification

by column chromatography. Lactam *rac*-**81** is a 1:1 mixture of *cis* and *trans* isomers, which were inseparable by column chromatography whereas, *rac*-**80** was obtained only in *trans*-isomer. The reaction with *rac*-**70** was repeated in fixed tin hydride condition and the yield of *rac*-**81** was 33%. The yield of *rac*-**81** in fixed Bu_3SnH concentration did not differ substantially from the yield obtained in syringe pump condition.

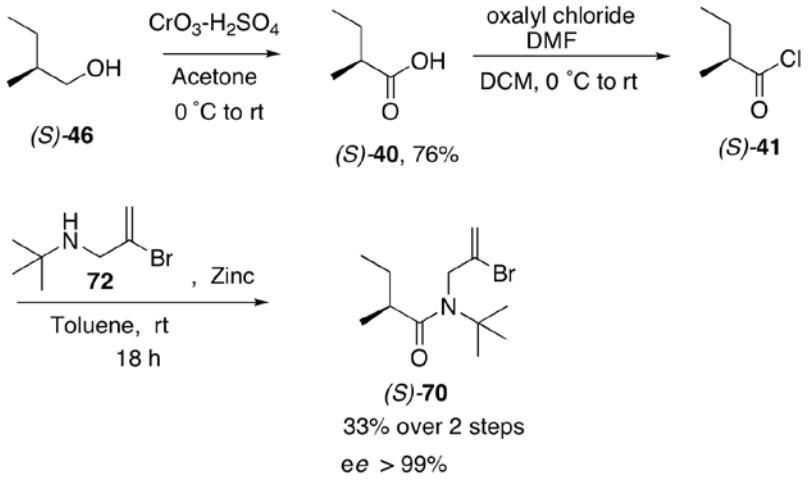


Scheme 2.17 Radical translocation/cyclization of amide *rac*-69 and *rac*-70

The reaction of amide *rac*-**70** with tin hydride and AIBN was repeated in different molar concentrations such as 0.005 M, 0.05 M, and 0.1 M, and the yields obtained for *rac*-**81** were 34%, 31%, and 36% respectively. The best yield (36%) was obtained while the reaction was performed in 0.01 M solution of amide *rac*-**70** in refluxing toluene under syringe pump condition.

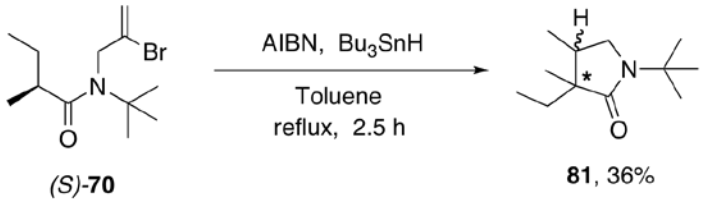
2.5 ENANTIOPURE SUBSTRATE WITH *TERT*-BUTYL SUBSTITUENT ON NITROGEN

To study the radical cyclization of enantioenriched amide, we made amide *(S)*-**70**. We have already prepared (*S*)-2-methylbutyric acid *(S)*-**40** from commercially available (*S*)-2-methylbutanol *(S)*-**46** (**Scheme 2.4**). Acid *(S)*-**40** was converted to acid chloride *(S)*-**41** by treatment with oxalyl chloride and DMF in DCM. Synthesis of amide *(S)*-**70** in >99% *ee* was accomplished by coupling between acid chloride *(S)*-**40** and sec-amine **72** in presence of activated metallic zinc in toluene with 33% yield over two steps (**Scheme 2.18**).



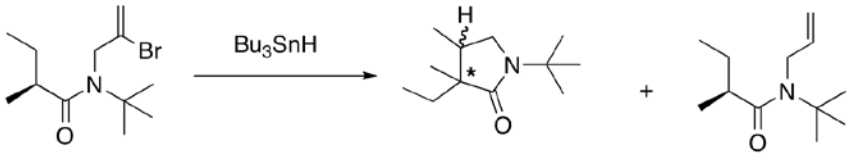
Scheme 2.18 Synthesis of enantiopure amide *(S)*-**70**

Amide *(S)*-**70** was reacted with tin hydride and AIBN under syringe pump conditions in refluxing toluene to give 5-membered lactam **81** in 36% yield (**Scheme 2.19**) after flash chromatography.



Scheme 2.19 Radical translocation/cyclization of enantiopure amide *(S)*-70

The radical reaction of *(S)*-**70** to obtain γ-lactam **81** was repeated in various different conditions. The results of radical reactions of amide *(S)*-**70** are summarized in **Table 2.1**. At room temperature with 15 mol percent of triethylborane in toluene, reduced product *(S)*-**82** was obtained in 83% yield with lactone **81** in 11% yield. When α,α,α-trifluorotoluene was used as a solvent with triethylborane in 60 ˚C, only *(S)*-**82** was obtained in 73% yield. The reaction was repeated with AIBN initiator and *(S)*-**82** was obtained in 58% yield with **81** in less than 5% yield. With AIBN initiator in refluxing toluene *(S)*-**70** gave only lactam **81** in 39% yield. For all the cases the reactions were performed in fixed tin hydride concentration (0.01 M). Entry 3 and 4 were repeated in syringe pump condition and the yield did not differ in significant extent.



(S)-**70** **81** *(S)*-**82**

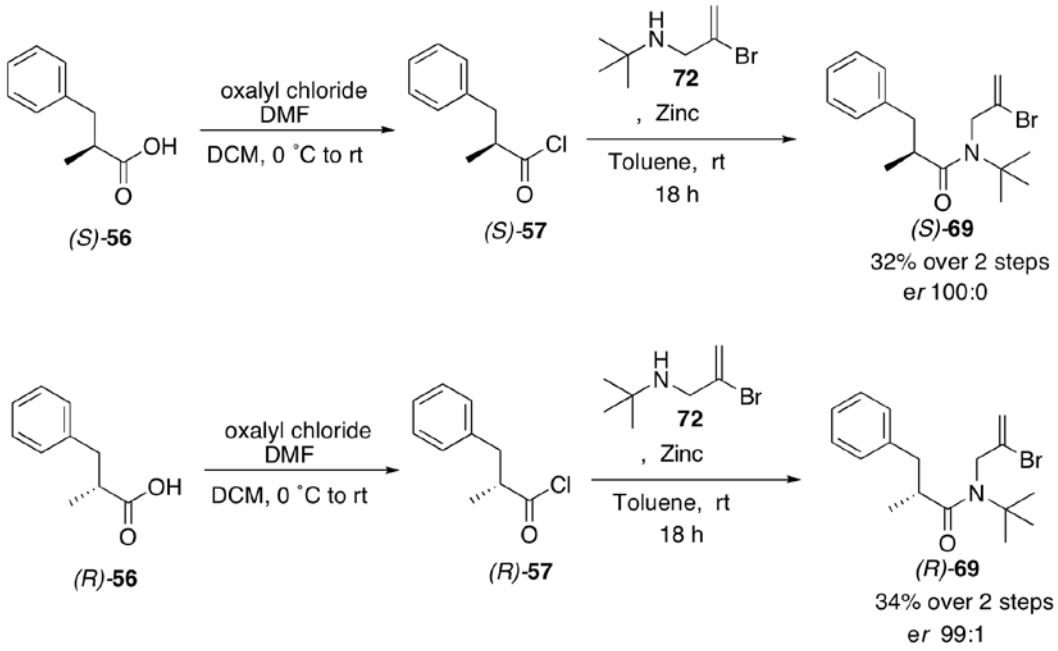
Entry	Solvent	Initiator	Temp. (°C)	Yield of **81***	Yield of (*S*)-**82***
1	Toluene	Et_3B	25	11%	83%
2	α,α,α–trifluorotoluene	Et_3B	60	0%	73%
3	α,α,α–trifluorotoluene	AIBN	60	< 5%	58%
4	Toluene	AIBN	110	39%	0%

*Isolated by column chromatography

Table 2.1. Radical reaction of *(S)*-70 in fixed Bu_3SnH concentration in presence of various initiators and solvents.

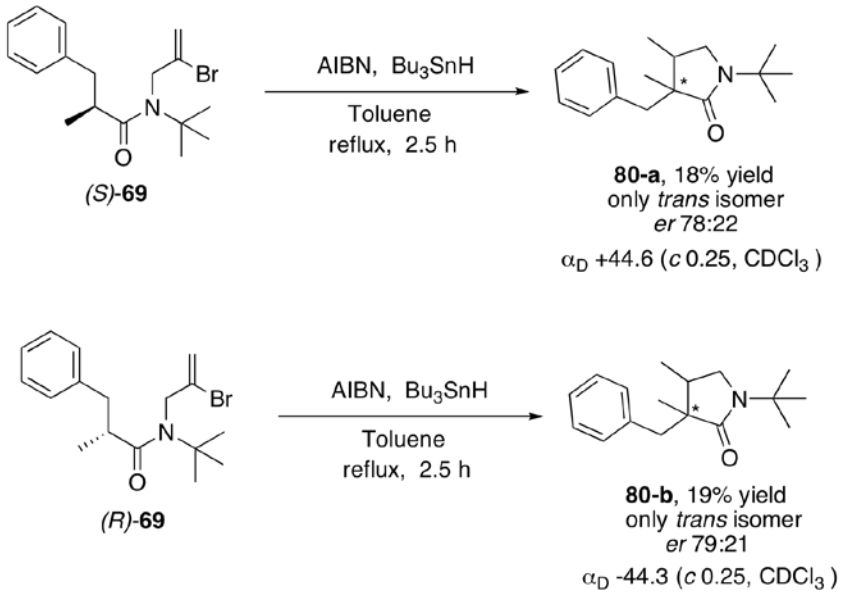
The results show that at lower temperatures irrespective of solvents and initiators, amide *(S)*-**70** gives reductively debrominated amide *(S)*-**82** as a major product. A moderate yield of cyclized product **81** was obtained at refluxing condition. The 6-*endo* cyclized product was not obtained in any case.

After successfully attempting the radical cyclization of enantioenriched amide *(S)*-**70** we set our focus on amides, i.e, *(R)*- and *(S)*-**69**. First, enantiopure acids *(R)*- and *(S)*-**56,** which were prepared following the literature procedure [37,38] were chlorinated using oxalyl chloride to yield the acid chlorides *(R)*- and *(S)*-**57**. The acid chlorides thus obtained were coupled with amine **72** in presence of equimolar amount of activated zinc in a solution of toluene to give the amide *(R)*- and *(S)*-**69** in 34% and 32% yield respectively with high enantiomeric excess (**Scheme20**).



Scheme 2.20 Synthesis of enantiopure amide *(R)*- and *(S)*-69

Amide *(R)*- and *(S)*-**69** were subjected to radical reaction in presence of tin hydride and AIBN under syringe pump conditions in a 0.01 M solution of refluxing toluene to give γ-lactam **80-b** and **80-a** in 19% and 18% yield respectively (**Scheme 2.21**) after flash chromatography. ^{1}HNMR study showed that the lactams were obtained only as *trans* isomers.



Scheme 2.21 Radical translocation/cyclization of enantiopure amide *(R)*- and *(S)*-69

We developed chiral GC analysis to determine the isomeric purity of the precursors **69**, **70** and products **80-a**, **80-b**, and **81**. For this purpose CP-7502 Chirasil-DEX CB column was used. The column phase consists of a cyclodextrin molecule that is directly bonded to a dimethylpolysiloxane and serves as stationary phase. Injection of *rac*-**70** into GC column gave two well-resolved peaks (49.7 min and 50.3 min) in about 1:1 ratio. In contrast, injection of *(S)*-**70** produced a major single peak at 50.3 min (**Figure 2.4**). Accordingly the formation of the acid chloride and the Yadav's coupling occurred with little racemization.

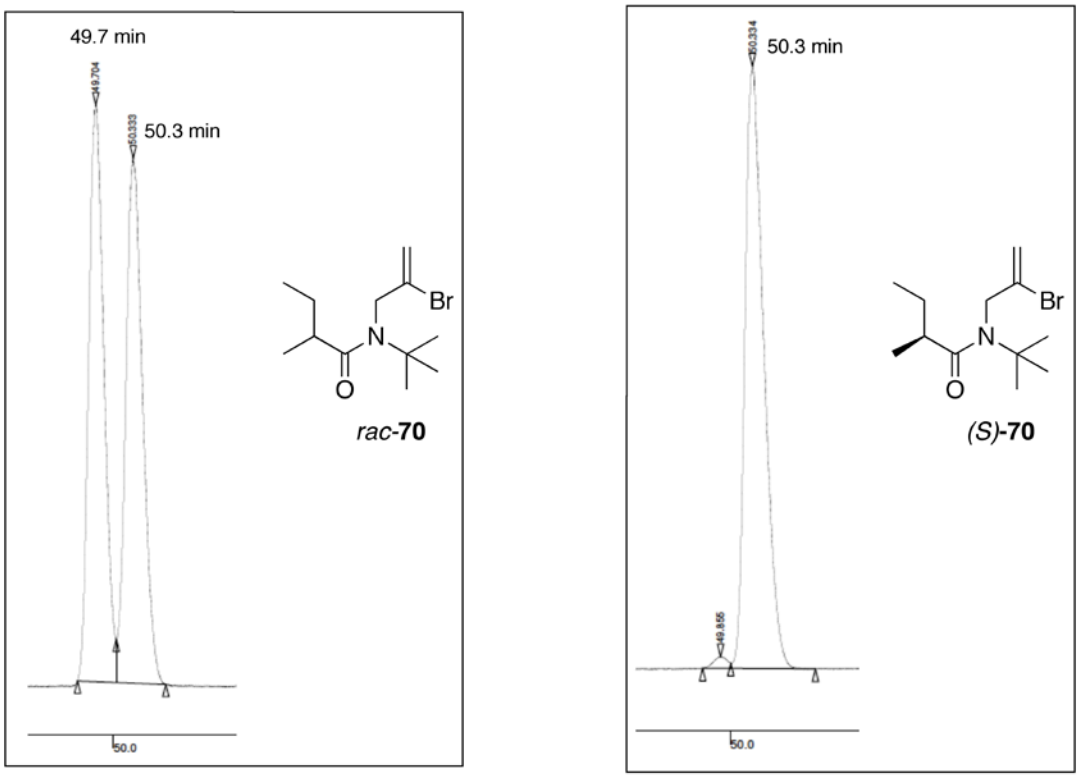


Figure 2.4. Chiral GC condition: *Flow rate 3.5 mL/min, initial oven temperature 80 ˚C, temperature ramp 0.5 ˚C/min upto 130 ˚C, then hold for 5 min*

Injection of cyclized product *rac*-**81** into the same column (CP-7502 Chirasil-DEX CB column) produced four peaks in 1:1:1:1 ratio at 43.9, 44.7, and 47.5, 50.1 min (**Figure 2.5**). When **81** was injected in chiral GC column, four peaks at 43.6, 44.2, 47.2, and 49.6 min were obtained in 6:1:5:1 ratio (**Figure 2.5**).

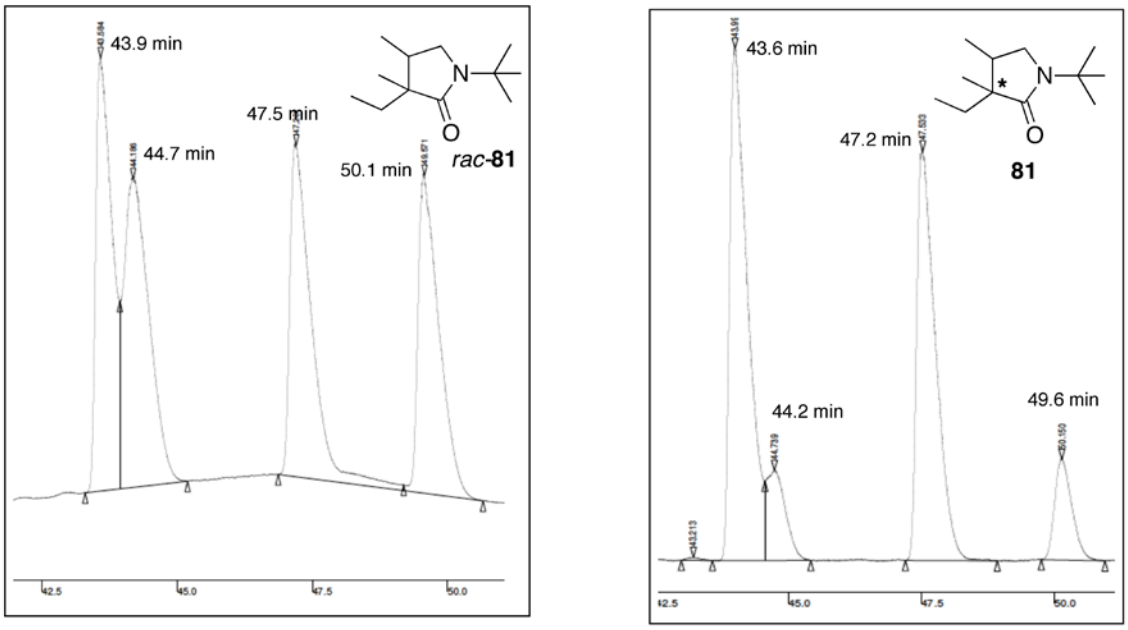


Figure 2.5. Chiral GC condition: *Flow rate 3.5 mL/min, initial oven temperature 80 ˚C, temperature ramp 0.3 ˚C/min upto 130 ˚C, then hold for 5 min.*

Though the peaks have not been assigned, we suspect that the peaks at 43.6 and 44.2 min are a pair of enantiomers, as are the peaks at 47.2 min and 49.6 min. Then the enantiomeric ratio is about 5:1 for each diastereomers.

More promising results were obtained when we studied amide **69** and lactam **80** in chiral GC. Injection of amide *rac*-**69** in chiral GC gave two well-separated peaks (at 48.57 and 49.32 min) in 1:1 ratio where as *(R)*-**69** gave the two peaks (at 48.59 and 49.17 min) but in 99:1 ratio and *(S)*-**69** gave only one peak (at 49.26 min) **(Figure 2.6)**. These results implicate that the amides *(R)*- and *(S)*-**69** are substantially entioenriched or enantiopure.

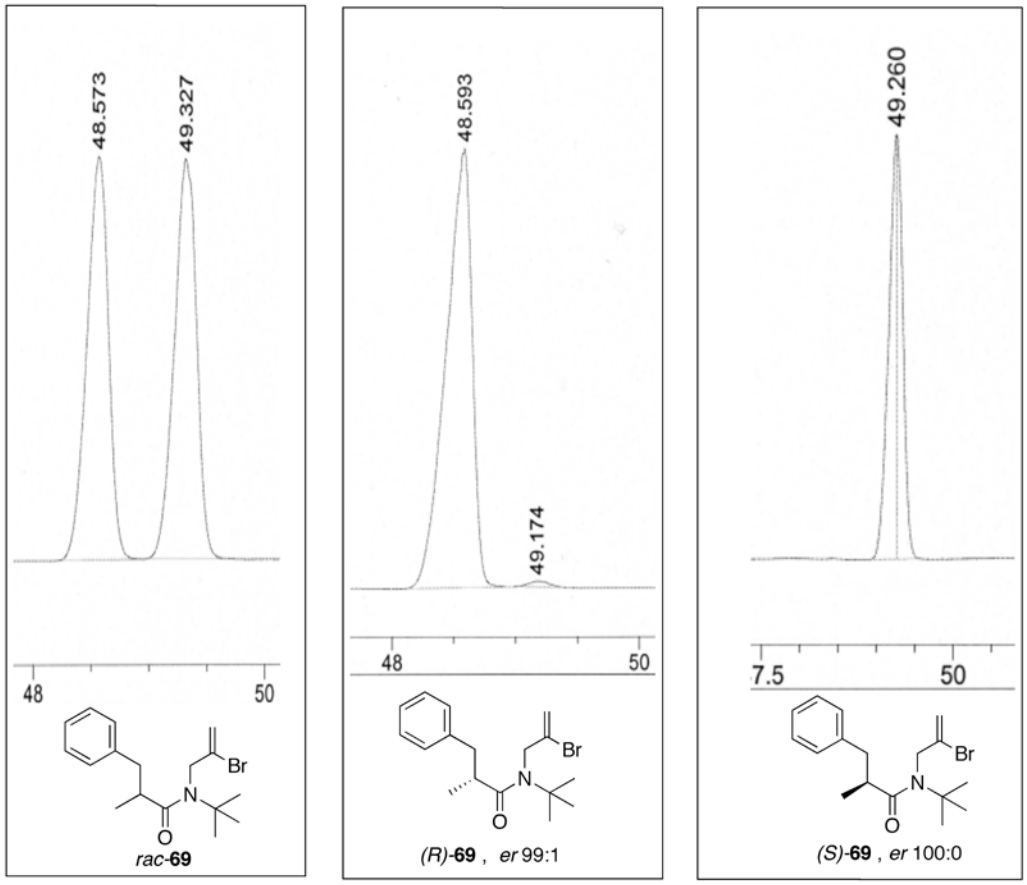


Figure 2.6. Chiral GC condition: *Flow rate 3.5 mL/min, initial oven temperature 80 ˚C, temperature ramp 0.3 ˚C/min upto 130 ˚C, then hold for 5 min.*

In the same chiral GC column the lactam **80** was injected and two peaks (at 39.56 and 40.05 min) were obtained in 1:1 ratio as expected. The injection of lactam **80-a** and **80-b** produced two peaks almost at same retention time but with different area-ratio. Lactam **80-a** produced two peaks (at 39.46 and 39.92 min) in 78:22 ratios whereas lactam **80-b** produced two peaks (at 39.41 and 39.92 min) at almost same retention time but in the ratio of 21:79.

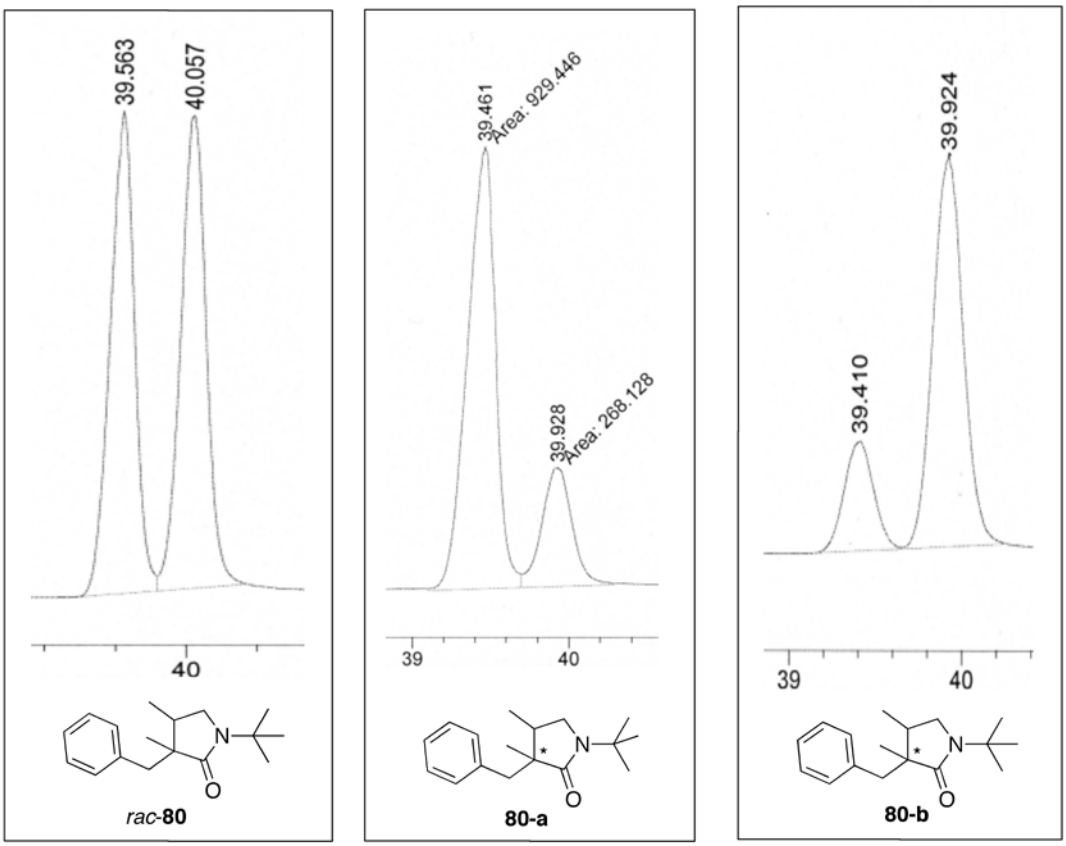
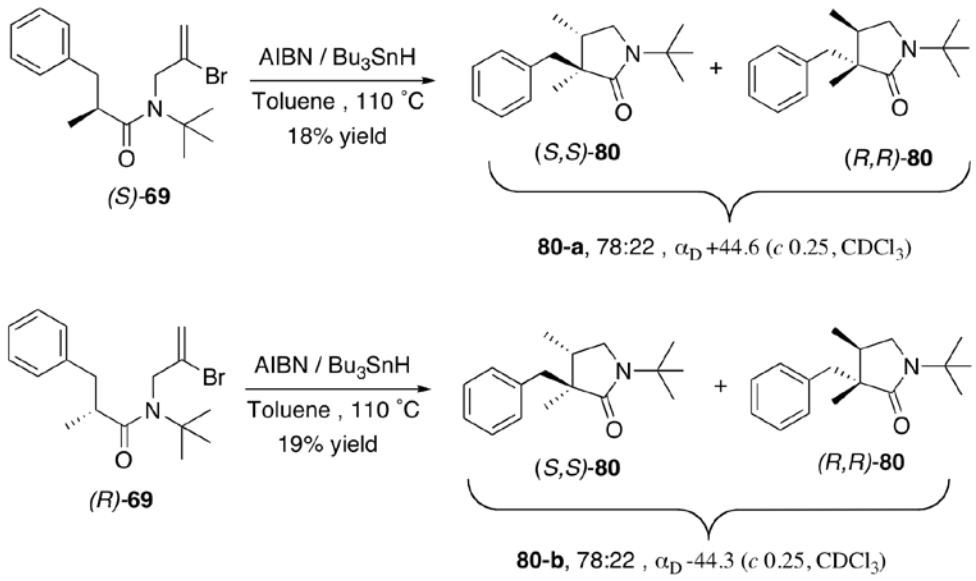


Figure 2.7. Chiral GC condition: *Flow rate 3.5 mL/min, initial oven temperature 80 ˚C, temperature ramp 0.3 ˚C/min upto 130 ˚C, then hold for 5 min.*

The chiral GC analysis of lactams **80-a** and **80-b** clearly shows that the radical translocation and cyclization of amides *(R)*- and *(S)*-**69** occur with enantio-preference. Though the peaks obtained in chiral GC analysis cannot be assigned with their respective structures, it is evident that the major enantiomer present in lactam **80-a** is certainly the minor one present in lactam **80-b** and vice-versa**.** Hence we establish that memory of chirality operates during the radical reaction of amide *(R)*- and *(S)*-**69** and we envision that the radical cyclization of amide *(S)*-**70** also followed the same route.

As assigning the peaks obtained from chiral GC with their structures appeared to be problematic, a theoretical calculation of optical rotation of (3*S*,4*S*)-3-benzyl-1-*tert*-butyl-3,4-

dimethylpyrrolidin-2-one (*(S,S)*-**80**) was performed. The theoretical value of specific rotation ($[\alpha]^{25}_{D}$) of *(S), (S)*-**80** turned out to be +124.4. The lactam **80-a** has $[\alpha]^{25}_{D}$ (*c* 0.25, $CDCl_3$) of +44.6 and lactam **80-b** has $[\alpha]^{25}_{D}$ (*c* 0.25, $CDCl_3$) of -44.3 (**Scheme 2.22**).



Scheme 2.22 Optically active components present in lactam 80-a-**and 80**-b

Both the lactams **80-a** and **80-b** are formed with 56% enantiomeric excess (chiral GC analysis), which implies that the $[\alpha]^{25}_{D}$ of the major enantiomer present in **80-a** is +79.6 and the $[\alpha]^{25}_{D}$ of the major enantiomer present in **80-b**, is -79.6. Now comparing the theoretical and experimental $[\alpha]^{25}_{D}$'s we are confirmed that the major enantiomer present in **80-a** is *(S), (S)*-**80** and *(R), (R)*-**80** is the major counterpart in lactam **80-b**. So, amide *(S)*-**69** underwent radical cyclization to give lactam *(S), (S)*-**80 as major enantiomer** and *(R)*-**69** under same condition produced lactam *(R), (R)*-**80** as major enantiomer. We can conclude that the memory of chirality operates during the radical translocation and cyclization of amide *(R)*- and *(S)*-**69** with the retention of configuration.

2.6 CONCLUSIONS

We validated the results of experiments done by Heiba and Dessau. The observations from that reaction might be considered as an early example of MOC in ester substrates. An unexpected instance of competitive 1,5-hydrogen transfer and 1,4-radical phenyl migration has been observed while we tried radical cyclization in *N*-benzyl substituted amide substrate. In addition, we successfully synthesized and cyclized both racemic and enantiopure *N*-*tert*-butyl substituted amides. Lactams obtained upon cyclization of enantiopure *N*-*tert*-butyl substituted amides showed enantiomeric components in different ratio in chiral GC analysis. Specific rotation calculation established that the radical cyclization of *N*-*tert*-butyl substituted amide occurs with memory of chirality and in this process the configuration is retained.

To conclude, we are the first to discover the first instance of memory of chirality in radical translocation-cyclization process of tertiary amide with retention of configuration.

3.0 EXPERIMENTAL SECTION

GENERAL SECTION

Chemicals and solvents were purchased from commercial suppliers and used as received, excepting as follows. Dichloromethane, THF, ether, and toluene were dried by passing through an activated alumina column. All reactions were carried out under an inert atmosphere of dry argon unless mentioned.

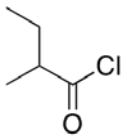
Reactions were monitored by TLC (0.25 mm E. Merck precoated silica gel plates) or ^{1}H NMR Spectroscopy or Gas chromatography analysis. For TLC analysis visualization was accomplished with a 254 nm UV lamp or by staining with phosphomolybdic acid, *p*-anisaldehyde, or potassium permanganate solutions. Gas chromatography analysis was performed in an Agilent 6850 GC System (CP-7502 Chirasil-DEX CB column) with condition: flow rate 3.5 mL/min, initial oven temperature 80 ˚C and hold at this temperature for 10 min, then temperature ramp 0.5 ˚C/min upto 130 ˚C and hold for 5 min. Flash column chromatography was performed with silica gel 60 (particle size 0.040 – 0.063 mm) purchased from EMD Chemicals Inc. as the stationary phase or by Combiflash® R_f.

Infrared (IR) spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer as thin film (CH_2Cl_2) or neat on sodium chloride plates. Low and high-resolution mass spectra were obtained on Waters LC/Q-Tof and reported in *m/z* units. High resolution mass spectra were

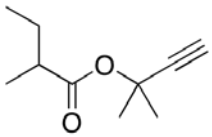
obtained on Fisons Autospec high-resolution magnetic sector mass spectrometer and reported in *m/z*. Proton (^{1}H) nuclear magnetic resonance (NMR) spectra were measured on Bruker Advance 300 ™ or Bruker Advance 400 ™ instrument at 300 and 400 MHz respectively. Carbon (^{13}C) NMR were measured on Bruker Advance 400™ instrument at 100 MHz. The chemical shifts in spectra were measured in parts per million (ppm) on the delta (δ) scale relative to the resonance of the solvent peak ($CDCl_3$: ^{1}H = 7.26 ppm, ^{13}C = 77.2 ppm). Unless otherwise noted, NMR spectra were recorded in $CDCl_3$ at 298 K. The following abbreviations were used to describe coupling: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad; app = apparent. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at the Na D-line (λ= 589 nm) using a 1 dm cell at 20 ˚C.

General procedure (A) for preparation of acid chlorides:

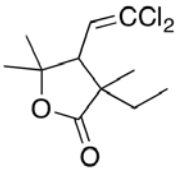
Oxalyl chloride (1.2 equiv) was added dropwise to a solution of the acid (1 equiv) and 2-3 drops of DMF in dry methylene chloride at 0 ˚C. The mixture was stirred for 2 h at room temperature and then the solvent was evaporated under *vacuo*. The crude acid chloride was used for the subsequent reaction without any further purification.



2-Methylbutyryl chloride (*rac*-**41):** The title compound (1.42 g) was prepared from 2-methylbutyric acid *rac*-**40** (1.5 g, 14.6 mmol) by following general procedure **A** and used crude.

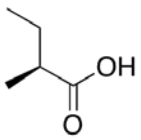


2-Methylbut-3-yn-2-yl 2-methylbutanoate (*rac*-36):[39] 2-methylbut-3-yn-2-ol **42** (1.98 g, 23.5 mmol) solution of anhydrous benzene (15 mL) was cooled (0 ˚C) and were added 4-DMAP (0.015 g, 0.12 mmol) and crude 2-methylbutyryl chloride *rac*-**41** (1.42 g, 11.7 mmol). Then the mixture was gradually warmed to room temperature and was refluxed for 18 h. The organic solution was then washed sequentially with saturated $NaHCO_3$ solution (2 × 20 mL) and brine and dried over $MgSO_4$. The solution was then filtered through a cotton plug and concentrated in *vacuo*. Purification of the residue by flash chromatography (1:50 EtOAc/hexane) afforded ester *rac*-**36** (1.27 g, 41% yield over 2 steps) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.51 (s, 1H), 2.35-2.26 (m, 1H), 1.67 (s, 6H), 1.69-1.62 (m, 1H), 1.51-1.42 (m, 1H), 1.13 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 84.0, 81.2, 67.9, 41.1, 28.7, 26.6, 16.8, 10.9.

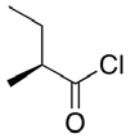


4-(2,2-Dichlorovinyl)-3-ethyl-3,5,5-trimethyldihydrofuran-2(3*H*)-one (*rac*-39):[26] A mixture of propargyl ester *rac*-**36** (0.1 g, 0.60 mmol), benzoyl peroxide (0.007 g, 0.029 mmol) and anhydrous carbon tetrachloride (3 mL, 50 equiv) in a sealed tube was flushed with argon. The mixture was heated at 125 ˚C for 4 h. Upon cooling the mixture was treated with saturated aqueous solution of $Na_2S_2O_5$ and then organic layer was washed subsequently with saturated

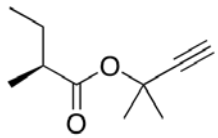
$NaHCO_3$ and brine. The organic layer was then separated, dried over $MgSO_4$, and concentrated in *vacuo*. The residue was purified by flash chromatography (1:20 EtOAc/hexane) to obtain title compound (0.034 g, 23%) as colorless oil, in 1.3:1 ratio of two diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ more polar isomer: 5.88 (d, *J* = 10.8 Hz, 1H), 3.89 (d, *J* = 10.5 Hz, 1H), 1.46 (s, 3H), 1.38 (s, 3H), 1.27 (s, 3H), 1.04 (t, *J* = 7.5 Hz, 3H); less polar isomer: 5.92 (d, *J* = 10.8 Hz, 1H), 3.20 (d, *J* = 11.1 Hz, 1H), 1.45 (s, 3H), 1.39 (s, 3H), 1.28 (s, 3H), 0.91 (t, *J* = 7.5 Hz, 3H); overlapping resonances: 1.82-1.65 (m, 2H), 1.64-1.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.1, 128.7, 128.4, 122.4, 79.8, 79.5, 51.9, 41.5, 41.2, 30.1, 25.6, 25.3, 20.4, 8.2.



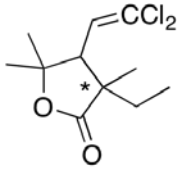
(*S*)-2-Methylbutanoic acid (*(S)*-40): To a stirred and cooled solution of *(S)*-2-methylbutanol *(S)*-**46** (2.5 g, 28.36 mmol) in acetone, Jones reagent (37 mmol) was added dropwise at 0 ˚C and the mixture was stirred for 2 h at room temperature. The reaction was then quenched by the addition of 2-propanol and the mixture was concentrated in *vacuo*. The residue was diluted with water and extracted with diethyl ether. The organic phase was washed with dilute HCl and brine, dried over $MgSO_4$, and concentrated. After distillation (80 ˚C) at reduced pressure (15 mmHg) the title product (2.18 g, 76%) was obtained as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (q, *J* = 6.9 Hz, 1H), 2.02-1.36 (m, 2H), 1.12 (d, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H).



(*S*)-2-Methylbutyryl chloride (*(S)*-41): Following general procedure **A** acid chloride (S)-**41** was obtained (1.40 g) from (*S*)-2-methylbutyric acid *(S)*-**40** (1.5 g, 14.6 mmol) and used crude for subsequent reaction.

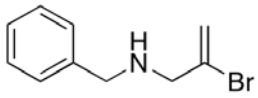


(*S*)-2-Methylbut-3-yn-2-yl 2-methylbutanoate (*(S)*-36):[39] Ester *(S)*-**36** (1.16 g, 37% yield over 2 steps) isolated as colorless oil: $[\alpha]^{25}_{D}$ = +20.5 (*c* = 1.4, ethanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.51 (s, 1H), 2.35-2.26 (m, 1H), 1.69-1.62 (m, 1H), 1.67 (s, 6H), 1.51-1.42 (m, 1H), 1.13 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 84.0, 81.2, 67.9, 41.1, 28.7, 26.6, 16.8, 10.9.

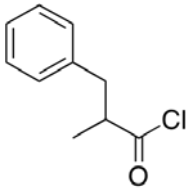


4-(2,2-Dichlorovinyl)-3-ethyl-3,5,5-trimethyldihydrofuran-2(3*H*)-one (39):[26] Title compound (0.032 g, 17%)was obtained as colorless oil: For more polar isomer $[\alpha]^{25}_{D}$ = +0.7 (*c* = 1.1, ethanol).^{1}H NMR (300 MHz, $CDCl_3$) δ more polar isomer: 5.87 (d, *J* = 10.8 Hz, 1H), 3.89 (d, *J* = 10.5 Hz, 1H), 1.46 (s, 3H), 1.38 (s, 3H), 1.27 (s, 3H), 1.04 (t, *J* = 7.5 Hz, 3H); less polar

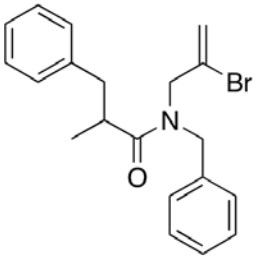
isomer: 5.91 (d, J = 10.8 Hz, 1H), 3.20 (d, J = 11.1 Hz, 1H), 1.45 (s, 3H), 1.39 (s, 3H), 1.28 (s, 3H), 0.91 (t, J = 7.5 Hz, 3H); overlapping resonances: 1.82-1.65 (m, 2H), 1.64-1.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.1, 128.7, 128.4, 122.4, 79.8, 79.5, 51.9, 41.5, 41.2, 30.1, 25.6, 25.3, 20.4, 8.2.



***N*-Benzyl-2-bromoprop-2-en-1-amine (55):**[40] To a solution of benzylamine (2.02 g, 18.9 mmol) in presence of potassium carbonate in DMF (12 mL) was slowly added a solution of 2,3-dibromopropene (1.26 g, 6.45 mmol) in DMF (3 mL) at 0 ˚C. Then the solution was stirred overnight at room temperature. The reaction mixture was diluted with ether and washed with water, dried over $MgSO_4$ and concentrated in *vacuo*. The crude product (1.38 g) was directly used for subsequent reaction. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.32 (m, 5H), 5.80 (d, J = 1.2 Hz, 1H), 5.60 (d, J = 1.2 Hz, 1H), 3.74 (s, 2H), 3.47 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 133.5, 128.6, 128.5, 128.3, 127.1, 117.9, 56.6, 51.1; FTIR (thin film, CH_2Cl_2, cm^{-1}) 3062, 3027, 2912, 2835, 1626, 1494, 1453.



2-Methyl-3-phenylpropanoyl chloride (57): Following general procedure **A,** acid chloride **57** was obtained (1.1 g) from 2-methyl-3-phenylpropanoic acid **56** (1.4 g, 8.52 mmol) and used crude for subsequent reaction.

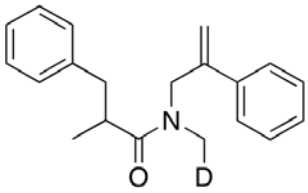


***N*-Benzyl-*N*-(2-bromoallyl)-2-methyl-3-phenylpropanamide (58):** To a stirred solution of N-benzyl-2-bromoprop-2-en-1-amine **55** (1.36 g, 6.01 mmol) and triethylamine (0.61 g, 6.04 mmol) in diethyl ether (18 mL) was added dropwise 2-methyl 3-phenylpropionyl chloride **57** (1.1 g, 6.02 mmol) at 0 ˚C. The resulting mixture was stirred at room temperature for 3 h. The reaction mixture was filtered, and the precipitated triethylammonium hydrochloride was washed with diethyl ether. The combined filtrates were washed successively with saturated $NaHCO_3$ solution, water, and brine. After drying with $MgSO_4$ and evaporating the solvent, the crude product was purified by flash chromatography (1:25 EtOAc/Hexane) to obtain title product (1.1 g, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) 7.25-6.91 (m, 10H), 5.51 (s, 2H), 5.46 (s, 2H), 4.66 (d, *J* = 15.0 Hz, 1H), 4.48 (d, *J* = 17.4 Hz, 1H), 4.42 (d, *J* = 14.4 Hz, 1H), 4.41 (d, *J* = 17.7 Hz, 1H), 4.32 (d, *J* = 15.6 Hz, 1H), 4.10 (d, *J* = 15.9 Hz, 1H), 3.82 (d, *J* = 18.6 Hz, 1H), 3.73 (d, *J* = 18.0

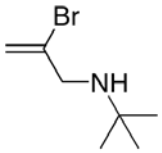
Hz, 1H), 1.23 (d, *J* = 6.6 Hz, 3H), 3.12-2.89 (m, 4H), 2.74-2.62 (m, 2H), 1.19 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 140.0, 139.8, 136.9, 136.3, 129.3, 129.2, 128.9, 128.6, 128.5, 128.4, 128.2, 128.1, 127.6, 127.4, 126.4, 126.3, 126.2, 118.1, 117.5, 53.8, 52.6, 50.0, 48.2, 40.8, 40.4, 38.7, 38.5, 18.7, 18.5; FTIR (thin film, CH_2Cl_2, cm^{-1}) 3053, 2985, 1650, 1495, 1466, 1453, 1422, 1265.

***N*,2-Dimethyl-3-phenyl-*N*-(2-phenylallyl)propanamide (61):** Under argon atmosphere the amide **58** (0.2 g, 0.54 mmol) was dissolved in toluene (25 mL) and the solution was brought to reflux. A solution of Bu_3SnH (0.3 g, 1.05 mmol) and AIBN (0.008 g, 0.049 mmol) in toluene (25 mL) was added via syringe pump over 2.5 h, and the mixture was refluxed for an additional 1 h. Upon cooling to room temperature, the solvent was evaporated in *vacuo* and the residue was diluted with ether (30 mL) and stirred with 8% potassium fluoride solution (50 mL) for 18 h. The aqueous layer was removed, and the organic layer was dried over $MgSO_4$, filtered through a celite pad, and the solvent was removed. After purification by column chromatography (2:25 EtOAc/hexane) gave title product (0.073 g, 50%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.11 (m, 10H), 5.40 (d, *J* = 0.6 Hz, 1H), 5.33 (app s, *J* = 1H), 4.98 (d, *J* = 0.9 Hz, 1H), 4.78 (t, *J* = 1.5 Hz, 1H), 4.58 (d, *J* = 11.4 Hz, 1H), 4.38 (d, *J* = 10.8 Hz, 1H), 4.03 (dt, *J* = 13.5 Hz, *J* = 1.2 Hz, 1H), 3.95 (dt, *J* = 13.5 Hz, *J* = 1.2 Hz, 1H), 3.03-2.90 (m, 2H), 2.93 (s, 3H), 2.72 (s, 3H), 2.67-2.56 (m, 2H), 1.15 (d, *J* = 5.1 Hz, 3H), 1.04 (d, *J* = 4.8 Hz, 3H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 176.8, 175.9, 144.1, 142.8, 140.3, 138.9, 138.5, 138.2, 130.5-125.9, 114.4, 112.5, 53.0, 50.6, 42.3, 40.9, 40.2, 38.5, 34.0, 32.6, 18.4, 17.5; FTIR (thin film, CH_2Cl_2, cm^{-1}) 3053, 3028, 2970, 2931, 1681, 1641, 1495, 1453, 1265; HRMS (EI) cald for $C_{20}H_{23}NO$, 293.1779 $[M]^+$, found: 293.1769.

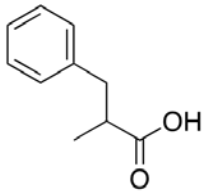


***N*-methyl-d-2-methyl-3-phenyl-*N*-(2-phenylallyl)propanamide (*d*-61):** The title compound (0.036 g, 44%) was obtained as colorless viscous liquid. HRMS (EI) cald for $C_{20}H_{22}NOD$, 294.1842 $[M]^+$, found: 294.1820.

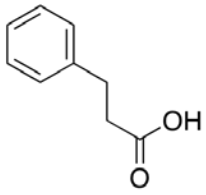


2-Bromo-*N*-*tert*-butylprop-2-en-1-amine (72): A mixture of *tert*-butylamine **71** (5.5 g, 74.9 mmol) and water was stirred in a 3-necked round-bottom flask fitted with reflux condenser. 2,3-Dibromopropene **54** (4.9 g, 24.6 mmol) was added dropwise for a period of 15 min. The stirring was continued for 6 h at room temperature, then homogeneous solution was allowed to stand 18 h. The solution was cooled in an ice-bath, NaOH (1.5 g) was added with stirring, and the resulting mixture was extracted with ether. The combined organic layer was dried over NaOH, and the excess tert-butylamine and ether were removed in *vacuo*. The crude product (4.01 g) was

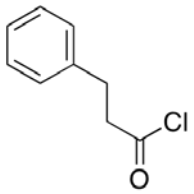
obtained as orange liquid and used for subsequent reactions without purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (d, *J* = 1.2 Hz, 1H), 5.49 (d, *J* = 1.2 Hz, 1H), 3.42 (s, 2H), 1.21 (s, 9H).



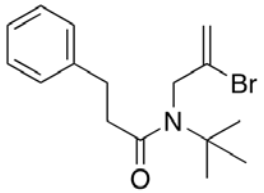
2-Methyl-3-phenylpropanoic acid (56): A solution of α-methylcinnamic acid **73** (5.0 g, 30.82 mmol) in absolute ethanol (30 mL) was stirred and 10% Pd/C (0.5 g) was added. The dark solution was evacuated thrice and then H_2-balloon was inserted. The reaction mixture was stirred for stirred at room temperature for 5 hr. The mixture was filtered through celite and the solvent was removed in *vacuo*. Vacuum distillation gave title product (2.98 g, 59%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (d, *J* = 6.9 Hz, 3H), 2.66 (tq, *J* = 7.2 Hz, *J* =6.9 Hz, 1H), 3.07-2.94 (m, 2H), 7.82 - 7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.0, 139.1, 129.1, 128.5, 126.6, 41.4, 39.4, 16.6.



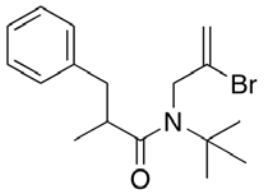
3-Phenylpropanoic acid (75): The title product (2.7 g, 88%) was prepared from cinnamic acid **74** (3 g, 20.25 mmol) following the same procedure for compound **56.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73-7.30 (m, 5H), 2.49 (t, *J* = 7.2 Hz, 2H), 2.97 (t, *J* = 7.2 Hz, 2H).



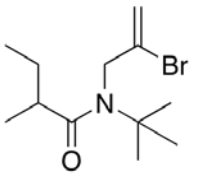
3-Phenylpropanoyl chloride (76): To prepare title product (0.5 g) from acid **75** (0.5 g, 33.29 mmol), general procedure **A** was followed and used crude for subsequent reaction.



***N*-(2-Bromoallyl)-*N*-*tert*-butyl-3-phenylpropanamide (77):** Under argon atmosphere 3-phenylpropanoyl chloride **76** (0.5 g, 3.32 mmol) was added to a solution of amine **72** (0.64 g, 3.33 mmol), triethylamine (0.34 g, 3.34 mmol) and DMAP (0.04 g, 0.33 mmol) in DCM (10 mL) at 0 ˚C. The reaction mixture was stirred and warmed to rt (12 h). The reaction mixture was filtered, and the precipitate was washed with diethyl ether. The combined filtrates were washed successively with saturated $NaHCO_3$ solution, water, and brine. After drying with $MgSO_4$ and evaporating the solvent, the crude product was purified by flash chromatography (2:25 EtOAc/hexane) to obtain title product (0.19 g, 18%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.15 (m, 5H) 5.67 (q, *J* = 2.4 Hz, 1H), 5.57 (q, *J* = 2.4 Hz, 1H), 3.97 (dd, *J* = 1.8 Hz, *J* = 1.8 Hz, 2H), 2.95 (t, *J* = 7.5 Hz, 2H), 2.55 (t, *J* = 7.8 Hz, 2H), 1.43 (s, 9H).

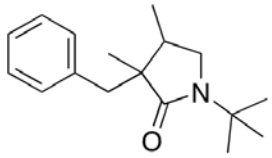


***N*-(2-Bromoallyl)-*N*-*tert*-butyl-2-methyl-3-phenylpropanamide (69):** Under argon atmosphere the acid chloride **57** (0.81 g, 4.43 mmol) and activated zinc powder (0.3 g, 4.58 mmol) were stirred in toluene (10 mL) for l0 minutes at room temperature. A solution of amine **72** (0.86 g, 4.47 mmol) in toluene (5 mL) was added slowly, and the mixture was stirred for overnight. After completion of the reaction, the reaction mixture was filtered and the solid was washed with ether (20 mL). The combined filtrate was washed with 10% $NaHCO_3$ solution, water and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product, which was then purified by column chromatography (2:25 EtOAc/hexane) to afford title compound (0.38 g, 25%) as pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.15 (m, 5H) 5.40 (br, 2H), 3.72 (br, 2H), 3.06-2.97 (m, 1H), 2.72-2.54 (m, 2H), 1.35 (s, 9H), 1.14 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.2, 177.5, 140.2, 138.5, 131.0, 129.4, 129.1, 128.6, 128.4, 128.3, 126.7, 126.4, 126.3, 116.6, 60.3, 57.8, 52.4, 42.4, 41.1, 39.8, 39.1, 28.4, 19.1, 16.1.

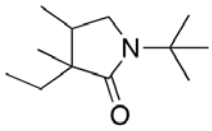


***N*-(2-bromoallyl)-*N*-*tert*-butyl-2-methylbutanamide (*rac*-70):** The title compound (1.02g, 41%) was obtained as pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (d, *J* = 3.9 Hz, 1H) 5.68 (d, *J* = 3.6 Hz, 1H), 4.11 (d, *J* = 9 Hz, 1H), 4.04 (d, *J* = 10 Hz, 1H), 2.33-2.30 (m, 1H),

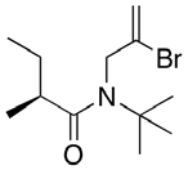
1.77-1.59 (m, 1H), 1.49-1.32 (m, 1H), 1.44 (s, 9H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 131.9, 116.6, 57.8, 53.0, 39.6, 28.7, 28.0, 18.6, 12.3; FTIR (thin film, CH_2Cl_2, cm^{-1}) 3383, 1650, 1644, 1466, 1463.



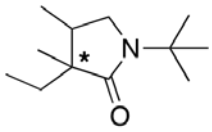
3-Benzyl-1-*tert*-butyl-3,4-dimethylpyrrolidin-2-one (80): Under argon atmosphere a solution of Bu_3SnH (0.13 g, 0.45 mmol) and AIBN (0.007 g, 0.043 mmol) in toluene (10 mL) was added via syringe pump for 20 min to a boiling solution of amide **69** in toluene (20 mL). The reaction mixture was stirred for 3 h at reflux and then cooled to room temperature. The solvent was evaporated in *vacuo* and ether was added. The organic layer was stirred with 8% aqueous potassium fluoride solution (50 mL) for 18 h. The aqueous layer was removed and the organic layer was dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (3:50 EtOAc/hexane) to afford title compound (0.02 g, 7%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.23 (m, 5H) 3.25 (dd, *J* = 9.3 Hz, *J* = 7.2 Hz, 1H), 3.14 (d, *J* = 13.5, 1H), 2.82 (dd, *J* = 9.3 Hz, *J* = 9.3 Hz, 1H), 2.58 (d, *J* = 13.5, 1H), 2.12-1.99 (m, 1H), 1.39 (s, 9H), 1.02 (s, 3H), 0.87 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 138.7, 130.5, 128.2, 126.3, 53.7, 49.6, 49.2, 42.6, 32.3, 27.8, 18.0, 12.8.



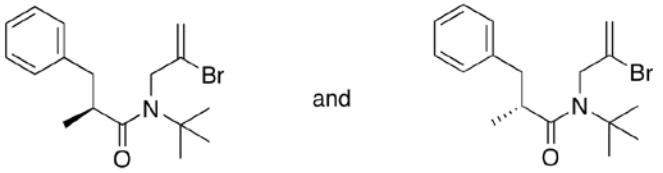
1-*tert*-Butyl-3-ethyl-3,4-dimethylpyrrolidin-2-one (*rac*-81): Under argon atmosphere a solution of Bu_3SnH (0.22 g, 0.75 mmol) and AIBN (0.012 g, 0.07 mmol) in toluene (15 mL) was added via syringe pump for 30 min to a boiling solution of amide *rac*-**70** (0.2 g, 0.73 mmol) in toluene (57 mL). The reaction mixture was stirred for 2.5 h at reflux condition and then cooled to room temperature. The solvent was evaporated in rotary evaporator and ether (50 mL) was added. The organic layer was stirred with 8% aqueous potassium fluoride solution (50 mL) for overnight. The aqueous layer was removed and the organic layer was dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (3:50 EtOAc/hexane) to afford title compound (0.055 g, 39%) as colorless oil, in 1:1 ratio of inseparable diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.42 (dd, *J* = 7.5 Hz, *J* = 5.4 Hz, 1H), 3.39 (dd, *J* = 7.5 Hz, *J* = 5.4 Hz, 1H), 2.91 (dd, *J* = 8.7 Hz, *J* = 8.7 Hz, 1H), 2.83 (dd, *J* = 8.7 Hz, *J* = 8.7 Hz, 1H), 2.16-2.08 (m, 1H), 2.02-1.95 (m, 1H), 1.59-1.49 (m, 2H), 1.43-1.35 (m, 2H), 1.37 (s, 9H), 1.36 (s, 9H), 1.03 (s, 3H), 0.97 (d, *J* = 7.2 Hz, 3H), 0.93 (d, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 7.5 Hz, 3H), 0.86 (s, 3H), 0.85 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.8, 60.5, 53.3, 50.1, 47.8, 47.3, 38.2, 32.6, 29.1, 27.8, 25.6, 21.4, 21.2, 16.3, 14.5, 9.2, 9.0; FTIR (thin film, CH_2Cl_2, cm^{-1}) 2968, 2934, 2877, 1674, 1463, 1410, 1382; HRMS (TOF ES) cald for $C_{12}H_{23}NO$, 220.1682 $[M+Na]^+$, found: 220.1701.



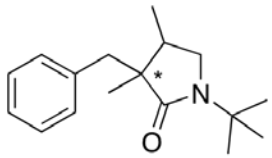
(*S*)-*N*-(2-bromoallyl)-*N*-*tert*-butyl-2-methylbutanamide ((*S*)-70): The title compound (0.67 g, 33%) was obtained as pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (d, *J* = 3.9 Hz, 1H) 5.68 (d, *J* = 3.6 Hz, 1H), 4.11 (d, *J* = 9 Hz, 1H), 4.04 (d, *J* = 10 Hz, 1H), 2.33-2.30 (m, 1H), , 1.77-1.59 (m, 1H), 1.49-1.32 (m, 1H), 1.44 (s, 9H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 131.9, 116.6, 57.8, 53.0, 39.6, 28.7, 28.0, 18.6, 12.3; FTIR (thin film, CH_2Cl_2, cm^{-1}) 3381, 1653, 1644, 1464, 1460.



1-*tert*-Butyl-3-ethyl-3,4-dimethylpyrrolidin-2-one (81): The title compound (0.038 g, 36%) was obtained as colorless oil, in 1:1 ratio of inseparable diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.42 (dd, *J* = 7.5 Hz, *J* = 5.4 Hz, 1H), 3.39 (dd, *J* = 7.5 Hz, *J* = 5.4 Hz, 1H), 2.91 (dd, *J* = 8.7 Hz, *J* = 8.7 Hz, 1H), 2.83 (dd, *J* = 8.7 Hz, *J* = 8.7 Hz, 1H), 2.16-2.08 (m, 1H), 2.02-1.95 (m, 1H), 1.59-1.49 (m, 2H), 1.43-1.35 (m, 2H), 1.37 (s, 9H), 1.36 (s, 9H), 1.03 (s, 3H), 0.97 (d, *J* = 7.2 Hz, 3H), 0.93 (d, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 7.5 Hz, 3H), 0.86 (s, 3H), 0.85 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.8, 60.5, 53.3, 50.1, 47.8, 47.3, 38.2, 32.6, 29.1, 27.8, 25.6, 21.4, 21.2, 16.3, 14.5, 9.2, 9.0; FTIR (thin film, CH_2Cl_2, cm^{-1}) 2968, 2934, 2877, 1674, 1463, 1410, 1382; HRMS (TOF ES) cald for $C_{12}H_{23}NO$, 220.1682 $[M+Na]^+$, found: 220.1699.



(*S*) and ***(R)*-*N*-(2-bromoallyl)-*N*-*tert*-butyl-2-methyl-3-phenylpropanamide (** *(S)*- and *(R)*-**69**): The title compound (0.29 g and 0.32 g, 32% and 34%) was obtained as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.15 (m, 5H) 5.40 (br, 2H), 3.72 (br, 2H), 3.06-2.97 (m, 1H), 2.72-2.54 (m, 2H), 1.35 (s, 9H), 1.14 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.2, 177.5, 140.2, 138.5, 131.0, 129.4, 129.1, 128.6, 128.4, 128.3, 126.7, 126.4, 126.3, 116.6, 60.3, 57.8, 52.4, 42.4, 41.1, 39.8, 39.1, 28.4, 19.1, 16.1.



3-Benzyl-1-*tert*-butyl-3,4-dimethylpyrrolidin-2-one (80-a and **80-b):** The title compounds (0.01 g and 0.008 g, 18% and 19%) were obtained as thick colorless oil and lactam **80-a** was crystallized from pentane. For **80-a**: $[\alpha]^{25}_{D}$ = +44.6 (*c* 0.25, $CDCl_3$) and for **80-b**: $[\alpha]^{25}_{D}$ = -44.3 (*c* 0.25, $CDCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.23 (m, 5H) 3.25 (dd, *J* = 9.3 Hz, *J* = 7.2 Hz, 1H), 3.14 (d, *J* = 13.5, 1H), 2.82 (dd, *J* = 9.3 Hz, *J* = 9.3 Hz, 1H), 2.58 (d, *J* = 13.5, 1H), 2.12-1.99 (m, 1H), 1.39 (s, 9H), 1.02 (s, 3H), 0.87 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 138.7, 130.5, 128.2, 126.3, 53.7, 49.6, 49.2, 42.6, 32.3, 27.8, 18.0, 12.8.

Pyrrolidinone $[\alpha]^{25}_{D}$ calculations:

polar=optrot cphf=rdfreq b3lyp/6-311++g(2d,p)

DPC2_M1:

E(RB3LYP) = -793.10690920 (-497682.1 kcal/mol); rel. E = 0 kcal/mol

[Alpha] (5890.0 A) = 134.20 deg

DPC2_M2:

E(RB3LYP) = -793.102753878 (-497679.5 kcal/mol); rel. E = 2.6 kcal/mol

[Alpha] (5890.0 A) = 53.33 deg

DPC2_M3:

E(RB3LYP) = -793.100548943 (-497678.1 kcal/mol); rel. E = 4 kcal/mol

[Alpha] (5890.0 A) = -27.32 deg

Boltzmann weighted average: 124.7

DPC_M1:

E(RB3LYP) = -793.100863835 (-497678.3 kcal/mol); rel. E = 3.8 kcal/mol

[Alpha] (5890.0 A) = -20.70 deg

DPC_M2:

E(RB3LYP) = -793.100417203 (-497678.0 kcal/mol); rel. E = 4.1 kcal/mol

[Alpha] (5890.0 A) = 44.97 deg

DPC_M3:

E(RB3LYP) = -793.098196358 (-497676.6 kcal/mol); rel. E = 5.5 kcal/mol

[Alpha] (5890.0 A) = 92.79 deg

Boltzmann weighted average: 124.4

The (*S*,*S*)-configuration of the pyrroldine **80** was arbitrarily selected and a conformational search at the RHF 6-311G* level in Spartan 10 (Wavefunction, Inc.) provided 6 energy minima. Each minimized conformation was submitted to an optical rotation calculation (b3lyp/6-311++G(2d,p)) on reoptimized geometry (b3lyp/6-32G(d)) using Gaussian 09, Revision A.02 (M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009).[41] The 6 starting conformations were found to have relative energies of 0, 2.6, 3.8, 4.0, 4.1 and 5.5 kcal/mol, and specific rotations of 134.2, 53.3, -20.7, -27.3, 45.0, and 92.8, respectively. After Boltzmann averaging (300 K), the specific rotation was determined as +124.4 for the (*S*, *S*)-**80**.

For a comparison with the experimental value, calculated as approx. +78, it is pertinent to point out the well-known fact that nonhybrid DFT functionals underestimate the lowest electronic excitation energies for delocalized π-systems and, consequently, often cause an overestimation of $[\alpha]^{25}_{D}$.[42]

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