Asymmetric Alkenyl Zirconocene/Zinc Additions to Aldehydes and Synthetic Efforts Toward Pseudotrienic Acid A

by

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Abstract

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The *in situ* hydrozirconation-transmetalation-aldehyde addition process is a convenient method for the generation of allylic alcohols. Ongoing research has focused on enhancing the enantioselectivity and substrate scope of this process and will be the focus of Chapter 1. Investigations have shown that both amino alcohols and amino thiols show moderate to high enantioselectivity. Non-linear effects were analyzed in order to gain mechanistic insight into the asymmetric addition process. Additionaly, analogues of both classes of ligands have been synthesized and evaluated. Amino thiol ligands tend to show the highest enantioselectivities due to the higher affinity of sulfur for zinc over zirconium. A new class of valine-based ligands was identified to be quite effective, in terms of ligand loading and % ee in the formation of allylic alcohols.

In Chapter 2, progess toward pseudotrienic acid A is discussed. The goal of this project was the synthesis of pseudotrienic acid A utilizing alkenylzirconium/zinc methodology cultivated in the Wipf group and to elucidate the absolute configuration at C(20) of the target molecule. A brief summary of the only reported synthesis of pseudotrienic acid B by Cossy *et al*. is outlined, followed by the retrosynthetic plan and synthesis of the 3 main fragments of this molecule. Lastly, the current progress towards the coupling of these fragments is examined.

Acknowledgements

I would like to extend my sincere gratitude towards my research advisor, Dr. Peter Wipf, for his guidance and patience during my Ph.D. studies. His genuine dedication to the success of his students is unquestionable. I would also like to extend thanks to Professors Brummond, Nelson, Cohen, Koide, and Beckman for their assistance and discussions regarding my proposal examination and dissertation studies. I have also had the pleasure of interacting with many talented individuals in the Wipf group and owe many thanks to them. In particular, I would like to acknowledge my former lab mates; Joshua Pierce, Dr. Steve Lynch, Dr. Graciela Mahler, and Marija Manojlovic for discussions, encouragement, music, and laughs. I have made many life long friends during my graduate studies and I would especially like to acknowledge Dr. Jamie M^{c}Cabe, Dr. Corey Stephenson, Julia Vargas, and Michelle Paul for being there for me through the good and not so good times. I would also like to acknowledge Dr. Fu-Tyan Lin and Dr. Damodaran Krishnan for help with NMR experiments and Dr. Kasi Somayajula and Dr. John Williams for mass spectral analysis.

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List of Abbreviations

Ac.....acetyl
Ac_2O.....acetic anhydride
BH_3•DMS .....borane dimethylsulfide complex
Boc .....*t*-butoxycarbonyl
Bn.....benzyl
Bu.....butyl
Cbz .....benzyloxycarbonyl
Cp.....cyclopentadienyl
DAIB.....dimethylaminoisoborneol
DEAD .....diethylazodicarboxylate
DIAD.....diisopropylazodicarboxylate
DIBAL .....diisobutylaluminum hydride
DIEA .....diisopropylethyl amine
DMAP 4-dimethylaminopyridine
DMF .....*N*,*N*-dimethylformamide
DMI.....1,3-dimethylimidazolidinone
Dpm.....diphenylmethyl
DMP .....Dess-Martin periodane
DMSO .....methyl sulfoxide
DPPA .....diphenylphosphoryl azide
ee.....enantiomeric excess
Et.....ethyl
HOBT.....1-hydroxybenzotriazole
HMDS .....hexamethyldisilazane
HMPA .....hexamethylphosphoramide
Imid .....imidazole
LAH .....lithium aluminum hydride
LDA .....lithium diisopropylamide
MIB .....morpholinoisoborneol
MIC .....minimum inhibitory concentration
Ms .....methanesulfonyl
Nap.....naphthyl
NBS.....*N*-bromosuccinimide
PCC .....pyridinium chlorochromate
PDC.....pyridinium dichromate

Ph .....phenyl
PIDA… .....phenyliodine diacetate
PIFA.....phenyliodine bistrifluoracetate
POPd .....$[(t\text{-Bu})_2P(OH)]_2PdCl_2$
PPTS .....pyridinium p-toluenesulfonate
Red-Al.....sodium bis(2-methoxyethoxy)aluminum hydride
TBAF .....tetrabutylammonium fluoride
TBDPS .....*t*-butyldiphenylsilyl
TBS .....*t*-butyldimethylsilyl
TDMPP .....tris(2,6-dimethoxyphenyl)phosphine
TEMPO.....2,2,6,6-tetramethylpiperidinooxy
Tf.....trifluoromethanesulfonyl
TFA.....trifluoroacetic acid
TFAA .....trifluoroacetic anhydride
THF .....tetrahydrofuran
TIPS… .....triisopropylsilyl
Tol.....*p*-tolyl
TMSQ .....trimethylsilyl quinidine
Ts.....*p*-toluenesulfonyl

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1.0 Asymmetric Alkenylzirconocene/Zinc Additions To Aldehydes

1.1 Introduction

1.1.1 Reactivity of Carbonyl Groups

The carbonyl group is a key functional group in organic synthesis. It can act as either an electrophile or nucleophile (Figure 1.1). Electrophilicity is generally expressed at the carbon atom whereas its nucleophilic character is most obvious in the enolate form. When used as an electrophile, the carbonyl moiety serves as a precursor to alcohol functionality. Organometallic reagents, such as Grignard and alkyllithium reagents add to aldehydes and ketones to produce secondary and tertiary alcohols in a 1,2-addition manner. Hydrides can react with carbonyls to produce the reduced product, an alcohol. Electrophilic carbonyl compounds also provide useful precursors to amines. Primary amines react with carbonyls to form imines whereas secondary amines condense to form enamines. Carbonyls exhibit both electrophilic and nucleophilic character in aldol condensations, when the enolate is used to produce α,β-unsaturated compounds or β-hydroxy ketones and aldehydes.

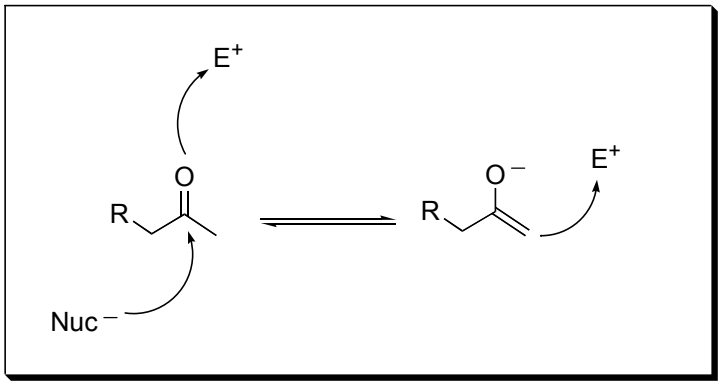
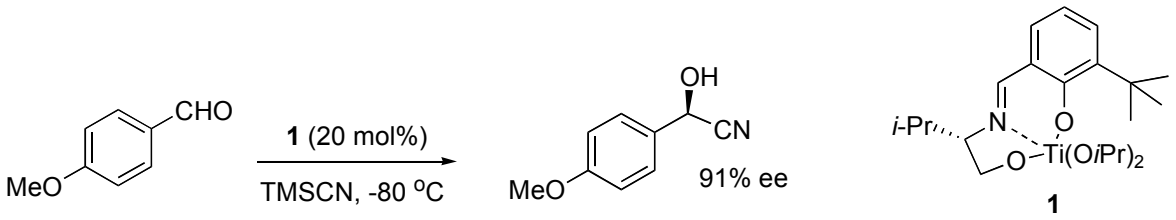


Figure 1.1. Sites for electrophilic and nucleophilic attack.

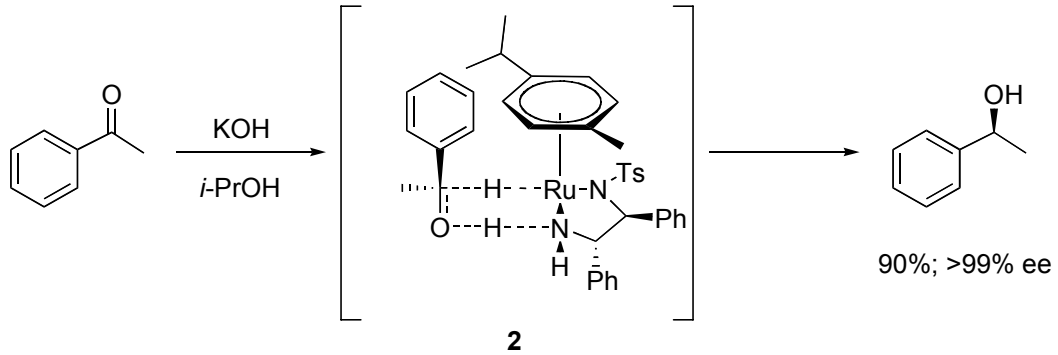
1.1.2 Asymmetric Additions to Carbonyl Compounds

A wide variety of reactions mentioned above can now be performed in an asymmetric fashion. The first asymmetric cyanohydrin formation was reported by Reetz *et al*. in 1986; their best result involved using 20 mol% of an (*S*)-binaphthol-based Ti complex in the addition of TMSCN to an aliphatic aldehyde to give the cyanohydrin adduct in 85% yield and 82% ee.[1] Another report by Narasaka *et al.* showed that by using 1 equivalent of an alkoxy titantium(IV) complex, both aromatic and aliphatic aldehydes could be coverted to the corresponding cyanohydrins in more than 85% yield and up to 96% ee.[2] Hayashi *et al*. have proposed a catalytic asymmetric variant using 20 mol% of complex **1**. The asymmetric addition of TMSCN to *p*-methoxy benzaldehyde resulted in an ee of 91% (Scheme 1.1).[3]



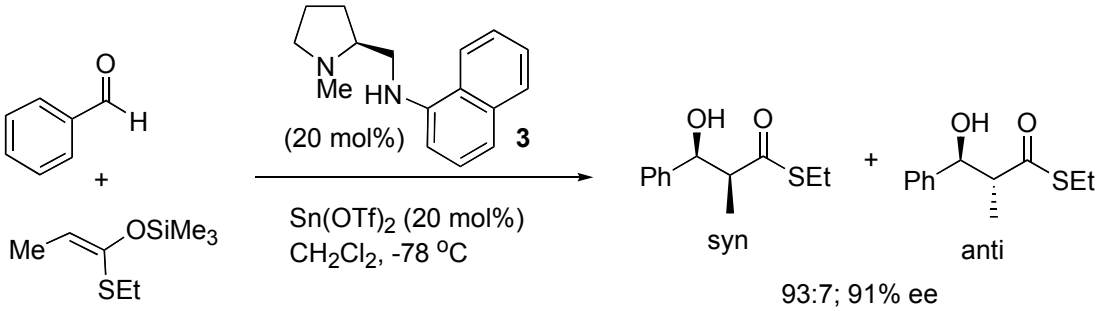
Scheme 1.1. Asymmetic cyanohydrin formation using a (*S*)-binaphthol-based Ti complex.

Noyori *et al*. have reported an asymmetric variant of a transfer hydrogenation using a ruthenium complex as a catalyst (Scheme 1.2).[4] In this reaction, a prochiral ketone can be converted to a chiral alcohol in the presence of a ruthenium catalyst and potassium hydroxide in isopropanol. This process occurs through six-membered transition state **2**, where hydride and proton are simultaneously delivered from MH and NH, respectively.



Scheme 1.2. Asymmetric transfer hydrogenation using ruthenium catalysis.

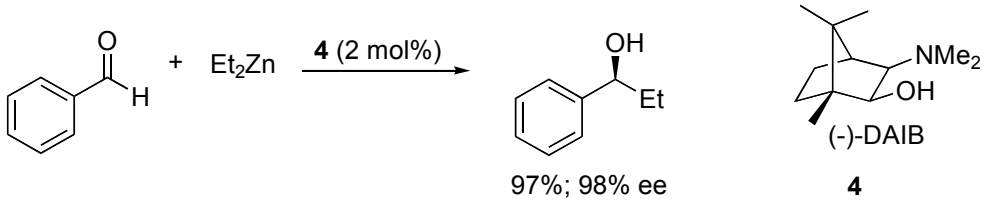
Mukaiyama *et al*. have discovered that in the presence of 20 mol% of catalyst **3**, different aldehydes react with the silyl enol ether of (*S*)-ethyl propanethiolate to produce aldol adducts with excellent relative and absolute stereochemical control (Scheme 1.3).[5] These chiral products are formed in a procedure that utilizes amine ligand and tin(II) triflate.



Scheme 1.3. Asymmetric Mukaiyama aldol.

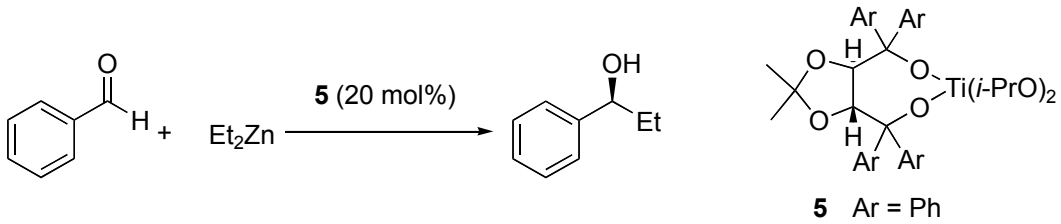
1.1.3 Organozinc Additions to Carbonyl Groups

Research on asymmetric organozinc additions to carbonyl compounds has expanded dramatically in the past 20 years.[6] Most of the work in this area has focused on alkylzinc additions to aldehydes. Ordinarily, dialkylzinc compounds are inert to carbonyl substrates, but in the presence of certain additives, their reactivity can be enhanced. The first noteworthy observation in this field was that of Oguni and Omi in 1984.[7] In the presence of 20 mol% (*S*)-leucinol, the reaction of diethylzinc with benzaldehyde provided optically enriched (*R*)-1-Phenyl-1-propanol in 49% ee and 96% yield. This significant discovery led to a rapid growth of research in this area. In 1986, Noyori *et al.* discovered the first highly efficient ligand for enantioselective dialkylzinc additions to aldehydes.[8] In the presence of 2 mol% of **4**, the reaction of diethylzinc with benzaldehyde gave (*S*)-1-phenylethanol in 98% ee (Scheme 1.4).



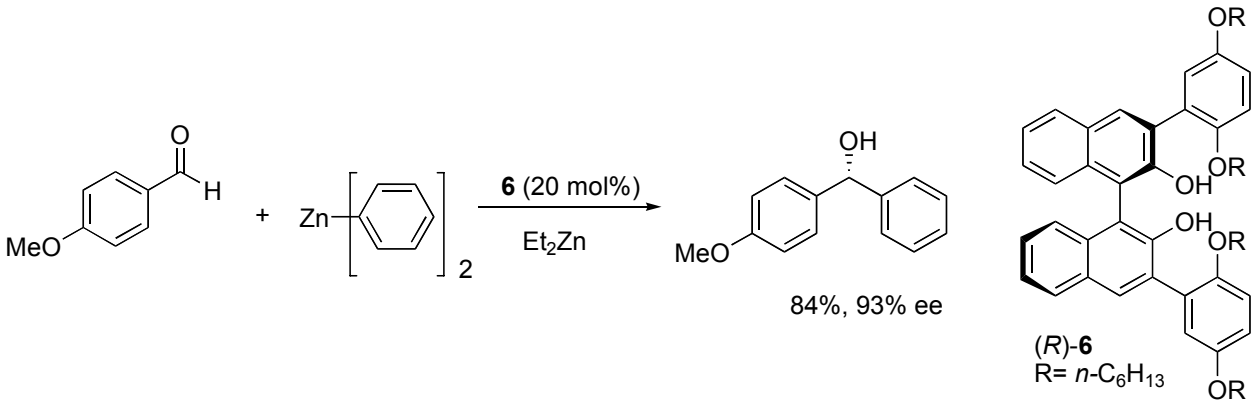
Scheme 1.4. Asymmetric diethylzinc addition catalyzed by (-)-DAIB.

TADDOL complexes are also effective catalysts for the asymmetric addition of organozinc reagents to aldehydes, as reported by Ito *et al*.[9] Enantioselectivities of 95-99% ee were obtained using a mixture of 20 mol% of chiral titanium TADDOLate **5** and excess Ti(O*i*Pr)$_4$ (Scheme 1.5).



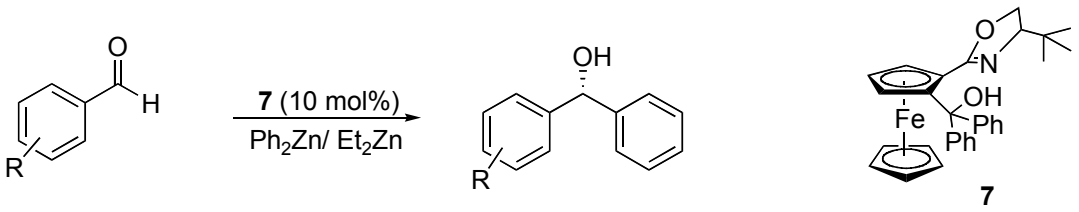
Scheme 1.5. Asymmetric diethylzinc addition catalyzed by TADDOLate **5**.

In contrast, it is more challenging to develop an enantioselective arylzinc addition because of the fast background reaction even in the absence of catalyst. The faster background reaction produces racemic product, thus lowering the enantioselectivity of the reaction. There are only a few enantioselective variants of this reaction. In 1999, Huang and Pu found that 20 mol% binaphthyl ligand **6** was enantioselective for the addition of diphenyl zinc to aldehydes (Scheme 1.6).[10] Initially, low ee's were obtained due to the competitive background reaction but they soon discovered that pretreating **6** with diethylzinc led to ee's of up to 98%.



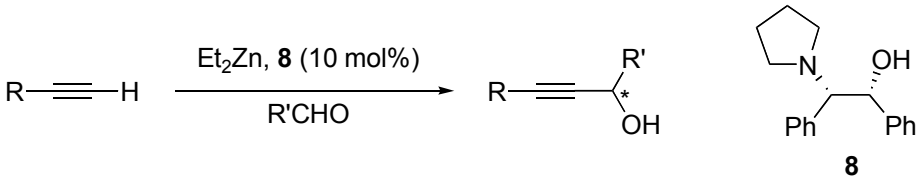
Scheme 1.6. Asymmetric diphenylzinc addition catalyzed by binaphthyl ligand **6**.

Bolm *et al*. also reported a similar finding in their research of diphenylzinc addition to aldehydes (Scheme 1.7).[11] Using 10 mol% of ligand **7,** diphenylzinc additions proceeded in 3-75% ee, but with the use of a 1:2 mixture of diphenylzinc and diethylzinc the ee of the product was increased to 83-99% ee.



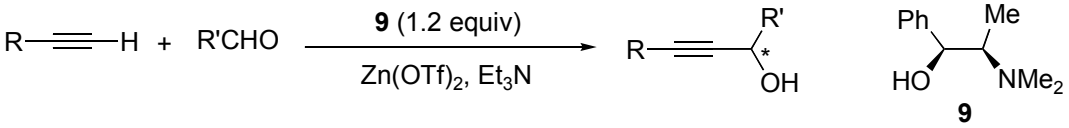
Scheme 1.7. Asymmetric diphenylzinc addition catalyzed by ferrocenyl **7**.

Alkynylzinc additions to aldehydes lead to the formation of propargyl alcohols. Li *et al.* have described this process in the presence of amino alcohol ligand **8** (Scheme 1.8). Using 10 mol% of this ligand and 1.2 equiv. of dimethylzinc, ee of up to 85% and yields in the range of 65-94% were observed.[12] It was also possible to suppress the methyl addition product in this reaction by using a mixture of toluene and THF (2.75:1).



Scheme 1.8. Asymmetric alkynylzinc addition catalyzed by amino alcohol **8**.

Carreira *et al.* have used 1.2 equivalents of **9** in the presence of $Zn(OTf)_2$ with a variety of aromatic and aliphatic aldehydes and observed ee's ranging from 92-99% (Scheme 1.9).[13] An interesting aspect of this reaction is that it can be carried out in air using reagent grade solvents without loss of enantioselectivity of the propargylic alcohol formed.



Scheme 1.9. Asymmetric alkynylzinc addition catalyzed by pseudoephederine-derived **9**.

1.1.4 Non-Linear Effects

An interesting aspect of a ligand-accelerated catalytic asymmetric process is the possibility for non-linear stereoinduction. The observance of a non-linear effect offers insight into the reaction mechanism, specifically relating to species involved in the catalytic cycles and species present in solution. Non-linear effects were first discovered by Kagan and Agami in 1984.[14] The first reactions studied in this context were asymmetric oxidation, asymmetric epoxidation and the proline-catalyzed Hajos-Parrish reaction. All of these processes resulted in a substantial departure from the linear correlation of the enantiomeric excess of the ligand and the enantiomeric excess of the product.[15] This anomaly can arise when more than one chiral ligand participates in the stereoselectivity-determining step of the catalytic cycle. Kagan has developed mathematical models to explain this behavior.[16] The use of a ligand that shows a (+)-NLE can be quite beneficial, as it allows the use of lower ee ligand while still retaining a high enantiomeric excess in the product. Tedious resolutions or absolute control in ligand synthesis become unnecessary when a small enantiomeric excess in the ligand is sufficient for a high enantiocontrol of the asymmetric transformation. This benefit, however, comes often at the expense of a slower rate of reaction due to the decreased concentration of catalyst available to take part in the catalytic cycle. In 1989, Noyori *et al*. published a mechanistic study on the addition of dialkylzinc reagents to benzaldehyde.[17] They demonstrated that diethylzinc additions to benzaldehyde in the presence of (-)-DAIB ligand of only 15% ee produced 95% ee of the alkylated alcohol product. This is the most pronounced asymmetric amplification reported to date with an asymmetric amplification value (I) of 32 in the presence of 15% ligand ee (Figure 1.2). I equals the enantiomeric excess of the observed product divided by the enantiomeric excess of the linear product (the expected enantiomeric excess based on a linear relationship with ligand ee).

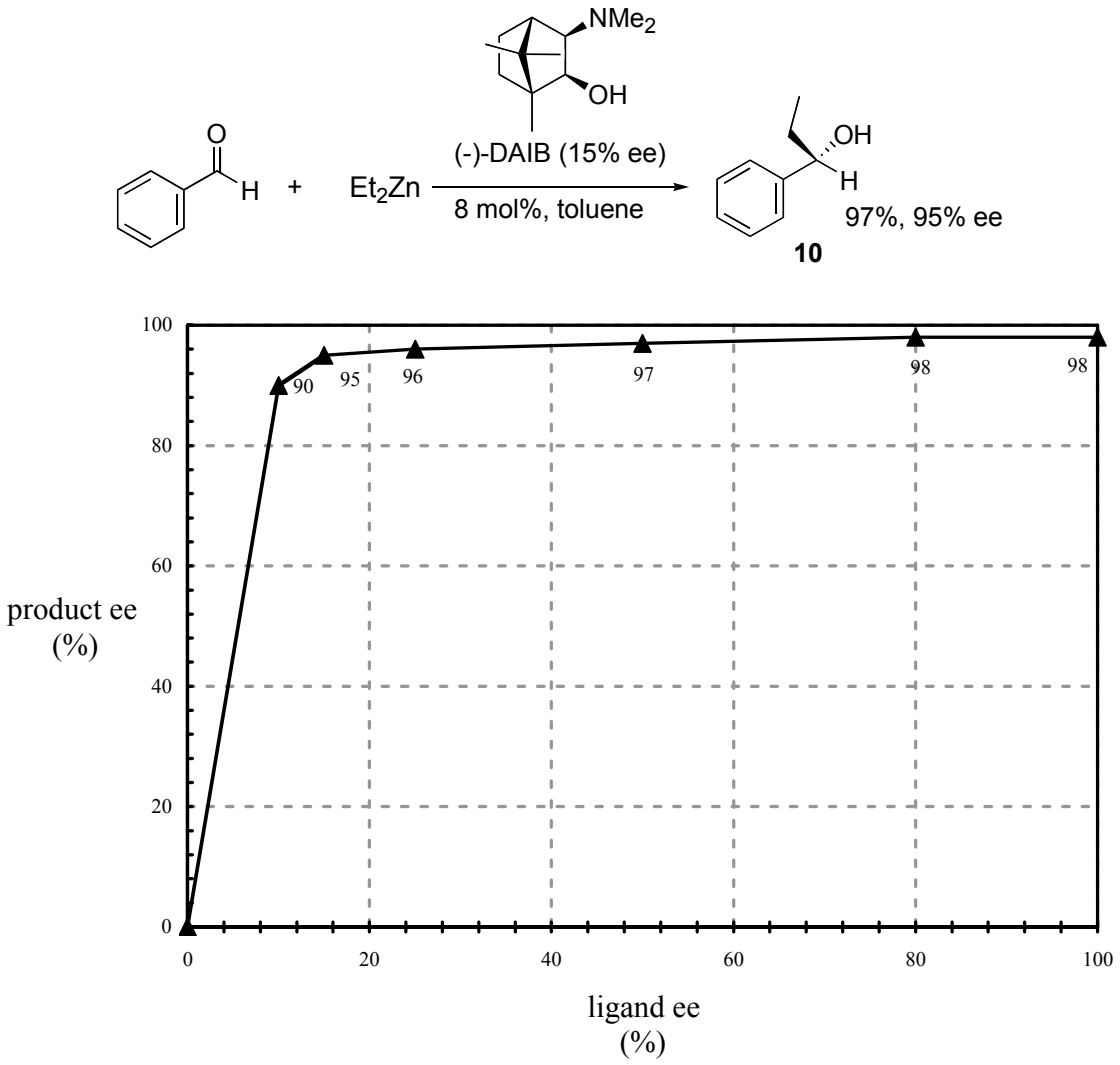


Figure 1.2. Non-linear dependence of product ee vs. ligand ee for the Et_2Zn addition to benzaldehyde.

Noyori concluded that this strong (+)-NLE was a result of the association between DAIB and the organozinc reagent. In solution, this association leads to the formation of dimeric complexes. When a mixture of (R) and (S)-DAIB was used, two types of dimeric complexes were formed: homochiral (R)·(R)-**11** or (S)·(S)-**11** and heterochiral (R)·(S)-**11** (Figure 1.3).[18] The departure from linearity is due in part to the stability of these complexes. Noyori did extensive work with NMR and X-ray diffraction analysis to determine the stability of the homochiral-**11** vs. heterochiral-**11**.[17] It was concluded that the heterochiral-**11** is more stable, thus it is the homochiral-**11** that dissociates at a faster rate and its monomer is the active catalyst in this

reaction. A (+)-NLE is observed while the minor enantiomer of the ligand is retained in the heterochiral-**11**.

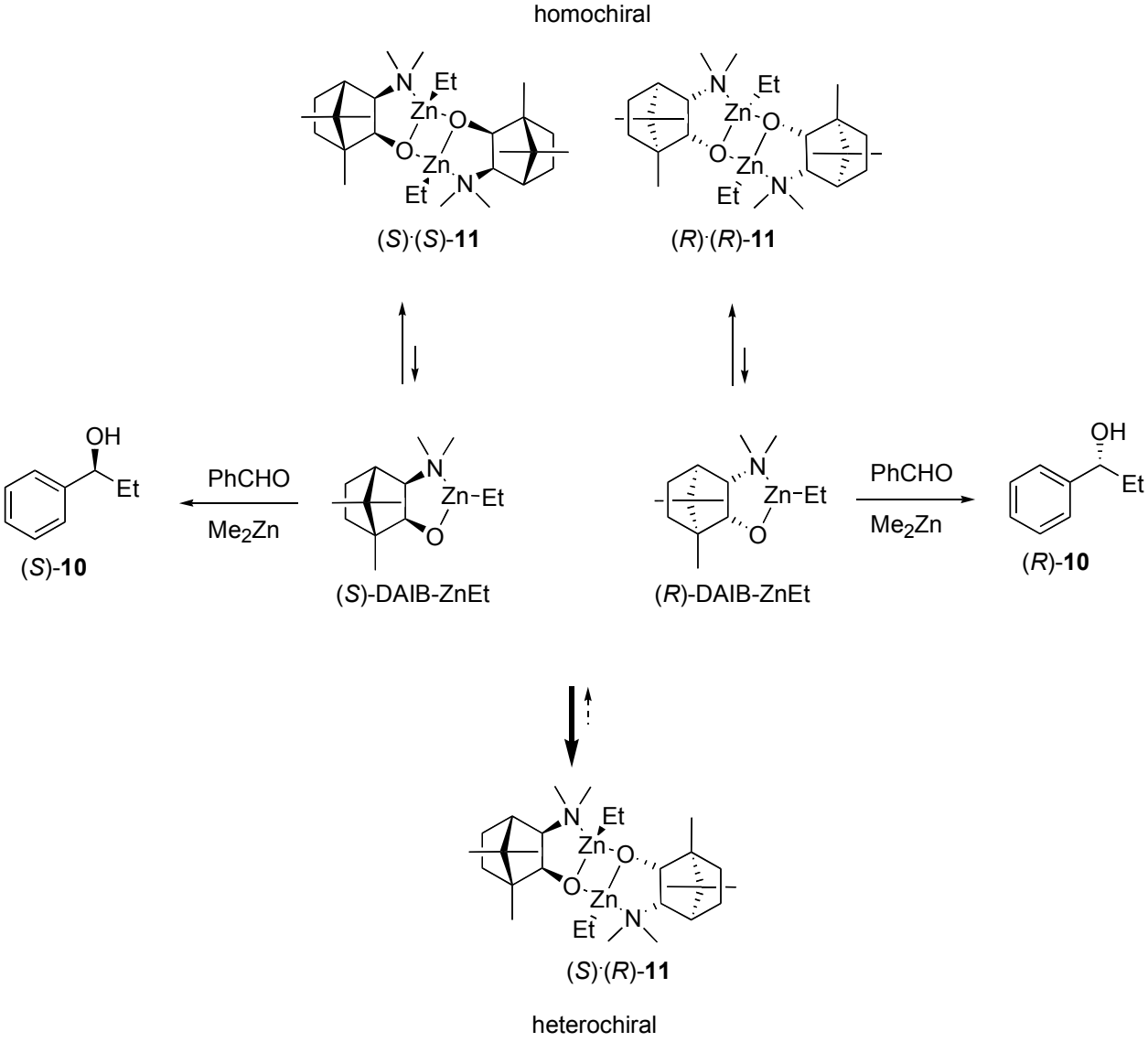


Figure 1.3. Homochiral and heterochiral aggregates formed in the ligand-accelerated diethylzinc addition to benzaldehyde.

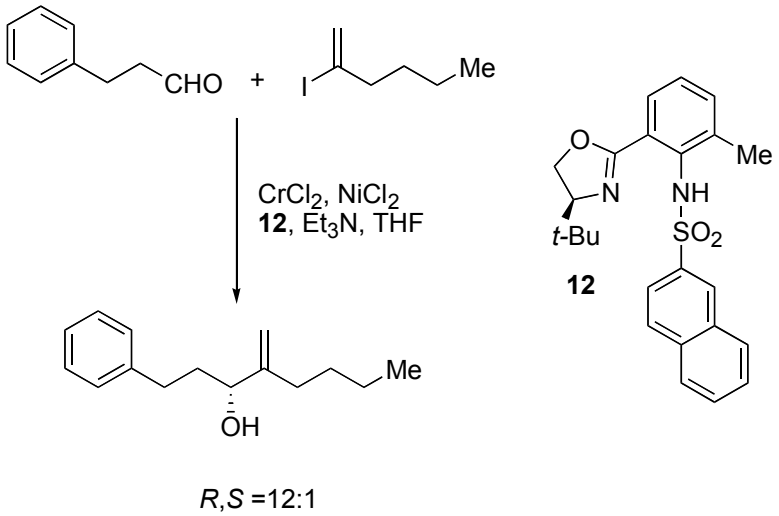
1.1.5 Alkenylmetal Additions to Carbonyl Compounds

Transition metal-mediated coupling reactions which rely on the addition of an alkenylmetal reagent to a carbonyl group represent a popular route for the generation of allylic alcohols. These processes have a strategic advantage because both a new C-C bond and a new stereogenic center are formed in one step. Many of these alkenylmetal reagents are generated *in situ* and then immediately reacted with the corresponding carbonyl compound.

In the Nozaki-Hiyama-Kishi reaction, an alkenyl halide or triflate is reacted with a carbonyl acceptor in the presence of a nickel catalyst and excess $CrCl_2$, Mn, or Zn to produce an allylic alcohol (Scheme 1.10).[19]

Scheme 1.10. Nozakai-Hiyama-Kishi reaction.

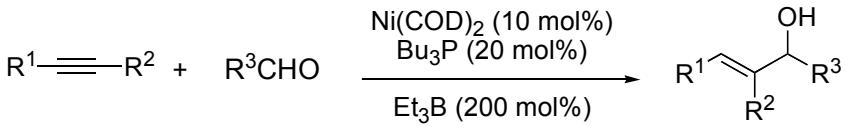
Kishi et al. has extended this protocol to a stoichiometric asymmetric process by employing a chiral sulfonamide ligand (Scheme 1.11).[20] Moderate asymmetric induction is observed in the presence of ligand **12**.



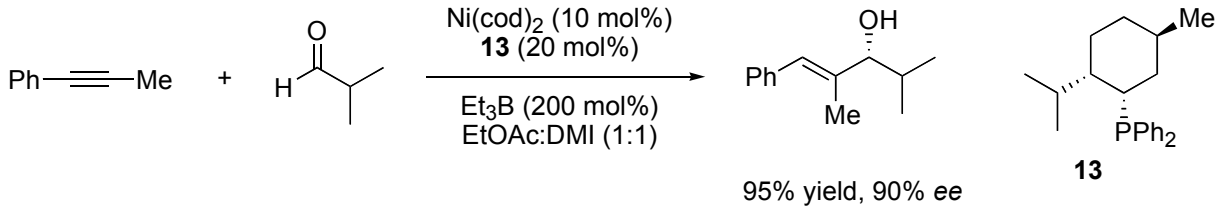
R,*S* =12:1

Scheme 1.11. Asymmetric Ni(II)/Cr(II)-mediated coupling reaction.

Jamison *et al*. has developed a catalytic intermolecular reductive coupling of alkynes and aldehydes to yield di- and trisubstituted allylic alcohols in high stereo- and regioselectivity (Scheme 1.12).[21] This work has been extended to an asymmetric protocol utilizing a (+)-(neomenthyl)diphenylphosphine **13** as the chiral phosphine.[22] Aliphatic as well as aromatic aldehydes show moderate to high enantioselectivity in the coupling process. Functional groups such as protected alcohols, protected amines, and silyl groups are inert to the reaction conditions.

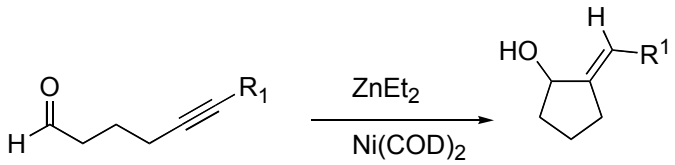


Scheme 1.12. Formation of allylic alcohols *via* nickel-catalyzed reductive coupling**.**



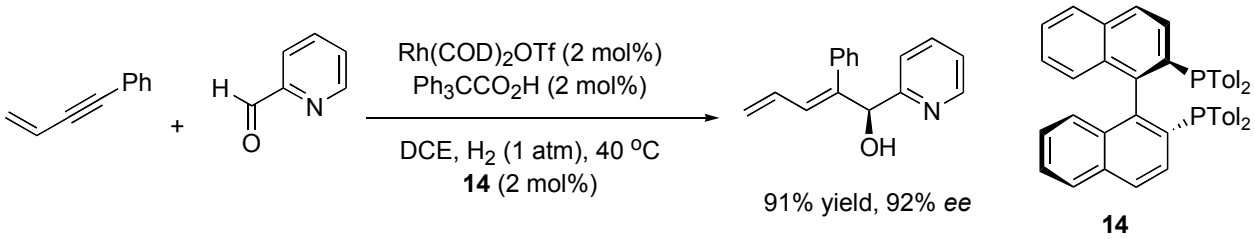
Scheme 1.13. Asymmetric reductive coupling employing the chiral phosphine ligand **13**.

Related to this method is work reported by Montgomery *et al*., where a protocol has been developed for the nickel-catalyzed cyclization and alkylation of ynals with organozincs to produce cyclic allylic alcohols and also effect a three component coupling of alkynes, aldehydes, and organozincs to produce acyclic allylic alcohols with complete control of alkene stereochemistry.[23] This process is envisioned to occur via an oxametallacycle, which in the presence of organozinc reagent would produce a common vinyl nickel intermediate for both alkylative and reductive cyclization products (Scheme 1.14).



Scheme 1.14. Nickel-catalyzed cyclization/alkylation of ynals with organozinc reagents.

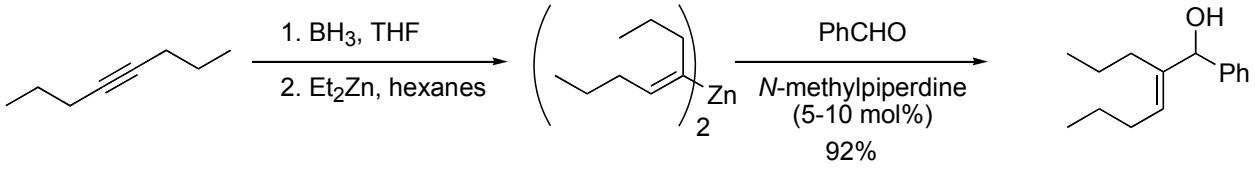
A different approach towards allylic alcohols was taken by Krische *et al.* in the development of an enantioselective reductive coupling of 1,3-enynes to heterocyclic aromatic aldehydes and ketones *via* rhodium catalysis. In the presence of a chiral phosphoric acid derived from BINOL **14**, highly optically active products are obtained under standard coupling conditions (Scheme 1.15).[24]



Scheme 1.15. Enantioselective hydrogen-mediated coupling.

1.1.6 Asymmetric Addition of Alkenylzinc Reagents to Aldehydes

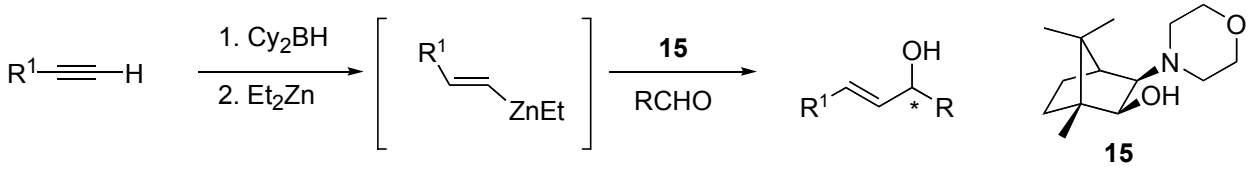
Allylic alcohols can also be accessed via alkenylzinc additions to aldehydes. Compared to alkylzinc addition, asymmetric alkenyl zinc additions are more challenging and only a few reported cases have been published. Srebnik illustrated the first preparation of bis(alkenyl) zinc reagents via hydroboration of an alkyne followed by subsequent transmetalation to form an organozinc reagent.[25] These reagents were successfully added to aldehydes in the presence of a catalytic amount of *N*-methylpiperdine to afford the allylic alcohols in good yields (Scheme 1.16).



Scheme 1.16. Srebnik's hydroboration followed by transmetalation protocol.

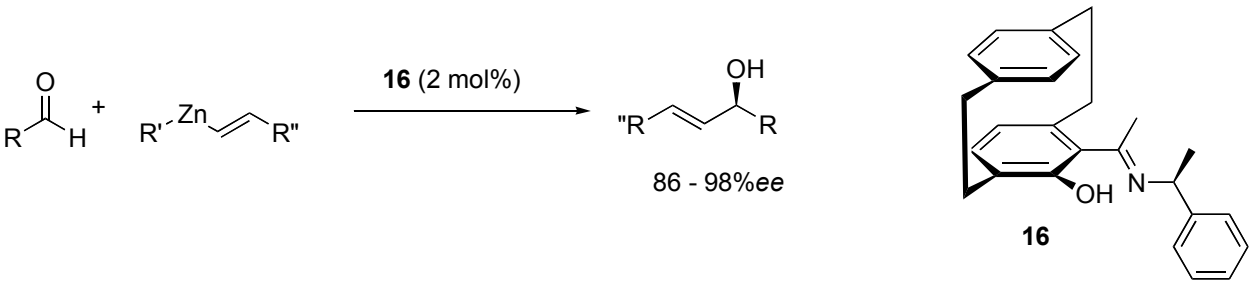
Inter- and intramolecular variants of this reaction as well as a chiral ligand catalyzed enantioselective addition have been shown to work successfully.[26] In the latter process, Oppolzer *et al*. has taken advantage of Noyori's (+)-DAIB ligand to promote an enantioselective addition with a variety of aldehydes with ee's in the range of 73-96% using 4.5 mol% of the

chiral ligand.[27] In recent years, Walsh *et al.* has shown that 2 mol% of the morpholino analogue of the (+)-DAIB ligand, Nugent's (-)-MIB, also shows promotion of the enantioselective addition reaction of a variety of terminal alkynes with ee's between 88-97% (Scheme 1.17).[28]



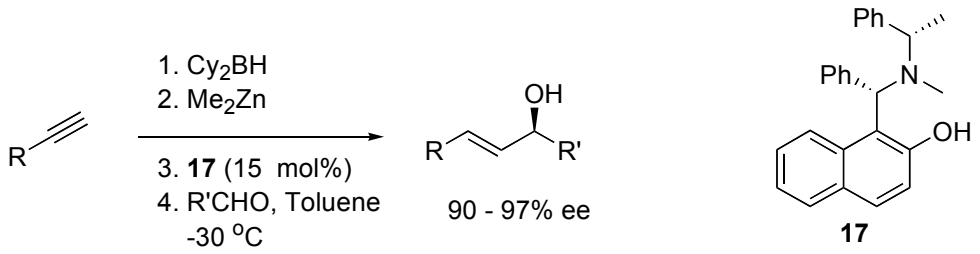
Scheme 1.17. Hydroboration/transmetalation protocol.

Bräse *et al*. has established a successful application of paracyclophane based ketimine ligands in the enantioselective alkenylation.[29] High enantioselectivities are realized for straight-chain aliphatic as well as branched aliphatic aldehydes with utilization of **16** (Scheme 1.18). A survey of transmetallating agents for this process was also examined.



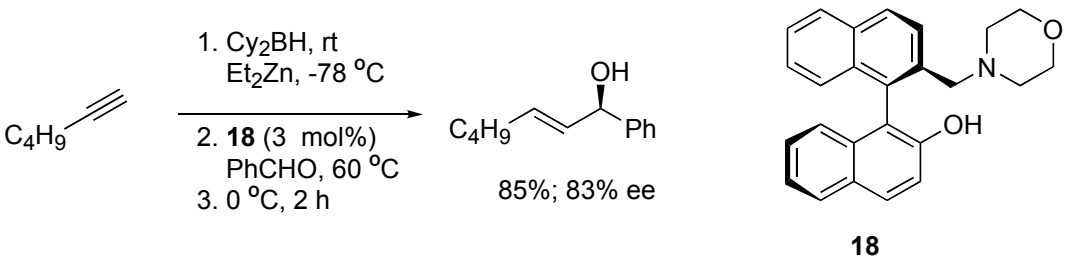
Scheme 1.18. Asymmetric addition of alkenylzincs catalyzed by chiral paracyclophane ketimines.

Chan *et al.* has also reported an effective aminonaphthol ligand for asymmetric vinylzinc addition reactions.[30] The ligand is conveniently made in one step from the multicomponent reaction of 2-naphthol, benzaldehyde, and (*S*)-*N*-α-dimethylbenzylamine **17** to afford the optically active tertiary amino naphthol in high purity. Yields and enantioselectivities are quite high for the addition process which works effectively not only with aromatic aldehyde but also with aliphatic aldehydes (Scheme 1.19).



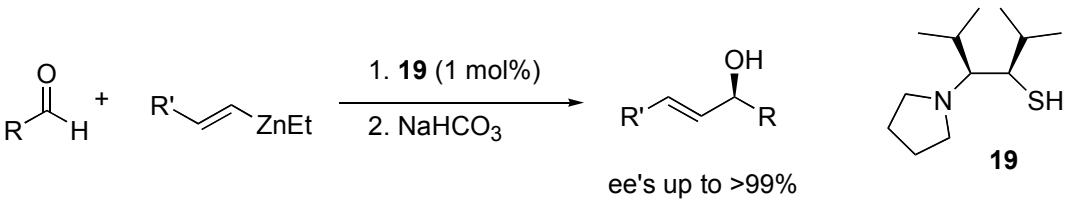
Scheme 1.19. Utilization of chiral aminonaphthol ligand in the asymmetric vinylzinc additions.

A morpholino derivative of a binaphthyl-based *N*,*O*-ligand has been disclosed by Ha *et al*.[31] Utilization of ligand **18** resulted in moderate enantioselectivity (72-82%) with aromatic aldehydes and a decrease in enantioselectivity for aliphatic aldehydes (32-55%) (Scheme 1.20).



Scheme 1.20. Utilization of a morpholino-derived binaphthyl ligand in the asymmetric vinylzinc additions.

Recently, Yang *et al*. have reported a new β–amino thiol scaffold for the enantioselective addition of alkenylzinc reagents to aldehydes.[32] Using amino thiol ligand **19,** high enantioselectivities are observed even at 1 mol% loading (Scheme 1.21).



Scheme 1.21. Utilization of a chiral β–amino alcohol ligand in the asymmetric vinylzinc additions.

1.1.7 Allylic Alcohols

Allylic alcohols represent convenient building blocks for a variety of synthetic applications. These transformations include [3,3] sigmatropic rearrangements,[33] enantio- and diastereoselective hydroxyl-directed additions to alkenes,[34] S_N2'-displacements with cuprates,[35] palladium catalyzed π-allyl substitution,[36] and cationic cyclizations (Figure 1.4).[37] Due to this versatility, our lab has also sought efficient ways to synthesize allylic alcohols.

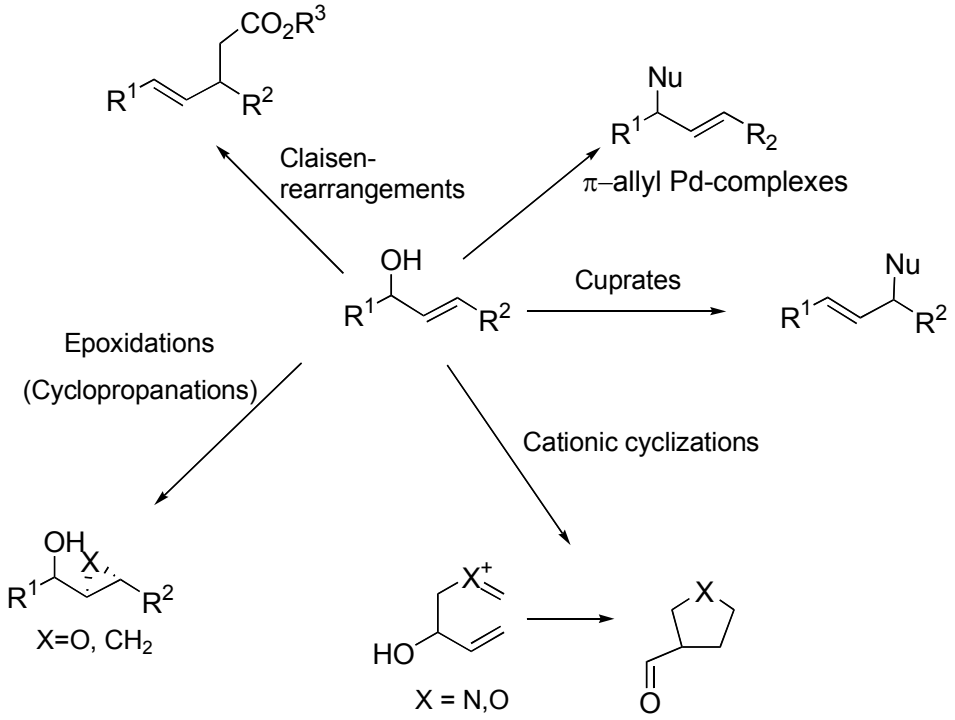
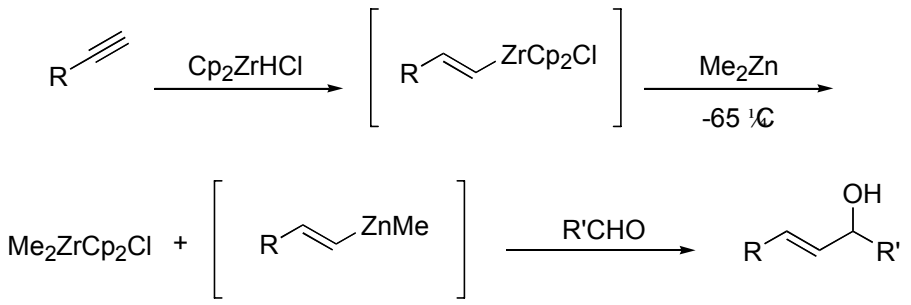


Figure 1.4. Versatility of allylic alcohols in synthetic methodology.

1.1.8 Alkenylzirconocene/Zinc Addition to Aldehydes

The *in situ* hydrozirconation-transmetalation process pioneered in our labs is another method for the convenient generation of allylic alcohols. In this method, hydrozirconation of an alkyne is followed by transmetalation at –65 ºC; upon reaction with an aldehyde the corresponding allylic alcohol product is generated in a one-pot reaction and in high yields (Scheme 1.22).[38]



Scheme 1.22. The *in situ* hydrozirconation-transmetalation addition protocol.

This methodology has been used in the synthesis of a variety of natural products by the Wipf as well as other groups. For example, the syntheses of leucascandrolide A[39] and (+)-curacin A[40] by the Wipf group, (+)-halichlorine by the Danishefsky group[41], lobatamide C by the Porco group[42], and (+)-acutiphycin[43] by Jamison showcase this methodology (Figure 1.5).

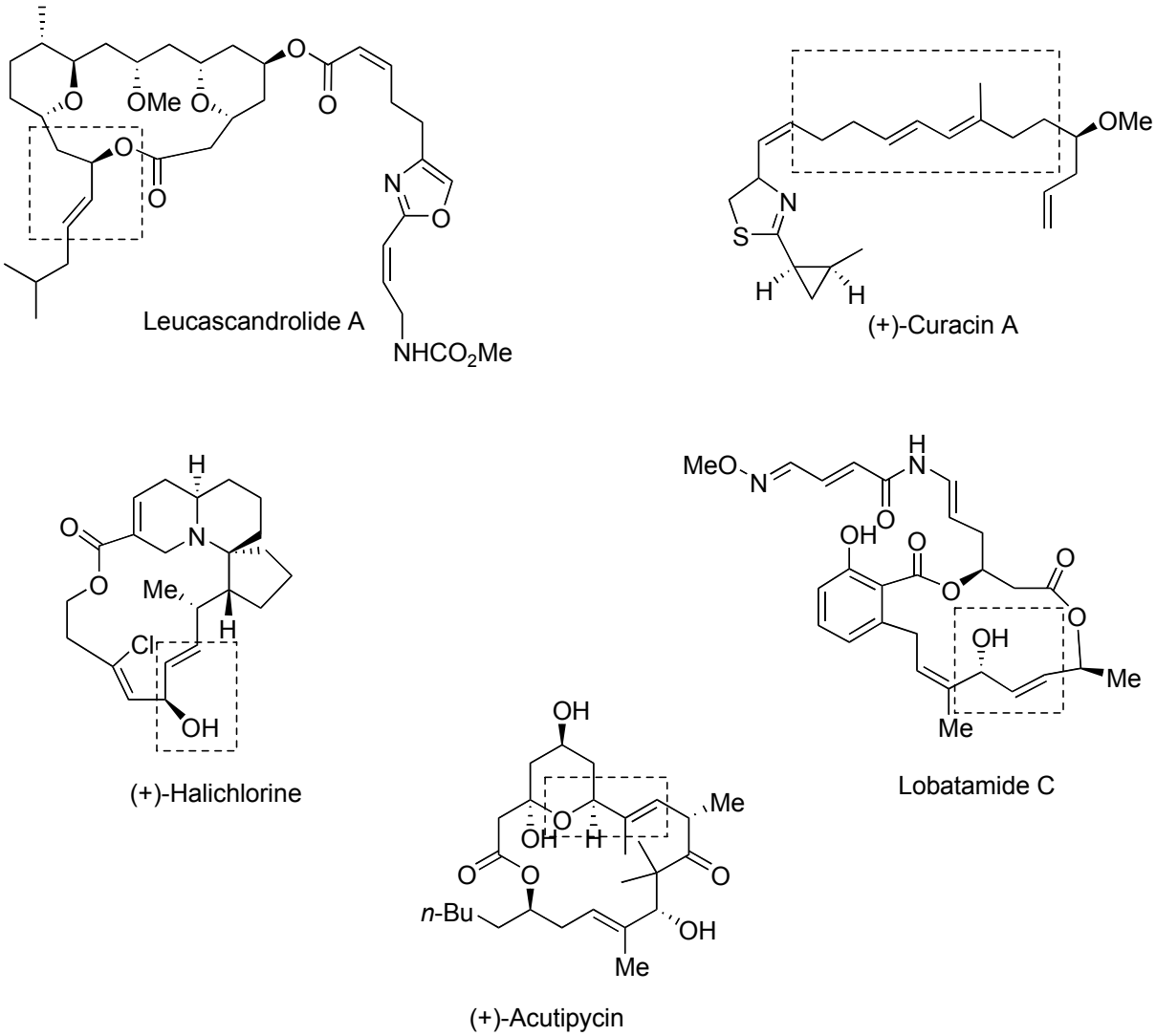
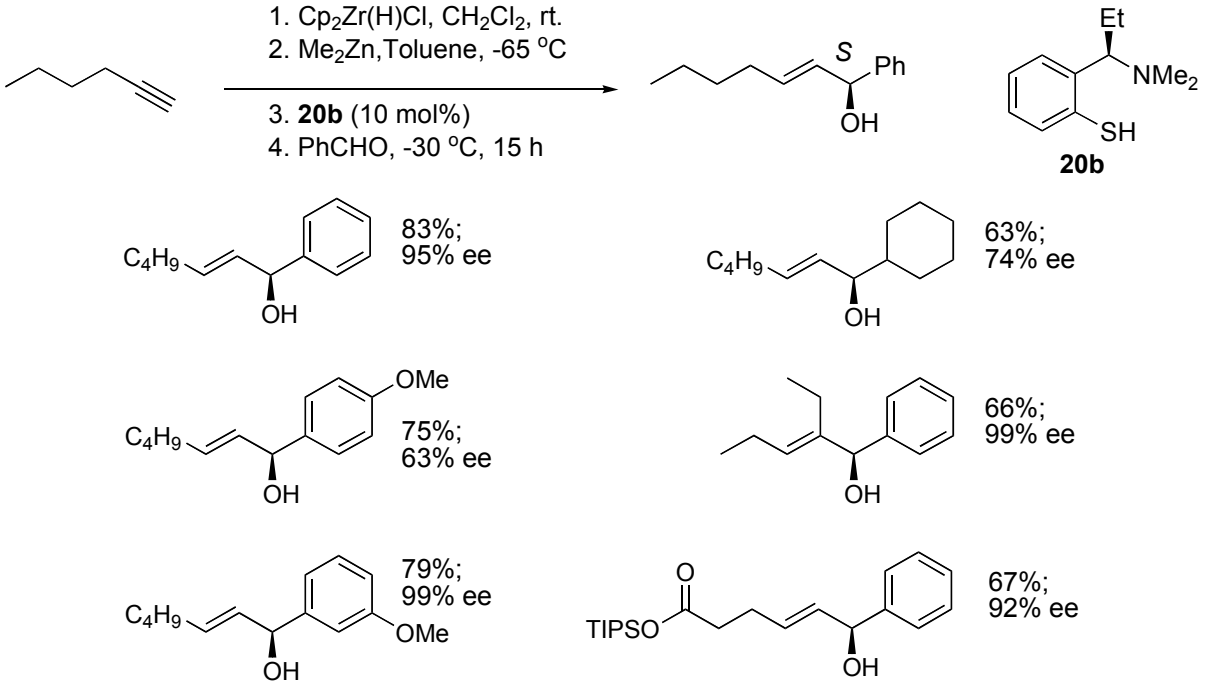


Figure 1.5. Natural products synthesized using alkenylzirconium/zinc methodology.

In order to increase the scope of this reaction, a chiral ligand which provides allylic alcohol products in uniformly high ee would be desirable. This ligand would dictate the specific enantiomer of the allylic alcohol that is formed. Although, countless ligands have shown superior enantioselectivity in simple alkylzinc additions to aldehydes, a ligand that affects the *in situ* hydrozirconation-transmetalation-aldehyde addition process with high asymmetric induction for all substrates remains to be identified.

1.1.9 Previous Wipf Group Work

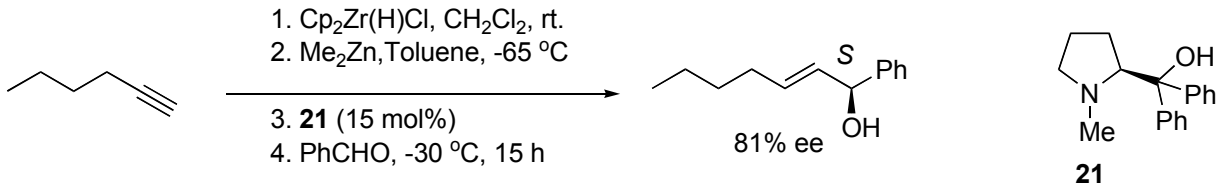
Past work in our group has lead to the discovery of a class of thiol-containing ligands that show high enantioselectivity in the alkenyl zirconium-zinc addition to most aromatic aldehydes.[44] Thiols proved to have a higher affinity towards zinc than zirconium.[45] This selectivity is quite important since in our *in situ* method both zinc and zirconium are present in the reaction medium and differential affinity of the ligand for zinc is desirable. Thiolates also have less of a tendency to lower the Lewis acidity of a metal than alcoholates. This feature is important since the Lewis acidity of the metal activates the carbonyl group towards addition. Specifically, the amino thiol **20b** has been shown to provide high enantioselectivity in the addition of vinylzinc species to electron-poor aromatic aldehydes.[46] However, lower ee's (64-74%) were found for aliphatic and aromatic aldehydes with electron-donating groups in the *para*- or *ortho*-positions (Scheme 1.23).



Scheme 1.23. Scope of the alkenylzirconium/zinc addition using ligand **20b**.

Proline-based amino alcohols are another class of ligands that have been shown to provide satisfactory enantioselectivity in the hydrozirconation-transmetalation addition to

aldehydes. We were able to determine that in the presence of 10-15 mol% of the proline-derived amino alcohol **21** the benzaldehyde-derived allylic alcohol was formed in 81% ee (Scheme 1.24).[44]



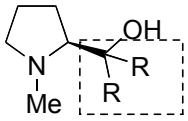
Scheme 1.24. The alkenylzirconium/zinc addition to benzaldehyde using ligand **21**.

Thus, we decided that further modifications of these two classes of ligands were warranted with the hope of identifying a ligand that shows high asymmetric induction with a wide variety of aldehydes and alkynes.

1.2 Proline-Based Amino Alcohol Ligands

1.2.1 Synthesis of Proline-Based Analogues

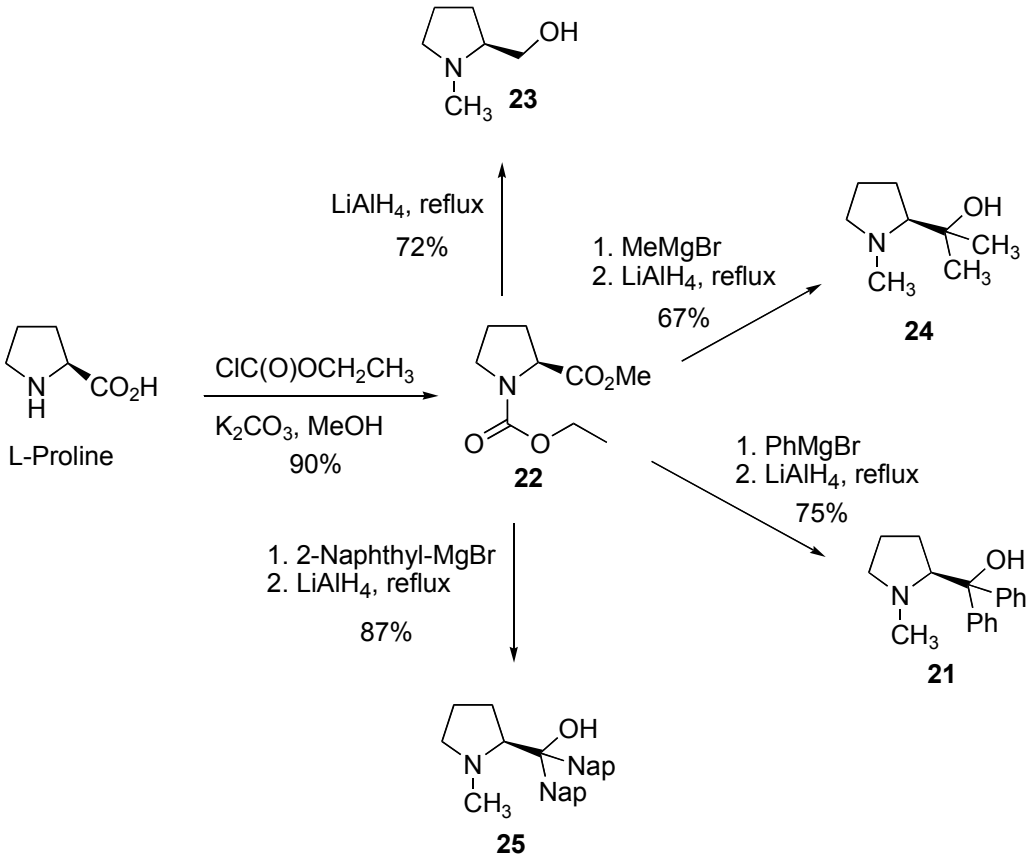
Based on the promising preliminary data obtained with the proline-derived amino alcohol, substitution of the diphenyl moiety for smaller and larger substituents was further explored in hopes of increasing the enantioselectivity above the current maximum of 81% ee (Figure 1.6).



R = H, Me. naphthyl

Figure 1.6. Modification of the diphenyl moiety of ligand **21** (R = Ph).

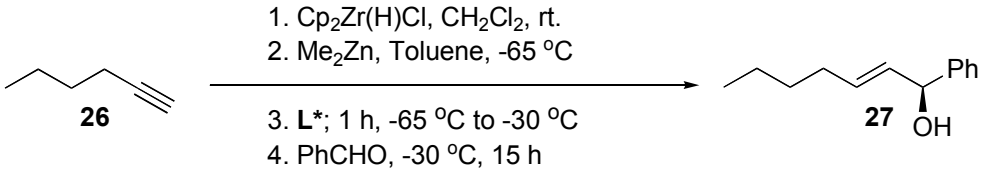
This series of amino alcohols was accessed quite conveniently starting from L-proline (Scheme 1.25). Conversion to the *N*-carbamate proline methylester **22** using ethyl chloroformate in the presence of potassium carbonate and MeOH proceeded in 90% yield.[47] Double reduction of the carbamate and the methylester using $LiAlH_4$ gave **23** in 72% yield. Grignard addition of a variety of nucleophiles to the methylester **22** afforded the corresponding tertiary alcohols. Reduction of the carbamate with $LiAlH_4$ gave the *N*-methylated amino alcohols **24**, **21**, and **25** in 67-87% yield.



Scheme 1.25. Synthesis of analogues at the diphenyl moiety of ligand **21**.

Amino alcohols **21,23-25** were tested at 10 and 15 mol% loading (Table 1.1). Ligand **21** showed the most promise, providing alcohol **27** with 81% ee at 15 mol% loading (Entry 6). A possible rationale for the dramatic difference between ligands **23, 24, 21** and **25** is that the side chain substituents strongly influence the nature of the dimerization equilibria that lead to catalytically active species. Ligands **23** and **24** might be too small to bias the facial selectivity in the alkenyl zinc addition to the aldehyde moiety; on the other hand, the naphthyl substituents on **25** may also be too bulky to allow tight substrate binding in the transition state, resulting in lower facial selectivity.

Table 1.1. Asymmetric additions of **26** to benzaldehyde in the presence of ligands **21** and **23-25**.



Entry	Ligand (**L***)	Ligand loading (mol%)	Yield (%) of **27**	ee (%)[a] of **27**
1	**23**	10	79	17
2	**23**	15	78	18
3	**24**	10	85	17
4	**24**	15	78	17
5	**21**	10	73-77	40 [b]
6	**21**	15	74-76	81 [b]
7	**25**	10	81	20
8	**25**	15	80	20

[a]ee's were determined by chiral HPLC analysis (Chiralcel OD, flow rate 1 mL/min using *i*-PrOH/hexanes (1:99)) with a Dynamax UV-1 absorbance detector, [b]ee given is the average of 2 runs.

Due to its relative promise, loading studies of ligand **21** from 5 to 50 mol% were performed. The graph in Figure 1.7 demonstrates that 15 mol% loading is indeed the optimal loading for this ligand while lower and higher loadings show a decrease in ee of product **26**.

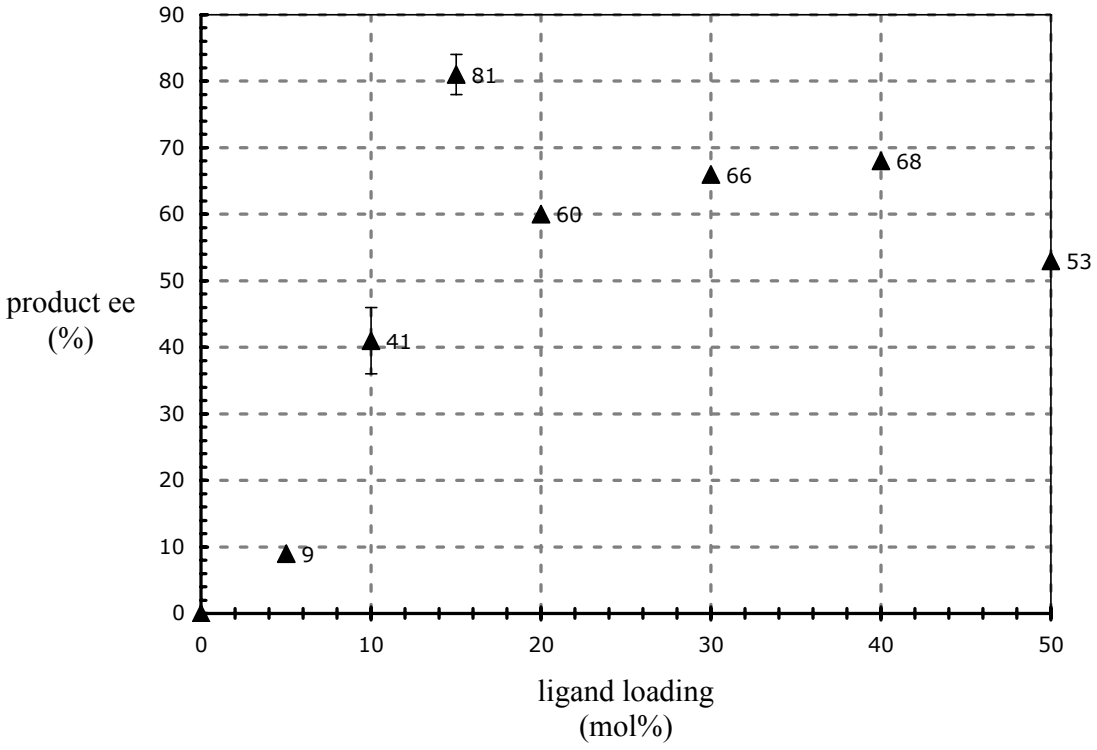
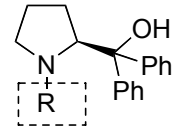


Figure 1.7. Loading effects of ligand **21** on the ee of allylic alcohol **27**.

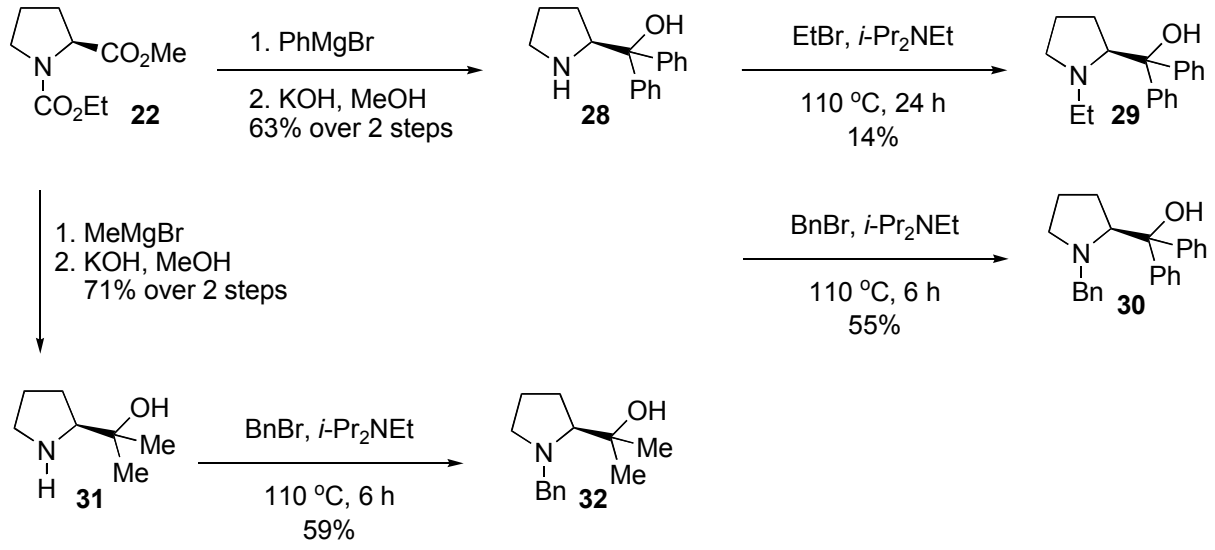


R = Et, Bn

Figure 1.8. Modification of substituents at amine site of ligand **21** (R = Me).

Further modifications to proline ligand **21** were examined, targeting modifications at the amine site (Figure 1.8). The synthesis of the analogues commenced with phenyl magnesium bromide addition to *N*-carbamate proline methylester **22** followed by hydrolysis of the ethyl carbamate with KOH to give **28** in 63% yield over 2 steps (Scheme 1.26). Alkylation of the amine with either benzyl bromide or ethyl bromide in the presence of Hünig's base resulted in the desired analogues **29** and **30** in 55% and 14% yield, respectively. Analogously, methyl magnesium bromide addition to *N*-carbamate proline methyl ester **22** and subsequent hydrolysis

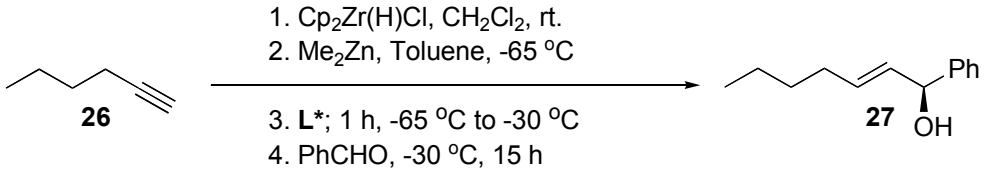
yielded **31** in 71% yield. Alkylation of the secondary amine with benzyl bromide in the presence Hünig's base afforded **32** in 59% yield.



Scheme 1.26. Synthesis of analogues at amine site of ligand **21**.

The analogues synthesized were tested at 10 and 15 mol% loading in the alkenylzirconocene/zinc addition process (Table 1.2). Disappointingly, the enantioselectivity observed for **29**, **30**, and **32** was low in all cases (3-20%). Based on this data, substitution at the amine is an important factor in determining enantioselectivity. Methyl substitution seems to be ideal while larger alkyl groups (ethyl and benzyl) at this site decrease the enantioselectivity drastically.

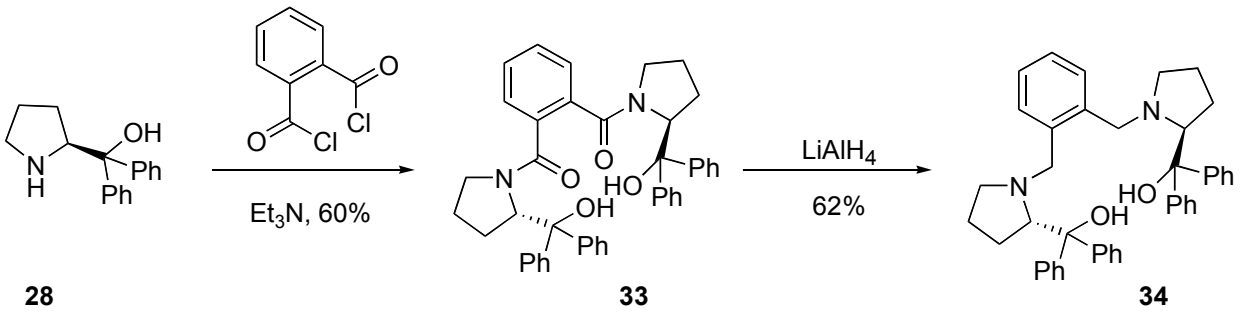
Table 1.2. Asymmetric additions of 26 to benzaldehyde in the presence ligands **29**, **30**, and **32**.



Entry	Ligand (**L***)	Ligand loading (mol%)	Yield (%) of **27**	ee (%)[a] of **27**
1	**29**	10	82	3
2	**29**	15	83	13
3	**30**	10	76	4
4	**30**	15	78	6
5	**32**	5	79	20
6	**32**	10	78	4

[a]ee's were determined by chiral HPLC analysis (Chiralcel OD, flow rate 1 mL/min using *i*-PrOH/hexanes (1:99)) with a Dynamax UV-1 absorbance detector.

Proline-derived C_2-symmetric bis-β-amino alcohol **33** has been reported by Chan *et al.* to catalyze enantioselective diethylzinc additions to aldehydes.[48] The high enantioselectivity observed is attributed to the rigid and bulky nature of the ligand. It was hoped that this sterically more demanding ligand would enhance enantioselectivity in our protocol. C_2-symmetrical bis-β-amino alcohol was conveniently prepared starting from (*S*)-(+)-diphenyl-pyrrolidin-2-yl-methanol **28** (Scheme 1.27). The amine was reacted with phthaloyl dichloride in the presence of triethylamine to afford the diamide **33,** followed by reduction of the amides using $LiAlH_4$ to afford **34** in 62% yield over 2 steps. Utilization of ligand **34** in the alkenyl zirconium/zinc addition protocol resulted in no enantiodifferentiation with an enantiomeric excess of only 2 % at 5 mol% and 4% at 10 mol%.



28 **33** **34**

Scheme 1.27. Synthesis of C_2-symmetric bis-β-amino alcohol **34**.

Shibasaki *et al*. disclosed a strategy for the development of poly-coordinating ligands for the enantioselective dimethylzinc addition to ketoesters.[49] This ligand strategy relies on the need for both Lewis acid activation of the substrate as well as Lewis base activation of the reagent to efficiently promote the reaction (Figure 1.9). Through dual activation of nucleophilic dimethylzinc and a catalytic amount of *i*-PrOH, high enantioselectivities were afforded. The multicenter approach was appealing and could possibly improve the enantioselectivity of alkenylzirconium-zinc addition reaction by providing an extra Lewis basic site.

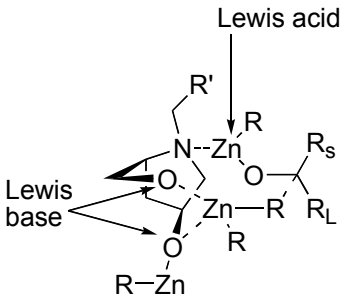
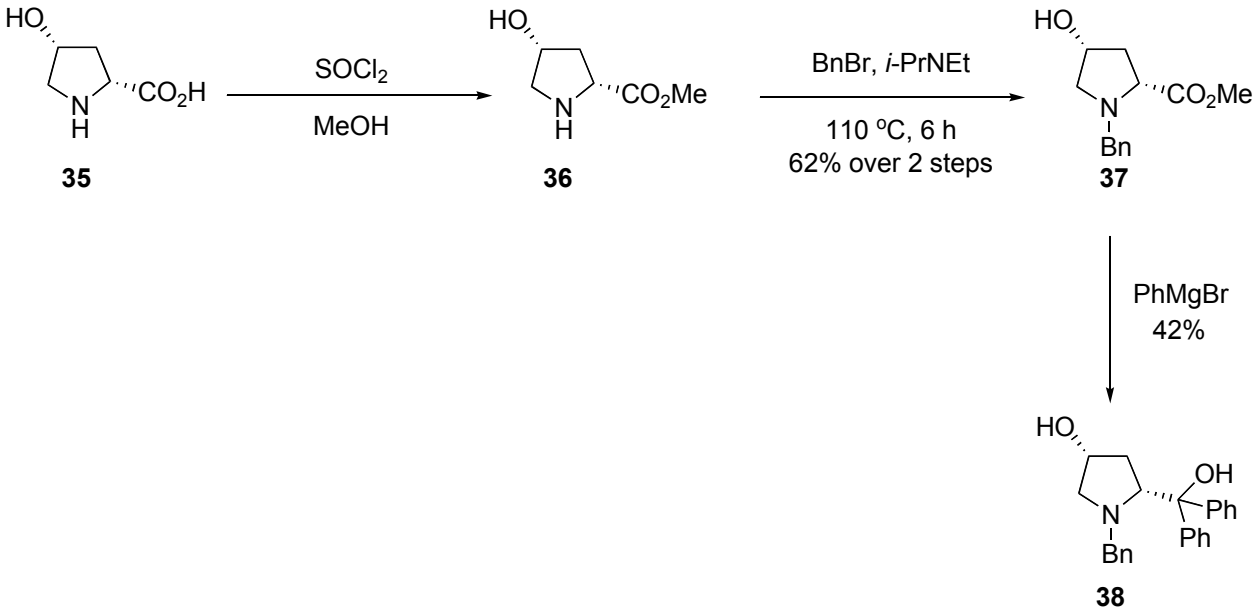


Figure 1.9. Multicenter approach in activation of substrate and reagent.

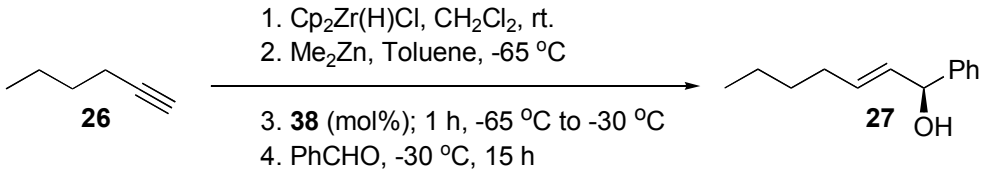
Ligand **38** was synthesized as reported by Shibasaki *et al*., 2,4-*cis*-4-hydroxy-D-proline was converted to the methylester in the presence of thionyl chloride and MeOH to afford **36**, which was alkylated with benzyl bromide to give **37** in 62% yield over 2 steps. Lastly, phenyl magnesium bromide addition to the methylester **37** resulted in the formation of **38** in 42% yield.



Scheme 1.28. Synthesis of ligand **38**.

The multicentered approach with ligand **38** did not show useful levels of enantioselectivity under our reaction conditions (Table 1.3).

Table 1.3. Asymmetric additions of **26** to benzaldehyde in the presence of ligand **38**.



Entry	Ligand	Ligand loading (mol%)	Yield (%) of **27**	ee (%)[a] of **27**
1	**38**	10	78	9
2	**38**	20	85	21

[a]ee's were determined by chiral HPLC analysis (Chiralcel OD, flow rate 1 mL/min using *i*-PrOH/hexanes (1:99)) with a Dynamax UV-1 absorbance detector.

In the proline-derived scaffold, ligand **21** shows the highest enantioselectivity. The proposed transition state model for this reaction using ligand **21** is shown below (Figure 1.10). All analogues synthesized using the proline scaffold afforded a drastic decrease in enantioselectivity. Both the diphenyl moiety and the methyl-substituted amine are vital

components of this ligand and any manipulation of these moieties leads to almost no enantiodifferentiation and results in low enantioselectivity.

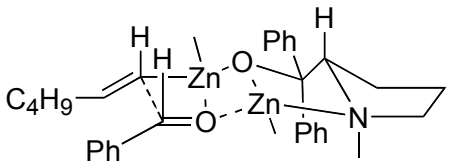


Figure 1.10. Possible transition state model for the proline-derived amino alcohol ligand **21** catalyzed alkenyl zirconocene/zinc addition to benzaldehyde.

1.2.2 Detemination of Non-linear Effect with Ligand 21

The use of ligand **21** resulted in the highest enantioselectivity of 81% ee at 15 mol% loading and thus this ligand was used in the ensuing mechanistic investigation. In order to gain more information about the aggregation state of ligand **21,** a study of non-linear effects was conducted. Using the optimal loading of 15 mol%, the reaction with 1-hexyne and benzaldehyde was studied while varying the %ee of the ligand. Each reaction was repeated 2 times and the data point shown is the average of the runs. The ee of the resulting alcohol **27** was measured by chiral HPLC[50] and plotted against the ligand ee%.

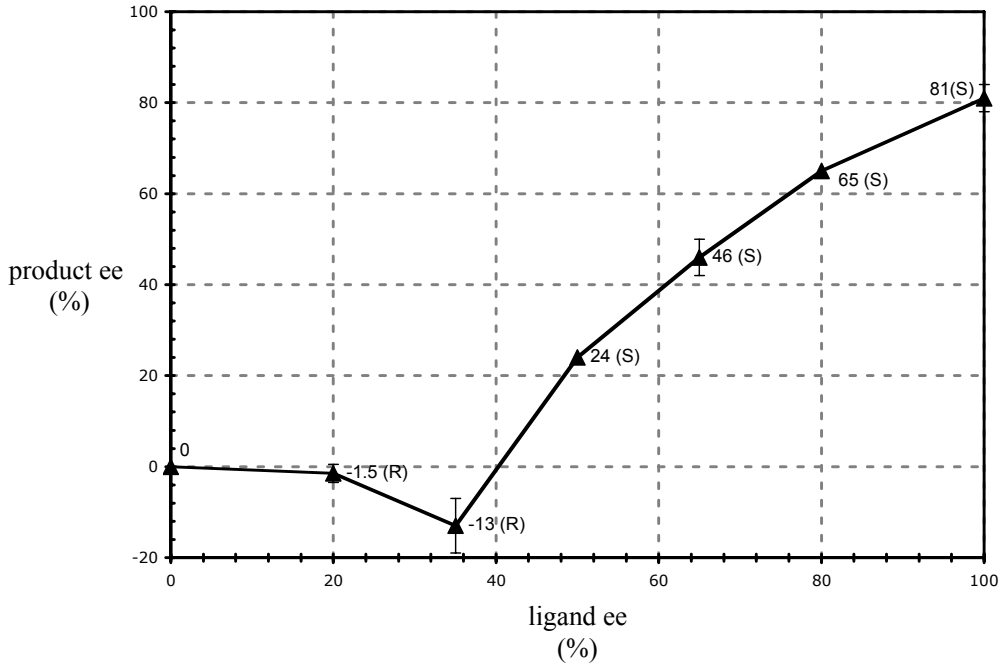


Figure 1.11. Non-linear effect for ligand **21** at 15 mol% loading in the formation of allylic alcohol **27**.

When the ee of the resulting allylic alcohol was plotted as a function of the %ee of ligand **21**, a linear decrease from 81% to 24% ee of product resulted at 100% to 50% ligand ee (Figure 1.11). At 35% ligand ee, a dramatic reversal of enantioselectivity, now favoring the opposite enantiomer of the allylic alcohol product, was seen. This reversal of selectivity diminished with 20% ligand ee.

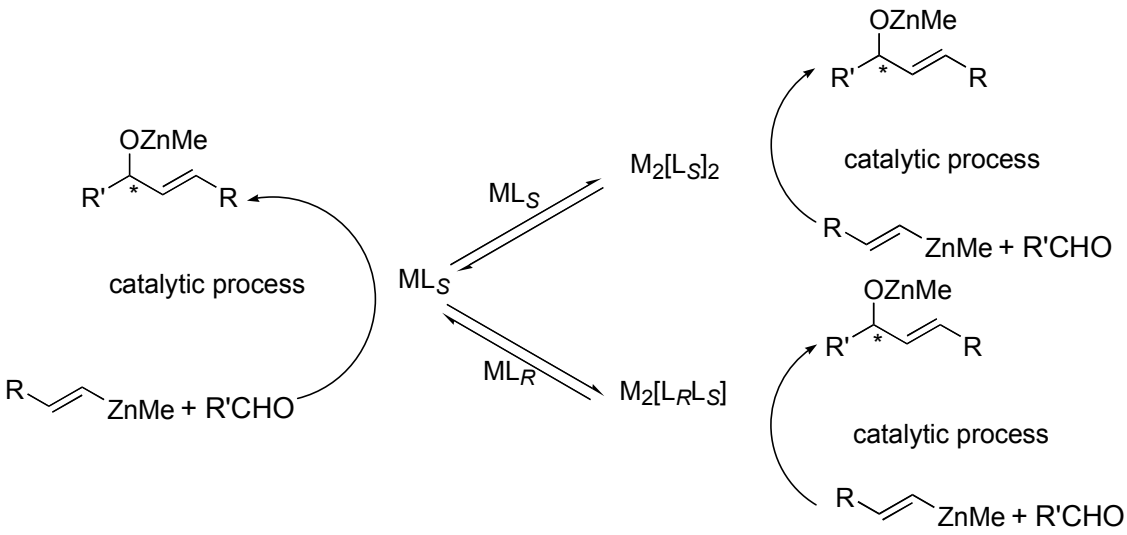


Figure 1.12. Formation of homo- and heterochiral metal-ligand complexes that are in equilibrium with the catalytically active monomeric complex in the presence of ligand **21**.

We interpret this unusual dependence on chiral loading and the switch in the product configuration by the participation of both monomeric and aggregated metal-ligand species in the catalytic cycle (Figure 1.12). This complex mechanism could result from the presence of Lewis-acidic zirconocene coordinating to the alcohol and perturbing the dynamic equilibria of aggregates that are formed in solution. This abnormal behavior is unique for ligand **21** and quite in contrast to the non-linear studies performed by Seth Ribe on the methyl amino thiol ligand **20a** (Figure 1.13).[51]

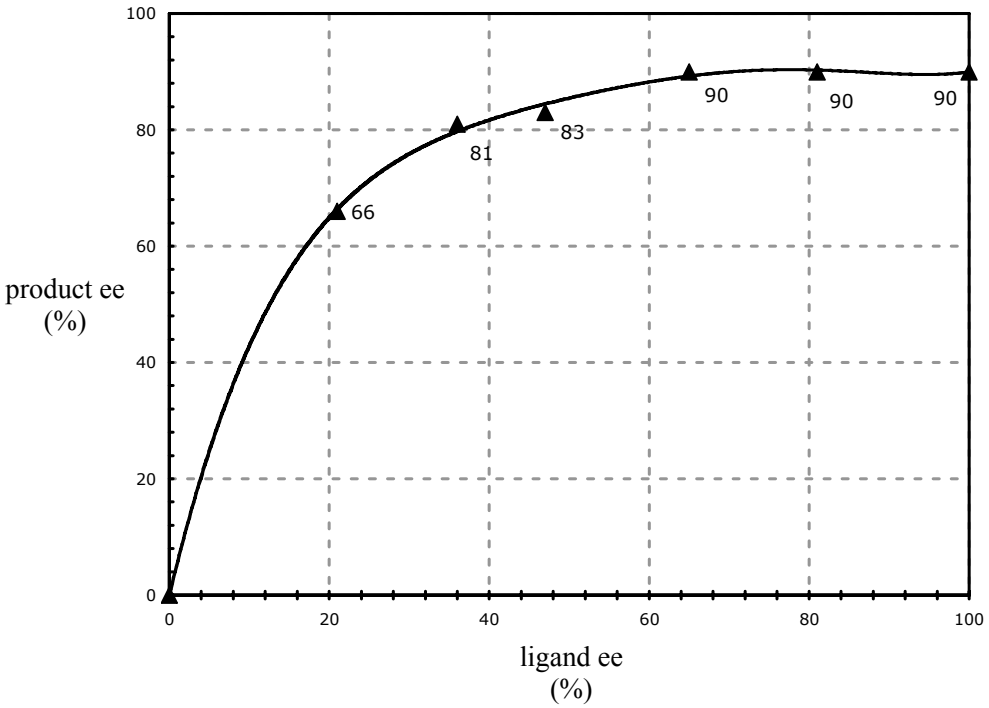


Figure 1.13. Positive non-linear effect for ligand **20a** at 10 mol% loading in the formation of allylic alcohol **27**.

In the presence of ligand **20a,** a positive non-linear effect was observed in agreement with Kagan's ML_2 model (Figure 1.14). This behaviour is indicative of a fast ligand exchange at the metal center of a reactive species bearing two chiral ligands. We postulate that with ligand **20a**, zirconocene byproducts do not affect the aggregates that are formed due to the high affinity that sulfur has for zinc.[45] Based on the strong asymmetric amplification effect it is reasonable to assume that the heterochiral dimer is more stable than the homochiral dimer. The instability of the homochiral dimer results in its rapid dissociation into monomeric species, which then take part in the catalytic cycle. Because the homochiral dimer is composed of a single enantiomer of the ligand, an asymmetric amplification is observed.

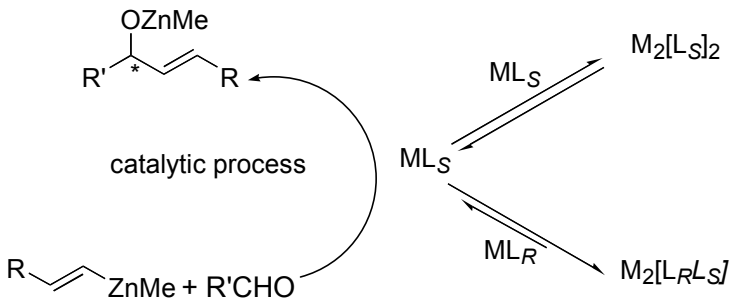
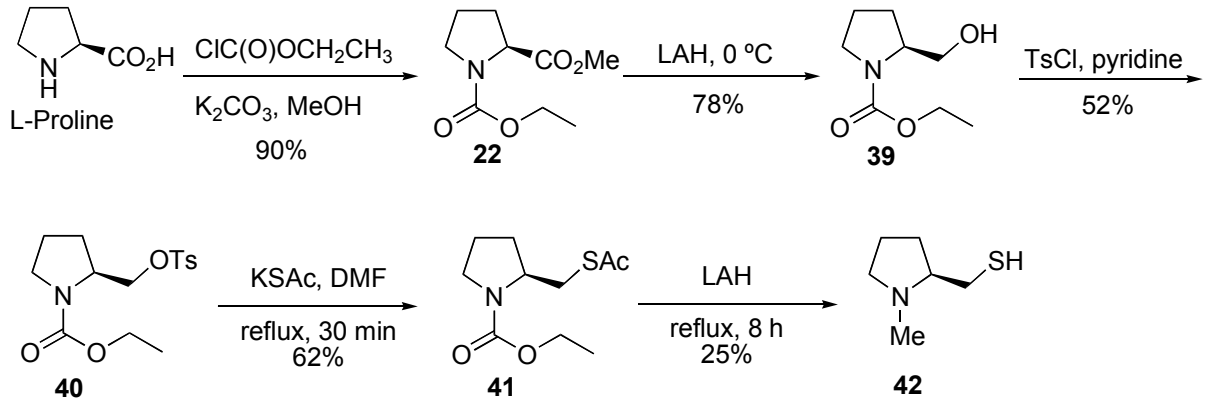


Figure 1.14. Formation of homo- and heterochiral metal-ligand complexes that are in equilibrium with the catalytically active monomeric complex in the presence of ligand **20a**.

In comparison, the aminoalcohol ligand **21** is inferior to the sulfur containing ligands **20a** and **20b.** Much of the enhancement of the chiral induction appears to be an effect of the presence of a sulfur ligand, and therefore our next avenue of exploration was to convert the proline-based amino alcohols into amino thiols in the hope of improving the enantioselectivity of the alkenylzinc addition process and decrease chiral ligand loading.

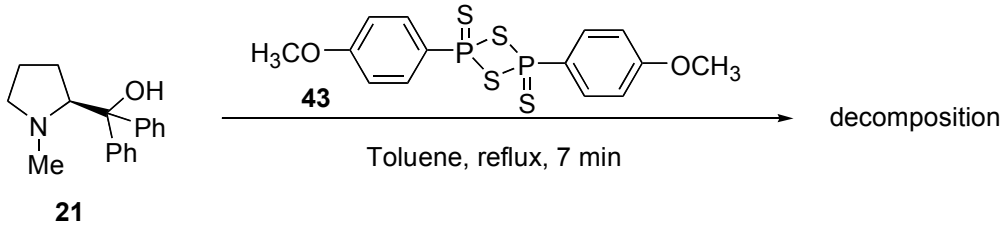
1.2.3 Synthesis of Thiol Analogues of Proline-based Amino Alcohols

Amino thiol **42** was synthesized from the common intermediate **22**, prepared as part of the initial series of proline-based amino alcohols. The methyl ester **22** was reduced to the corresponding alcohol **39** in 78% yield using $LiAlH_4$. The alcohol was then converted to tosylate **40** in 52% yield and subsequent displacement with potassium thioacetate furnished thioacetate **41** in 62% yield. This reaction was followed by a low yielding double reduction of the acetate as well as the carbamate to provide thiol **42**. Using ligand **42,** the addition of hexenylzinc to benzaldehyde at a loading of 10 mol% gave product of 83% ee; at 15 mol% ligand loading, product of 84% ee was obtained. This was a significant improvement over the enantioselectivity (17% ee and 18% ee) observed with the corresponding amino alcohol analogue **23**.



Scheme 1.29. Synthesis of ligand **42**.

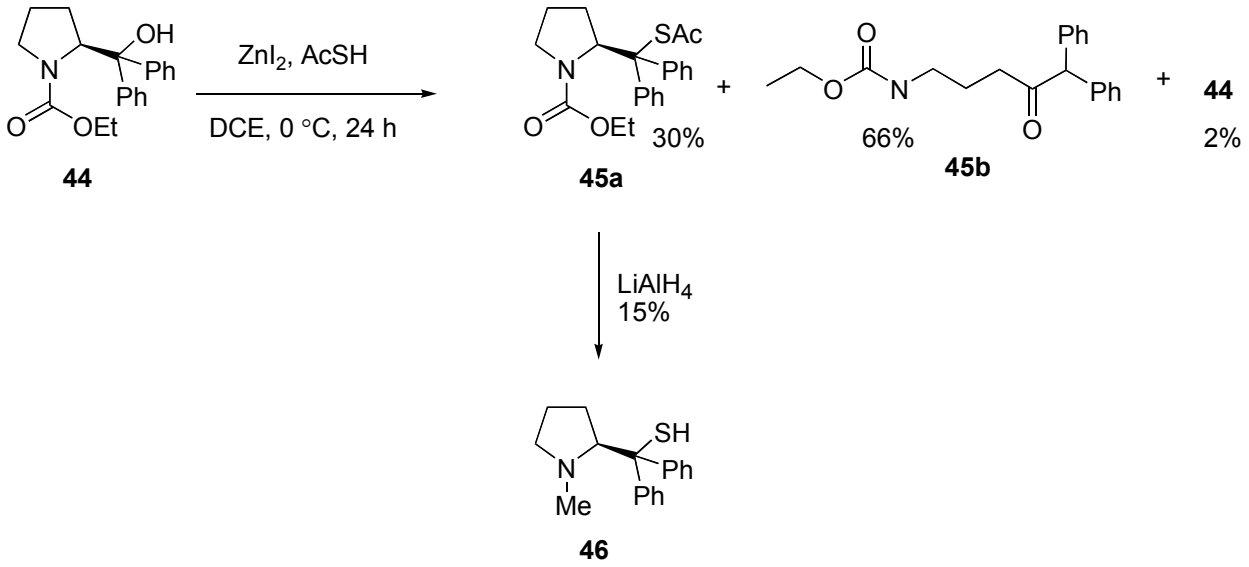
Encouraged by these results, transformation of diphenylamino alcohol **21** into the corresponding thiol **45a** was investigated. Compound **45a** was previously synthesized from **21** by Gibson et al. using Lawesson's reagent **43** by heating the reaction mixture at reflux for 7 min (Scheme 1.30).[52] Disappointingly, in our hands these conditions resulted in decomposition of the starting material.



Scheme 1.30. Conversion of alcohol **21** to corresponding thioacetate using Lawesson's reagent.

An alternative route was also proposed whereby in the presence of zinc iodide and thioacetic acid the tertiary alcohol **44** is converted to the corresponding thioacetate. Initially, this reaction at room temperature cleanly afforded the acyclic compound **45b** as the only product. Cooling the reaction to 0 °C for 5 h, afforded the desired product **45a**, acyclic product **45b**, and starting material. To ensure complete conversion, the reaction mixture was stirred for 24 h at 0 °C to give 30% of the desired product **45a**, 66% of the acyclic product **45b**, and a trace of starting material. Further attempts to inhibit the formation of the acyclic product **45b** were not pursued. Disappointingly, application of ligand **46** in the alkenylzirconocene/zinc addition led to

a low enantioselectivity of 18% ee at 10 mol% loading. It is unclear at this time what causes the dismal enantioselectivity shown by the tertiary thiol ligand **46**.



Scheme 1.31. Conversion of alcohol **44** to thioacetate to **45** using an activation/displacement protocol.

1.3 Thiol Benzylamines

1.3.1 Preparation of 2-(1-dimethylamino-2-methylpropyl)benzenethiol

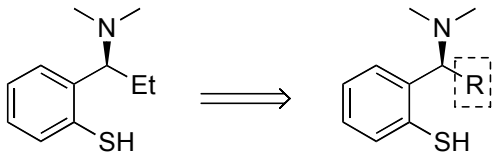
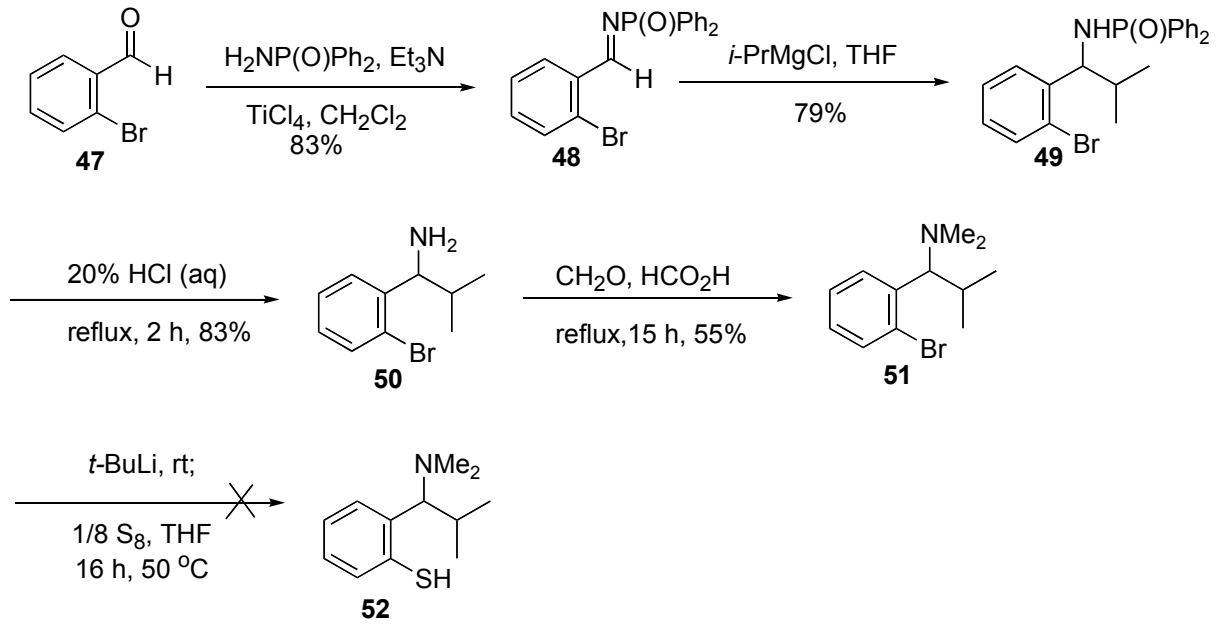


Figure 1.15. Modification to ethyl-substituted aminothiol **20b**.

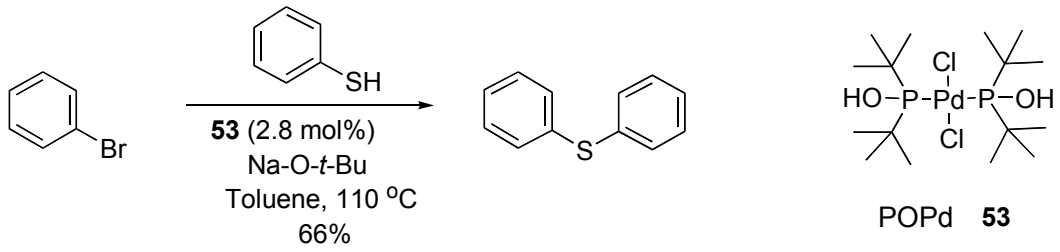
After further examination of the data reported by Seth Ribe for the enantioselectivity obtained using methyl-(**20a**) and ethyl-substituted (**20b**) aminothiols, it was postulated that increasing the steric bulk of the R group from an ethyl to an isopropyl substituent would increase the enantioselectivity beyond the current maximum of 95% ee (Figure 1.15). In attempts to access this isopropyl amino thiol ligand, we felt that installation of the sulfur moiety at a late stage would be beneficial due to the chemical instability of free thiols. Introduction of the sulfur moiety would be performed analogously to the synthesis of the methyl- and ethylaminothiol ligands (Scheme 1.32). We felt installation of bromine at the *ortho*-position would facilitate the introduction of the thiol. Although there are no enantiomerically pure building blocks for this synthesis, we were confident that a resolution at some point along the route would be feasible.



Scheme 1.32. Synthesis of 2-(1-dimethylamino-2-methylpropyl)benzenethiol (**52**).

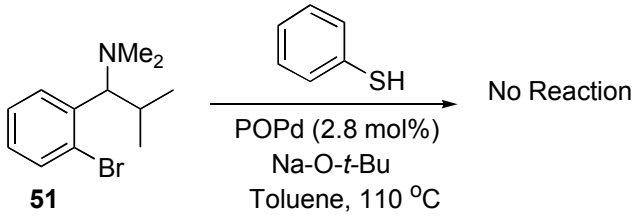
Addition of *ortho*-bromobenzaldehyde to diphenylphosphinamide in the presence of $TiCl_4$ and Et_3N resulted in an 83% yield of imine **48**. Isopropyl magnesium chloride addition to the imine resulted in a 79% yield of **49**. Treatment of **49** with 20% aq. HCl at reflux furnished the free amine **50** in 83% yield. Eschweiler-Clarke methylation of the resulting amine provided the dimethylated product **51** in 55% yield. Finally, halogen-metal exchange using *t*-BuLi, followed by reaction of the aryllithio species with elemental sulfur was expected to furnish the *ortho*-substituted thiol **52**. Unfortunately, this last step proved to be very problematic. Varying

the lithiating agent and also varying reaction times for the halogen-metal exchange still afforded no product. This could be due to the added steric bulk of the isopropyl group compared to the ethyl and methyl analogues. At this point, an alternate method for conversion of the bromine to the thiol was required. A possible solution was through the use of the air-stable palladium catalyst **53**, introduced by Li (Scheme 1.33).[53]



Scheme 1.33. Synthesis of thioethers using POPd (**53**).

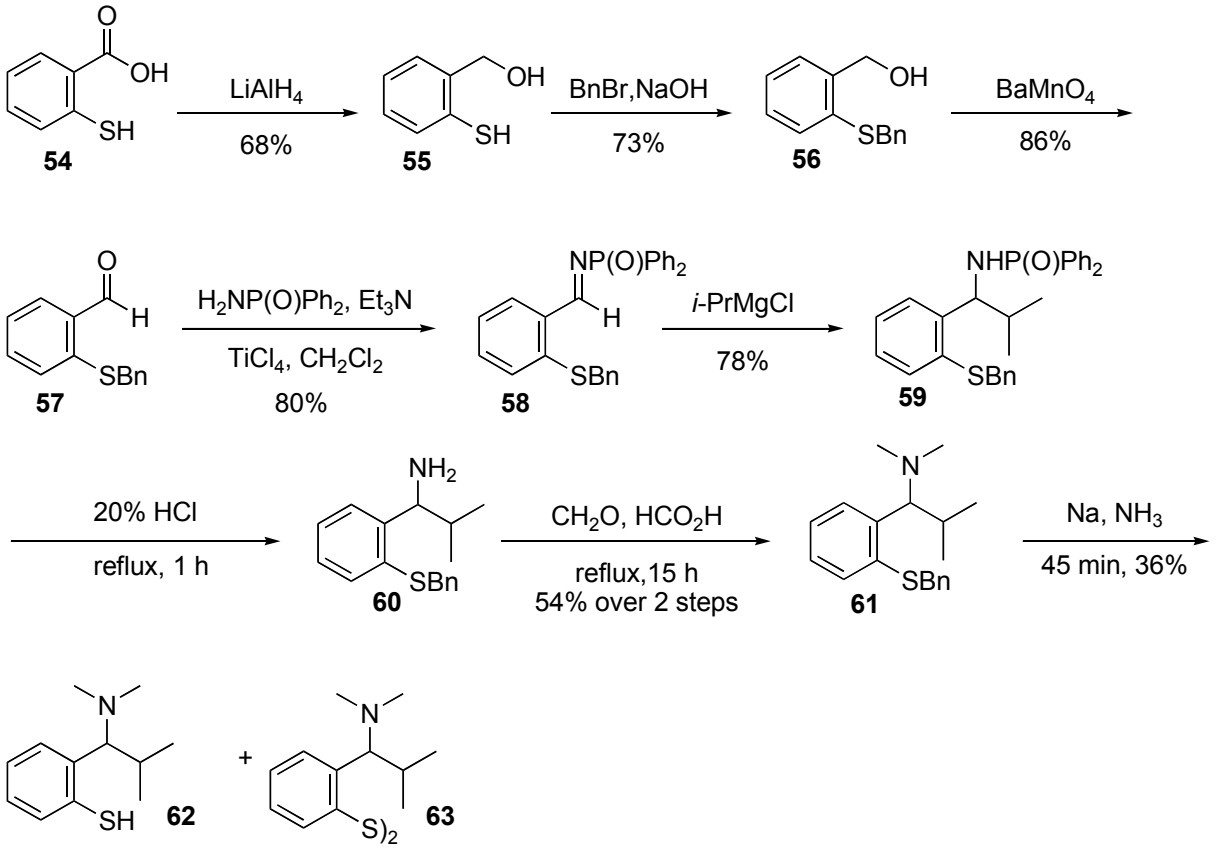
It has been shown that in the presence of a catalytic amount of POPd **53**, an aryl halide can be coupled to thiophenol to give the thioether in 66% yield. However, in our substrate no reaction resulted (Scheme 1.34). This lack of reactivity could be partially due to the added steric bulk present in **51**. Thus, coupling of the thiol at the *ortho*-position might present a significant challenge.



Scheme 1.34. Conversion of aryl bromide **51** to thioether using POPd **53**.

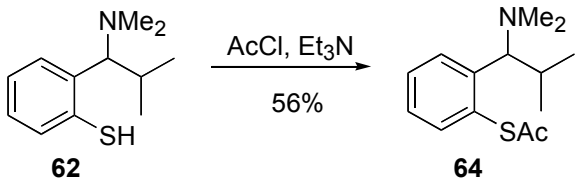
The route was thus modified in order to install the thiol functionality at an earlier stage (Scheme 1.35). The most convenient solution was to start from thiosalicylic acid followed by protection of the thiol. This enabled further elaboration of the ligand while not affecting the thiol group.

Thiosalicylic acid was treated with $LiAlH_4$ to afford the reduced product **55** in 68% yield.[82] Protection of thiol **55** with benzylbromide and NaOH gave **56** in 73% yield. Oxidation of the alcohol with barium manganate furnished aldehyde **57** in 86% yield. This aldehyde was then reacted with diphenylphosphinamide in the presence of $TiCl_4$ and Et_3N to afford imine **58** in 80% yield. Isopropyl magnesium chloride addition to the imine afforded the alkylated **59** in 78% yield. Treatment of **59** with 20% aq. HCl at reflux furnished the free amine **60**.[54] Eschweiler-Clarke methylation of the amine afforded the dimethylated product **61** in 54% yield over 2 steps. Deprotection of the benzyl group with Na/NH_3 gave isopropyl aminothiol ligand **62** in 36% yield.[55] Low yields in the deprotection of **61** were obtained due to the instability of the free thiol product **62** upon exposure to air. After workup, crude NMR analysis revealed <10% disulfide formation. But after purification by column chromatography on SiO_2, the amount of disulfide formed was increased. Thus, exposure to air facilitates formation of disulfide **63**.



Scheme 1.35. Revised synthesis of 2-(1-dimethylamino-2-methylpropyl)benzenethiol **62**.

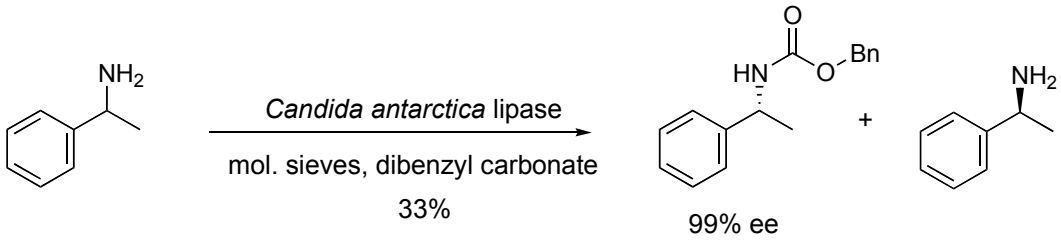
Due to the instability of the free thiol, a more stable analogue was desired. Transformation of **62** to the acetate **64** was carried out using acetyl chloride and triethylamine to give **64** in 56% yield (Scheme 1.36). With a viable route to **62** and **64** in hand, separation of racemic intermediates was necessary.



62 **64**

Scheme 1.36. Conversion of thiol **62** to thioacetate **64**.

Resolution of racemic amine **60** was explored first. (*R,S*)-Tartaric acid, camphorsulfonic acid, and (S)-mandelic acid were used as potential resolving agents in the presence of different solvents. Recrystallization from $CHCl_3$, EtOH, and 20% Et_2O/EtOH was attempted. However, the resolution of the amine failed while a solvent with the ideal properties for resolution was not found. The solvents and salts examined did not differentiate between the enantiomers in order for a resolution to be viable. Next, an enzymatic resolution using *Candida antarctica* lipase was tried. It has been shown by the group of Wong that primary amines can be resolved quite easily using *Candida antarctica* lipase and dibenzylcarbonate (Scheme 1.37).[56] However, the resolution via this route was unsuccessful since no enzymatic protection of either enantiomer of amine was observed.



Scheme 1.37. Enzymatic resolution of amines.

Another technique for separation of enantiomers involves using chiral HPLC. Using both OD and AD-H analytical columns,[57] intermediates **59-61** were tested for adequate separation. It was found that intermediate **59** could be separated to baseline resolution using 30% *i*-propanol/hexanes at a flow rate of 1 mL/min (Figure 1.16) on the Chiralcel AD-H analytical column.

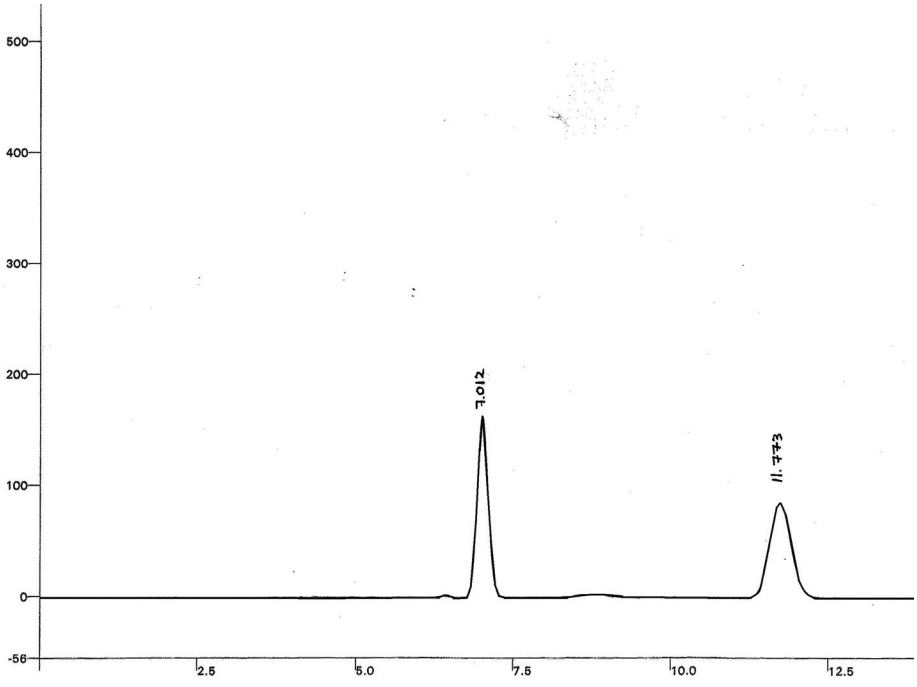
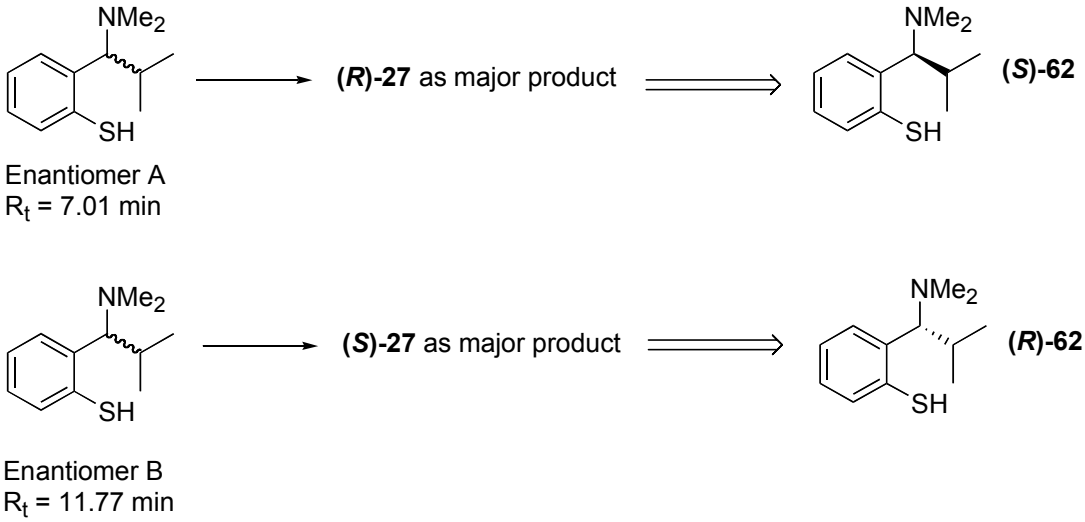


Figure 1.16. HPLC chromatogram of **59**. R_t enantiomer A = 7.01 min and R_t enantiomer B = 11.77 min.

Separation of racemic-**59** on an AD-H Chiralpack Semi-Prep column (2 cm x 25 cm) at a flow rate of 10 mL/min with 30% *i*-propanol/hexanes afforded each enantiomer in >99% ee.[58] The pure enantiomers were then further elaborated to give optically pure 2-(1-dimethylamino-2-methylpropyl)benzenethiols, **(*R*)-** and **(*S*)-62**. The assignment of (*R*)- and (*S*)- to this new ligand is based on the data for the ethyl analogue **20**. In the case of **20**, the (*R*)-configuration of the ligand gave the (*S*)-configuration of allylic alcohol **27**. Based on the major enantiomer of allylic alcohol **27** formed, it was therefore possible to assign the configuration of the ligand (Scheme 1.38).



Scheme 1.38. Assigment of configuration to enantiomers of **62**.

Table 1.4. Asymmetric additions of **26** to benzaldehyde in the presence ligands **62-64**.

Entry	Ligand (**L***)	Ligand Loading (mol%)	**63:62**[b]	Yield (%) of **27**	ee (%)[a] of **27**
1	**(*S*)-62**	5	1:4	78	56
2	**(*S*)-62**	10	1:4	74	66
3	**(*S*)-62**[b]	10	1:10	80	62
4	**(*R*)-62**	5	1:7	70	68
5	**(*R*)-62**	10	1:7	76	96
6	**(*R*)-62**	10	1:15	79	99
7	**(*R*)-62**[b]	5	1:10	82	87
8	**(*R*)-62**[b]	10	1:10	80	97
9	**(*S*)-63**	5	1:0	45	26
10	**(*S*)-63**	10	1:0	65	27
11	**(*R*)-64**	5	-	75	11
12	**(*R*)-64**	10	-	79	18

[a]ee's were determined by chiral HPLC analysis (Chiralcel OD, 1 mL/min using *i*-PrOH/hexanes (1:99)) with a PL-ELS 1000 detector, [b]ligand was used crude, before chromatographic purification, [c]ratio of free thiol to disulfide by NMR was determined by measuring doublet at 3.82 ppm (**63**) and 3.50 ppm (**62**).

The preliminary data with ligand **62** in the alkenyl zirconocene/zinc addition to aldehydes is shown in Table 1.4. At a ligand loading of 10 mol%, **(*S*)-62** shows enantioselectivities between 62-66% for the allylic alcohol **(*R*)-27** (Entry 2, 3). This is in sharp contrast to enantioselectivities between 96-99% observed for **(*R*)-62** (Entry 5,6,8). This discrepancy is quite puzzling since both enantiomers should show similar enantioselectivities in forming allylic alcohol **19**. It is unclear at this time if the enantioselectivity of the reaction is perturbed by the presence of disulfide. The disulfide **(*R*)-63** was also tested because of its stability compared to the free thiol but showed a low enantioselectivity of ~27% ee (Entry 9, 10). The thioacetate **(*R*)-64** showed low enantioselectivities of 11 and 18% ee (Entry 11, 12).

After preliminary data with ligand **62** were obtained, Wipf *et al*. reported on the inherent discrepancy between enantiomeric ratios formulated from ELSD and UV detectors.[59] By comparing values for enantiomeric excess of a mixture of standards, the UV detector in all cases

showed more accurate results. The ELSD grossly exaggerated the enantiomeric excess of the standards. This difference can potentially be derived from the non-linear response of the ELS detector.

In light of this inconsistency, the reactions with isopropyl thiol benzylamine **62** were repeated and the enantiomeric excess was determined using both ELSD and UV detectors. Disappointingly, the enantiomeric excesses were inflated when ELSD was used as the method of detection. The enantiomeric excess detected by the UV was much lower, 31% ee using **(*S*)-62** and 84% ee using (***R***)-**62** (Table 1.5). The divergence in enantioenrichment of product between **(*R*)**- and **(*S*)-62** are still apparent even with UV detection. At this time, no clear reason for this effect can be given. The discrepancy can be as a result of varying amounts of disulfide in the ligand mixture, which can possibly perturb the asymmetric system.

Table 1.5. Chiral HPLC analysis of **27** with tandem detection by ELSD and UV.

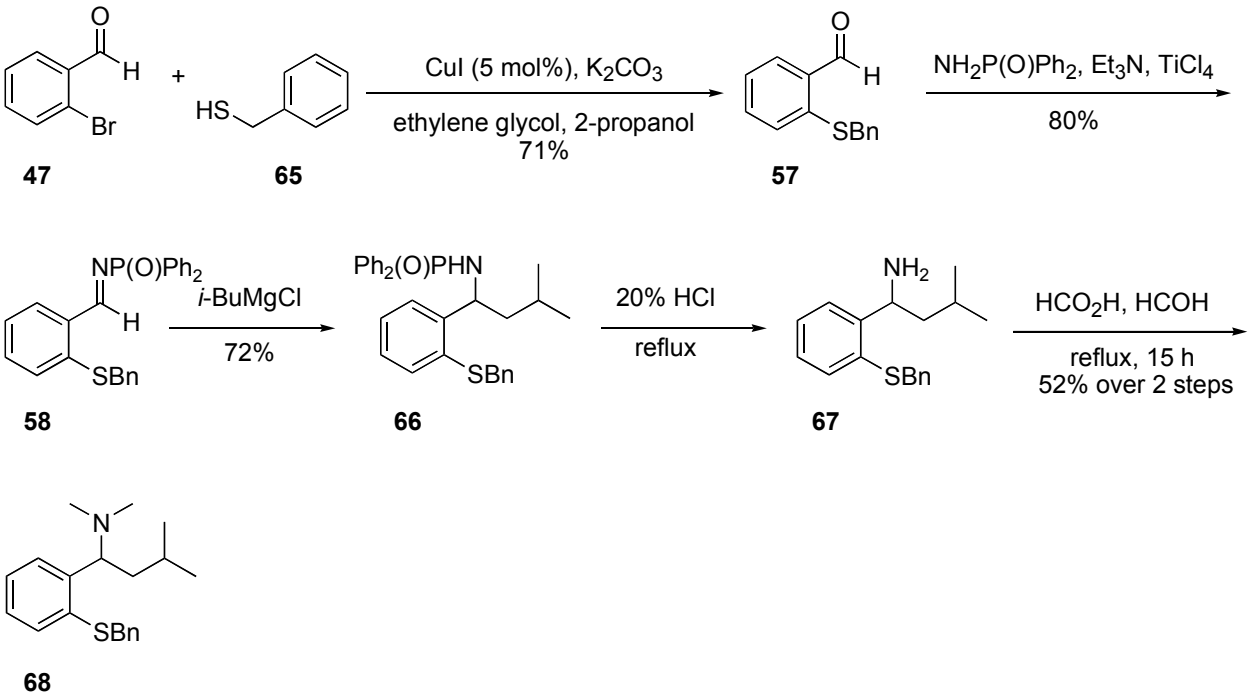
Entry	Ligand	Ligand Loading (mol%)	Yield (%) of **27**	ee (%)[a] of **27** **ELSD**	ee (%)[a] of **27** **UV**
1	**(*S*)-62**	10	82	76	31
2	**(*R*)-62**	10	80	99	84

[a]ee's were determined by chiral HPLC analysis (Chiralcel OD, flow rate 1 mL/min using *i*-PrOH/hexanes (1:99)) with a Dynamax UV-1 absorbance detector followed in tandem with PL-ELS 1000 detector. The UV detector was connected to the ELSD in a tandem manner.

1.3.2 Preparation of 2-(1-Dimethylamino-2-methylbutyl)benzenethiol

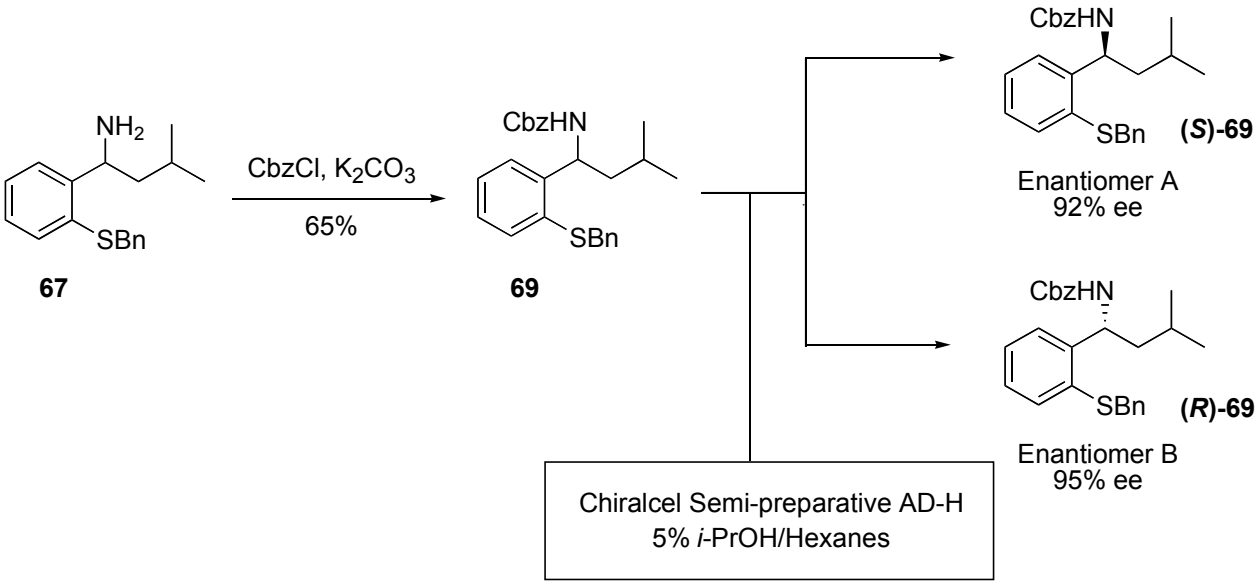
An isobutyl analogue was synthesized analogously to the isopropyl analogue, **70**. Aldehyde **57** was improved by employing a copper mediated coupling between *ortho*-bromobenzaldehyde and benzylmercaptan to afford **57** in 71% yield.[60] This aldehyde was then reacted with diphenylphosphinamide in the presence of $TiCl_4$ and Et_3N to afford imine **58** in 80% yield. Isobutyl magnesium chloride addition to the imine afforded the alkylated product **66** in 72% yield. Treatment of **66** with 20% aq. HCl at reflux furnished the free amine **67**.[61]

Eschweiler-Clarke methylation of the amine afforded the dimethylated product **68** in 52% yield over 2 steps.



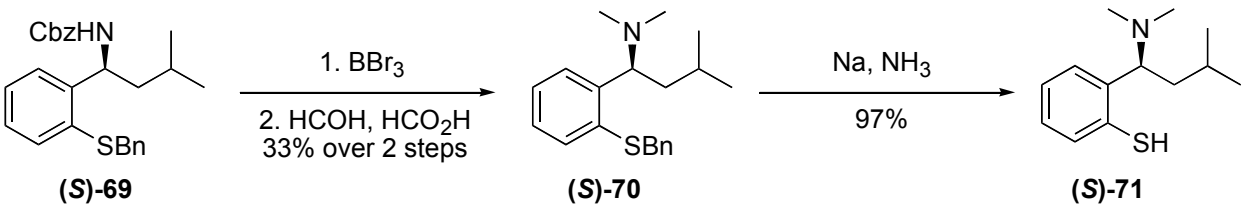
Scheme 1.39. Synthesis of benzylamine **68**.

Using both OD and AD-H analytical columns, intermediates **66-68** were tested for adequate separation. It was found that intermediate **66** could be separated to baseline resolution using 5% *i*-propanol/hexanes at a flow rate of 1 mL/min (Figure 10) on the Chiralcel OD analytical column. However, transferring these conditions to the semi-preparative AD column resulted in no baseline separation. Cbz-protected amine was examined as an alternative intermediate to be examined on HPLC. Inital protection of amine **67** using benzylchlorofomate and K_2CO_3 resulted in **69** in 65% yield (Scheme 1.40). It was found that intermediate **69** could be separated to baseline separation using 5% *i*-PrOH/hexanes at a flow rate of 1 mL/min on the Chiralcel OD analytical column. Gratifyingly, separation of racemic-**69** on an AD-H Chiralpack Semi-Prep column (2 cm x 25 cm) at a flow rate of 10 mL/min with 5% *i*-propanol/hexanes afforded each enantiomer in >92% ee.[62]



Scheme 1.40. Synthesis and separation of Cbz-intermediate **69**.

The pure enantiomers were then further elaborated to give enantiomerically enriched 2-(1-dimethylamino-3-methylbutyl)-benzenethiol, **(*R*)-** and **(*S*)-71** (Scheme 1.41). The configuration of ligand **71** was assigned based on the rationale previously used to assign the configuration of ligand **62** (Scheme 1.38).



Scheme 1.41. Synthesis of thiol benzylamine (*S*)-**71**.

The preliminary data obtained with both enantiomers of ligand 71 in the alkenyl zirconocene/zinc addition to aldehydes is shown in Table 1.6. At a ligand loading of 10 mol%, (*S*)-71 and (*R*)-71 show ee's between 61-69% for the formation of allylic alcohol 27 (Entry 2, 3).

Table 1.6. Asymmetric additions of **26** to benzaldehyde in the presence of ligands **71**.

Entry	Ligand	Ligand Loading (mol%)	Yield (%) of **27**	ee (%)[a] of **27**
1	**(*S*)-71**	5	81	44
2	**(*S*)-71**	10	78	61
3	**(*R*)-71**	10	84	69
4	**(*R*)-71**	15	80	70

[a]ee's were determined by chiral HPLC analysis (Chiralcel OD, flow rate 1 mL/min using *i*-PrOH/hexanes (1:99)) with a Dynamax UV-1 absorbance detector.

Unfortunately, increasing the steric bulk of the R group to isopropyl and isobutyl showed no further increase in enantioselectivity. The proposed transition state model for using this ligand scaffold is shown in Figure 1.17. The increase in added steric bulk of the R group must inhibit to some degree the formation of this transition state. This could possibly arise from steric crowding of the R group with the amine substituents and thus disrupting the rigidity of the transition state.

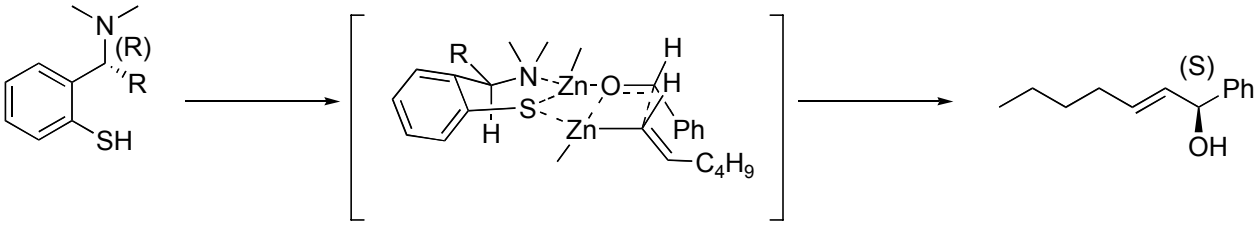


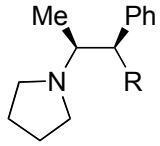
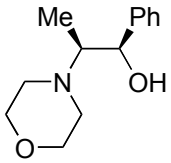
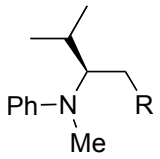
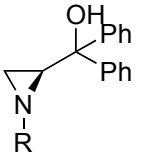
Figure 1.17. Possible transition state model for the thiol benzylamine catalyzed alkenyl zirconocene/zinc addition to benzaldehyde.

1.4 Alternative Ligand Scaffolds

1.4.1 Alternate Ligand Survey

Alternate ligands surveyed in the alkenylzirconocene/zinc addition to aldehydes are shown in Tables 1.7, 1.8, and 1.9. Norephedrine-based amino alcohols and thiocarboxylates ligands have shown promise in diethylzinc addition to aldehydes with ee's of up to 99%.[63] The data shown below indicates little selectivity with this ligand scaffold although an increase in enantioselectivity was observed between the alcohol **72** and thioacetate **73** (entry 1). This slight increase might again be due to the higher affinity of zinc for thiolates as compared to the corresponding alcoholates. Anderson et al. have demonstrated the importance of the substituents on nitrogen in chiral amino thiol ligands for the asymmetric addition of diethylzinc to aromatic aldehydes.[64] These valine-based ligands, **77-79**, were tested in our methodology and showed very little selectivity (entry 3). Aziridine-based β-amino alcohols also have proven to be successful in the enantioselective addition of diethylzinc to aromatic aldehydes.[65] Ligands of this type also posses the diphenylalcohol moiety that was so effective in the proline-based ligands. However, as shown below, no significant enantioselectivity in the alkenyl zirconocene/zinc addition to benzaldehyde was observed with ligands **83**, **85**, and **86** (entry 4).

Table 1.7. Asymmetric additions of **26** to benzaldehyde in the presence of ligands **72-86**.

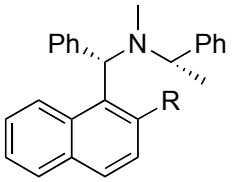
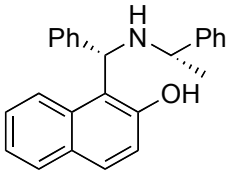
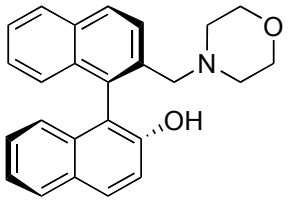
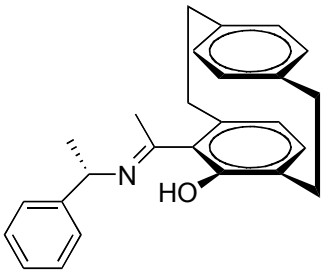
Entry	Ligand	Ligand Loading (mol%)	Yield (%) of **27**	ee (%)[a] of **27**
1		**72**, R = OH; 10	85	19
		73, R = SAc; 15	81	46
2		**74**; 10	80	20
3		**77**, R = OH; 10	74	10
		78, R = SAc; 15	75	16
		79, R = SH; 15	80	17
4		**83**, R = Trt; 15	85	8
		85, R = Bn; 15	74	12
		86, R = Dpm; 10	80	48

[a]ee's were determined by chiral HPLC analysis (Chiralcel OD, flow rate 1 mL/min using *i*-PrOH/hexanes (1:99)) with a Dynamax UV-1 absorbance detector.

In 2003, Chan *et al.* reported on the alkenylations of aldehydes using aminonaphthol **87**. This ligand was easily prepared via a one step procedure and used in Oppolzers' hydroboration-transmetalation to zinc followed by addition to aldehyde that resulted in high ee's of up to 99%.[30] This methodology is quite similar to ours and thus this ligand was considered as a viable candidate for further exploration. Unfortunately, these ligands did not provide significant stereoinduction in our methodology (Table 1.8, entries 1 and 2). Possibly, B-Zn and Zr-Zn allylic alcohol formations occur via different mechanisms and the presence of zirconocene byproducts plays a crucial role in the overall control of the catalytic asymmetric process. A binaphthyl backbone was also considered as a viable option since ligands of this type have shown moderated enantioselectivity in asymmetric alkenylzinc addition to aldehydes.[31]

Unfortunately, racemic **27** was afforded with ligand **92** (entry 3). Dahmen has used paracyclophanes-based ketimine ligands in asymmetric alkylzinc additions as well as alkenylzinc additions.[29] In our reaction manifold, a low enantioselectivity of 6% was observed with ligand **96** (entry 4).

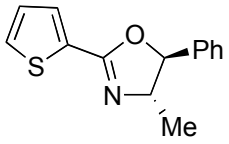
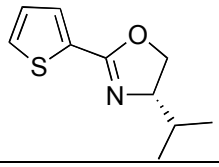
Table 1.8. Asymmetric additions of **26** to benzaldehyde in the presence of ligands **87**-**89**, **92**, and **96**.

Entry	Ligand	Ligand loading (mol%)	Yield (%) of **27**	ee (%)[a] of **27**
1		**87**, R = OH; 15	76	2
		88, R = SH; 15	81	28
2		**89**; 15	79	17
3		**92**; 10	76	1
4		**96**; 10	60	6

[a]ee's were determined by chiral HPLC analysis (Chiralcel OD, flow rate 1 mL/min using *i*-PrOH/hexanes (1:99)) with a Dynamax UV-1 absorbance detector.

Oxazolines have shown good stereochemical control properties in metal-mediated catalysis.[66] Ligands of this type, **97** and **98**, also contain a second donor group in the form of a thiophene. Incorporation of sulfur via a thiophene moiety might induce some extra rigidity which may have positive effects on the enantioselective addition of alkenylzinc reagents. Ligand **97** proved to be slightly more enantioselective in the alkenyl zirconocene/zinc addition to benzaldehyde than ligand **98,** but neither showed the desired level of enantioselectivity (Table 1.9, entries 1 and 2).

Table 1.9. Asymmetric additions of **26** to benzaldehyde in the presence of ligands **97** and **98**.

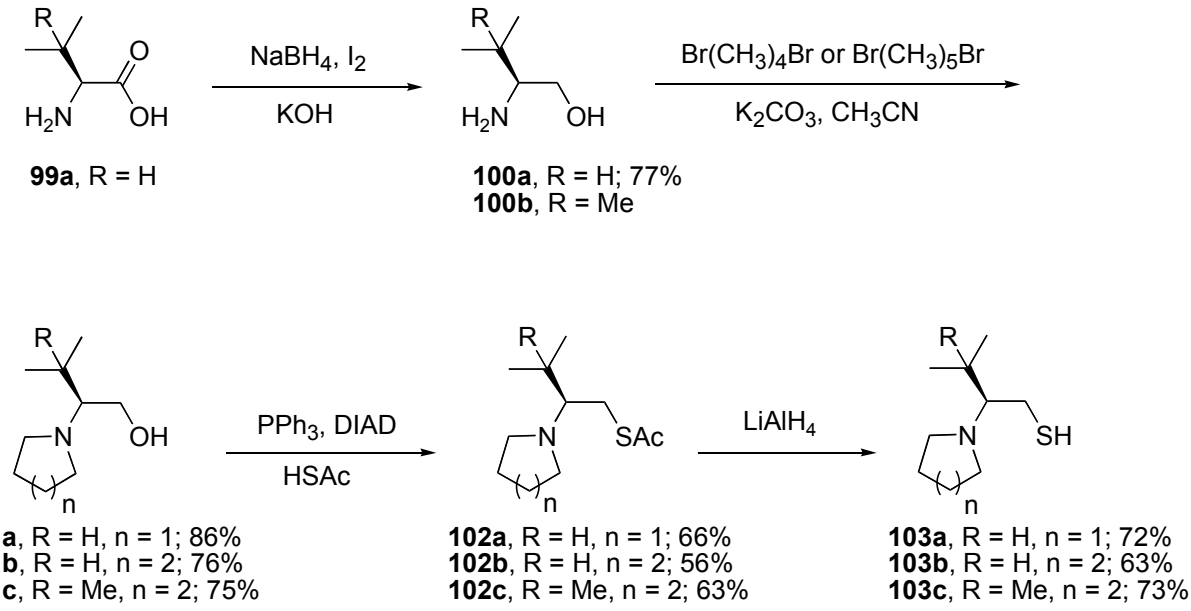
Entry	Ligand	Ligand Loading (mol%)	Yield (%) of **27**	ee (%)[a] of **27**
1		**97**; 15	83	21
2		**98**; 15	79	7

[a]ee's were determined by chiral HPLC analysis (Chiralcel OD, flow rate 1 mL/min using *i*-PrOH/hexanes(1:99)) with a Dynamax UV-1 absorbance detector.

1.4.2 Synthesis and Evaluation of β–Amino Thiol Ligands

In an effort to investigate alternate ligand scaffolds, conformationally relatively restricted compounds containing the amino and thiol moieties in a 1,2-relationship were considered. The desired analogues were synthesized starting from (*L*)-valine and (S)-*t*-leucinol (Scheme 1.42). (*L*)-Valine was reduced using Meyer's reduction protocol to afford (*L*)-valinol **100a** in 77% yield.[67] Dialkylation of the amine employing 1,4-dibromobutane and 1,5-dibromopentane in the presence of K_2CO_3 resulted in the formation of **101a** and **101b** in 86% and 76% yield,

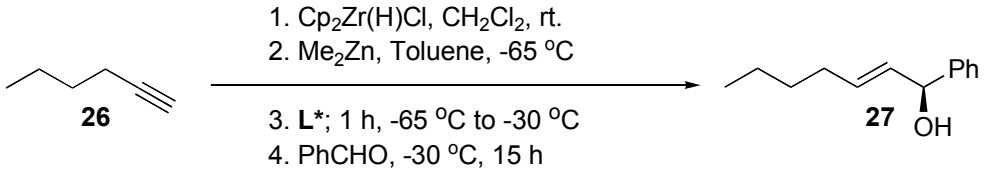
respectively. Conversion of the hydroxy moiety to the thioacetate utilizing Mitsunobu reaction conditions followed by $LiAlH_4$ reduction afforded the desired ligands **103a** and **103b**.[68] Analogously, ligand **103c** was synthesized starting from (*S*)-*t*-leucinol in the manner described above.



Scheme 1.42. Synthesis of β-amino alcohol and thiol ligands.

The β-amino thiol ligands **103a**, **103b**, and **103c** were screened in the alkenyl zirconium/zinc addition. Initial results showed good yields (80-81%) and moderate enantioselectivities (71-77%) in the presence of ligands **103b** and **103c** at 15 mol% ligand loading (Table 1.10). Thiol **103a** was rather ineffective (22% ee). Not unexpectedly, the corresponding β-amino alcohol ligands also showed a dramatic decrease in enantioselectivity (2-3%). The latter effect can be attributed to the characteristics of sulfur atoms and the presence of at least two metal complexes as previously mentioned.

Table 1.10. Asymmetric addition of **26** to benzaldehyde in the presence of ligands **103a-103c**.



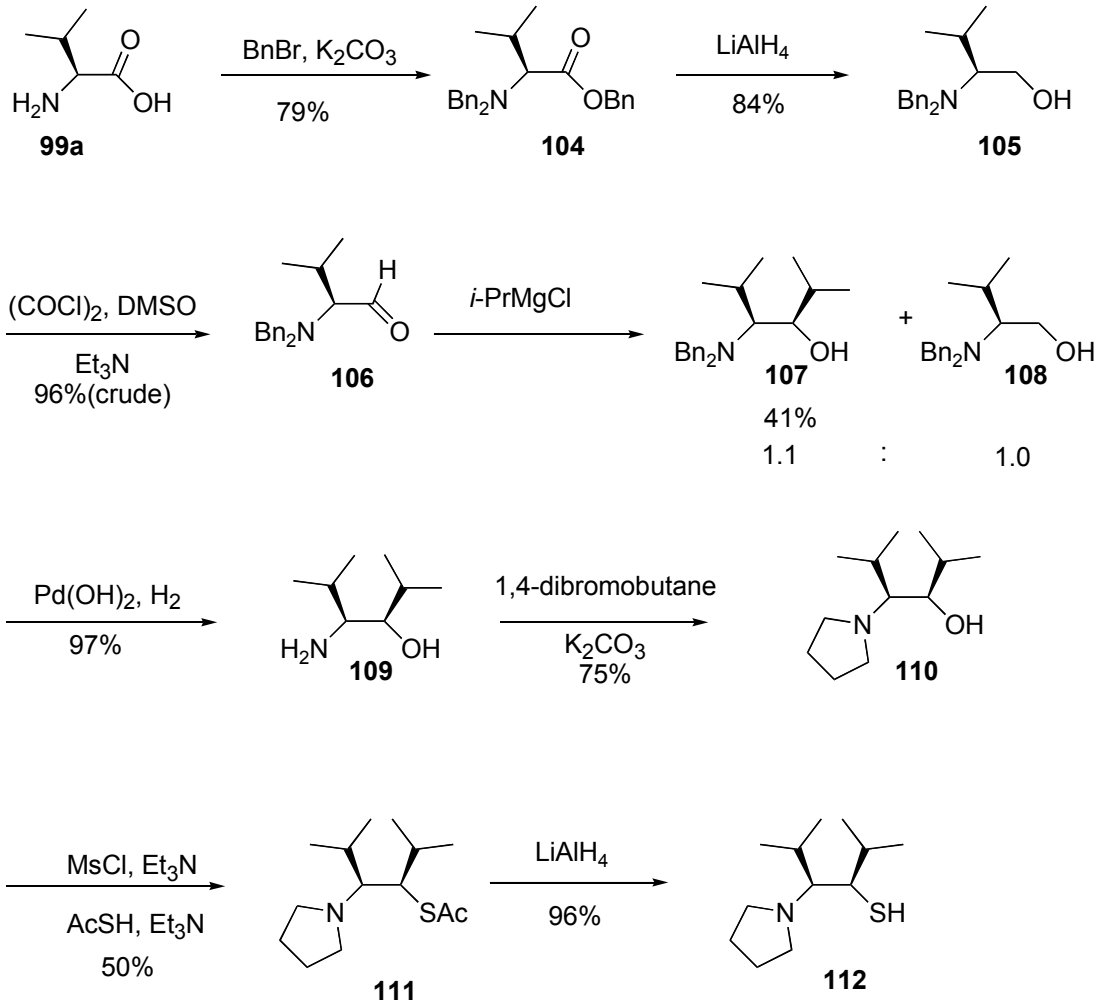
Entry	Ligand (**L***)	Ligand Loading (mol%)	Yield (%)	ee (%)[a] of **27**
1	**103a**	10	69	22
2	**103b**	10	75	64
3	**103b**	15	82	77
4	**103b**	20	79	76
5	**103c**	10	75	61
6	**103c**	15	81	71

[a]*ee*'s were determined by chiral HPLC analysis (Chiralcel OD, flow rate 1 mL/min using *i*-PrOH/hexanes (1:99)).

Our preliminary results with these rather simple β–amino thiol ligands prompted a further exploration of the β–amino alcohol scaffold. In the hope of increasing the enantioselectivity to appreciable levels, steric bulk was introduced at the α–carbon next to the thiol. Ligands with this specific substitution pattern have previously been reported by Yang *et al.* for the alkenylboron/zinc addition to aldehydes.[32] High enantioselectivity was observed by Yang when employing β–amino alcohol **112**.

β–Amino alcohol **112** was synthesized and examined in the alkenylzirconocene/zinc addition protocol. The amino thiol ligand was synthesized from readily available (*L*)-valine (Scheme 1.43). Using benzyl chloride in the presence of NaOH gave the *N*,*N*-dibenzylamino benzyl ester **104** in 79% yield. Reduction of the benzyl ester using $LiAlH_4$ afforded the resulting alcohol, which was further oxidized to the corresponding aldehyde **106** using Swern oxidation conditions in 96% yield. Isopropylmagnesium bromide addition to the aldehyde resulted in the bis-isopropyl amino alcohol **107** with high diastereoselectivity in 27% yield. A major byproduct of the Grignard reaction was the reduced alcohol **108**. Cleavage of the benzyl group employing hydrogenolysis conditions using $Pd(OH)_2$ afforded the free amine **109** in 97% yield. Alkylation of the amine using 1,4-dibrombutane resulted in the formation of the pyrrolidine alcohol **110** in

75% yield. In order to install the thiolacetate, the alcohol **110** was converted to the mesylate followed by displacement with thiolacetic acid. This process occurs via initial displacement of the mesylate by the tertiary amine to form the intermediate aziridine. The aziridine undergoes facile ring opening in the presence of thiolacetate to give the corresponding thiolacetate. Finally, $LiAlH_4$ reduction results in the amino thiol ligand **112** in 96% yield.

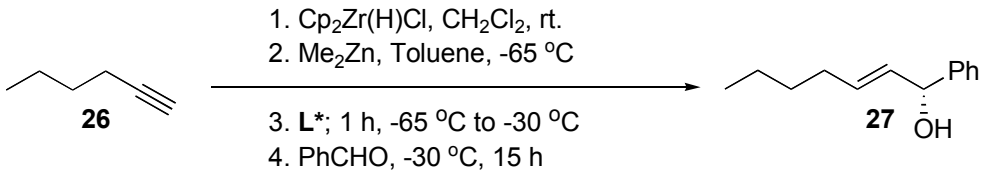


Scheme 1.43. Synthesis of β–amino alcohol **112**.

In our standard reaction, β–amino thiol **112** showed the highest enantioselectivity at 94% ee at a ligand loading of 10 mol% (Table 1.11, entry 6). A high enantioselectivity for the formation of **27** could be retained even at 2.5 mol% loading. In comparison to the corresponding

amino alcohol ligand **110**, the amino thioacetate and amino thiol ligands both showed higher enantioselectivities (entries 1,2, and 6).

Table 1.11. Asymmetric additions of **26** to benzaldehyde in the presence of ligands **110-112**.

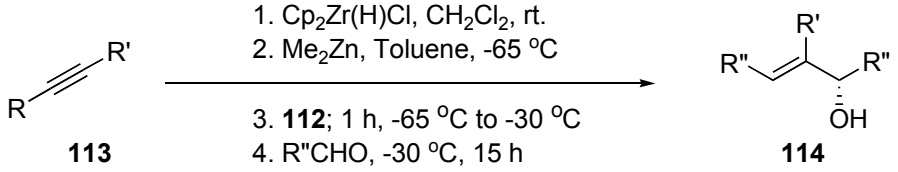


Entry	Ligand (**L***)	Loading Loading (mol%)	Yield (%)	ee (%)[a] of **27**
1	**110**	10	81	7
2	**111**	10	77	84
3	**112**	1	75	66
4	**112**	2.5	82	90
5	**112**	5	79	93
6	**112**	10	81	94
7	**112**	15	76	94

[a]*ee*'s were determined by chiral HPLC analysis (Chiralcel OD, flow rate 1 mL/min using *i*-PrOH/hexanes (1:99)).

The scope of the alkenylzirconocen/zinc addition process in the presence of the β-aminothiol ligand **112** is further illustrated in Table 1.12. It was observed that amino thiol **112** catalyzed reactions resulted in moderate enantioselectivity for aliphatic aldehydes (73-79% ee, entries 1 and 8). A decrease in enantioselectivity was found for the electron rich *p*-anisaldehyde (entry 3). Attempts at optimizing this reaction resulted in no appreciable increase in enantioselectivity (entries 4-6). The reaction scope was further investigated using internal alkynes. Promising results were obtained in the reaction of 3-hexyne with benzaldehyde, which resulted in an 89% yield and 90% ee for the corresponding allylic alcohol **118** (entry 10). The analogous reaction with *p*-anisaldehyde resulted in 87% ee, although at a lower yield of 63% (entry 12). Utilization of a silyl ester functionalized alkyne provided the substituted allylic alcohol **122** in 72% yield with an enantioselectivity of 71% (entry 13).

Table 1.12. Asymmetric addition in the presence of ligand **112**.



113 **114**

Entry	Alkyne (R, R')	Aldehyde (R")	Ligand Loading (mol%)	Product	Yield (%)	ee (%)[e] of **114**
1	*n*-C_4H_9, H	Ph CH_2CH_2	5	**115**	78	79
2	*n*-C_4H_9, H	(*p*-OMe)C_6H_4	5	**116**	72	36
3	*n*-C_4H_9, H	(*p*-OMe)C_6H_4	10	**116**	65	42
4[a]	*n*-C_4H_9, H	(*p*-OMe)C_6H_4	10	**116**	60	14
5[b]	*n*-C_4H_9, H	(*p*-OMe)C_6H_4	10	**116**	62	5
6[c]	*n*-C_4H_9, H	(*p*-OMe)C_6H_4	10	**116**	15	10
7	*n*-C_4H_9, H	C_6H_{11}	5	**117**	65	72[f]
8	*n*-C_4H_9, H	C_6H_{11}	10	**117**	70	73[f]
9[d]	*n*-C_4H_9, H	C_6H_{11}	10	**117**	23	24[f]
10	CH_3CH_2, CH_3CH_2	Ph	10	**118**	89	90[g]
11	CH_3CH_2, CH_3CH_2	Ph CH_2CH_2	10	**119**	65	53[g]
12	CH_3CH_2, CH_3CH_2	(*p*-OMe)C_6H_4	10	**120**	63	87[g]
13	TIPSOC(O)CH_2CH_2, H	Ph	10	**122**	72	71[h]

[a]no premixing of ligand, [b]reaction mixture was stirred at –50 °C for 15 h, [c]reaction mixture was stirred for 1 h, [d]ligand was premixed at 0 °C and stirred at 0 °C for 15 h, [e]*ee*'s were determined by chiral HPLC analysis (Chiralcel OD, flow rate 1 mL/min using *i*-PrOH/hexanes (1:99)), [f]*ee*'s were determined by ^{1}H NMR analysis of the derivatized product using Mosher's ester, [g]*ee*'s were determined by chiral HPLC analysis (Chiralcel AD-H, flow rate 1 mL/min using *i*-PrOH/hexanes (1:99)), [h]the corresponding allylic alcohol was treated with $LiAlH_4$ followed by *ee* determination of the resulting diol by chiral HPLC analysis (Chiralcel AD-H, flow rate 1 mL/min using *i*-PrOH/hexanes (5:95)).

The proposed transition state with ligand **112** is shown below in Figure 1.18. While simple β–amino thiol ligands, **103b** and **103c**, displayed mediocre enantioselectivity, the bis-isopropyl β-amino thiol ligand afforded the best enantioselectivity. This is also the first ligand that has shown promising results in both our hydrozirconation/transmetalation protocol as well as the reported hydroboration/transmetalation protocol.

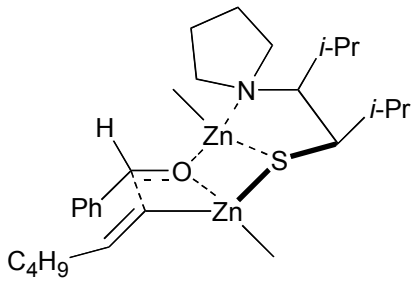
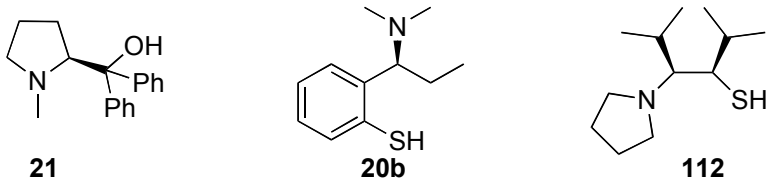


Figure 1.18. Possible transition state model for the β–amino thiol **112** catalyzed alkenyl zirconocene/zinc addition to benzaldehyde.

1.5 Conclusions

Among the ligands surveyed in the alkenyl zirconium-zinc addition to aldehydes, proline-derived **21**, thiol benzylamine **20b**, and β-amino thiol **112** show the most promise (Figure 1.19). The amino thiol ligand **20b** has demonstrated a positive NLE and remains the optimal ligand investigated thus far. The amino alcohol ligand **21** shows an unusual dependence on ligand ee% and loading, but it offers an attractive alternative due to its ease of synthesis and inherent stability. Ligand **112** represents a new β-amino thiol scaffold that was found to be effective in the alkenylzirconium/zinc addition process. In comparison to thiol benzylamine **20b**, β-amino thiol **112** shows comparable enantioselectivity at a lower ligand loading of 5 mol%. Proline-based **21** and β-amino thiol **112** can potentially increase the asymmetric induction in substrates where ligand **20b** has been shown to be mediocre.

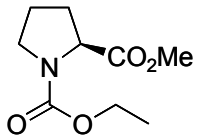


21 **20b** **112**

Figure 1.19. Ligands effective in the asymmetric alkenylzirconium/zinc addition to aldehydes.

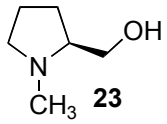
1.6 Experimental

General: All moisture-sensitive reactions were performed under an atmosphere of N_2. Glassware was dried in an oven at 140 ºC prior to use. THF and Et_2O were dried by distillation over Na/benzophenone. CH_2Cl_2 was purified by filtration through activated alumina. Me_2Zn was purchased from the Aldrich Chemical Company and Cp_2ZrHCl was prepared according to a modification of a literature protocol.[69] Unless otherwise stated, solvents and reagents were used as received. Analytical thin layer choromatography was performed on pre-coated silica gel 60 F-254 plates (particle size 0.040-0.055 mm, 230-400 mesh) and visualization was accomplished with a 254 nm UV light or by staining with an anisaldehyde solution (7.5 mL of *p*-anisaldehyde, 25 mL of concentrated H_2SO_4 and 7.5 mL of glacial acetic acid in 675 mL of 95% ethanol) or a $KMnO_4$ solution (1.5 g of $KMnO_4$, 10 g of potassium carbonate and 2.5 mL of 5% aqueous NaOH in 150 mL of H_2O). Flash chromatography on SiO_2 was used to separate and purify the crude reaction mixtures. NMR spectra were recorded at 300 MHz/75 MHz (^{1}H NMR/^{13}C NMR) at 21 ºC in $CDCl_3$ unless otherwise noted. Chemical shifts (δ) are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, sx=sextet, sp=septet, o=octet, dt=doublet of triplet, dq=doublet of quartet, m=multiplet, b=broad), integration, and coupling constants. Mass spectra were obtained on a double focusing instrument. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at T= 25 ºC. IR spectra obtained on a Nicolet AVATAR 360 FT-IR E.S.P. Spectrometer. Chiral HPLC analysis was performed on a Dynamax SD-200 delivery system in conjunction with a Dynamax UV-1 absorbance detector or PL-ELS 1000 detector. A Chiralcel OD (0.46 cm x 2.5 cm) or AD-H (0.46 cm x 25 cm) column was used for analytical separation, and a Chiralcel AD-H (2 cm x 25 cm) column for semi-preparative separations.



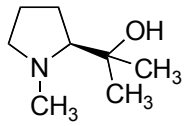
22

***N*-Ethoxycarbonyl-*L*-proline methyl ester (22).**[70] To a solution of 2.50 g (21.7 mmol) of *L*-proline and 3.00 g (21.7 mmol) of K_2CO_3 in 40 mL of MeOH at 0 ºC was added 4.48 mL (46.9 mmol) of ethyl chloroformate over 10 min. The resulting solution was stirred for 15 h at room temperature, concentrated *in vacuo,* diluted with 30 mL of H_2O, and extracted with 25 mL of $CHCl_3$ (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield 4.47 g (90%) of **22** as a clear, oily mixture of rotamers (1:1) that was used without further purification: $[\alpha]_D^{25}$ -59.1 (*c* 1.0, $CHCl_3$); lit.[70] $[\alpha]_D^{25}$ -60.3 (*c* 1.3, $CHCl_3$); ^{1}H NMR δ 4.36-4.26 (m, 1 H), 4.21-3.99 (m, 2 H), 3.72 (s, 1.5 H), 3.70 (s, 1.5 H), 3.62-3.52 (m, 1 H), 3.52-3.40 (m, 1 H), 2.26-2.11 (m, 1 H), 2.04-1.80 (m, 3 H), 1.25 (t, 1.5 H, *J* = 7.1 Hz), 1.18 (t, 1.5 H, *J* = 7.1 Hz); MS (EI) *m/z* (rel intensity) 201 (M^+, 19), 142 (100), 128 (20), 114 (13).



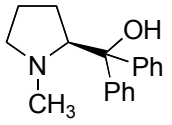
23

(*S*)-1-Methyl-2-pyrrolidinemethanol (23). To a solution of 2.00 g (9.94 mmol) of **22** in 20 mL of THF at 0 ºC was added 1.13 g (29.8 mmol) of $LiAlH_4$. The reaction mixture was heated at reflux for 4 h, cooled to 0 ºC, quenched with H_2O, acidified to pH 3 with 1 N HCl, diluted with Et_2O, and filtered through a plug of celite. The celite was washed with EtOAc and the organic layer was separated. The aqueous layer was re-extracted with CH_2Cl_2 (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (20% EtOAc/Hexanes) to yield 1.05 g (72%) of **23** as a colorless oil: $[\alpha]_D^{25}$ -49.0 (*c* 1.0, $CHCl_3$); lit.[70] $[\alpha]_D^{25}$ -49.5 (*c* 5.0, CH_3OH); ^{1}H NMR δ 3.62 (dd, 1 H, *J* = 3.5, 10.8 Hz), 3.48-3.39 (m, 1 H), 3.12-3.00 (m, 1 H), 2.30-2.18 (m, 3 H), 2.31 (s, 3 H), 1.95-1.75 (m, 2 H), 1.74-1.60 (m, 2 H); MS (EI) *m/z* (rel intensity) 115 (M^+, 26), 84 (100).



24

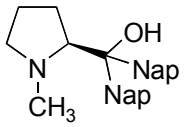
(*S*)-(+)-Dimethyl(1-methylpyrrolidin-2-yl)methanol (24).[71] To a solution of 9.71 g (48.3 mmol) of **22** in 60 mL of THF at 0 ºC was added 64.0 mL (193 mmol) of a 3 M solution of methyl magnesium bromide in THF. The reaction mixture was stirred for 4 h at 0 ºC, quenched with NH_4Cl, and extracted with $CHCl_3$ (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield an orange oil. This oil was used in the subsequent step without further purification. A solution of the oil in 75 mL of THF at 0 ºC was treated portionwise with 3.60 g (43.9 mmol) of $LiAlH_4$, heated at reflux for 3 h, cooled to 0 ºC, quenched with H_2O, acidified to pH 3 with 1 N HCl, diluted with Et_2O, and filtered through a plug of celite. The celite was washed with EtOAc and the organic layer was separated. The aqueous layer was re-extracted with CH_2Cl_2 (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (20% EtOAc/Hexanes) to yield 4.64 g (67%) of **24** as a slightly orange oil: $[\alpha]_D^{25}$ +6.7 (*c* 0.15, $CHCl_3$); lit.[71] $[\alpha]_D^{25}$ -5.8 (*R*) (*c* 0.4, $CHCl_3$); ^{1}H NMR δ 3.07-2.99 (m, 1 H), 2.47 (s, 3 H), 2.45-2.30 (m, 2 H), 1.87 -1.73 (m, 1 H), 1.74-1.62 (m, 3 H), 1.17 (s, 3 H), 1.08 (s, 3 H); MS (EI) *m/z* (rel intensity) 145 (M^+, 11), 128 (14), 84 (100).



21

(*S*)-(+)-Diphenyl(1-methylpyrrolidin-2-yl)methanol (21).[72] To a solution of 4.47 g (21.9 mmol) of **22** in 30 mL of THF at 0 ºC was added 87.8 mL (87.8 mmol) of 1 M phenyl magnesium bromide in THF. The reaction mixture was stirred for 4 h at 0 ºC, quenched with NH_4Cl, and extracted with $CHCl_3$ (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield 8.50 g of an orange oil. This oil was used in the subsequent step without further purification. A solution of the oil in 60 mL of THF at 0 ºC was treated portionwise with 1.60 g (43.9 mmol) of $LiAlH_4$, heated at reflux for 3 h, cooled to 0 ºC, quenched with H_2O, acidified to pH 3 with 1 N HCl, diluted with Et_2O, and filtered through a

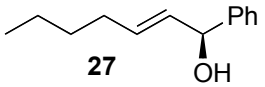
plug of celite. The celite washed with EtOAc and the organic layer was separated. The aqueous layer was re-extracted with CH_2Cl_2 (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (20% EtOAc/Hexanes), and further purified by Kugelrohr distillation at 180 ºC (0.1 Torr) to yield 4.40 g (75%) of **21** as a beige solid: Mp 64-66 ºC (EtOAc/Hexanes, lit. 68.5-68.9); $[\alpha]_D^{25}$ +53.4 (*c* 0.9, $CHCl_3$); lit.[72] $[\alpha]_D^{23}$ +57.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.80-7.70 (m, 2 H), 7.62-7.52 (m, 2 H), 7.48-7.30 (m, 4 H), 7.25-7.12 (m, 2 H), 4.88 (bs, 1 H), 3.70 (dd, 1 H, *J* = 5.2, 9.5 Hz), 3.22-3.18 (m, 1 H), 2.60-2.45 (m, 1 H), 2.00-1.90 (m, 1 H), 1.91 (s, 3 H), 1.85-1.75 (m, 1 H); MS (EI) *m/z* (rel intensity) 268 (M^+, 7), 249 (14), 190 (27), 181 (129), 165 (27), 152 (22), 105 (17).



25

(*S*)-(+)-Dinaphthyl(1-methylpyrrolidin-2-yl)methanol (25). To a solution of 1.26 g (6.26 mmol) of **22** in 35 mL of THF at 0 ºC was added 50.0 mL (25.0 mmol) of a 0.5 M solution of 2-naphthyl magnesium bromide in THF. The reaction mixture was stirred for 4 h at 0 ºC, quenched with NH_4Cl, extracted with $CHCl_3$ (3x), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield 2.00 g of an orange oil. This oil was used in the subsequent step without further purification. A solution of the oil in 50 mL of THF at 0 ºC was treated portionwise with 0.360 g (9.40 mmol) of $LiAlH_4$, heated at reflux for 4 h, cooled to 0 ºC, quenched with H_2O, acidified to pH 3 with 1 N HCl, diluted with Et_2O, and filtered through a plug of celite. The celite was washed with EtOAc and the organic layer was separated. The aqueous layer was re-extracted with CH_2Cl_2 (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was precipitated from 50% EtOAc/Hexanes to give 2.00 g (87%) of off-white solid **25**: Mp 202-204 ºC (EtOAc/Hexanes); $[\alpha]_D^{25}$ +65.2 (*c* 1.0, $CHCl_3$); IR (KBr) 3525, 3008, 2900, 1210, 1071, 935 cm^{-1}; ^{1}H NMR δ 8.24 (s, 1 H), 8.11 (s, 1 H), 7.82 (td, 2 H, *J* = 1.4, 7.3 Hz), 7.76-7.66 (m, 6 H), 7.46-7.33 (m, 4 H), 3.87 (dd, 1 H, *J* = 4.4 Hz, 9.2 Hz), 3.19-3.09 (m, 1 H), 2.47 (td, 1 H, *J* = 6.8, 9.8 Hz), 2.06-1.92 (m, 1 H), 1.83 (s, 3 H), 1.82-1.59 (m, 3 H); ^{13}C NMR δ 135.7, 133.3, 132.1, 128.3, 127.7, 127.4, 125.9, 125.6, 124.5, 124.5, 124.3,

124.0, 58.9, 43.2, 30.0, 24.1; MS (EI) *m/z* (rel intensity) 349 ($[M-H_2O]^+$, 30), 282 (28), 252 (8), 155 (20), 127 (21); HRMS (EI) Calcd for $C_{26}H_{23}N$ (M-H_2O) 349.1831, found 349.1819.



27

General Protocol for formation of allylic alcohol, (*S*)-1-Phenylhept-2-en-1-ol (27) using 15 mol% of ligand 21. To a suspension of 500 mg (1.93 mmol) of zirconocene hydrochloride in 4 mL of CH_2Cl_2 under N_2 was added 175 µL (1.52 mmol) of 1-hexyne at room temperature. After 5 min, an additional 80 µL (0.70 mmol) of 1-hexyne was added. The reaction mixture was stirred for an additional 10 min, and the solution was concentrated in *vacuo*. To a solution of the resulting orange oil in 4 mL of toluene at -65 ºC was added 650 µL (1.29 mmol) of Me_2Zn (2.0 M solution in toluene). After 10 min, 52 mg (0.19 mmol) of ligand **21** was added. The reaction mixture was then warmed to -30 ºC over a period of 1 h, and 134 µL (1.29 mmol) of freshly distilled benzaldehyde was added. The solution was stirred for 15 h at -30 ºC, quenched by addition of $NaHCO_3$ solution, filtered through a plug of florisil and extracted with EtOAc. The organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (10% EtOAc/Hexanes) to yield 190 mg (80%) of **27** as a colorless oil. The enantiomeric excess was determined using chiral HPLC (Chiralcel OD) using 1% *i*-PrOH/hexane at a flow rate of 1 mL/min (R_t minor = 18.1 min, R_t major = 26.8 min) with a Dynamax UV-1 absorbance detector: ^{1}H NMR δ 7.37-7.22 (m, 5 H), 5.70 (dt, 1 H, *J* = 6.2, 15.3 Hz), 5.61 (dd, 1 H, *J* = 6.5, 15.4 Hz), 5.13 (d, 1 H, *J* = 6.3 Hz), 2.10-2.00 (m, 2 H), 1.83 (bs, 1 H), 1.41-1.24 (m, 4 H), 0.85 (t, 3 H, *J* = 6.8 Hz).

(*S*)-1-Phenylhept-2-en-1-ol (27) using 10 mol% of ligand 23. According to the general protocol, 500 mg (1.93 mmol) of zirconocene hydrochloride, 175 µL (1.52 mmol) of 1-hexyne, 650 µL (1.29 mmol) of Me_2Zn (2.0 M solution in toluene), 15 mg (0.13 mmol) of ligand **23**, and 134 µL (1.29 mmol) of freshly distilled benzaldehyde provided 197 mg (79%) of **27** with an ee of 17%.[73]

(*S*)-1-Phenylhept-2-en-1-ol (27) using 15 mol% of ligand 23. According to the general protocol, 500 mg (1.93 mmol) of zirconocene hydrochloride, 175 µL (1.52 mmol) of 1-hexyne,

650 μL (1.29 mmol) of Me_2Zn (2.0 M solution in toluene), 22 mg (0.19 mmol) of ligand **23**, and 134 μL (1.29 mmol) of freshly distilled benzaldehyde provided 195 mg (78%) of **27** with an ee of 18%.

(*S*)-1-Phenylhept-2-en-1-ol (27) using 10 mol% of ligand 24. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 μL (0.76 mmol) of 1-hexyne, 325 μL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 9.2 mg (0.06 mmol) of ligand **24**, and 66 μL (0.65 mmol) of freshly distilled benzaldehyde provided 105 mg (85%) of **27** with an ee of 17%.

(*S*)-1-Phenylhept-2-en-1-ol (27) using 15 mol% of ligand 24. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 μL (0.76 mmol) of 1-hexyne, 325 μL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 14 mg (0.09 mmol) of ligand **24**, and 66 μL (0.65 mmol) of freshly distilled benzaldehyde provided 96 mg (78%) of **27** with an ee of 17%.

(*S*)-1-Phenylhept-2-en-1-ol (27) using 10 mol% of ligand 21. According to the general protocol, 500 mg (1.93 mmol) of zirconocene hydrochloride, 175 μL (1.52 mmol) of 1-hexyne, 650 μL (1.29 mmol) of Me_2Zn (2.0 M solution in toluene), 43 mg (0.13 mmol) of ligand **21**, and 134 μL (1.29 mmol) of freshly distilled benzaldehyde provided 180 mg (73%) of **27** with an ee of 46%. Run 2 was conducted on the same scale to yield 190 mg (77%) of **27** with an ee of 35%.

(*S*)-1-Phenylhept-2-en-1-ol (27) using 15 mol% of ligand 21. According to the general protocol, 500 mg (1.93 mmol) of zirconocene hydrochloride, 175 μL (1.52 mmol) of 1-hexyne, 650 μL (1.29 mmol) of Me_2Zn (2.0 M solution in toluene), 63 mg (0.19 mmol) of ligand **21**, and 134 μL (1.29 mmol) of freshly distilled benzaldehyde provided 185 mg (76%) of **27** with an ee of 79%. Run 2 was conducted on the same scale to yield 180 mg (74%) of **27** with an ee of 83%.[73]

(*S*)-1-Phenylhept-2-en-1-ol (27) using 10 mol% of ligand 25. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 μL (0.76 mmol) of 1-hexyne,

325 μL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 22 mg (0.06 mmol) of ligand **25**, and 66 μL (0.65 mmol) of freshly distilled benzaldehyde provided 100 mg (81%) of **27** with an ee of 20%.

(*S*)-1-Phenylhept-2-en-1-ol (27) using 15 mol% of ligand 25. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 μL (0.76 mmol) of 1-hexyne, 325 μL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 33 mg (0.09 mmol) of ligand **25**, and 66 μL (0.65 mmol) of freshly distilled benzaldehyde provided 98 mg (80%) of **27** with an ee of 20%.

Chiral loading: (*S*)-1-Phenylhept-2-en-1-ol (27) using 5 mol% of ligand (*S*)-21: According to the general protocol, 510 mg (1.98 mmol) of zirconocene hydrochloride, 179 μL (1.55 mmol) of 1-hexyne, 660 μL (1.32 mmol) of Me_2Zn (2.0 M solution in toluene), 22 mg (0.08 mmol) of **(*S*)-21**, and 134 μL (1.32 mmol) of freshly distilled benzaldehyde provided 192 mg (75%) of **27** with an ee of 9%. The numerical value of each data point is listed below (Table 8).

Table 1.13. Enantioselective formation of **27** using ligand **21**.

ligand loading (mol%) of **(*S*)-21**	ee[73] (%) of **(*S*)-27**
0	0
5	9
10	41[a]
15	81[a]
20	60
30	66
40	68
50	53

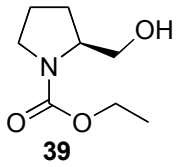
[a] At the specified chiral ligand loading, 2 runs were conducted and the average was reported.

Non-linear effect: (*S*)-1-Phenylhept-2-en-1-ol (27) using 15 mol% of ligand (*S*)-21 (65% ee): According to the general protocol, 500 mg (1.93 mmol) of zirconocene hydrochloride, 179 μL (1.54 mmol) of 1-hexyne, 660 μL (1.31 mmol) of Me_2Zn (2.0 M solution in toluene), 52 mg

(0.19 mmol) of **(*S*)-21** and 11 mg (0.04 mmol) of **(*R*)-21**, and 134 μL (1.29 mmol) of freshly distilled benzaldehyde provided 180 mg (74%) of **27** with an ee of 41%. Data points in Figure 1.13 are the average of 2 or 3 runs conducted at the specified %ee of ligand. The numerical value of each data point is listed below (Table 9).

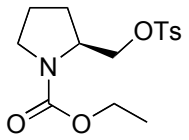
Table 1.14. Enantioselective formation of **27** using ligand **21** at 15 mol% loading**.**

ee (%) of **(*S*)-21**	ee[73] (%) of **27**
100	81 (S)
80	65 (S)
65	46 (S)
50	24 (S)
35	13 (R)
20	1.5 (R)
0	0



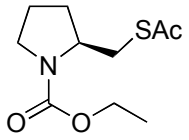
39

(*S*)-2-Hydroxymethylpyrrolidine-1-carboxylic acid ethyl ester (39).[74] To a solution of 3.50 g (15.2 mmol) of **22** in 100 mL of Et_2O at 0 ºC was added portionwise 421 mg (11.1 mmol) of $LiAlH_4$. The resulting slurry was stirred for 5 h at 0 ºC and quenched with EtOAc and 20% potassium hydroxide. The organic layer was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting 2.4 g (78%) of clear oil were found to contain a 6:1 mixture of **39** and **22** and used in subsequent steps without further purification. A portion of this crude oil was purified by chromatography on SiO_2 (10% EtOAc/Hexanes) to yield pure **39** for characterization purposes: ^{1}H NMR δ 4.16 (q, 2 H, J = 7.1 Hz), 4.05-3.95 (m, 1 H), 3.70-3.56 (m, 2 H), 3.55-3.47 (m, 1 H), 3.41-3.30 (m, 1 H), 2.10-1.98 (m, 1 H), 1.97-1.73 (m, 2 H), 1.70-1.50 (bs, 1 H), 1.28 (t, 3 H, J = 7.1 Hz); MS (EI) *m/z* (rel intensity) 173 (M^+, 2), 142 (88), 128 (12), 114 (14), 98 (38).



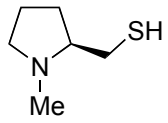
40

(*S*)-2-Toluene-4-sulfonyloxymethylpyrrolidine-1-carboxylic acid ethyl ester (40).[52] To a solution of 2.40 g (11.9 mmol) of a 6:1 mixture of **39** and **22** in 20 mL of pyridine at room temperature was added 3.17 g (16.6 mmol) of *p*-toluenesulfonyl chloride. The reaction mixture was stirred for 4 h, diluted with CH_2Cl_2, washed with 1 M HCl, $NaHCO_3$, and H_2O, dried ($MgSO_4$), filtered and concentrated *in vacuo.* Chromatography of the crude residue on SiO_2 (50% EtOAc/Hexanes) yielded 2.45 g (52%) of a 1:10 mixture of **22** and **40** as a clear oil. This mixture was used without further purification in subsequent steps. A sample of this mixture was re-purified by chromatography on SiO_2 (33% EtOAc/Hexanes) to yield pure **40** as a 1:1 mixture of rotamers for characterization purposes: ^{1}H NMR δ 7.77 (d, 2 H, *J* = 8.2 Hz), 7.38-7.30 (m, 2 H), 4.20-3.85 (m, 6 H), 3.45-3.25 (m, 2 H), 2.45 (s, 3 H), 2.05-1.86 (m, 3 H), 1.85-1.75 (m, 1 H), 1.22 (t, 1.5 H, *J* = 7.1 Hz), 1.13 (t, 1.5 H, *J* = 6.8 Hz); MS (EI) *m/z* (rel intensity) 327 (M^+, 9), 297 (17), 155 (12), 142 (100).



41

(*S*)-2-Acetylsulfanylmethylpyrrolidine-1-carboxylic acid ethylester (41). A solution of 2.45 g (6.79 mmol) of a 10:1 mixture of **40** and **22** in 50 mL of DMF was treated with 3.92 g (34.4 mmol) of potassium thioacetate. The resulting solution was heated at reflux for 1 h, diluted with H_2O, and extracted with CH_2Cl_2 (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo.* The resulting residue was purified by chromatography on SiO_2 (10% EtOAc/Hexanes) to yield 1.07 g (62%) of **41** as an orange, oily 2:1 mixture of rotamers: $[\alpha]_D^{25}$ +59.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 4.25-4.03 (m, 2 H), 3.93 (bs, 1 H), 3.38 (bs, 2 H), 3.19 (d, 1 H, *J* = 3.6 Hz), 2.32 (s, 3 H), 1.96-1.67 (m, 5 H), 1.25 (t, 3 H, *J* = 7.1 Hz); MS (EI) *m/z* (rel intensity) 232 (M^+, 7), 224 (43), 188 (27), 155 (25), 142 (100), 114 (14).

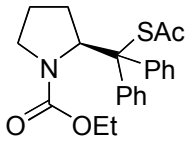


42

(*S*)-(1-Methylpyrrolidin-2-yl)-methanethiol (42). A solution of 1.07 g (4.62 mmol) of **41** in 40 mL of THF was added dropwise to a slurry of 1.07 g (20.8 mmol) of $LiAlH_4$ in 60 mL of THF. The resulting solution was heated at reflux for 8 h, cooled to 0 ºC, quenched with 1.3 mL of H_2O and 16 mL of 1 M HCl, dried ($MgSO_4$), filtered through celite, and concentrated *in vacuo.* The resulting oil was purified by chromatography on SiO_2 (10% EtOAc/Hexanes) to yield 151 mg (25%) of **42** as a clear oil: $[\alpha]_D^{25}$ -84.0 (*c* 0.5, $CHCl_3$); lit.[71] $[\alpha]_D^{20}$ -85.7 (*c* 0.9, $CHCl_3$); ^{1}H NMR δ 3.04 (t, 1 H, *J* = 9.4 Hz), 3.02 (dd, 1 H, *J* = 3.4, 12.9 Hz), 2.72 (dd, 1 H, *J* = 8.2, 12.9 Hz), 2.45-2.37 (m, 1 H), 2.36 (s, 3 H), 2.30-2.21 (m, 1 H), 2.10-1.90 (m, 1 H), 1.85-1.60 (m, 3 H).

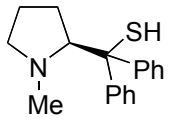
(*S*)-1-Phenylhept-2-en-1-ol (27) using 10 mol% of ligand 42. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 µL (0.76 mmol) of 1-hexyne, 325 µL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 7.9 mg (0.065 mmol) of ligand **42**, and 66 µL (0.65 mmol) of freshly distilled benzaldehyde provided 100 mg (81%) of **27** with an ee of 83%.

(*S*)-1-Phenylhept-2-en-1-ol (27) using 15 mol% of ligand 42. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 µL (0.76 mmol) of 1-hexyne, 325 µL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 12 mg (0.090 mmol) of ligand **42**, and 66 µL (0.65 mmol) of freshly distilled benzaldehyde provided 120 mg (98%) of **27** with an ee of 84%.



45a

(*S*)-2-(Acetylsulfanyldiphenylmethyl)-pyrrolidine-1-carboxylic acid ethyl ester (45a).[52] To 2.00 g (6.13 mmol) of **44** and 2.15 g (6.74 mmol) of ZnI_2 at 0 °C in 110 mL of dichloroethane was added 0.94 mL (13.3 mmol) of thiolacetic acid. The resulting reaction was stirred for 26 h, diluted with H_2O, extracted with CH_2Cl_2, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (100% Hexanes-30% EtOAc/Hexanes) to yield 700 mg (30%) of **45a** as white solid: Mp 136-140 °C (EtoAc/Hexanes); $[\alpha]_D^{25}$ –229.1.0 (*c* 0.5, $CHCl_3$); lit.[52] $[\alpha]_D^{25}$ –231.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.54 (d, 2 H, *J* = 7.5 Hz), 7.45-7.19 (m, 8 H), 5.74 (d, 1 H, *J* = 8.4 Hz), 4.30-3.90 (m, 2 H), 3.58-3.20 (bs, 1 H), 2.70 (dt, 1 H, *J* = 3.9, 10.2 Hz), 2.35-2.10 (m, 1 H), 2.14 (s, 3 H), 2.06-1.90 (m, 1 H), 1.45-1.18 (m, 5 H), 0.3-0.0 (bs, 1 H); MS (EI) *m/z* (rel intensity) 307 ([M-C_2H_3OS]$^+$, 15), 234 (11), 206 (10), 165 (11), 142 (100), 115 (7), 105 (25), 84 (25); HRMS (EI) Calcd for $C_{22}H_{25}NO_3S$-C_2H_3OS 307.1572, found 307.1569.



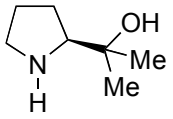
46

(*S*)-(1-Methylpyrrolidin-2-yl)diphenylmethanethiol (46).[52] To 225 mg (5.92 mmol) of $LiAlH_4$ in 14 mL of THF at 0 °C was added 650 mg (1.69 mmol) of **45** in 19 mL of THF. The reaction was heated at reflux for 7 h, cooled, quenched with 9 mL of H_2O, 4.5 mL of 1 N HCl, filtered through celite, washed with 50 mL of CH_2Cl_2, dried ($MgSO_4$), and concentrated in vacuo. The crude residue was purified by chromatography on neutral alumina (100% Hexanes) to yield 70 mg (15%) of **46** as a colorless oil: ^{1}H NMR δ 7.60-7.45 (m, 2 H), 7.40-7.30 (m, 2H), 7.29-7.15 (m, 6 H), 3.54 (dd, 1 H, *J* = 3.1, 9.1 Hz), 3.09 (t, 1 H, *J* = 7.5 Hz), 2.45-2.25 (m, 1 H), 2.22-2.05 (m, 2 H), 1.95-1.59 (m, 2 H), 1.63 (s, 3 H); MS (EI) *m/z* (rel intensity) 283 (M^+, 6), 250 (17), 220 (10), 198 (64), 182 (30), 165 (100), 152 (12), 121 (85), 115 (20); HRMS (EI) Calcd for $C_{18}H_{21}NO_1S$ 283.1395, found 283.1388.

(*S*)-1-Phenylhept-2-en-1-ol (27) using 5 mol% of ligand 46. According to the general protocol, 500 mg (1.93 mmol) of zirconocene hydrochloride, 175 µL (1.52 mmol) of 1-hexyne, 650 µL (1.29 mmol) of Me_2Zn (2.0 M solution in toluene), 18 mg (0.065 mmol) of ligand **46**,

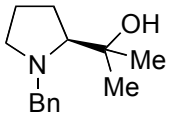
and 134 μL (1.29 mmol) of freshly distilled benzaldehyde provided 204 mg (83%) of **27** with an ee of 5%.

(*S*)-1-Phenylhept-2-en-1-ol (27) using 10 mol% of ligand 46. According to the general protocol, 500 mg (1.93 mmol) of zirconocene hydrochloride, 175 μL (1.52 mmol) of 1-hexyne, 650 μL (1.29 mmol) of Me_2Zn (2.0 M solution in toluene), 36 mg (0.13 mmol) of ligand **46**, and 134 μL (1.29 mmol) of freshly distilled benzaldehyde provided 197 mg (83%) of **27** with an ee of 18%.



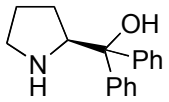
31

(*S*)-(+)-Dimethylpyrrolidin-2-yl-methanol (31).[75] To 2.00 g (9.94 mmol) of **22** in 30 mL of THF at 0 ºC was added 13.3 mL (39.8 mmol) of 3 M methyl magnesium bromide in Et_2O. The resulting reaction was stirred for 6 h at 0 ºC. The reaction was quenched with NH_4Cl, extracted with $CHCl_3$, washed with NaCl, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (100% Hexanes) to yield 1.5 g (68%) of ethyl carbamate as a colorless oil. To 700 mg (3.12 mmol) of the resulting oil in 6.25 mL of MeOH was added 1.75 g (3.12 mmol) of KOH. The reaction was heated at reflux for 4 h, cooled, and concentrated *in vacuo* to remove MeOH. The resulting residue was dissolved in H_2O, extracted with $CHCl_3$, washed with NaCl, dried ($MgSO_4$), and concentrated *in vacuo* to yield 550 mg (63%) of **31** as an orange oil. The crude material was used without purification in the next step: $[\alpha]_D^{25}$ –14.2 (*c* 0.5, $CHCl_3$); lit.[76] $[\alpha]_D^{25}$ –16.6 (*c* 0.57, CH_2Cl_2); ^{1}H NMR δ 3.64 (dt, 1 H, *J* = 7.8, 11.1 Hz), 3.51 (dd, 1 H, *J* = 5.4, 10.5 Hz), 3.19 (ddd, 1 H, *J* = 3.3, 9.0, 11.4 Hz), 2.14-2.04 (m, 1 H), 1.95-1.86 (m, 1 H), 1.85-1.74 (m, 1 H), 1.70-1.58 (m, 1 H), 1.55 (s, 3 H), 1.39 (s, 3 H); MS (EI) *m/z* (rel intensity) 155 (7), 142 (12), 113 (12), 110(24), 96 (20), 91 (39), 82 (66), 69 (100), 63 (9), 53 (48).



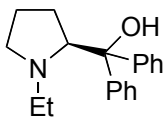
32

(S)-(+)-2-(1-Benzylpyrrolidin-2-yl)propan-2-ol (32).[78] To 550 mg (3.6 mmol) of **31** in 30 mL of toluene was added 0.47 mL (4.0 mmol) of diisopropylethylamine and 1.6 mL (9.0 mmol) of benzyl bromide. The solution was heated at 110 ºC for 4 h, cooled, quenched with $NaHCO_3$, extracted with EtOAc, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (75% EtOAc/Hexanes) to yield 450 mg (59 %) of **32** as a colorless oil: $[\alpha]_D^{25}$ –39.2 (*c* 0.5, $CHCl_3$); lit.[76] $[\alpha]_D^{25}$ –40.2 (*c* 2.45, CH_2Cl_2); ^{1}H NMR δ 7.47-7.10 (m, 5 H), 4.15 (d, 1 H, *J* = 13.9 Hz), 3.60 (d, 1 H, *J* = 13.9 Hz), 2.94-2.85 (m, 1 H), 2.80-2.72 (m, 1 H), 2.67 (s, 1 H), 2.48 –2.30 (m, 1 H), 1.97-1.63 (m, 4 H), 1.27 (s, 3 H), 1.18 (s, 3 H); MS (EI) *m/z* (rel intensity) 294 (5), 210 (M^+, 90), 181 (19), 160 (18), 106 (19), 91 (100).



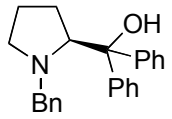
28

(*S*)-(+)-Diphenylpyrrolidin-2-yl-methanol (28).[77] To 2.00 g (9.94 mmol) of **22** in 25 mL of THF at ºC was added 13.3 mL (39.8 mmol) of 3 M phenyl magnesium bromide in Et_2O. The reaction mixture was stirred for 3 h at 0 ºC, quenched with NH_4Cl, extracted with $CHCl_3$, washed with NaCl, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield 2.30 g of ethyl carbamate as an off white solid. The crude material was used without purification in the next step. To 2.30 g of crude ethylcarbamate in 20 mL of MeOH was added 5.6 g (10 mmol) of KOH. The reaction was heated at reflux for 4 h, cooled, and concentrated *in vacuo* to remove MeOH. The resulting residue was dissolved in H_2O, extracted with $CHCl_3$, washed with NaCl, dried ($MgSO_4$), and concentrated *in vacuo* to yield 1.60 g (63%) of **28** as off white solid: Mp 75-78 °C ($CHCl_3$); $[\alpha]_D^{25}$ –71.0 (*c* 0.5, $CHCl_3$); lit.[77] $[\alpha]_D^{25}$ –68.1 (*c* 3.17, CH_3OH); ^{1}H NMR δ 7.58 (s, 2 H, *J* = 7.2 Hz), 7.50 (d, 2 H, *J* = 7.5 Hz), 7.34-7.20 (m, 4 H), 7.20-7.12 (m, 2 H), 4.27 (t, 1 H, *J* = 7.8 Hz), 3.10-3.88 (m, 2 H), 1.81-1.50 (m, 4 H); MS (EI) *m/z* (rel intensity) 254 (M^+, 42), 234 (64), 206 (61), 191 (11), 165 (15), 152 (7), 105 (17), 77 (20), 70 (100).



29

(S)-(+)-(1-Ethylpyrrolidin-2-yl)-diphenylmethanol (29).[48] To 500 mg (1.98 mmol) of **28** in 15 mL of toluene at rt was added 0.86 mL (4.94 mmol) of diisopropylethylamine and 0.16 mL (2.17 mmol) of ethylbromide. The solution was heated at 120 ºC for 24 h, cooled, quenched with $NaHCO_3$, extracted with EtOAc, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (20% EtOAc/Hexanes) to yield 80 mg (14%) of **29** as a white solid: Mp 77-80 °C (EtOAc/Hexanes, lit.[48] 78-79 °C; $[\alpha]_D^{25}$ +6.1 (*c* 0.5, $CHCl_3$); lit.[48] $[\alpha]_D^{25}$ +6.3 (*c* 0.64, CH_2Cl_2); ^{1}H NMR δ 7.65-7.59 (m, 2 H), 7.58-7.52 (m, 2 H), 7.32-7.21 (m, 4 H), 7.20-7.10 (m, 2 H), 5.15-4.80 (bs, 1 H), 3.79 (dd, 1 H, *J* = 4.2, 9.1 Hz), 3.28-3.20 (m, 1 H), 2.42-2.34 (m, 1 H), 2.10-1.80 (m, 3 H), 1.80-1.60 (m, 3 H), 0.80 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR δ 146.6, 128.0, 127.9, 126.1, 125.7, 125.5, 70.7, 54.6, 49.8, 29.7, 24.3, 13.5; MS (EI) *m/z* (rel intensity) 305 (5), 282 (M^+, 6), 272 (8), 263 (25), 204 (45), 182 (24), 165 (30), 98 (100); HRMS (EI) Calcd for $C_{19}H_{23}NO$ (M-C_6H_5) 344.2000, found 344.2014.



30

(S)-(+)-(1-Benzylpyrrolidin-2-yl)-diphenylmethanol (30).[75] To 400 mg (1.58 mmol) of **28** in 15 mL of toluene was added 0.69 mL (3.95 mmol) of diisopropylethylamine and 0.21 mL (1.74 mmol) of benzylbromide. The solution was heated at 110 ºC for 4 h, cooled, quenched with $NaHCO_3$, extracted with EtOAc, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (100% Hexanes) to yield 300 mg (55%) of **30** as a white solid: Mp 120-124 °C (Hexanes, lit.[78] 120-122 °C); $[\alpha]_D^{25}$ (*c* 0.5, $CHCl_3$); lit.[78] $[\alpha]_D^{25}$ (*c*, CH_3OH); ^{1}H NMR δ 7.74 (d, 2 H, *J* = 8.1 Hz), 7.59 (d, 2 H, *J* = 7.8 Hz), 7.36-7.00 (m, 11 H), 4.95 (bs, 1 H), 3.99 (dd, 1 H, *J* = 4.5, 9.3 Hz), 3.24 (A of AB, 1 H, *J* = 12.6 Hz), 3.04 (B of AB, 1 H, *J* = 12.6 Hz), 2.92 (p, 1 H, *J* = 4.2 Hz), 2.37 (q, 1 H, *J* = 9.3 Hz), 2.08-1.90 (m, 1 H), 1.85-1.70 (m, 1 H), 1.70-1.56 (m, 3 H); ^{13}C NMR δ 148.0, 246.7, 139.7, 128.6, 128.2, 128.1, 128.1, 126.8, 126.4, 126.2, 125.6, 125.6, 70.7, 60.6, 55.5, 29.8, 24.2; MS (EI) *m/z* (rel intensity) 325 ([M-OH]$^+$, 7), 167 (10), 160 (100), 105 (15), 91 (73); HRMS (EI) Calcd for $C_{24}H_{25}NO$ 344.2000, found 344.2014.

(*S*)-1-Phenylhept-2-en-1-ol (27) using 10 mol% of ligand 29. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 μL (0.76 mmol) of 1-hexyne, 325 μL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 18 mg (0.065 mmol) of ligand **29**, and 66 μL (0.65 mmol) of freshly distilled benzaldehyde provided 101 mg (82%) of **27** with an ee of 3%.

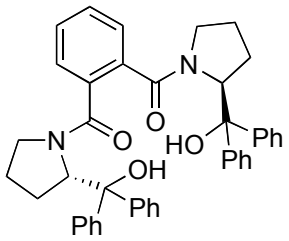
(*S*)-1-Phenylhept-2-en-1-ol (27) using 15 mol% of ligand 29. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 μL (0.76 mmol) of 1-hexyne, 325 μL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 27 mg (0.098 mmol) of ligand **29**, and 66 μL (0.65 mmol) of freshly distilled benzaldehyde provided 102 mg (83%) of **27** with an ee of 13%.[73]

(*S*)-1-Phenylhept-2-en-1-ol (27) using 10 mol% of ligand 30. According to the general protocol, 300 mg (1.16 mmol) of zirconocene hydrochloride, 105 μL (0.78 mmol) of 1-hexyne, 388 μL (0.78 mmol) of Me_2Zn (2.0 M solution in toluene), 27 mg (0.078 mmol) of ligand **30**, and 79 μL (0.78 mmol) of freshly distilled benzaldehyde provided 114 mg (76%) of **27** with an ee of 4%.

(*S*)-1-Phenylhept-2-en-1-ol (27) using 15 mol% of ligand 30. According to the general protocol, 300 mg (1.16 mmol) of zirconocene hydrochloride, 105 μL (0.78 mmol) of 1-hexyne, 388 μL (0.78 mmol) of Me_2Zn (2.0 M solution in toluene), 40 mg (0.116 mmol) of ligand **30**, and 79 μL (0.78 mmol) of freshly distilled benzaldehyde provided 117 mg (78%) of **27** with an ee of 6%.

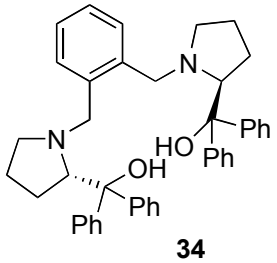
(*S*)-1-Phenylhept-2-en-1-ol (27) using 5 mol% of ligand 32. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 μL (0.76 mmol) of 1-hexyne, 325 μL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 14 mg (0.033 mmol) of ligand **32**, and 66 μL (0.65 mmol) of freshly distilled benzaldehyde provided 98 mg (79%) of **27** with an ee of 20%.[73]

(*S*)-1-Phenylhept-2-en-1-ol (27) using 10 mol% of ligand 32. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 μL (0.76 mmol) of 1-hexyne, 325 μL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 27 mg (0.065 mmol) of ligand **32**, and 66 μL (0.65 mmol) of freshly distilled benzaldehyde provided 96 mg (78%) of **27** with an ee of 4%.



33

***N,N*'-Phthaloyl-bis-((*S*)-2-(1-hydroxy-1,1-diphenylmethyl)pyrolidine) (33).**[48] To 0.51 mL (3.62 mmol) of phthaloyl chloride in 1 mL of benzene was added 360 mg (1.42 mmol) of **28** in 3 mL of benzene. The resulting solution was stirred for 4 h at rt, filtered through celite, washed with Et_2O, $NaHCO_3$, NaCl, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (25% EtoAc/Hexanes) to yield 270 mg (60%) of **33** as a white solid: Mp 114-117 °C (EtOAc/Hexanes, lit.[48] 114-116 °C); $[\alpha]_D^{25}$ +12.9 (*c* 0.5, $CHCl_3$); lit.[48] $[\alpha]_D^{25}$ +13.6 (*c* 1.00, CH_2Cl_2); ^{1}H NMR δ 7.62-7.23 (m, 24 H), 6.95 (s, 2 H), 6.71 (dd, 2 H, *J* = 3.9, 6.7 Hz), 3.76 (t, 2 H, *J* = 6.0 Hz), 3.28 (t, 2 H, *J* = 7.8 Hz), 2.80-2.65 (m, 2 H), 2.30-2.14 (m, 2 H), 2.04-1.80 (m, 2 H), 1.79-1.46 (m, 2H), 1.45-1.30 (m, 2 H); HRMS (EI) Calcd for $C_{42}H_{40}N_2O_4$ (M+Na) 659.2886, found 659.2863.

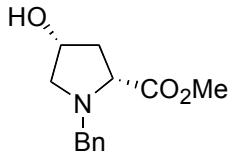


34

N,N'-α,α'-*o*-Xylene-bis-((*S*)-2-(1-hydroxy-1,1-diphenylmethyl)pyrrolidine) (34).[48] To 250 mg (0.39 mmol) of **33** in 9 mL of THF at 0 °C was added 61 mg (1.61 mmol) of $LiAlH_4$ portionwise. The gray slurry was heated at reflux for 2 h, quenched with H_2O, filtered, filtrate washed with EtOAc, washed with NaCl, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (25% EtoAc/Hexanes) to yield 148 mg (62%) of **34** as a white solid: Mp 112-113 °C (EtOAc/Hexanes, lit.[48] 110-112 °C); $[\alpha]_D^{25}$ +5.1 (*c* 0.5, $CHCl_3$); lit.[48] $[\alpha]_D^{25}$ +4.5 (*c* 0.53, CH_2Cl_2); ^{1}H NMR δ 7.67 (d, 4 H, *J* = 7.5 Hz), 7.58 (d, 4 H, *J* = 7.2 Hz), 7.40-7.05 (m, 10 H), 3.97 (dd, 2 H, *J* = 4.5, 9.0 Hz), 3.05 (A of AB, 2 H, *J* = 13.5 Hz), 2.95 (B of AB, 2 H, *J* = 13.2 Hz), 2.78-2.68 (m, 2 H), 2.37 (s, 2 H), 2.22 (q, 2 H, *J* = 8.4 Hz), 2.07-1.90 (m, 2 H), 1.80-1.45 (m, 4 H); MS (EI) *m/z* (rel intensity) 711 (23), 609 (M^+, 100), 458 (27), 356 (30), 236 (28), 167 (20).

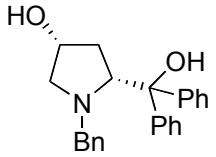
(*S*)-1-Phenylhept-2-en-1-ol (27) using 5 mol% of ligand 34. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 μL (0.76 mmol) of 1-hexyne, 325 μL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 19 mg (0.033 mmol) of ligand **34**, and 66 μL (0.65 mmol) of freshly distilled benzaldehyde provided 97 mg (78%) of **27** with an ee of 2%.[73]

(*S*)-1-Phenylhept-2-en-1-ol (27) using 10 mol% of ligand 34. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 μL (0.76 mmol) of 1-hexyne, 325 μL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 39 mg (0.065 mmol) of ligand **34**, and 66 μL (0.65 mmol) of freshly distilled benzaldehyde provided 91 mg (73%) of **27** with an ee of 4%.



37

1-Benzyl-4-hydroxypyrrolidine-2-carboxylic acid methyl ester (37).[49] To 1.00 g (7.62 mmol) of *cis*-4-hydroxy-D-proline in 7.64 mL of MeOH was added 0.56 mL (7.62 mmol) of thionyl chloride at 0 ºC. The reaction was heated at reflux for 4.5 h, cooled, and concentrated *in vacuo* to yield 1.10 g (100%) of **36** as a white solid. The crude material was used without purification in the next step. To 1.00 g (6.89 mmol) of **36** in 7 mL of toluene was added 3.00 mL (17.2 mmol) of diisopropylethylamine and 0.91 mL (7.58 mmol) of benzylbromide. The solution was heated at 110 ºC for 6 h, cooled, quenched with $NaHCO_3$, extracted with EtOAc, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (50% EtOAc/Hexanes) to yield 1.1 g (62%) of **37** as an orange/brown oil: $[\alpha]_D^{25}$ +90.0 (*c* 0.5, $CHCl_3$); lit. $[\alpha]_D^{25}$ +92.5 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 7.40-7.20 (m, 2 H), 4.32-4.24 (m, 1 H), 3.91 (A of AB, 1 H, *J* = 13.1 Hz), 3.75 (B of AB, 1 H, *J* = 13.1 Hz), 3.65 (s, 3 H), 3.38 (dd, 1 H, *J* = 3.9, 10.0 Hz), 3.21 (bd, 1 H, *J* = 10.1 Hz), 3.06 (d, 1 H, *J* = 9.9 Hz), 2.67 (dd, 1 H, *J* = 3.9, 9.8 Hz), 2.30-2.50 (m, 1 H), 1.93-2.03 (m, 1 H); MS (EI) *m/z* (rel intensity) 258 (6), 235 (M^+, 45), 215 (47), 176 (85), 91 (99), 65 (19); HRMS (EI) Calcd for $C_{13}H_{17}NO_3$ 235.1219, found 235.1208.



38

1-Benzyl-5-(hydroxydiphenylmethyl)pyrrolidin-3-ol (38).[49] 1.00 g (4.25 mmol) of **37** in 12 mL of THF at 0 ºC was added 5.67 mL (17.0 mmol) of a 3 M solution of phenyl magnesium bromide in Et_2O. The resulting reaction was stirred for 3 h at 0 ºC, quenched with $NaHCO_3$, extracted with EtOAc, dried ($MgSO_4$), filtered, and concentrated *in vacuo.* The resulting crude residue was purified by chromatography on SiO_2 (100% Hexanes) to yield 700 mg (46%) of **38** as off white solid: Mp 126-128 °C (Hexanes, lit.[79] 127-130°C); $[\alpha]_D^{25}$ +128.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 7.74 (d, 2 H, *J* = 7.5 Hz), 7.56 (d, 2 H, *J* = 7.5 Hz), 7.40-7.10 (m, 9 H), 7.01 (d, 2 H, *J* =

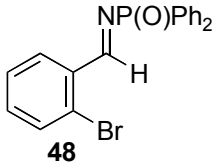
6.3 Hz), 4.16 (dd, 1 H, *J* = 3.0, 10.5 Hz), 4.14-4.05 (m, 1 H), 3.27 (A of AB, 1 H, *J* = 12.6 Hz), 3.05 (B of AB, 1 H, *J* = 12.6 Hz), 3.00 (d, 1 H, *J* = 10.5 Hz), 2.49 (dd, 1 H, *J* = 3.6, 10.2 Hz), 2.40 (ddd, 1 H, *J* = 6.0, 10.5, 16.5 Hz), 1.76 (d, 1 H, *J* = 15 Hz), 1.57 (bs, 1 H); MS (EI) *m/z* (rel intensity) 358 (M^+, 7), 341 (22), 232 (14), 246 (8), 176 (100), 159(12), 105 (26).

(*S*)-1-Phenylhept-2-en-1-ol (27) using 10 mol% of ligand 38. According to the general protocol, 500 mg (1.93 mmol) of zirconocene hydrochloride, 175 µL (1.52 mmol) of 1-hexyne, 650 µL (1.29 mmol) of Me_2Zn (2.0 M solution in toluene), 46 mg (0.13 mmol) of ligand **38**, and 134 µL (1.29 mmol) of freshly distilled benzaldehyde provided 186 mg (76%) of **27** with an ee of 9%.

(*S*)-1-Phenylhept-2-en-1-ol (27) using 20 mol% of ligand 38. According to the general protocol, 500 mg (1.93 mmol) of zirconocene hydrochloride, 175 µL (1.52 mmol) of 1-hexyne, 650 µL (1.29 mmol) of Me_2Zn (2.0 M solution in toluene), 93 mg (0.26 mmol) of ligand **38**, and 134 µL (1.29 mmol) of freshly distilled benzaldehyde provided 208 mg (85%) of **27** with an ee of 21%.[73]

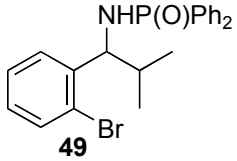
$Ph_2P(O)NH_2$

***P,P*-Diphenylphosphinamide.**[80] A solution of 20.0 g (84.6 mmol) of diphenylphosphinyl chloride in 150 mL of CH_2Cl_2 was cooled to -78 ºC, treated with ~50.0 g (3.0 mmol) of liquid ammonia, warmed to room temperature and stirred for 16 h, diluted with $CHCl_3$, filtered, and concentrated *in vacuo.* The resulting solid residue was recrystalized from toluene to yield 15.5 g (84%) of **63** as a white solid: Mp 164-165 ºC (toluene, lit.[81] 164-166 ºC); ^{1}H NMR δ 8.00-7.80 (m, 4 H), 7.55-7.35 (m, 6 H), 3.55 (bs, 2 H); MS (EI) *m/z* (rel intensity) 216 (M^+, 100), 199 (82), 140 (57), 124 (67).



48

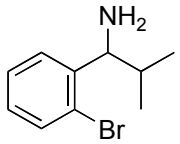
2-Bromo-*P*,*P*-diphenylphosphinamide (48). A suspension of 3.00 g (13.9 mmol) of *o*-bromobenaldehyde, 2.51 g (21.5 mmol) of *P,P*-Diphenylphosphinamide, and 5.75 mL (41.3 mmol) of triethylamine in 50 mL of CH_2Cl_2 was cooled to 0 ºC, treated dropwise with a solution of 832 µL (7.55 mmol) of $TiCl_4$ in 10 mL of CH_2Cl_2 over 30 min, gradually warmed to room temperature and stirred for 8 h. The reaction mixture was poured into 150 mL of Et_2O, stirred for 5 min, filtered through a plug of celite, washed with 300 mL of Et_2O, and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (10% EtOAc/Hexanes) to yield 3.80 g (83%) of **48** as a yellow solid: Mp 198-200 ºC (EtOAc/Hexanes); IR (KBr) 3431, 3057, 2360, 1635, 1203, 1123, 1026 cm^{-1}; ^1H NMR δ 9.62 (d, 1 H, J = 31.2 Hz), 8.25 (dd, 1 H, J = 2.2, 7.4 Hz), 8.00-7.84 (m, 3 H), 7.57 (dd, 1 H, J = 1.6, 5.9 Hz) 7.50-7.28 (m, 9 H); ^{13}C NMR δ 172.5, 134.4, 134.0, 133.7, 133.3, 131.8, 131.4, 129.6, 128.4, 127.9, 127.5; MS (EI) *m/z* (rel intensity) 386 (53), 384 (M^+, 55), 348 (8), 306 (4), 201 (100), 183 (7); HRMS (EI) Calcd for $C_{19}H_{16}NOPBr$ 384.0153, found 384.0137.



49

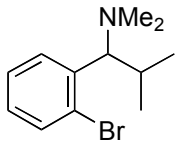
1-(2-Bromophenyl)-2-methylpropyl-*P*,*P*-diphenylphosphinamide (49). A solution of 4.00 g (4.90 mmol) of **48** in 40 mL of THF was added to 13.0 mL of a 2 M solution of isopropyl magnesium chloride in THF at 0 ºC. The resulting reaction mixture was gradually warmed to room temperature and stirred for 5 h, cooled to 0 ºC, quenched with NH_4Cl, and extracted with CH_2Cl_2 (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield 3.5 g (79%) of **49** as a white solid that was used without further purification: Mp 198-200 ºC; IR (KBr) 3057, 2961, 1590, 1359, 1105 cm^{-1}; ^1H NMR (CD_3OD) δ 7.73-7.66 (m, 2 H), 7.52-7.42 (m, 4 H), 7.41-7.32 (m, 4 H), 7.31-7.23 (2 H), 7.22-7.15 (m, 1 H), 7.04-6.96 (m, 1 H), 5.64 (bt, 1 H, J = 10.5 Hz), 4.23 (bq, 1 H, J = 10.8 Hz), 1.98-1.81 (m, 1 H), 1.04 (d, 3 H, J = 6.7 Hz), 0.71 (d, 3 H, J = 6.8 Hz); ^{13}C NMR δ 144.1, 133.8, 132.7, 132.6, 132.5, 132.3, 131.8,

131.7, 131.6, 131.6, 131.4, 130.9, 128.4, 128.2, 128.1, 127.9, 127.1, 34.3, 19.8, 18.2; MS (EI) *m/z* (rel intensity) 430 (3), 428 (M^+, 4), 386 (10), 384 (10), 338 (15), 294 (11), 248 (12), 201 (22), 127 (16), 107 (32), 91 (100); HRMS (EI) Calcd for $C_{22}H_{23}NOPBr$ (M– C_3H_7) 384.0153, found 384.0157.



50

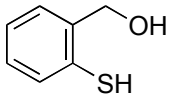
1-(2-Bromophenyl)-2-methylpropylamine (50). A solution of 1.00 g (2.34 mmol) of **49** in 10 mL of 20% aqueous HCl was heated at reflux for 1 h, cooled to 0 ºC, and extracted with Et_2O. The aqueous layer was basified with NaOH, and extracted with Et_2O (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield 440 mg (75%) of **50** as a light yellow oil that was used without further purification: IR (neat) 3251, 3010, 1605, 1098, 924 cm^{-1}; ^1H NMR δ 7.60 (d, 1 H, *J* = 7.4 Hz), 7.52 (d, 1 H, *J* = 7.9 Hz), 7.25 (t, 1 H, *J* = 3.9 Hz), 7.11 (t, 1 H, *J* = 7.2 Hz), 4.10 (d, 1 H, *J* = 7.5 Hz), 1.99-1.92 (m, 1 H), 0.95 (d, 3 H, *J* = 6.7 Hz), 0.86 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR δ 138.4, 133.2, 129.4, 128.4, 127.9, 124.2, 60.1, 33.2, 19.4, 18.5; MS (EI) *m/z* (rel intensity) 226 (M^+, 6), 224 (5), 212 (7), 184 (100), 182 (98), 130 (8), 115 (6), 104 (30); HRMS (EI) Calcd for $C_{10}H_{11}NBr$ 224.0070, found 224.0075.



51

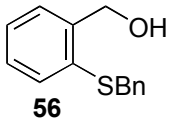
1-(2-Bromophenyl)-2-methylpropyldimethylamine (51). To 150 mg (0.650 mmol) of **50** was added 220 µL (2.92 mmol) of a 37% aqueous solution of formaldehyde, 260 µL (6.06 mmol) of aqueous 88% formic acid, and 3 mL of H_2O. The reaction mixture was heated at reflux for 16 h, cooled to 0 ºC, basified with NaOH, and extracted with Et_2O (3x). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield 93 mg (55%) of **51** as a clear oil: IR (neat) 3054, 2930, 1245, 1120, 654 cm^{-1}; ^1H NMR δ 7.53 (d, 1 H, *J* = 7.9 Hz), 7.31-7.18

(m, 2 H), 7.08- 6.98 (m, 1 H), 3.77 (d, 1 H, J = 8.6 Hz), 2.21-2.09 (m, 1 H), 2.15 (s, 6 H), 0.98 (d, 3 H, J = 6.6 Hz), 0.71 (d, 3 H, J = 6.7 Hz); ^{13}C NMR δ 137.6, 132.9, 129.5, 128.0, 126.9, 126.5, 72.2, 41.7, 29.7, 20.1, 18.6; MS (EI) *m/z* (rel intensity) 257 (19), 255 (M^+, 21), 214 (98), 212 (100), 198 (6), 169 (7), 132 (37), 115 (10).



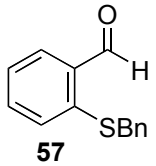
55

(2-Mercaptophenyl)methanol (55).[82] A solution of 10.0 g (64.8 mmol) of thiosalicylic acid in 50 mL of THF was added portionwise to a slurry of 4.50 g (112 mmol) of LAH in 100 mL of THF at 0 ºC. The reaction mixture was slowly warmed to room temperature, stirred for 15 h, cooled to 0 ºC, diluted with 22 mL of EtOAc and 90 mL of H_2SO_4, filtered through a pad of celite, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (5% EtOAc/Hexanes) to yield 6.20 g (68%) of **55** as a clear oil: ^{1}H NMR δ 7.40-7.33 (m, 2 H), 7.30-7.13 (m, 2 H), 5.16 (s, 2 H), 3.47 (s, 1 H), 2.09 (s, 1 H); MS (EI) *m/z* (rel intensity) 122 ([M-H_2O]$^+$, 100), 111 (18).



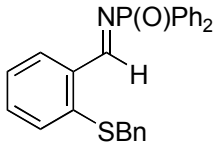
56

(2-Benzylsulfanylphenyl)methanol (56).[83] A solution of 6.20 g (44.3 mmol) of **55** in 75 mL of 95% EtOH was added to a solution of 1.86 g (1.05 mmol) of NaOH in 100 mL of 95% EtOH. The resulting solution was stirred at room temperature for 45 min, followed by the addition of 5.27 mL (44.3 mmol) of benzyl bromide in 100 mL of 95% EtOH at 0 ºC. The reaction mixture was heated at reflux for 15 h, cooled to 0 ºC, concentrated *in vacuo,* diluted with H_2O, and extracted with Et_20 (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo.* The resulting residue was purified by chromatography on SiO_2 (20% EtOAc/Hexanes) to yield 7.40 g (73%) of **56** as a white solid: Mp 48-49 ºC (EtOAc/Hexanes, lit. 48-49 ºC); ^{1}H NMR δ 7.42-7.32 (m, 2 H), 7.29-7.13 (m, 7 H), 4.62 (d, 2 H, J = 6.0 Hz), 4.07 (s, 2 H); MS (EI) *m/z* (rel intensity) 182 ([M-?]$^+$, 23), 139 (15), 122 (100), 109 (10).



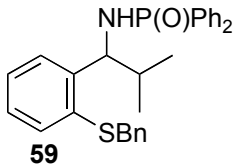
57

2-Benzylsulfanylbenzaldehyde (57). To 4.50 g (19.5 mmol) of **56** in 200 mL of CH_2Cl_2 at 0 ºC was added portionwise 25.0 g (97.5 mmol) of barium manganate. The resulting black solution was stirred for 15 h at room temperature, filtered through a pad of celite, and concentrated *in vacuo* to yield 3.60 g (86%) of **57** as a white solid: Mp 78-79 ºC (CH_2Cl_2, lit. 78-79 ºC); MS (EI) *m/z* (rel intensity) 230 (M^+, 7), 212 (7), 139 (100), 121 (9), 111 (22), 109 (9); ^{1}H NMR δ 10.26 (s, 1 H); 7.80 (d, 1 H, *J* = 7.9 Hz); 7.50-7.38 (m, 3 H); 7.37-7.20 (m, 5 H); 4.18 (s, 2 H).



58

2-Benzylsulfanyl-*P,P*-diphenylphosphinamide (58). A suspension of 3.77 g (16.5 mmol) of **57**, 2.30 g (10.6 mmol) of, and 4.41 mL (31.7 mmol) of triethylamine in 50 mL of CH_2Cl_2 was cooled to 0 ºC, treated dropwise over 20 min with a solution of 640 μL of (5.79 mmol) $TiCl_4$ in 10 mL of CH_2Cl_2, gradually warmed to room temperature, and stirred for 8 h. The reaction mixture was poured into 150 mL of Et_2O, stirred for 5 min, filtered through a plug of celite, washed with 300 mL of Et_2O, and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (10% EtOAc/Hexanes) to yield 3.8 g (83%) of **58** as a yellow solid: Mp 116-118 ºC (EtOAc/Hexanes); IR (KBr) 3058, 3028, 1690, 1585, 2738, 2359, 1264, 829 cm^{-1}; ^{1}H NMR δ 9.69 (d, 1 H, *J* = 31.9 Hz), 8.13-7.98 (m, 5 H), 7.58-7.43 (m, 8 H), 7.40-7.27 (m, 5 H), 7.25-7.18 (m, 1 H), 4.18 (s, 2 H); ^{13}C NMR δ 172.0, 141.3, 136.2, 134.6, 134.3, 133.9, 133.0, 132.2, 131.6, 129.8, 128.9, 128.4, 128.2, 127.3, 126.0, 39.1; MS (EI) *m/z* (rel intensity) 428 (M^+, 9), 336 (12), 201 (24), 91 (79), 77 (100).

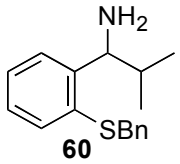


59

1-(2-Benzylsulfanylphenyl)-2-methylpropyl-*P*,*P*-diphenylphosphinamide (59). A solution of 2.10 g (4.90 mmol) of **58** in 50 mL of THF was added to 6.13 mL of a 2 M solution of isopropyl magnesium chloride in THF at 0 ºC. The reaction mixture was gradually warmed to room temperature and stirred for 5 h, cooled to 0 ºC, quenched with NH_4Cl, and extracted with CH_2Cl_2 (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (50% EtOAc/Hexanes) to yield 1.80 g (78%) of **59** as an off white solid. The enantiomers were separated using Chiral HPLC (Chiralcel AD-H semi-prep column) with ~85 mg/injection of **59** and eluting with 30% *i*-PrOH/Hexanes at a flow rate of 10 mL/min.

(*S*)-59: Mp 133-138 ºC (*i*-PrOH/Hexanes); R_t = 11.2 min; $[\alpha]_D^{25}$ -31.6 (*c* 0.5, $CHCl_3$); IR (KBr) 3050, 2945, 1558, 1248, 1346, 1156 cm^{-1}; ^1H NMR (CD_3OD) δ 7.74-7.62 (m, 2 H), 7.57-7.28 (m, 6 H), 7.19-6.97 (m, 11 H), 5.46 (bt, 1 H, *J* = 10.6 Hz), 4.54 (bs, 1 H), 3.67 (bd, 1 H, *J* = 11.9 Hz), 3.50 (m, 1 H), 1.91-1.70 (m, 1 H), 0.96 (d, 3 H, *J* = 6.7 Hz), 0.66 (d, 3 H, *J* = 6.4 Hz); ^{13}C NMR δ 144.2, 137.0, 132.7, 132.6, 131.9, 131.8, 131.6, 131.4, 129.0, 128.4, 128.1, 127.9, 127.0, 126.6, 64.2, 39.9, 34.8, 25.4, 20.2; MS (EI) *m/z* (rel intensity) 471 (M^+, 10), 428 (69), 336 (19), 306 (77), 270 (42), 201 (100); HRMS (EI) Calcd for $C_{29}H_{30}NOPS$ 471.1785, found 471.1807.

(*R*)-59: Mp 132-135 ºC; $[\alpha]_D^{25}$ +45.3 (*c* 0.8, $CHCl_3$); R_t = 20.2 min; ^1H NMR (CD_3OD) δ 7.75-7.65 (m, 2 H); 7.57-7.29 (m, 6 H), 7.23-6.97 (m, 11 H), 5.48 (bt, 1 H, *J* = 10.7 Hz), 4.53 (bs, 1 H), 3.70 (bd, 1 H, *J* = 12.1 Hz), 3.40-3.60 (m, 1 H), 1.90-1.71 (m, 1 H), 0.98 (d, 3 H, *J* = 6.7 Hz), 0.68 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR δ 144.2, 137.0, 132.6, 132.5, 131.8, 131.6, 131.3, 129.0, 128.3, 128.0, 127.8, 127.1, 126.9, 126.6, 39.9, 34.7, 22.5, 20.1; MS (EI) *m/z* (rel intensity) 471 (M^+, 20), 428 (75), 270 (35), 201 (88), 136 (18); HRMS (EI) Calcd for $C_{29}H_{30}NOPS$ 471.1785, found 471.1785.

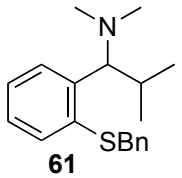


60

1-(2-Benzylsulfanylphenyl)-2-methylpropylamine (60). A solution of 900 mg (1.91 mmol) of **59** in 10 mL of 20% aqueous HCl was heated at reflux for 45 min, cooled to 0 ºC, diluted with Et_2O, and filtered. The filtrate was extracted with Et_2O, the aqueous layer was basified with NaOH, and extracted with Et_2O (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting yellow oil **60** was used without further purification.

(*S*)-60: $[\alpha]_D^{25}$ +52.5 (*c* 0.3, $CHCl_3$); IR (neat) 3444, 3060, 2361, 1650, 1472, 1361 cm^{-1}; ^1H NMR δ 7.55-7.42 (m, 2 H), 7.39-7.10 (m, 9 H), 4.19 (d, 1 H, *J* = 7.4 Hz), 4.16, 4.11 (AB, 2 H, *J* = 12.6 Hz), 1.92 (o, 1 H, *J* = 6.8 Hz), 1.02 (d, 3 H, *J* = 6.6 Hz), 0.83 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR δ 146.6, 137.5, 133.5, 130.9, 128.9, 128.4, 127.2, 127.0, 126.9, 126.6, 57.9, 40.1, 34.5, 20.1, 18.4; MS (EI) *m/z* (rel intensity) 271 (M^+, 30), 254 (43), 228 (100), 163 (17), 136 (29), 106 (32); HRMS (EI) Calcd for $C_{17}H_{21}NS$ 271.1380, found 271.1395.

(*R*)-60: $[\alpha]_D^{25}$ -44.3 (*c* = 0.6, $CHCl_3$); IR (neat) 3430, 2967, 2122, 1590, 1266, 1190 cm^{-1}; ^1H NMR δ 7.43-7.37 (m, 2 H), 7.31-7.14 (m, 7 H), 4.16 (d, 1 H, *J* = 7.4 Hz), 4.09, 4.04 (AB, 2 H, *J* = 12.7 Hz), 1.86 (o, 1 H, *J* = 6.8 Hz), 0.97 (d, 3 H, *J* = 6.6 Hz), 0.77 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR δ 146.4, 137.5, 134.5, 130.9, 128.8, 128.4, 127.1, 126.9, 126.8, 126.6, 57.8, 40.0, 34.5, 20.1, 18.3; MS (EI) *m/z* (rel intensity) 270 (M^+, 20), 254 (33), 244 (43), 228 (100), 136 (32), 106 (18).

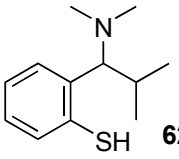


61

1-(2-Benzylsulfanylphenyl)-2-methylpropyldimethylamine (61). To 450 mg (1.66 mmol) of **60** was added 652 μL (7.80 mmol) of a 37% aqueous formaldehyde solution, 752 μL (15.4 mmol) of 88% aqueous formic acid, and 5 mL of H_2O. The resulting solution was heated at reflux for 20 h, cooled to 0 ºC, basified with NaOH, and extracted with $CHCl_3$ (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield 310 mg (54%) of **61** over 2 steps as a clear oil.

(*S*)-61: $[\alpha]_D^{25}$ +87.0 (*c* 0.4, $CHCl_3$); IR (neat) 3145, 2899, 2710, 1704, 1211, 754 cm^{-1}; ^1H NMR δ 7.43-7.36 (m, 1 H), 7.32-7.12 (m, 8 H), 4.07 (s, 2 H), 3.91 (d, 1 H, *J* = 8.2 Hz), 2.27-2.04 (m, 1 H), 2.13 (s, 6 H), 0.95 (d, 3 H, *J* = 6.6 Hz), 0.70 (d, 3 H, *J* = 6.7 Hz); ^{13}C NMR δ 138.8, 137.4, 130.3, 128.9, 128.5, 128.4, 127.1, 126.9, 125.6, 69.7, 42.1, 39.9, 29.6, 20.3, 18.5; MS (EI) *m/z* (rel intensity) 299 (M^+, 33), 256 (100), 179 (27), 164 (32), 150 (19); HRMS (EI) Calcd for $C_{19}H_{25}NS$ 299.1697, found 299.1708.

(*R*)-61: $[\alpha]_D^{25}$ -30.7 (*c* 0.3, $CHCl_3$); IR (neat) 3053, 2802, 2705, 1625, 1287 cm^{-1}; ^1H NMR δ 7.43-7.37 (m, 1 H), 7.33-7.11 (m, 8 H), 4.07 (s, 2 H), 3.95 (d, 1 H, *J* = 8.3 Hz), 2.29-2.05 (m, 1 H), 2.15 (s, 6 H), 1.00 (d, 3 H, *J* = 6.6 Hz), 0.74 (d, 3 H, *J* = 6.7 Hz); ^{13}C NMR δ 138.8, 137.3, 130.1, 128.8, 128.3, 128.3, 127.0, 126.7, 125.4, 69.6, 42.0, 39.8, 29.6, 20.3, 18.6; MS (EI) *m/z* (rel intensity) 298 (M^+, 8), 256 (100), 209 (37), 164 (21).



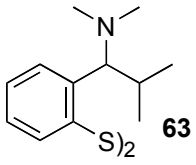
62

(*R*)-2-(1-Dimethylamino-2-methylpropyl)benzenethiol (62). A solution of 140 mg (0.47 mmol) of **61** in 5 mL of THF at -78 ºC was treated with 27 mL of liquid NH_3, followed by addition of 432 mg (0.187 mmol) of Na, stirred for 45 min at -78 ºC, and quenched with solid NH_4Cl. The resulting solution was evaporated under N_2, the residue dissolved in H_2O, and

extracted with $CHCl_3$ (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (25% EtOAc/Hexanes) to yield 35 mg (36%) of crude **62** as a clear oil and 10 mg (10%) of disulfide compound **63**.

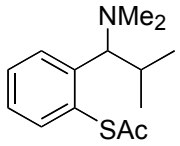
(*S*)-62: ^{1}H NMR δ 7.34 (d, 1 H), 7.10-6.90 (m, 3 H), 3.50 (d, 1 H, *J* = 6.7 Hz), 2.40 (s, 6 H), 2.50-2.30 (m, 1 H), 0.99 (d, 3 H, *J* = 6.7 Hz), 0.87 (d, 3 H, *J* = 6.7 Hz)

(*R*)-62: $[\alpha]_D^{25}$ -30.7 (*c* 0.3, $CHCl_3$); ^{1}H NMR δ 7.34 (d, 1 H, *J* = 9.4 Hz), 7.11-6.95 (m, 3 H), 3.50 (d, 1 H, *J* = 6.7 Hz), 2.40 (s, 6 H), 2.44-2.25 (m, 1 H), 1.00 (d, 3 H, *J* = 6.7 Hz), 0.87 (d, 3 H, *J* = 6.7 Hz); MS (EI) *m/z* (rel intensity) 208 (M^+, 44), 166 (64), 149 (18), 125 (20), 111 (34), 97 (48); HRMS (EI) Calcd for $C_{12}H_{18}NS$ 208.1155, found 208.1160.



63

(*S*)-(1-(2-(2-(1-Dimethylamino-2-methylpropyl)-phenyldisulfanyl)phenyl)-2-methyl-propyl)dimethylamine) (63). IR (KBr) 3060, 2955, 2816, 1585, 1459, 1248, 1152, 872, 524 cm $^{-1}$; ^{1}H NMR δ 7.60 (d, 2 H, *J* = 8.0 Hz), 7.25-7.08 (m, 6 H), 3.82 (d, 2 H, *J* = 8.8 Hz), 2.30-2.08 (m, 2 H), 2.16 (s, 12 H), 0.96 (d, 6 H, *J* = 6.6 Hz), 0.74 (d, 3 H, *J* = 7.0 Hz), 0.72 (d, 3 H, J = 7.0 Hz).



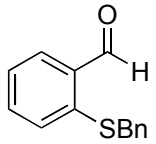
64

2-(1-Dimethylamino-2-methylpropyl)benzenethiolacetate (64). To 140 mg (0.67 mmol) **61** in 5 mL of CH_3CN was added 0.10 mL (0.74 mmol) of triethylamine. The resulting solution was stirred for 5 min, followed by addition of 47.5 μL (0.679 mmol) of acetyl chloride and continued to stir at room temperature for 6 h. The reaction mixture was diluted with H_2O and extracted

with CH_2Cl_2 (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (5% MeOH/CH_2Cl_2) to yield 95 mg (56%) of **64** as a clear oil: $[\alpha]_D^{25}$ -30.7 (*c* 0.3, $CHCl_3$); ^{1}H NMR δ 7.45-7.37 (m, 3 H), 7.33-7.27 (m, 1 H), 3.69 (d, 1 H, *J* = 8.4 Hz), 2.43 (s, 3 H), 2.27-2.10 (m, 1 H), 2.12 (s, 6 H), 0.94 (d, 3 H, *J* = 6.6 Hz), 0.70 (d, 3 H, *J* = 6.6 Hz); MS (EI) *m/z* (rel intensity) 224 (M^+-?, 7), 208 (39), 166 (42), 91 (34).

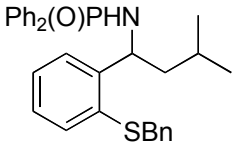
(*R*)-1-Phenylhept-2-en-1-ol (27) using ligand (*S*)-62, (*S*)-63. According to the general protocol, runs were conducted on a 500 mg or 250 mg scale of Schwartz reagent at both 5 and 10 mol% chiral ligand loading. Resulting yields and %ee of **27** are listed in Table 2.

(*S*)-1-Phenylhept-2-en-1-ol (27) using of ligand (*R*)-62, (*R*)-64. According to the general protocol, runs were conducted on a 500 mg or 250 mg scale of Schwartz reagent at both 5 and 10 mol% chiral ligand loading. Resulting yields and %ee[84] of **27** are listed in Table 2.



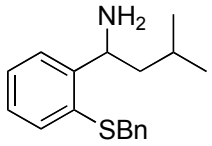
57

2-Benzylsulfanylbenzaldehyde (57). A suspension of 9.5 mg (0.5 mmol) of CuI, 0.12 mL (1.0 mmol) of 2-bromobenzaldehyde (1.00 mmol), and 276 mg (2.0 mmol) of K_2CO_3 was added to a screw-capped sealed tube. The tube was evacuated and backfilled with nitrogen (3 cycles). 1.0 mL of *i*-PrOH, 0.11 mL of ethylene glycol, and 0.12 mL (1.0 mmol) of benzylmercaptan were added at rt. The tube was heated to 80 ºC for 20 h, cooled, filtered through frit, and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (100% hexanes) to yield 200 mg (71%) of **57** as a yellow solid: Mp 78-79 ºC (CH_2Cl_2, lit. 78-79 ºC); MS (EI) *m/z* (rel intensity) 230 (M^+, 7), 212 (7), 139 (100), 121 (9), 111 (22), 109 (9); ^{1}H NMR δ 10.26 (s, 1 H), 7.80 (d, 1 H, *J* = 7.9 Hz), 7.50-7.38 (m, 3 H), 7.37-7.20 (m, 5 H), 4.18 (s, 2 H).



66

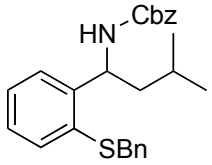
1-(2-Benzylsulfanylphenyl)-3-methylbutyl-*P*,*P*-diphenylphosphinamide (66). A solution of 2.70 g (6.31 mmol) of **59** in 50 mL of THF was added to 7.90 mL (15.8 mmol) of a 2 M solution of isobutyl magnesium chloride in THF at 0 ºC. The reaction mixture was stirred for 5 h at 0 ºC, quenched with NH_4Cl, and extracted with CH_2Cl_2 (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (25% EtOAc/Hexanes) to yield 2.20 g (72%) of **66** as a white foamy solid: Mp 109-111 ºC; IR (KBr) 3193, 3056, 2952, 2866, 2360, 1437, 1188, 1122, 722 cm^{-1}; ^1H NMR δ 7.92 (dd, 2 H, *J* = 7.8, 11.7 Hz), 7.77 (dd, 2 H, *J* = 7.8, 11.7 Hz), 7.52-7.31 (m, 5 H), 7.30-7.19 (m, 6 H), 7.18-7.07 (m, 4 H), 4.79 (bs, 1 H), 3.95-3.70 (m, 3 H), 1.93-1.64 (m, 2 H), 1.64-1.45 (s, 1 H), 0.95 (d, 3 H, *J* = 6.0 Hz), 0.87 (d, 3 H, *J* = 6.3 Hz); ^{13}C NMR δ 145.5, 137.0, 134.0, 133.1, 132.9, 132.40, 132.3, 131.9, 131.8, 131.7, 131.4, 131.4, 131.2, 131.2, 128.7, 128.5, 128.2, 128.2, 128.0, 128.0, 127.8, 127.1, 126.9, 51.8, 39.8, 24.7, 22.9, 21.8; MS (EI) *m/z* (rel intensity) 485 (M^+, 20), 428 (37), 362 (14), 306 (50), 284 (98), 201 (96), 135 (20), 91 (100), 77 (47); HRMS (EI) Calcd for $C_{30}H_{32}NOPS$ 485.1942, found 485.1936.



67

1-(2-Benzylsulfanylphenyl)-3-methylbutylamine (67). A solution of 2.2 g (mmol) of **66** in 20 mL of 20% aqueous HCl was heated at reflux for 1 h, cooled to 0 ºC, diluted with Et_2O, and filtered. The filtrate was extracted with Et_2O, the aqueous layer was basified with NaOH, and extracted with Et_2O (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting yellow oil **67** was used without further purification: IR (KBr) 3280, 3124, 2956, 2675, 1280, 567 cm^{-1}; ^1H NMR δ 7.58 (d, 1 H, *J* = 7.2 Hz), 7.40 (d, 1 H, *J* = 7.5 Hz), 7.35-7.15 (m, 7 H), 5.54 (bs, 2 H), 4.78 (s, 1 H), 4.10 (dt, 2 H, *J* = 4.5, 12.6 Hz), 1.80-1.65 (m, 1 H), 1.66-1.50 (m, 2 H), 0.94 (d, 6 H, *J* = 3.0 Hz); ^{13}C NMR δ 143.5, 137.4,

134.1, 132.3, 128.9, 128.4, 127.8, 127.7, 127.1, 126.4, 50.2, 45.9, 40.4, 24.9, 22.9, 22.1; MS (EI) *m/z* (rel intensity) 286 (M^+, 12), 285 (45), 269 (12), 268 (40), 228 (64), 211 (25), 194 (61), 135 (41), 91 (100); HRMS (EI) Calcd for $C_{18}H_{23}NS$ 285.1551, found 285.1541.

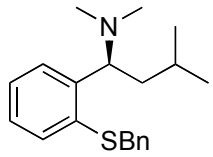


69

[1-(2-Benzylsulfanylphenyl)-3-methylbutyl]carbamic acid benzyl ester (69). To 2.2 g (7.72 mmol) of **67** in 10 mL of THF was added 1.60 g (11.6 mmol) of K_2CO_3 followed by 1.21 mL (8.49 mmol) of benzyl chloroformate. The resulting reaction was stirred for 15 h at rt, quenched with H_2O, extracted with Et_2O, washed with NaCl, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (50% EtOAc/Hexanes) to yield 2.10 g (65%) of **67** as an off white solid:

(*S*)-69: Mp 63-64 °C (EtOAc/Hexanes); $[\alpha]_D^{25}$ +12.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 7.43-7.12 (m, 14 H), 5.38-5.25 (m, 1 H), 5.30 (s, 2 H), 5.08 (d, 2 H, *J* = 5.4 Hz), 4.14 (s, 2 H), 1.70-1.50 (m, 1 H), 0.97 (d, 3 H, *J* = 6.0 Hz), 0.92 (d, 3 H, *J* = 6.0 Hz); ^{13}C NMR δ 155.5, 144.5, 137.4, 136.5, 133.7, 132.9, 129.0, 128.4, 128.1, 127.5, 127.4, 127.1, 126.5, 66.7, 51.9, 45.9, 40.2, 25.3, 23.1, 21.9; MS (EI) *m/z* (rel intensity) 419 (M^+, 25), 362 (13), 318 (27), 284 (50), 268 (30), 211 (19), 179 (20), 150 (41), 123 (30), 91 (100); HRMS (EI) Calcd for $C_{26}H_{29}NO_2S$ 419.1919, found 419.1934.

(*R*)-69: Mp 61-65 °C; $[\alpha]_D^{25}$ –11.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 7.40-7.10 (m, 14 H), 5.35-5.15 (m, 2 H), 5.30 (d, 2 H, J = 5.4 Hz), 4.14 (s, 2 H), 1.60-1.50 (m, 1 H), 0.97 (d, 3 H, J = 6.0 Hz), 0.92 (d, 3 H, J = 6.3 Hz); ^{13}C NMR δ 155.5, 144.4, 137.4, 136.5, 133.7, 132.9, 129.0, 128.4, 128.1, 127.5, 127.4, 127.1, 126.5, 66.6, 51.9, 45.9, 40.2, 25.2, 23.1, 21.9; MS (EI) *m/z* (rel intensity) 419 (M^+, 25), 362 (13), 318 (27), 284 (50), 268 (30), 211 (19), 179 (20), 150 (41), 123 (30), 91 (100); HRMS (EI) Calcd for $C_{26}H_{29}NO_2S$ (M+Na) 442.1817, found 442.1852.



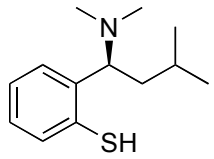
70

1-(2-Benzylsulfanylphenyl)-3-methylbutyldimethylamine (70). To 1.00 g (2.38 mmol) of **69** in 50 mL of CH_2Cl_2 at –10 ºC was added of 11.9 mL (11.9 mmol) of a 1M solution of BBr_3 in CH_2Cl_2. The resulting reaction was stirred at –10 ºC for 1 h, rt for 15 h, cooled to 0 ºC, quenched with H_2O, extracted with CH_2Cl_2, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was used without further purification.

To 760 mg (2.67 mmol) of amine was added 1.05 mL (12.6 mmol) of a 37% aqueous formaldehyde solution, 1.21 mL (24.8 mmol) of 88% aqueous formic acid, and 10 mL of H_2O. The resulting solution was heated at reflux for 20 h, cooled to 0 ºC, basified with NaOH, and extracted with $CHCl_3$ (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield 250 mg (33%) of **70** over 2 steps as a clear oil.

(*S*)-70: $[\alpha]_D^{25}$ +1.7 (*c* 0.9, $CHCl_3$); IR (neat) 3190, 3145, 2886, 1620, 1301, 760, 642 cm^{-1}; ^1H NMR δ 7.42-7.15 (m, 9 H), 4.13 (s, 2 H), 4.11 (t, 1 H, *J* = 7.5 Hz), 2.20 (s, 6 H), 1.68 (t, 2 H, *J* = 6.9 Hz), 1.31-1.18 (sp, 1 H, *J* = 6.3 Hz), 0.89 (d, 3 H, *J* = 6.6 Hz), 0.83 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR δ 141.0, 137.4, 137.4, 129.5, 129.0, 128.5, 127.8, 127.2, 127.1, 125.9, 62.8, 42.2, 40.8, 39.4, 25.2, 23.9, 22.5; MS (EI) *m/z* (rel intensity) 313 (M^+, 25), 256 (67), 222(35), 164 (33), 135 (54), 91 (90); HRMS (EI) Calcd for $C_{20}H_{27}NS$ 313.1853, found 313.1864.

(*R*)-70: $[\alpha]_D^{25}$ –7.3 (*c* 0.02, $CHCl_3$); IR (KBr) 3205, 3156, 2863, 1560, 1309, 927 cm^{-1}; ^1H NMR δ 7.45-7.10 (m, 9 H), 4.13 (s, 2 H), 4.10 (t, 1 H, *J* = 9.9 Hz), 2.19 (s, 6 H), 1.67 (t, 2 H, *J* = 7.5 Hz), 1.32-1.17 (m, 1 H), 0.89 (d, 3 H, *J* = 6.3 Hz), 0.83 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR δ 140.9, 137.4, 137.3, 129.4, 129.0, 128.5, 127.7, 127.2, 127.1, 125.8, 62.7, 42.2, 40.8, 39.3, 25.2, 23.9, 22.5; MS (EI) *m/z* (rel intensity) 313 (M^+, 8), 268 (8), 256 (100), 222 (65), 164 (30), 135 (60), 91 (95); HRMS (EI) Calcd for $C_{20}H_{27}NS$ 313.1854, found 313.1864.

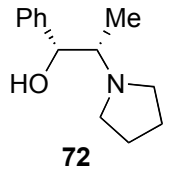


71

2-(1-Dimethylamino-3-methylbutyl)benzenethiol (71). A solution of 160 mg (0.51 mmol) of **70** in 5 mL of THF at -78 ºC was treated with 26.0 mL of liquid NH_3, followed by addition of 345 mg (0.15 mmol) of Na, stirred for 45 min at -78 ºC, and quenched with solid NH_4Cl. The resulting solution was evaporated under N_2, the residue dissolved in H_2O, and extracted with $CHCl_3$ (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (25% EtOAc/Hexanes) to yield 120 mg (97%) of crude **71** as a clear oil.

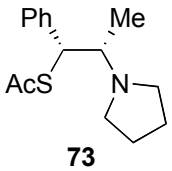
(*S*)-71: $[\alpha]_D^{25}$ +9.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 7.75-7.65 (m, 1 H), 7.33-7.10 (m, 3 H). 3.91 (dd, 1 H, *J* = 4.2, 6.2 Hz), 2.25 (s, 6 H), 1.83 (qd, 1 H, *J* = 3.9, 9.9 Hz), 1.67 (qd, 1 H, *J* = 4.2, 9.3 Hz), 1.43-1.28 (m, 1 H), 0.94 (d, 3 H, *J* = 6.6 Hz), 0.89 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR δ 140.6, 138.3, 128.4, 127.6, 127.4, 125.9, 63.9, 41.8, 39.0, 25.3, 24.0, 22.3; MS (EI) *m/z* (rel intensity) 233 (5), 222 (48), 190 (10), 177 (24), 166 (70), 149 (58), 135 (100), 123 (42).

(*R*)-71: $[\alpha]_D^{25}$ –6.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 7.76-7.64 (m, 1 H), 7.38-7.10 (m, 3 H), 3.91 (dd, 1 H, *J* = 4.2, 10.5 Hz), 2.25 (s, 6 H), 1.85 (qd, 1 H, *J* = 3.9, 9.9 Hz), 1.67 (qd, 1 H, *J* = 4.2, 9.3 Hz), 1.45-1.30 (m, 1 H), 0.95 (d, 3 H, *J* = 6.3 Hz), 0.89 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR δ 140.6, 138.3, 128.4, 127.6, 127.4, 125.9, 63.9, 41.8, 39.0, 25.3, 24.0, 22.3; MS (EI) *m/z* (rel intensity) 233 (4), 222 (40), 190 (10), 177 (20), 166 (68), 149 (58), 135 (100), 123 (38).



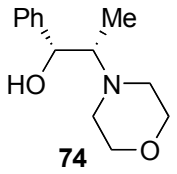
72

(1*R*,2*S*)-1-Phenyl-2-(1-pyrrolidinyl)propan-1-ol (72).[85] A solution of 500 mg (3.30 mmol) of (1*R*,2*S*)-(-)-norephedrine, 0.79 mL (6.6 mmol)of 1,4-dibromobutane, and 2.28 g (16.5 mmol) of K_2CO_3 in 5 mL of EtOH was heated at reflux for 24 h. The resulting heterogeneous solution was filtered and 345 mg (52%) of **72** was obtained as a solid: Mp 44-46 ºC (acetonitrile); $[\alpha]_D^{25}$ +13.0 (*c* 1.0, $CHCl_3$); lit.[85] $[\alpha]_D^{25}$ +13.1 (*c* 2.0, $CHCl_3$); ^{1}H NMR δ 7.36-7.23 (m, 5 H), 5.08 (d, 1 H, *J* = 2.1 Hz), 3.60 (bs, 1 H), 2.91-2.88 (m, 2 H), 2.76-2.73 (m, 2 H), 2.63-2.55 (m, 1 H), 1.92-1.83 (m, 4 H), 0.85 (d, 3 H, *J* = 6.6 Hz); MS (EI) *m/z* (rel intensity) 204 (M^+, 25), 187 (33), 160 (14), 105 (21), 98 (100).



73

(1*R*, 2*S*)-1-Acetylthio-1-phenyl-2-(1-pyrrolidinyl)propane (73).[85] To a solution of 250 mg (1.22 mmol) of **72** and 0.260 mL (1.83 mmol) of triethylamine in 5 mL of CH_2Cl_2 at -78 ºC was added 0.100 mL (1.35 mmol) of methanesulfonylchloride. The reaction mixture was stirred for 30 min at -78 ºC, concentrated *in vacuo*, redissolved in 5 mL of H_2O, warmed to room temperature, treated with 418 mg (3.66 mmol) of potassium thioacetate, stirred for 2 h at room temperature, and extracted with CH_2Cl_2 (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (20% EtOAc/Hexanes) to yield 0.070 g (21%) of **73** as a clear oil: $[\alpha]_D^{25}$ +29.1 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 7.30-7.18 (m, 5 H), 4.94 (bs, 1 H), 2.65-2.49 (m, 5 H), 2.21 (s, 3 H), 1.75-1.55 (m, 4 H), 0.93 (d, 3 H, *J* = 6.4 Hz).



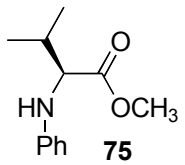
74

(1*R*,2*S*)-1-Phenyl-2-(1-morpholin)propan-1-ol (74).[85] A solution of 500 mg (3.30 mmol) of (1*R*,2*S*)-(-)-norephedrine, 0.420 mL (3.30 mmol) of 1,4-dibromoethylether, and 456 mg (3.30 mmol) of K_2CO_3 in 10 mL of CH_3CN was heated at reflux for 20 h. The heterogeneous solution was filtered and 350 mg (48%) of **74** was obtained as a beige solid: Mp 204-205 ºC (acetonitrile, lit.[85] 198-199); $[\alpha]_D^{25}$ -30.7 (*c* 0.3, $CHCl_3$); ^{1}H NMR (CD_3OD) δ 7.40-7.25 (m, 4 H), 7.24-7.15 (m, 1 H), 5.32 (s, 1 H), 4.10-3.85 (m, 2 H), 3.82-3.70 (m, 2 H), 3.65-3.51 (m, 2 H), 3.49-3.30 (m, 2 H), 3.22-3.11 (m, 1 H), 1.05 (d, 3 H, *J* = 6.8 Hz); MS (EI) *m/z* (rel intensity) 220 (M^+, 14), 203 (14), 176 (12), 144 (11), 114 (100), 105 (10).

(*R*)-1-Phenylhept-2-en-1-ol (27) using 10 mol% of ligand 72. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 μL (0.76 mmol) of 1-hexyne, 325 μL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 13 mg (0.060 mmol) of ligand **72**, and 66 μL (0.65 mmol) of freshly distilled benzaldehyde provided 104 mg (85%) of **27** with an ee of 19%.

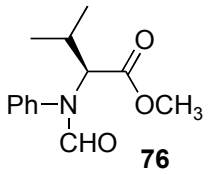
(*R*)-1-Phenylhept-2-en-1-ol (27) using 15 mol% of ligand 73. According to the general protocol, 125 mg (0.484 mmol) of zirconocene hydrochloride, 44 μL (0.38 mmol) of 1-hexyne, 0.16 μL (0.32 mmol) of Me_2Zn (2.0 M solution in toluene), 14 mg (0.050 mmol) of ligand **73**, and 38 μL (0.32 mmol) of freshly distilled benzaldehyde provided 50 mg (81%) of **27** with an ee of 46%.

(*R*)-1-Phenylhept-2-en-1-ol (27) using 10 mol% of ligand 74. According to the general protocol, 500 mg (1.93 mmol) of zirconocene hydrochloride, 175 μL (1.52 mmol) of 1-hexyne, 650 μL (1.29 mmol) of Me_2Zn (2.0 M solution in toluene), 29 mg (0.13 mmol) of ligand **74**, and 134 μL (1.29 mmol) of freshly distilled benzaldehyde provided 196 mg (80%) of **27** with an ee of 20%.[73]



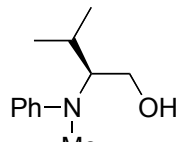
75

Methyl-(*S*)-[*N*-phenyl-2-amino-3-methyl]butanoate (75). To a solution of 4.00 g (34.1 mmol) of *L*-valine methylester hydrochloride and 3.59 mL (34.1 mmol) of phenylbromide in 60 mL of dimethylacetamide was added 0.650 g (3.41 mmol) of copper iodide (I) and 7.07 g (34.1 mmol) of potassium carbonate. The resulting solution was heated at reflux for 60 h, cooled to room temperature, diluted with 120 mL of EtOAc and 60 mL of H_2O, and adjusted to pH 3 using concentrated HCl. The organic layer was separated and aqueous layer extracted with EtOAc (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo.* The resulting residue was purified by chromatography on SiO_2 (10% EtOAc/Hexanes) to yield 7.00 g (99%) of **75** as a gray oil: $[\alpha]_D^{25}$ -94 (*c* 1.0, $CHCl_3$); lit.[86] $[\alpha]_D^{22}$ -92 (*c* 0.8, $CHCl_3$); ^{1}H NMR δ 7.25-7.10 (m, 2 H), 6.72 (t, 1 H, *J* = 8.0 Hz), 6.63 (d, 2 H, *J* = 9.6 Hz), 4.11 (bs, 1 H), 3.86 (d, 1 H, *J* = 5.9 Hz), 3.70 (s, 3 H), 2.29-2.00 (m, 1 H), 1.03 (d, 3 H, *J* = 6.8 Hz), 1.01 (d, 3 H, *J* = 6.8 Hz).



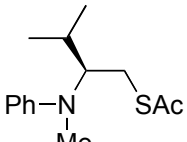
76

Methyl-(*S*)-[*N*-formyl-*N*-phenyl-2-amino-3-methyl]butanoate (76). To 8.18 mL (86.5 mmol) of acetic anhydride was added 4.07 mL of 88% aqueous formic acid at 0 ºC. The resulting solution was stirred at 60 ºC for 1 h, treated with a solution of 7.00 g (33.8 mmol) of **75** in 10 mL of THF, stirred for 2.5 h at 65 ºC, and concentrated *in vacuo.* The resulting residue was purified by chromatography on SiO_2 (20% EtOAc/Hexanes) to yield 5.40 g (67%) of **76** as an orange oil: $[\alpha]_D^{25}$ -80.1 (*c* 1.0, $CHCl_3$); lit.[86] $[\alpha]_D^{22}$ -82.5 (*c* 2.0, $CHCl_3$); ^{1}H NMR δ 8.28 (s, 1 H), 7.40-7.20 (m, 5 H), 4.57 (d, 1 H, *J* = 10.1 Hz), 3.65 (s, 3 H), 2.40-2.20 (m, 1 H), 0.94 (d, 3 H, *J* = 6.6 Hz), 0.85 (d, 3 H, *J* = 6.7 Hz); MS (EI) *m/z* (rel intensity) 235 (M^+, 8), 198 (17), 176 (70), 148 (100), 104 (81).



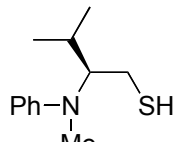
77

(*S*)-*N*-Methyl-*N*-phenyl-2-amino-3-methylbutan-1-ol (77). A solution of 4.00 g (17.0 mmol) of **76** in 60 mL of THF was added portionwise to a slurry of 3.22 g (85.1 mmol) of LAH in 60 mL of THF at 0 ºC. The resulting suspension was stirred for a further 15 min, quenched at 0 ºC with 3 mL of H_2O, 3 mL of aqueous NaOH, and 9 mL of H_2O, filtered through a pad of celite, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (5% EtOAc/Hexanes) to yield 6.20 g (68%) of **77** as a yellow solid: Mp 74-77 ºC (EtOAc/Hexanes, lit. 78-79 ºC); $[\alpha]_D^{25}$ -145.2 (*c* 0.41, $CHCl_3$); lit.[86] $[\alpha]_D^{22}$ -153.8 (*c* 2.0, $CHCl_3$); ^{1}H NMR δ 7.33-7.15 (m, 2 H), 6.91 (bd, 2 H, *J* = 8.0 Hz), 6.77 (bt, 1 H, *J* = 7.1 Hz), 3.90-3.72 (m, 1 H), 3.70-3.50 (m, 2 H), 2.79 (s, 3 H), 1.95-1.75 (m, 1 H), 0.94 (d, 3 H, *J* = 6.6 Hz), 0.77 (d, 3 H, *J* = 6.6 Hz); MS (EI) *m/z* (rel intensity) 193 (M^+, 27), 162 (100), 150 (46), 132 (32), 107 (44).



78

(*S*)-*N*-Methyl-*N*-phenyl-2-amino-3-methyl-1-thiolacetylbutane (78). To a solution of 2.19 g (8.33 mmol) of triphenylphosphine in 30 mL of THF at 0 ºC was added 1.64 mL (8.33 mmol) of diisopropyl azodicarboxylate. The resulting solution was stirred for 1 h at 0 ºC, followed by simultaneous addition of 0.59 mL (8.33 mmol) of thioacetic acid in 5 mL of THF and 800 mg (4.17 mmol) of **77** in 3 mL of THF. The reaction mixture was stirred for 1 h at 0 ºC, concentrated *in vacuo* to 1/3 its' volume, and washed with sodium bicarbonate. The organic layer was filtered through SiO_2 and concentrated *in vacuo.* The resulting residue was purified by chromatography on SiO_2 (5% EtOAc/Hexanes) to yield 548 mg (49%) of **78** as a yellow oil: ^{1}H NMR δ 7.22-7.10 (m, 2 H), 6.70 (d, 2 H, *J* = 8.3 Hz), 6.62 (t, 1 H, *J* = 7.3 Hz), 3.61 (td, 1 H, *J* = 3.8 Hz, 11.0 Hz), 3.47 (dd, 1 H, *J* = 3.8, 13.7 Hz), 2.96 (dd, 1 H, *J* = 11.1, 13.7 Hz), 2.69 (s, 3 H), 2.20 (s, 3 H), 2.20-1.99 (bs, 1 H), 1.98-1.82 (m, 1 H), 1.04 (d, 3 H, *J* = 6.6 Hz), 0.80 (d, 3 H, *J* = 6.7 Hz).



79

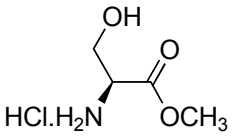
(*S*)-*N*-Methyl-*N*-phenyl-2-amino-3-methylbutan-1-thiol (79). A solution of 550 mg (2.03 mmol) of **78** in 21 mL of THF was added portionwise to a slurry of 307 mg (8.11 mmol) of LAH in 18 mL of THF at 0 ºC. The suspension was stirred at room temperature for 30 min, cooled to 0 ºC, quenched with 3 mL of H_2O, 3 mL of aqueous NaOH, and 9 mL of H_2O, filtered through a pad of celite, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (Hexanes) to yield 297 mg (70%) of **79** as a clear oil: $[\alpha]_D^{25}$ -89.5 (*c* 1.2, $CHCl_3$); lit.[86] $[\alpha]_D^{22}$ -93.8 (*c* 0.8, $CHCl_3$); ^{1}H NMR δ 7.21 (t, 2 H, *J* = 9.3 Hz), 6.84 (d, 2 H, *J* = 8.2 Hz), 6.70-6.60 (m, 1H), 3.58 (dt, 1 H, *J* = 5.0, 9.4 Hz), 2.85-2.77 (m, 2 H), 2.74 (s, 3 H), 1.92-1.78 (m, 1 H), 1.39 (dd, 1 H, *J* = 5.4, 8.8 Hz); 0.97 (d, 3 H, *J* = 6.6 Hz); 0.79 (d, 3 H, *J* = 6.7 Hz).

(*R*)-1-Phenylhept-2-en-1-ol (27) using 10 mol% of ligand 77. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 µL (0.76 mmol) of 1-hexyne, 325 µL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 12 mg (0.060 mmol) of ligand **77**, and 66 µL (0.65 mmol) of freshly distilled benzaldehyde provided 91 mg (74%) of **27** with an ee of 10%.

(*R*)-1-Phenylhept-2-en-1-ol (27) using 15 mol% of ligand 78. According to the general protocol, 500 mg (1.93 mmol) of zirconocene hydrochloride, 175 µL (1.52 mmol) of 1-hexyne, 650 µL (1.29 mmol) of Me_2Zn (2.0 M solution in toluene), 53 mg (0.19 mmol) of ligand **78**, and 134 µL (1.29 mmol) of freshly distilled benzaldehyde provided 183 mg (75%) of **27** with an ee of 16%.

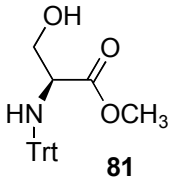
(*R*)-1-Phenylhept-2-en-1-ol (27) using 15 mol% of ligand 79. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 µL (0.76 mmol) of 1-hexyne, 325 µL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 19 mg (0.090 mmol) of ligand **79**,

and 66 μL (0.65 mmol) of freshly distilled benzaldehyde provided 98 mg (80%) of **27** with an ee of 17%.



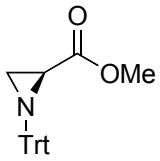
80

(*L*)-Serine methylester hydrochloride (80).[87] To a solution of 1.46 mL (20.0 mmol) of thionyl chloride in 20 mL of MeOH at 0 ºC was added 2.10 g (20.0 mmol) of *L*-serine. The reaction mixture was heated at reflux for 1 h and concentrated *in vacuo*. The resulting solid residue was resubjected to 2 M HCl as before, heated at reflux for an additional 1 h, and concentrated *in vacuo* to yield 3.00 g (97%) of **80** as a white solid: Mp 51-56 ºC (MeOH, lit. 163-166 ºC); $[\alpha]_D^{25}$ +3.7 (*c* 0.9, MeOH); lit.[87] $[\alpha]_D^{22}$ +4.0 (*c* 4.0, $CHCl_3$); ^{1}H NMR (CD_3OD) δ 4.03 (bt, 3 H, *J* = 4.2 Hz), 3.90, 3.80 (d of AB, 2 H, *J* = 4.5, 11.8 Hz), 3.75 (s, 3 H); MS (EI) *m/z* (rel intensity) 120 (M^+, 38), 88 (61), 74 (17), 60 (100).



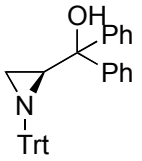
81

(*L*)-Triphenylmethyl serine methylester (81).[88] To a solution of 3.00 g (19.5 mmol) of **80** and 5.43 mL (5.54 mmol) of triethylamine in 10 mL of $CHCl_3$ at 0 ºC was added dropwise a solution of 5.43 mL (19.5 mmol) of chlorotriphenylmethane in 10 mL of $CHCl_3$. The resulting solution was stirred for 24 h and concentrated *in vacuo*. The residue was dissolved in EtOAc, washed with sodium chloride, 10% citric acid, sodium bicarbonate, and sodium chloride. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield 4.50 g (64%) of **81** as an off white solid. The solid was used in subsequent steps without further purification: ^{1}H NMR δ 7.55-7.45 (m, 6 H), 7.35-7.20 (m, 6 H), 7.19-7.10 (m, 3 H), 3.71-3.62 (m, 1 H), 3.57-3.47 (m, 2 H), 3.28 (s, 3 H), 3.10-2.90 (bs, 1 H), 2.2 (bs, 1 H).



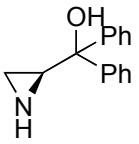
82

1-Tritylaziridine-2-carboxylate methyl ester (82). To a solution of 3.50 g (9.72 mmol) of **81** and 2.70 mL (21.4 mmol) of triethylamine in 21 mL of THF was added dropwise a solution of 0.69 mL (19.5 mmol) of methanesulfonyl chloride. The resulting solution was heated at reflux for 48 h at room temperature, and concentrated *in vacuo*. The residue was dissolved in EtOAc, washed with 10% citric acid and sodium bicarbonate solution, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by titration of the crude residue with hexanes, followed by filtration of the precipitate to yield 1.85 g (56%) of **82** as an off-white solid: Mp 105-106 ºC (hexanes, lit. 127-129 ºC); $[\alpha]_D^{25}$ -87.0 (*c* = 0.5, $CHCl_3$); lit.[88] $[\alpha]_D^{22}$ -96.8 (*c* 1.1, CH_3OH); ^{1}H NMR δ 7.60-7.40 (m, 5 H), 7.35-7.10 (m, 10 H), 3.75 (s, 3 H), 2.24 (dd, 1 H, *J* = 1.6, 2.7 Hz), 1.87 (dd, 1 H, *J* = 2.7, 6.2 Hz), 1.39 (dd, 1 H, *J* = 1.6, 6.2 Hz); MS (EI) *m/z* (rel intensity) 342 (M^+, 10), 302 (31), 266 (34), 243 (100), 165 (49), 115 (5).



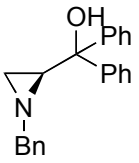
83

***N*-Tritylaziridin-2-yldiphenylmethanol (83).** A solution of 5.83 mL (11.7 mmol) of phenyl magnesium bromide in 50 mL of THF was added to 1.00 g (2.92 mmol) of **82** in 50 mL of THF at 0 ºC. The reaction mixture was stirred for 15 h at room temperature, quenched at 0 ºC with ammonium chloride, and extracted with CH_2Cl_2 (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (10% EtOAc/Hexanes) to yield 1.20 g (88%) of **83** as a white solid: Mp 130-132 ºC (EtOAc/ Hexanes, lit. 133.5-134.5 ºC); $[\alpha]_D^{25}$ -76.5 (*c* 0.5,$CHCl_3$); lit.[88] $[\alpha]_D^{22}$ -78.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.48-7.42 (m, 2 H), 7.38-7.29 (m, 8 H), 7.25-7.10 (m, 15 H), 4.46 (s, 1 H), 2.38 (dd, 1 H, *J* = 3.2, 6.2 Hz), 2.11 (bd, 1 H, *J* = 2.9 Hz), 1.36 (d, 1 H, *J* = 6.3 Hz); MS (EI) *m/z* (rel intensity) 390 ($[M-C_6H_5]^+$, 12), 243 (100), 183 (10), 165 (77), 105 (26).



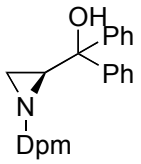
84

Aziridin-2-yldiphenylmethanol (84).[89] A solution of 300 mg (0.64 mmol) of **83** in a mixture of CH_2Cl_2 (1.5 mL) and MeOH (1.5 mL) was treated at 0 ºC with 1.13 mL of trifluoroacetic acid. The resulting suspension was concentrated *in vacuo*, washed with sodium bicarbonate, and extracted with CH_2Cl_2 (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield 140 mg (97%) of **84** as a white solid which was used without further purification in the next step: Mp 144-145 ºC (CH_2Cl_2, lit. 145-147 ºC; $[\alpha]_D^{25}$ -16.1 (*c* 0.5, $CHCl_3$); lit.[89] $[\alpha]_D^{22}$ -16.3 (*c* 0.2, $CHCl_3$); ^{1}H NMR δ 7.45-7.25 (m, 10 H), 3.37 (bt, 1 H, *J* = 5.9 Hz), 1.76 (d, 1 H, *J* = 3.5 Hz), 1.68 (d, 1 H, *J* = 3.9 Hz); MS (EI) *m/z* (rel intensity) 260 (M^+, 43), 206 (28), 183 (93), 154 (38), 105 (100).



85

***N*-Benzylaziridin-2-yldiphenylmethanol (85).** To a solution of 140 mg (0.620 mmol) of **84** and 172 mg (1.24 mmol) of potassium carbonate in 5.60 mL of THF was added 0.0700 mL (0.620 mmol) of benzyl bromide. The reaction mixture was stirred at room temperature for 20 h, diluted with H_2O and extracted with CH_2Cl_2 (3x). The combined organic layers were washed successively with 1 M HCl and H_2O, dried ($MgSO_4$), filtered, and concentrated *in vacuo.* The resulting solid was purified by chromatography on SiO_2 (5% EtOAc/Hexanes) to yield 88 mg (45%) of **85** as a white solid: Mp 86-91 ºC (EtOAc/Hexanes, lit. 88-92 ºC); $[\alpha]_D^{25}$ -33.6 (*c* 0.5, $CHCl_3$); lit.[89] $[\alpha]_D^{22}$ -35.4 (*c* 0.5, CH_2Cl_2); ^{1}H NMR δ 7.60-7.45 (m, 2 H), 7.40-7.26 (m, 15 H), 3.79 (d, 1 H, *J* = 13.2 Hz), 3.47 (d, 1 H, *J* = 13.3 Hz), 2.64-2.56 (m, 1 H), 2.07 (d, 1 H, *J* = 3.4 Hz), 1.57 (d, 1 H, *J* = 6.3 Hz); MS (EI) *m/z* (rel intensity) 315 (M^+, 42), 260 (47), 183 (95), 154 (37), 132 (34), 105 (100).



86

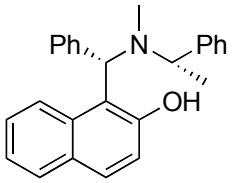
***N*-Benzhydrylaziridin-2-yldiphenylmethanol (86).** To a solution of 500 mg (2.20 mmol) of **84** and 590 mg (5.60 mmol) of potassium carbonate in 15 mL of THF was added 680 mg (3.31 mmol) of benzhydryl chloride. The reaction mixture was heated at reflux for 5 d, quenched with H_2O, and extracted with CH_2Cl_2 (3x). The combined organic layers were washed successively with 1 M HCl and H_2O, dried ($MgSO_4$), filtered, and concentrated *in vacuo.* The resulting solid was purified by chromatography on SiO_2 (5% EtOAc/Hexanes) to yield 300 mg (34%) of **86** as a white solid: Mp 192-193 ºC (CH_2Cl_2, lit. 192-194 ºC); $[\alpha]_D^{25}$ -36.2 (*c* 0.5, CH_2Cl_2); lit.[89] $[\alpha]_D^{22}$ -39.8 (*c* 0.3, CH_2Cl_2); ^{1}H NMR δ 7.45-7.33 (m, 5 H), 7.32-7.17 (m, 4 H), 7.15-7.09 (m, 2 H), 7.08-6.98 (m, 6 H), 6.97-6.89 (m, 3 H), 3.90 (s, 1 H), 3.84 (s, 1 H), 2.72 (dd, 1 H, *J* = 3.6, 6.4 Hz), 2.11 (d, 1 H, *J* = 3.6 Hz), 1.58 (d, 1 H, *J* = 6.4 Hz); MS (EI) *m/z* (rel intensity) 391 (M^+, 45), 314 (31), 224 (37), 196 (71), 167 (100), 152 (21), 105 (13).

(*S*)-1-Phenylhept-2-en-1-ol (27) using 15 mol% of ligand 83. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 µL (0.76 mmol) of 1-hexyne, 325 µL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 45 mg (0.090 mmol) of ligand **83**, and 66 µL (0.65 mmol) of freshly distilled benzaldehyde provided 105 mg (85%) of **27** with an ee of 8%.

(*S*)-1-Phenylhept-2-en-1-ol (27) using 15 mol% of ligand 85. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 µL (0.76 mmol) of 1-hexyne, 325 µL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 28 mg (0.090 mmol) of ligand **85**, and 66 µL (0.65 mmol) of freshly distilled benzaldehyde provided 91 mg (74%) of **27** with an ee of 12%.

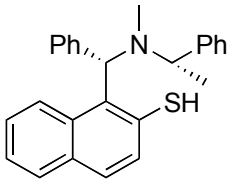
(*S*)-1-Phenylhept-2-en-1-ol (27) using 10 mol% of ligand 86. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 µL (0.76 mmol) of 1-hexyne, 325 µL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 25 mg (0.060 mmol) of ligand **86**,

and 66 μL (0.65 mmol) of freshly distilled benzaldehyde provided 98 mg (80%) of **27** with an ee of 48%.



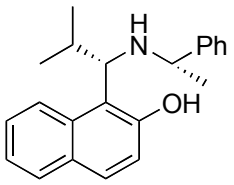
87

1-(*S*)-Phenyl(((1'*S*)-1'-phenylethyl)methylamino)methyl)-2-naphthol (87).[30] A solution of 500 mg (3.47 mmol) of 2-naphthol, 0.600 mL (4.13 mmol) of (*S*)-(-)-*N*,α-dimethylbenzylamine, and 0.440 mL (4.34 mmol) of benzaldehyde was stirred at 95 ºC for 30 h. The reaction mixture was treated with 1 mL of MeOH and stirred at room temperature for 15 h. The precipitated solid was washed with methanol and dried under *vacuo* to yield 360 mg (28%) of **87** as a light yellow solid: Mp 80–86 ºC (methanol, lit.[90] 128-129 ºC); $[\alpha]_D^{25}$ +230 (*c* 0.22, $CHCl_3$); ^{1}H NMR δ 7.95-7.75 (m, 1 H), 7.74-7.50 (m, 3 H), 7.45-7.30 (m, 5 H), 7.29-6.95 (m, 7 H), 5.48 (bs, 1 H), 4.36 (bd, 1 H, *J* = 5.3 Hz), 2.17 (bs, 3 H), 1.52 (bd, 3 H, *J* = 5.2 Hz); MS (EI) *m/z* (rel intensity) 349 ($[M-H_2O]^+$, 40), 287 (20), 246 (40), 120 (37).



88

1-(*S*)-Phenyl(((1'*S*)-1'-phenylethyl)methylamino)methyl)-2-thionaphthol (88).[30] A solution of 500 mg (3.12 mmol) of 2-thionaphthol, 0.540 mL (3.71 mmol) of (*S*)-(-)-*N*,α-dimethylbenzylamine, and 0.40 mL (3.90 mmol) of benzaldehyde was stirred at 95 ºC for 30 h. The reaction mixture was treated with 1 mL of MeOH and stirred at room temperature for 15 h. The precipitated solid was washed with methanol and dried under *vacuo* to yield 350 mg (30%) of **88** as a off white solid: Mp 132-133 ºC (MeOH); $[\alpha]_D^{25}$ +88.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 7.90-7.75 (m, 1 H), 7.74-7.45 (m, 3 H), 7.40-7.28 (m, 5 H), 7.27-6.80 (m, 7 H), 5.31 (bs, 1 H), 4.25-4.05 (m, 1 H), 3.51 (s, 3 H), 2.15 (bs, 3 H), 1.50 (bd, 3 H, *J* = 5.8 Hz); MS (EI) *m/z* (rel intensity) 231 ($[M-N(CH_3)CH_2(CH_3)Ph]^+$), 100), 202 (25), 120 (51), 164 (21).



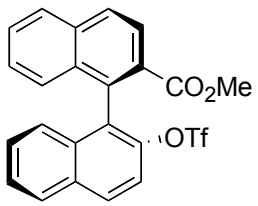
89

1-((*S*)-Propyl-(((1'*S*)-1'-phenylethyl)amino)methyl)-2-naphthol (89). To a solution of 0.390 mL (4.34 mmol) of isobutyraldehyde was added 500 mg (3.47 mmol) of 2-naphthol in 1 mL of EtOH followed by addition of 0.600 mL (4.13 mmol) of (*S*)-(-)-methylbenzylamine at 0 ºC. The reaction mixture was stirred at room temperature for 6 d. The reaction mixture was treated with 1 mL of MeOH and stirred at room temperature for 15 h. The precipitated solid was washed with methanol, and dried under *vacuo*. The resulting 350 mg (32%) of off white solid **89** were slightly contaminated with residual 2-naphthol and were used without further purification: Mp 133-134 ºC (MeOH, lit. 134-135 ºC); $[\alpha]_D^{25}$ +1.5 (*c* 0.8, $CHCl_3$); ^{1}H NMR δ 8.03-7.15 (m, 11 H), 4.22 (d, 1 H, *J* = 6.1 Hz), 3.73 (q, 1 H, *J* = 6.9 Hz), 2.21-2.14 (m, 1 H), 1.51 (d, 3 H, *J* = 6.7 Hz), 0.98 (d, 3 H, *J* = 6.7 Hz), 0.78 (d, 3 H, *J* = 7.0 Hz); MS (EI) *m/z* (rel intensity) 319 (M^+, 10), 276 (79), 198 (32), 144 (100), 115 (52), 105 (82).

(*R*)-1-Phenylhept-2-en-1-ol (27) using 15 mol% of ligand 87. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 µL (0.76 mmol) of 1-hexyne, 325 µL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 33 mg (0.09 mmol) of ligand **87**, and 66 µL (0.65 mmol) of freshly distilled benzaldehyde provided 98 mg (76%) of **27** with an ee of 2%.

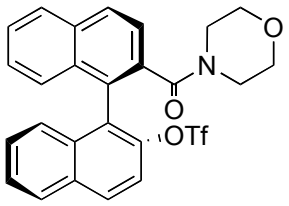
(*R*)-1-Phenylhept-2-en-1-ol (27) using 15 mol% of ligand 88. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 µL (0.76 mmol) of 1-hexyne, 325 µL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), \37 mg (0.09 mmol) of ligand **88**, and 66 µL (0.65 mmol) of freshly distilled benzaldehyde provided 101 mg (81%) of **27** with an ee of 28%.[73]

(*R*)-1-Phenylhept-2-en-1-ol (27) using 10 mol% of ligand 89. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 μL (0.76 mmol) of 1-hexyne, 325 μL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 31 mg (0.06 mmol) of ligand **89**, and 66 μL (0.65 mmol) of freshly distilled benzaldehyde provided 97 mg (80%) of **27** with an ee of 17%.[73]



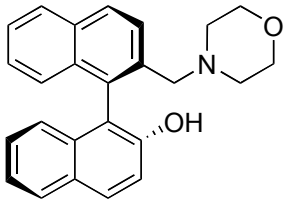
90

(*R*)-2'-Trifluoromethanesulfonyloxy-[1,1']binaphthalenyl-2-carboxylic acid methyl ester (90).[91] 3.6 mL of Methanol and 1.4 mL (mmol) of diisopropylethylamine were added to a solution of 1.00 g (1.83 mmol) of (*R*)-(-)-1,1'-Bis-2-naphthol bis(trifluoromethanesulfonate) in 10 mL of DMSO. The resulting solution was degassed by freeze-pump-thaw cycles and transferred to a 3-neck round bottom flask containing 61 mg (0.27 mmol) of $Pd(OAc)_2$ and 113 mg (0.27 mmol) of bisdiphenylphosphinopropane. The reaction was stirred under a CO atmosphere at 80 °C for 72 h. The resulting reaction mixture was diluted with NaCl, extracted with Et_2O, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (10% EtOAc/Hexanes) to yield 350 mg (42%) of **90** as an orange solid: $[\alpha]_D^{25}$ (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 8.24 (d, 1 H, *J* = 8.7 Hz), 8.10 (d, 1 H, *J* = 6.2 Hz), 8.06 (d, 1 H, *J* = 6.6 Hz), 7.99 (dd, 2 H, *J* = 2.8, 8.3 Hz), 7.64-6.55 (m, 4 H), 7.40-7.30 (m, 3 H), 7.17 (d, 1 H, *J* = 5.5 Hz), 7.14 (d, 1 H, *J* = 5.8 Hz), 3.56 (s, 3 H); MS (EI) *m/z* (rel intensity) 460 (M^+, 17), 327 (14), 311 (80), 268 (100), 239 (31), 119 (7).



91

(R)-Trifluoromethanesulfonic acid 2'-(morpholine-4-carbonyl)-[1,1']binaphthalenyl-2-yl ester (91).[92] To a solution of 100 mg (1.35 mmol) of Me_3Al in 0.67 mL of toluene at 0 °C was added 0.12 mL (1.35 mmol) of morpholine in 4 mL of toluene. The resulting solution was stirred at rt for 1 h followed by the addition of 310 mg (0.68 mmol) of **90**. The mixture was heated at reflux for 3 h, quenched with 1 N HCl, extracted with EtOAc, washed with NaCl, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (75% EtOAc/Hexanes) to yield 330 mg (95%) of **91** as a white solid: Mp 94-97 °C; $[\alpha]_D^{25}$ –24.1 (*c* 0.5, $CHCl_3$); lit.[93] $[\alpha]_D^{25}$ –25.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 8.60 (d, 2 H, *J* = 8.7 Hz), 7.97 (d, 2 H, *J* = 8.1 Hz), 7.70-7.50 (m, 4 H), 7.50-7.10 (m, 4 H), 3.80-3.40 (m, 8 H); MS (EI) *m/z* (rel intensity) 515 (M^+, 35), 429 (21), 382 (100), 366 (30), 297 (22), 239 (26), 114 (12), 91 (12), 70 (26).

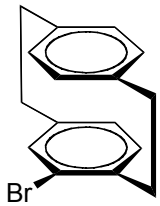


92

(R)-2'-Morpholin-4-ylmethyl-[1,1']binaphthalenyl-2-ol (92).[93] To 300 mg (0.58 mmol) of **91** in 11 mL of THF at 0 °C was added 88 mg (2.33 mmol) of $LiAlH_4$ portionwise. The solution was heated at reflux for 14 h, cooled, diluted with 40 mL of H_2O, filtered through celite, extracted with EtOAc, washed with NaCl, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (50% EtOAc/Hexanes) to yield 60 mg (28%) of **92** as an off-white solid: Mp 102-104 °C, $[\alpha]_D^{25}$ –83.2 (*c* 0.5, $CHCl_3$); lit.[93] $[\alpha]_D^{25}$ –84.8 (*c* 1.25, $CHCl_3$); ^{1}H NMR δ 8.00-7.84 (m, 4 H), 7.51 (d, 1 H, *J* = 8.4 Hz), 7.48-7.40 (m, 1 H), 7.42 (d, 1 H, *J* = 8.7 Hz), 7.35-7.25 (m, 3 H), 7.19 (ddd, 1 H, *J* = 1.2, 6.9, 8.4 Hz), 7.12

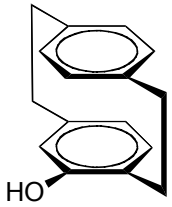
(ddd, 1 H, J = 1.2, 6.9, 8.4 Hz), 6.99 (d, 1 H, J = 8.4 Hz), 6.72 (d, 1 H, J = 8.4 Hz), 3.85-3.70 (m, 3 H), 3.70-3.58 (m, 2 H), 3.67 (d, 1 H, J = 12.0 Hz), 3.30 (d, 1 H, J = 12.0 Hz), 2.75-2.63 (m, 2 H), 2.37 (ddd, 2 H, J = 2.7, 6.3, 9.3 Hz); MS (EI) *m/z* (rel intensity) 369 (M^+, 49), 311 (4), 281 (43), 222 (100), 162 (55), 155 (76), 145 (88), 91 (61).

(*R*)-1-Phenylhept-2-en-1-ol (27) using 10 mol% of ligand 92. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 μL (0.76 mmol) of 1-hexyne, 325 μL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 24 mg (0.065 mmol) of ligand **92**, and 66 μL (0.65 mmol) of freshly distilled benzaldehyde provided 97 mg (80%) of **27** with an ee of 17%.[73]



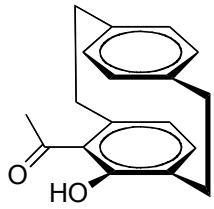
93

4-Bromo[2,2]paracyclophane (93).[94] To 0.51 mL (9.9 mmol) of Br_2 in 15 mL of CCl_4 was added 12 mg (0.2 mmol) of Fe powder and stirred for 15 min. The suspension was diluted with 45 mL of CH_2Cl_2 followed by the addition of 2.00g (9.6 mmol) of [2,2]-paracyclophane. The resulting solution was stirred for 2 h, washed with $NaHSO_3$, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield 2.8 g (99%) as an off-white solid **93** and was used without further purification in the next step: Mp 136-137 °C (CH_2Cl_2, lit.[94] Mp 134 °C); ^{1}H NMR δ 7.17 (d, 1 H, J = 6.9 Hz), 6.65-6.40 (m, 6 H), 3.48 (ddd, 1 H, J = 1.8, 10.5, 12.6 Hz), 3.27-3.02 (m, 5 H), 2.75-3.02 (m, 2 H); MS (EI) *m/z* (rel intensity) 288 (M^+, 10), 182 (12), 115 (6), 104 (100).



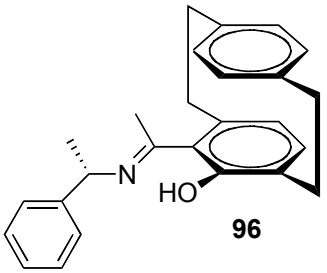
94

4-Hydroxy[2,2]paracyclophane (94).[95] To 2.7 g (9.4 mmol) of **93** in 118 mL of Et_2O at 0 °C was added 12.5 mL (18.8 mmol) of *n*-BuLi. The resulting reaction was stirred for 20 minutes at 0 °C followed by addition of 2.10 mL (18.8 mmol) of $B(OMe)_3$. The reaction was stirred for 1 h at rt, 2 mL of 0.5 M NaOH solution was added, 1.5 mL of 30% H_2O_2, extracted with Et_2O, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield 1.0 g (48%) of beige solid **94** and was used without further purification in the next step: Mp 220-223 °C (Et_2O, lit.[95] Mp 225 °C); ^{1}H NMR δ 7.01 (dd, 1 H, *J* = 6.3 Hz), 6.55 (dd, 1 H, *J* = 7.8 Hz), 6.45 (dd, 1 H, *J* = 7.8 Hz), 6.39 (d, 2 H, *J* = 8.1), 6.26 (dd, 1 H, *J* = 1.5, 7.5 Hz), 5.56 (s, 1 H), 3.38-3.26 (m, 1 H), 3.15-3.00 (m, 4 H), 3.00-2.85 (m, 2 H), 2.75-2.59 (m, 1 H); MS (EI) *m/z* (rel intensity) 224 (M^+, 43), 120 (100), 115 (14), 109 (17), 105 (23), 104 (56), 103 (15).



95

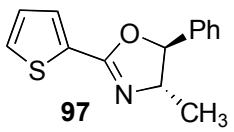
4-Acetyl-5-hydroxy[2.2]paracyclophane (95).[96] To 1.00 g (4.46 mmol) of **94** in 50 mL of CH_2Cl_2 at 0 °C was added 0.64 mL (5.80 mmol) of $TiCl_4$ followed by addition of 0.32 mL (4.46 mmol) of acetyl chloride. The resulting reaction was stirred at rt for 2 h, cooled to 0 °C, diluted with 50 mL of H_2O, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield 1.15 g (97%) of yellow/brown solid **95** and was used without further purification: Mp 112-115 °C (CH_2Cl_2, lit.[96] Mp 115-116 °C); ^{1}H NMR δ 6.98 (dd, 1 H, *J* = 1.9, 7.8 Hz), 6.63 (dd, 1 H, *J* = 1.9, 7.8 Hz), 6.54 (d, 1 H, *J* = 7.5 Hz), 6.46 (dd, 1 H, *J* = 1.8, 7.9 Hz), 6.32 (dd, 2 H, *J* = 2.1, 7.8 Hz), 3.65 (ddd, 1 H, *J* = 1.6, 9.6, 11.2 Hz), 3.45 (ddd, 1 H, *J* = 3.0, 10.1, 13.1 Hz), 3.25-3.10 (m, 2 H), 3.10-2.93 (m, 2 H), 2.76 (dd, 1 H, *J* = 7.7, 9.6 Hz), 2.72 (dd, 1 H, *J* = 7.7, 9.5 Hz), 2.65-2.50 (m, 1 H), 2.59 (s, 3 H); MS (EI) *m/z* (rel intensity) 266 (M^+, 42), 162 (71), 120 (20), 104 (100), 91 (27), 78 (20).



96

(*S,S*)-4-hydroxy-5-[1-(1-phenylethylamino)ethyl][2,2]paracyclophane.[96] To a solution of 1.15 g (4.3 mmol) of **95** in 100 mL of toluene was added 0.55 mL (4.3 mmol) of (*S*)-phenyl ethylamine and 53 mg (0.22 mmol) of Et_2SnCl_2. The resulting solution was heated at reflux for 28 h and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (40:1 Benzene/EtOH) to yield 450 mg (28%) of **96** as an orange solid: $[\alpha]_D^{25}$ –215 (*c* 0.5, $CHCl_3$); lit.[93] $[\alpha]_D^{25}$ –232 (*c* 0.4, C_6H_6); Mp 165-168 °C (Benzene/EtOH, lit.[96] Mp 165-166°C); ^{1}H NMR δ 7.53 (d, 2 H, *J* = 7.6 Hz), 7.45 (t, 2 H, *J* = 7.3 Hz), 7.39-7.28 (m, 1 H), 7.00 (d, 1 H, *J* = 7.7 Hz), 6.57 (d, 1 H, *J* = 7.8 Hz), 6.46 (d, 1 H, *J* = 7.8 Hz), 6.42 (d, 1 H, *J* = 8.9 Hz), 6.18 (d, 1 H, *J* = 7.6 Hz), 6.09 (d, 1 H, *J* = 7.7 Hz), 4.87 (q, 1 H, *J* = 6.5 Hz), 3.49-3.38 (m, 1 H), 3.29-3.13 (m, 2 H), 3.07-2.91 (m, 2 H), 2.90-2.79 (m, 1 H), 2.58-2.46 (m, 1 H), 2.44-2.32 (m, 1 H), 2.27 (s, 3 H), 1.68 (d, 3 H, *J* = 6.5 Hz); MS (EI) *m/z* (rel intensity) 404 (10), 370 (M^+, 100), 266 (25).

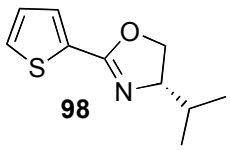
(*R*)-1-Phenylhept-2-en-1-ol (19) using 10 mol% of ligand 96. According to the general protocol, 500 mg (1.93 mmol) of zirconocene hydrochloride, 175 μL (1.52 mmol) of 1-hexyne, 650 μL (1.29 mmol) of Me_2Zn (2.0 M solution in toluene), 48 mg (0.13 mmol) of ligand **96**, and 134 μL (1.29 mmol) of freshly distilled benzaldehyde provided 194 mg (79%) of **27** with an ee of 16%.[84]



97

(4*S*,5*R*)-4-Methyl-5-phenyl-2-(2-thienyl)-1,3-oxazoline (97).[97] To 473 μL (5.09 mmol) of 2-thiophene carbonitrile and 1.00 g (6.61 mmol) of (1*S*,2*R*)-(+)-norephederine was added a solution of 34.7 mg (0.25 mmol) of $ZnCl_2$ in 15 mL of chlorobenzene. The solution was heated

at reflux for 48 h, cooled to 0 ºC, concentrated *in vacuo*, diluted with CH_2Cl_2, and extracted with H_2O (3x). The aqueous layer was re-extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (10% EtOAc/Hexanes) to yield 660 mg (53%) of **97** as a yellow oil: $[\alpha]_D^{25}$ -456 (*c* 0.5, $CHCl_3$); lit.[97] $[\alpha]_D^{22}$ -553 (*c* 0.3, $CHCl_3$); ^{1}H NMR δ 7.68 (dd, 1 H, *J* = 1.2, 3.6 Hz), 7.48 (dd, 1 H, *J* = 1.2, 5.0 Hz), 7.39-7.28 (m, 3 H), 7.26-7.18 (m, 2 H), 7.10 (dd, 1 H, *J* = 3.7, 5.0 Hz), 5.74 (d, 1 H, *J* = 9.7 Hz), 4.70-4.55 (m, 1 H), 0.86 (d, 3 H, *J* = 7.0 Hz); MS (EI) *m/z* (rel intensity) 243 (M^+, 21), 137 (100), 109 (32), 105 (12).

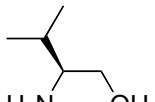


98

(4*S*)-4-Isopropyl-2-(2-thienyl)-1,3-oxazoline (98). To 695 µL (7.47 mmol) of 2-thiophene carbonitrile and 1.00 g (9.71 mmol) of L-valinol was added a solution of 51.0 mg (0.37 mmol) of $ZnCl_2$ in 15 mL of chlorobenzene. The reaction was heated at reflux for 48 h, cooled to 0 ºC, concentrated *in vacuo*, diluted with CH_2Cl_2, and extracted with H_2O (3x). The aqueous layer was re-extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (10% EtOAc/Hexanes) to yield 1.40 g (96%) of **98** as a clear oil: $[\alpha]_D^{25}$ -88.2 (*c* 0.5, $CHCl_3$); lit.[97] $[\alpha]_D^{22}$ -89.3 (*c* 0.3, $CHCl_3$); ^{1}H NMR δ 7.57 (dd, 1 H, *J* = 1.2, 3.7Hz), 7.41 (dd, 1 H, *J* = 1.2, 5.0 Hz), 7.05 (dd, 1 H, *J* = 3.7, 5.0 Hz), 4.44-4.31 (m, 1 H), 4.16-4.02 (m, 2 H), 1.93-1.77 (m, 1 H), 0.99 (d, 3 H, *J* = 6.8 Hz), 0.89 (d, 3 H, *J* = 6.8 Hz); MS (EI) *m/z* (rel intensity) 195 (M^+, 9), 152 (100), 124 (23), 111 (16).

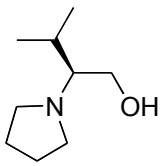
(*R*)-1-Phenylhept-2-en-1-ol (27) using 15 mol% of ligand 97. According to the general protocol, 500 mg (1.93 mmol) of zirconocene hydrochloride, 175 µL (1.52 mmol) of 1-hexyne, 650 µL (1.29 mmol) of Me_2Zn (2.0 M solution in toluene), 47 mg (0.19 mmol) of ligand **97**, and 134 µL (1.29 mmol) of freshly distilled benzaldehyde provided 203 mg (83%) of **27** with an ee of 21%.

(*S*)-1-Phenylhept-2-en-1-ol (27) using 15 mol% of ligand 98. According to the general protocol, 500 mg (1.93 mmol) of zirconocene hydrochloride, 175 μL (1.52 mmol) of 1-hexyne, 650 μL (1.29 mmol) of Me_2Zn (2.0 M solution in toluene), 37 mg (0.19 mmol) of ligand **98**, and 134 μL (1.29 mmol) of freshly distilled benzaldehyde provided 193 mg (79%) of **27** with an ee of 7%.[84]



99a

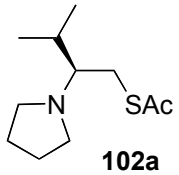
(*L*)-Valinol (100a).[98] To a solution of 2.00 g (17.1 mmol) of (*L*)-valine in 75 mL of THF at 0 ºC was added 1.30 g (34.1 mmol) of LAH over 15 min. The resulting solution was heated at reflux for 20 h, cooled to 0 ºC, quenched with 1 mL of H_2O, 1 mL of 15% NaOH, and 3 mL of H_2O, and filtered through celite. The celite was washed with Et_2O, and the combined solutions were concentrated in *vacuo* to yield 1.50 g (86%) of **100a** as a clear oil: $[\alpha]_D^{25}$ +12.3 (*c* 0.5, $CHCl_3$); lit.[98] $[\alpha]_D^{20}$ +12.4 (*c* 0.9, MeOH); ^{1}H NMR δ 3.60 (dd, 1 H, *J* = 4.0, 10.5 Hz), 3.26 (dd, 1 H, *J* = 8.8, 10.5 Hz), 2.60-2.45 (m, 1 H), 1.62- 1.43 (m, 1 H), 0.95-0.70 (m, 6 H); MS (EI) *m/z* (rel intensity) 128 ($[M-H_2O]^+$, 33), 114 (18).



101a

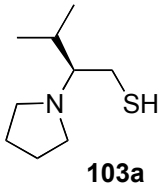
(*S*)-3-Methyl-2-pyrrolidin-1-yl-butan-1-ol (101a). To a solution of 2.00 g (19.4 mmol) of (*L*)-valinol in 80 mL of CH_3CN were added 5.36 g (38.8 mmol) of K_2CO_3 and 2.54 mL of 1,4-dibromobutane. The reaction mixture was heated at reflux for 18 h, cooled, filtered, and concentrated *in vacuo*. The resulting oil was diluted with H_2O, extracted with EtOAc, dried ($MgSO_4$), and concentrated *in vacuo* to yield 2.63 g (86%) of **101a** as a colorless oil: $[\alpha]_D^{25}$ +39.2 (*c* 1.5, $CHCl_3$); IR (KBr) 3406, 2960, 2874, 1463, 1387, 1111, 1010 cm^{-1}; ^{1}H NMR δ 3.63 (dd, 1 H, *J* = 4.8, 10.5 Hz), 3.41 (dd, 1 H, *J* = 6.9, 10.5 Hz), 2.73 (bs, 4 H), 2.34 (q, 1 H, *J* = 6.3 Hz), 1.92 (o, 1 H, *J* = 6.6 Hz), 1.88-1.70 (m, 4 H), 0.99 (d, 3 H, *J* = 6.9 Hz), 0.91 (d, 3 H, *J* = 6.6

Hz); ^{13}C NMR δ 67.0, 60.0, 49.4, 28.6, 23.7, 21.7, 18.7; MS (EI) *m/z* (rel intensity) 126 ([M-CH_2OH]$^+$, 100), 114 (98), 96 (19), 84 (40), 70 (53), 55 (32); HRMS (EI) Calcd for $C_9H_{19}NO$ 158.1545, found 158.1540.



102a

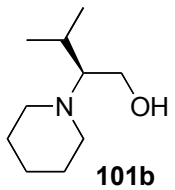
Thioacetic acid (*S*)-(3-methyl-2-pyrrolidin-1-yl-butyl) ester (102a). To a well stirred solution of 2.68 g (10.2 mmol) of PPh_3 in 75 mL of THF at 0 ºC was added 2.00 mL (10.2 mmol) of diisopropylazodicarboxylate. The resulting solution was stirred for 30 min, followed by simultaneous addition of 0.73 mL (10.2 mmol) of thiolacetic acid and 800 mg (5.10 mmol) of **101a**. The reaction mixture was stirred for 1 h at 0 ºC, 1 h at rt, and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (2% EtOAc/pet. Et_2O) to yield 725 mg (66%) of **102a** as an orange oil: $[\alpha]_D^{25}$ +52.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 3.17 (A of ABX, 1 H, *J* = 4.5, 13.8 Hz), 3.00 (B of ABX, 1 H, *J* = 5.4, 13.8 Hz), 2.68-2.55 (m, 4 H), 2.32 (s, 3 H), 2.04-1.88 (m, 1 H), 1.82-1.69 (m, 4 H), 1.34-1.24 (m, 1 H), 0.96 (d, 3 H, *J* = 7.2 Hz), 0.93 (d, 3 H, *J* = 6.9 Hz); ^{13}C NMR δ 196.0, 67.6, 50.7, 30.8, 30.5, 28.3, 23.5, 20.4, 17.8; HRMS (EI) Calcd for $C_{11}H_{21}NOS$ 216.1422, found 216.1409.



103a

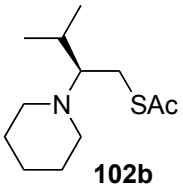
(*S*)-3-Methyl-2-pyrrolidin-1-yl-butane-1-thiol (103a). To a suspension of 42 mg (1.1 mmol) of $LiAlH_4$ in 4 mL of Et_2O at 0 ºC was added 60 mg (0.28 mmol) of **102a** in 2 mL of Et_2O. The resulting slurry was stirred for 45 min at rt, cooled to 0 ºC, and quenched with 1 mL of H_2O, 1 mL of 15% NaOH, 3 mL of H_2O, and filtered through celite. The resulting filtrate was concentrated *in vacuo* to yield 35 mg (72%) of **103a** as a colorless oil: $[\alpha]_D^{25}$ +31.8 (*c* 0.25, $CHCl_3$); IR (KBr) 2959, 2872, 2790, 1462, 1365, 1296, 1118 cm^{-1}; ^{1}H NMR δ 2.80-2.55 (m, 4

H), 2.33 (q, 1 H, J = 5.4 Hz), 1.96 (o, 1 H, J = 6.0 Hz), 1.82-1.68 (m, 4 H), 1.61 (bs, 1 H), 1.26 (s, 1 H), 0.96 (d, 3 H, J = 6.3 Hz), 0.94 (d, 3 H, J = 6.3 Hz); ^{13}C NMR δ 69.8, 50.1, 30.3, 24.0, 23.7, 20.6, 18.5; MS (EI) *m/z* (rel intensity) 173 (M^+, 43), 140 (36), 126 (100), 97 (13), 84 (6), 70 (17), 55 (8); HRMS (EI) Calcd for $C_9H_{19}NS$ 173.1238, found 216.1232.



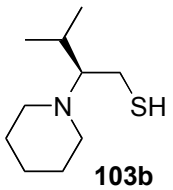
101b

(*S*)-3-Methyl-2-piperidin-1-yl-butan-1-ol (101b).[99] According to the preparation of **101a**, **101b** (76%) was obtained as a colorless oil: $[\alpha]_D^{25}$ +23.3 (*c* 0.25, $CHCl_3$); ^{1}H NMR δ 3.98 (s, 1 H), 3.56-3.45 (dd, 1 H, J = 5.4, 10.2 Hz), 3.16 (t, 1 H, J = 10.2 Hz), 2.91-2.78 (m, 2 H), 2.63-2.47 (m, 2 H), 2.35-2.21 (m, 1 H), 1.92-1.78 (m, 1 H), 1.68-1.42 (m, 6 H), 1.03 (d, 3 H, J = 6.6 Hz), 0.81 (d, 3 H, J = 6.6 Hz); MS (EI) *m/z* (rel intensity) 154 ([M-OH]+, 13), 140 (60), 128 (20), 98 (20), 91 (61), 84 (82), 69 (74), 63 (100).



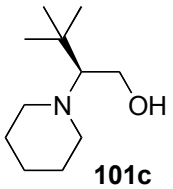
102b

Thioacetic acid (*S*)-(3-methyl-2-piperidin-1-yl-butyl) ester (102b). According to the preparation of **102a**, **102b** (56%) was obtained as an orange oil: $[\alpha]_D^{25}$ +42.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 3.07 (d, 2 H, J = 5.5 Hz), 2.62-2.53 (m, 2 H), 2.53-2.40 (m, 2 H), 2.32 (s, 3 H), 2.34-2.22 (m, 1 H), 1.83 (o, 1 H, J = 6.8 Hz), 1.53-1.46 (m, 4 H), 1.46-1.36 (m, 2 H), 0.95 (d, 3 H, J = 6.7 Hz), 0.92 (d, 3 H, J = 6.7 Hz); MS (EI) *m/z* (rel intensity) 229 (M^+, 31), 210 (80), 186 (93), 144 (76), 140 (100), 110 (49), 103 (70); HRMS (EI) Calcd for $C_{12}H_{23}NOS$ 229.1500, found 229.1507.



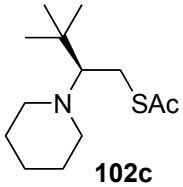
103b

(*S*)-3-Methyl-2-pyrrolidin-1-yl-butane-1-thiol (103b). According to the preparation of **103a**, **103b** (63%) was obtained as an orange oil: $[\alpha]_D^{25}$ +72.2 (*c* 0.6, $CHCl_3$); ^{1}H NMR δ 3.06 (A of ABX, 1 H, *J* = 7.2, 12.6 Hz), 3.04 (B of ABX, 1 H, *J* = 4.8, 12.9 Hz), 2.65-2.53 (m, 2 H), 2.53-2.44 (m, 2 H), 1.82 (o, 1 H, *J* = 6.6 Hz), 1.63-1.48 (m, 4 H), 1.48-1.35 (m, 2 H), 0.95 (d, 3 H, *J* = 6.6 Hz), 0.93 (d, 3 H, *J* = 6.3 Hz); ^{13}C NMR δ 70.7, 50.7, 39.2, 30.2, 26.7, 25.1, 21.2, 20.6; MS (EI) *m/z* (rel intensity) 188 (M^+, 7), 186 (10), 140 (100), 111 (16), 98 (6), 84 (18), 69 (7), 55 (13); HRMS (EI) Calcd for $C_{10}H_{21}NS$ 187.1395, found 187.1397.



101c

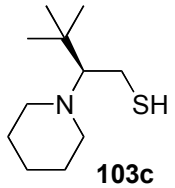
(*S*)-3,3-Dimethyl-2-piperidin-1-yl-butan-1-ol (101c). According to the preparation of **101a** except starting from (*S*)-tert-leucinol, **101c** (75%) was obtained as a white flaky solid: $[\alpha]_D^{25}$ +31.4 (*c* 0.5, $CHCl_3$); IR (KBr) 3269, 2931, 2801, 1043, 1041 cm^{-1};^{1}H NMR δ 3.58-3.40 (m, 2 H), 3.05-2.95 (m, 2 H), 2.75-2.60 (m, 2 H), 2.42 (dd, 1 H, *J* = 1.4, 10.8 Hz), 1.52-1.43 (m, 6 H), 0.97 (s, 9 H); ^{13}C NMR δ 74.8, 57.3, 51.6, 36.8, 29.1, 27.8, 24.9; MS (EI) *m/z* (rel intensity) 185 (M^+, 23), 170 (70), 154 (72), 128 (100), 98 (60), 83 (57), 68 (48); HRMS (EI) Calcd for $C_{11}H_{23}NO$ 185.1779, found 185.1780.



102c

Thioacetic acid (*S*)-(3,3-dimethyl-2-piperidin-1-yl-butyl) ester (102c). According to the preparation of **102a**, **102c** (63%) was obtained as an orange solid: $[\alpha]_D^{25}$ +114 (*c* 0.1, $CHCl_3$); IR (KBr) 3353, 2935, 2772, 2359, 1687, 1440, 1310, 1166 , 957 cm^{-1}; ^{1}H NMR δ 3.34 (dd, 1 H, *J* =

3.2, 13.6 Hz), 2.96 (dd, 1 H, *J* = 11.5, 13.6 Hz), 2.85-2.73 (m, 2 H), 2.63-2.52 (m, 2 H), 2.33 (s, 3 H), 2.28 (dd, 1 H, *J* = 3.1, 11.6 Hz), 1.57-1.40 (m, 6 H), 0.94 (s, 9 H); ^{13}C NMR δ 196.2, 73.0, 52.9; 38.0, 30.6, 27.7, 27.6, 27.1, 25.0; MS (EI) *m/z* (rel intensity) 228 ([M-CH_3]$^+$, 33), 200 (6),154 (15), 28 (144), 110 (9), 84 (100); HRMS (EI) Calcd for $C_{13}H_{26}NOS$ 244.1735, found 244.1724.



103c

(*S*)-(3,3)-Dimethyl-2-piperidin-1-yl-butane-1-thiol (103c). According to the preparation of **103a**, **103c** (73%) was obtained as a colorless oil: $[\alpha]_D^{25}$ +64.6 (*c* 0.85, $CHCl_3$); IR (KBr) 2934, 2852, 1476, 1389, 1250, 1002 cm^{-1}; ^{1}H NMR δ 2.91-2.78 (m, 4 H), 2.77 (d, 1 H, *J* = 5.4 Hz), 2.69-2.56 (m, 1 H), 2.29 (dd, 1 H, *J* = 3.0, 11.1 Hz), 1.95 (bs, 1 H), 1.56-1.39 (m, 6 H), 0.91 (s, 9 H); ^{13}C NMR δ 76.8, 52.4, 38.3, 28.9, 27.4, 25.1, 23.0; MS (EI) *m/z* (rel intensity) 343 (40), 232 (5), 200 ([M-CH_3]$^+$, 22), 154 (77), 142 (100), 111 (44), 96 (17), 83 (27), 68 (13); HRMS (EI) Calcd for $C_{12}H_{27}NS$-CH_3 200.1473, found 200.1478.

(*R*)-1-Phenylhept-2-en-1-ol (27) using 10 mol% of ligand 103a. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 μL (0.76 mmol) of 1-hexyne, 325 μL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 11 mg (0.065 mmol) of ligand **103a**, and 66 μL (0.65 mmol) of freshly distilled benzaldehyde provided 86 mg (69%) of **27** with an ee of 22%.

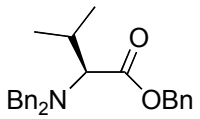
(*R*)-1-Phenylhept-2-en-1-ol (27) using 10 mol% of ligand 103b. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 μL (0.76 mmol) of 1-hexyne, 325 μL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 12 mg (0.065 mmol) of ligand **103b**, and 66 μL (0.65 mmol) of freshly distilled benzaldehyde provided 93mg (75%) of **27** with an ee of 64%.

(*R*)-1-Phenylhept-2-en-1-ol (27) using 15 mol% of ligand 103b. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 μL (0.76 mmol) of 1-hexyne, 325 μL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 17 mg (0.09 mmol) of ligand **103b**, and 66 μL (0.65 mmol) of freshly distilled benzaldehyde provided 101 mg (82%) of **27** with an ee of 77%.

(*R*)-1-Phenylhept-2-en-1-ol (27) using 20 mol% of ligand 103b. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 μL (0.76 mmol) of 1-hexyne, 325 μL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 24 mg (0.13 mmol) of ligand **103b**, and 66 μL (0.65 mmol) of freshly distilled benzaldehyde provided 98 mg (79%) of **27** with an ee of 76%.[73]

(*S*)-1-Phenylhept-2-en-1-ol (27) using 10 mol% of ligand 103c. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 μL (0.76 mmol) of 1-hexyne, 325 μL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 13 mg (0.065 mmol) of ligand **103c**, and 66 μL (0.65 mmol) of freshly distilled benzaldehyde provided 93 mg (75%) of **103c** with an ee of 61%.

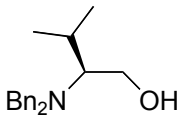
(*R*)-1-Phenylhept-2-en-1-ol (27) using 15 mol% of ligand 103c. According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 87 μL (0.76 mmol) of 1-hexyne, 325 μL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 18 mg (0.09 mmol) of ligand **10**, and 66 μL (0.65 mmol) of freshly distilled benzaldehyde provided 100 mg (81%) of **27** with an ee of 71%.



104

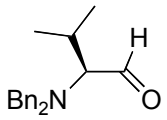
(*S*)-2-Dibenzylamino-3-methylbutyric acid benzyl ester (104).[100] A solution of 20.3 mL (171 mmol) of benzyl bromide in 40 mL of EtOH was slowly added to a solution of 5.00 g (42.7 mmol) of (*L*)-Valine and 23.6 g (171 mmol) of K_2CO_3 in a 5:1 mixture of EtOH-H_2O (250 mL). The reaction mixture was heated under reflux for 14 h, concentrated *in vacuo*, and the resulting

slurry was extracted with EtOAc (3 x 150 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (2.5% EtOAc/Hexanes) to yield 13.0 g (79%) of **104** as colorless oil: ^{1}H NMR δ 7.60-7.10 (m, 15 H), 5.31 (A of AB, 1 H, *J* = 12.0 Hz), 5.17 (B of AB, 1 H, *J* = 12.3 Hz), 3.97 (A of AB, 1 H, *J* = 13.8 Hz), 3.29 (B of AB, 1 H, *J* = 14.1 Hz), 2.92 (d, 1 H, *J* = 10.8 Hz), 2.28-2.12 (m, 1 H), 1.02 (d, 3 H, *J* = 6.6 Hz), 0.78 (d, 3 H, *J* = 6.6 Hz); MS (EI) *m/z* (rel intensity) 388 (M+, 5), 387 (13), 344 (50), 252 (90), 181 (29), 160 (30), 92 (80), 65 (100).



105

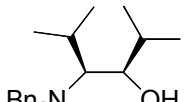
(*S*)-2-Dibenzylamino-3-methyl-butan-1-ol (105).[100] To a solution of 1.10 g (29.1 mmol) of $LiAlH_4$ in 75 mL of Et_2O at 0 ºC was added 1.10 g (24.3 mmol) of **104** in 25 mL of Et_2O. The reaction was stirred at rt for 1 h, quenched at 0 ºC with 1.1 mL of H_2O, 1.1 mL of NaOH, and 3.4 mL of H_2O. The resulting slurry was flitered through a plug of celite and washed with EtOAc. The filtrate was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (5% EtOAc/Hexanes) to yield 5.8 g (84%) of **105** as a light yellow oil: $[\alpha]_D^{25}$ +23.1 (*c* 1.0, $CHCl_3$); lit.[101] $[\alpha]_D^{25}$ +24.5 (*c* 0.8, $CHCl_3$); ^{1}H NMR δ 7.36-7.15 (m, 10 H), 3.90 (A of AB, 2 H, *J* = 13.2 Hz), 3.69 (B of AB, 2 H, *J* = 13.2 Hz), 3.64-3.52 (m, 1 H), 3.45 (t, 1 H, *J* = 10.2 Hz), 2.99 (s, 1 H), 2.09 (sp, 1 H, *J* = 6.9 Hz), 1.16 (d, 3 H, *J* = 6.7 Hz), 0.90 (d, 3 H, *J* = 6.6 Hz); MS (EI) *m/z* (rel intensity) 283 (M+, 12), 280 (10), 265 (56), 252 (37), 240 (20), 210 (38), 160 (7), 106 (11), 91 (100), 65 (21).



106

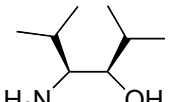
2-Dibenzylamino-3-methyl-butyraldehyde (106).[102] To a solution of 730 μL (8.47 mmol) of oxalyl chloride in CH_2Cl_2 at –60 ºC was added 1.00 mL (14.1 mmol) of DMSO in 10 mL of CH_2Cl_2 dropwise and was stirred for 15 min. 2.00 g (7.07 mmol) of **106** in 15 mL of CH_2Cl_2 was added. After the mixture was stirred for 30 min, 3.94 mL (28.2 mmol) of Et_3N was added. The

reaction was slowly warmed to rt, hydrolyzed by the addition of H_2O, and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. 1.90 g (96%) of the resulting yellow oil, **106**, was used without further purification in the next step: $[\alpha]_D^{25}$ +24.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 9.87 (d, 1H), 7.50-7.00 (m, 10 H), 4.03 (A of AB, 2 H, *J* = 13.8 Hz), 3.72 (B of AB, 2 H, *J* = 13.8 Hz), 2.73 (dd, 1 H, *J* = 3.3, 10.2 Hz), 2.25-2.40 (m, 1 H), 1.09 (d, 3 H, *J* = 6.6 Hz), 0.88 (d, 3 H, *J* = 6.6 Hz); MS (EI) *m/z* (rel intensity) 369 (4), 314 (5), 278 (3), 263 (3), 252 (45), 106 (44), 91 (100).



107

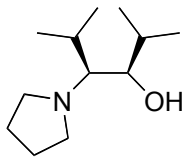
(3*R*,4*S*)-4-(Dibenzylamino)-2,5-dimethylhexan-3-ol (107).[32] To a stirred solution of 2.37 g (8.43 mmol) of **106** in 10 mL of THF at 0 ºC was added 8.43 mL (16.8 mmol) of a 2 M solution of isopropyl magnesium chloride in THF. The resulting reaction was stirred for 1 h at 0 ºC and warmed to rt. At rt, the reaction was quenched with NH_4Cl and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (100% Hexanes) to yield 1.12 g (41%) of **107** as colorless oil: $[\alpha]_D^{25}$ +20.3 (*c* 0.5, $CHCl_3$); $[\alpha]_D^{25}$ +20.4 (*c* 5.5, $CHCl_3$); ^{1}H NMR δ 7.40-7.10 (m, 10 H), 3.74 (A of AB, 2 H, *J* = 13.8 Hz), 3.73-3.65 (m, 1 H), 3.58 (B of AB, 2 H, *J* = 13.8 Hz), 2.39 (dd, 1 H, *J* = 4.8 Hz), 2.28 (o, 1 H, *J* = 6.6 Hz), 2.08 (o, 1 H, *J* = 6.3 Hz), 1.13 (d, 3 H, *J* = 6.9 Hz), 1.03 (d, 3 H, *J* = 6.6 Hz), 0.96 (d, 3 H, *J* = 6.9 Hz), 0.87 (d, 3 H, *J* = 6.6 Hz); MS (EI) *m/z* (rel intensity) 324 (M^+, 2), 282 (22), 252 (73), 210 (15), 181 (12), 160 (10), 91 (100), 65 (39).



109

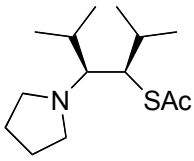
(3*R*,4*S*)-4-Amino-2,5-dimethylhexan-3-ol (109).[32] To a solution of 580 mg (1.78 mmol) of **108** in 10 mL of MeOH was added 192 mg of 20% $Pd(OH)_2$. An atmosphere of H_2 was introduced via a balloon (1 atm) and stirred for 3 h at rt. The resulting solution was filtered through celite and washed with MeOH. The filtrate was concentrated *in vacuo* to yield 250 mg (97%) of **109**

as a white solid and was used without further purification in the next step: Mp 86-89 °C; lit.[32] Mp 87-88 °C; $[\alpha]_D^{25}$ +6.1 (*c* 0.5, $CHCl_3$); lit.[32] $[\alpha]_D^{25}$ +6.8 (*c* 2.8, EtOH); ^{1}H NMR δ 3.31 (dd, 1 H, *J* = 4.4, 6.9 Hz), 2.63 (dd, 1 H, *J* = 4.0, 6.9 Hz), 2.06-1.87 (m, 2 H), 1.09 (d, 3 H, *J* = 6.6 Hz), 0.88 (d, 3 H, *J* = 6.6 Hz); MS (EI) *m/z* (rel intensity) 147 (10), 146 (M+), 102 (24), 72 (100), 55 (30).



110

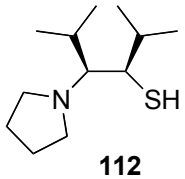
(3*R*,4*S*)-2,5-Dimethyl-4-(pyrolidin-1-yl)hexan-3-ol (110).[32] To a mixture of 624 mg (4.29 mmol) of **109** and 1.18 g (8.58 mmol) of potassium carbonate in 40 mL of CH_3CN was added 616 mg (5.15 mmol) of 1,4-dibromobutane. The reaction was heated at reflux for 16 h and filtered, and concentrated *in vacuo*. The resulting residue was diluted with H_2O, extracted with EtoAc, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (25% EtOAc/Hexanes) to yield 650 mg (76%) of **110** as a colorless oil.



111

(3*R*,4*S*)-2,5-Dimethyl-4-(pyrolidin-1-yl)hexan-3-yl ethanethioate (111).[32] To a solution of 550 mg (2.75 mmol) of **110** and 1.15 mL (8.24 mmol) of Et_3N in 20 mL of CH_2Cl_2 at 0 ºC was added 0.426 ml (5.50 mmol) of MsCl. The resulting solution was stirred for 1 h at 0 ºC and concentrated *in vacuo*. The resulting residue was dissolved in 20 mL of benzene followed by 1.15 mL (8.24 mmol) of Et_3N and 0.391 mL (5.50 mmol) of thiolacetic acid. The reaction was heated to reflux for 8 h and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (100% EtOAc/Hexanes) to yield 650 mg (76%) of **111** as a colorless oil: $[\alpha]_D^{25}$ +52.8 (*c* 0.5, $CHCl_3$); lit.[32] $[\alpha]_D^{25}$ +53.9 (*c* 1.21, $CHCl_3$); ^{1}H NMR δ 3.80 (t, 1 H, *J* = 6.3 Hz), 2.75-2.72 (m, 2H), 2.68 (t, 2 H, *J* = 6.3 Hz), 2.12-2.00 (m, 1 H), 2.00-1.85 (m, 1 H),

1.75-1.55 (m, 4 H), 0.95 (d, 6 H, *J* = 7.2 Hz), 0.93 (d, 3 H, *J* = 7.2 Hz), 0.88 (d, 3 H, *J* = 6.6 Hz). MS (EI) *m/z* (rel intensity) 215 ([M-C_2H_3O]$^+$,10), 214 (65), 138 (5), 126 (100), 110 (9), 96 (5), 70 (15).



112

(3*R*,4*S*)-2,5-Dimethyl-4-(pyrolidin-1-yl)hexan-3-thiol (112). To a suspension of 58 mg (1.5 mmol) of $LiAlH_4$ in 3 mL of Et_2O at 0 ºC was added 200 mg (0.77 mmol) of **111** in 6 mL of Et_2O. The resulting slurry was stirred for 1 h, quenched with 2M NaOH, and filtered through a pad of celite. The resulting filtrate was concentrated *in vacuo* to yield 160 mg (96%) of **112** as a yellow oil: $[\alpha]_D^{25}$ +13.0 (*c* 0.5, $CHCl_3$); lit.[32] $[\alpha]_D^{25}$ +13.7 (*c* 0.99, $CHCl_3$); ^{1}H NMR δ 3.00 (m, 1 H), 2.80-2.69 (q, 4 H, *J* = 6.0 Hz), 2.56 (dd, 1 H, *J* = 4.0, 7.8 Hz), 2.30-2.15 (m, 1 H), 2.07-1.80 (m, 1 H), 1.75-1.55 (m, 4 H), 1.01 (d, 1H, *J* = 4.4 Hz); 1.00 (d, 3 H, *J* = 4.0 Hz); 0.99 (d, 3 H, *J* = 3.4 Hz); 0.92 (d, 3 H, *J* = 6.6 Hz); MS (EI) *m/z* (rel intensity) 215 (M+, 10), 214 (20), 182 (22), 170 (48), 126 (95), 110 (55), 86 (83), 70 (90), 61 (100).

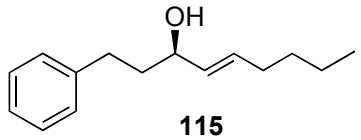
(*R*)-1-Phenylhept-2-en-1-ol (27) using 10 mol% of ligand 110. According to the general protocol, 500 mg (1.93 mmol) of zirconocene hydrochloride, 175 µL (1.52 mmol) of 1-hexyne, 650 µL (1.29 mmol) of Me_2Zn (2.0 M solution in toluene), 26 mg (0.13 mmol) of ligand **110**, and 134 µL (1.29 mmol) of freshly distilled benzaldehyde provided 200 mg (81%) of **27** with an ee of 7%.

(*R*)-1-Phenylhept-2-en-1-ol (27) using 10 mol% of ligand 111. According to the general protocol, 500 mg (1.93 mmol) of zirconocene hydrochloride, 175 µL (1.52 mmol) of 1-hexyne, 650 µL (1.29 mmol) of Me_2Zn (2.0 M solution in toluene), 33 mg (0.13 mmol) of ligand **111**, and 134 µL (1.29 mmol) of freshly distilled benzaldehyde provided 190 mg (77%) of **27** with an ee of 84%.

Chiral loading: (*R*)-1-Phenylhept-2-en-1-ol (27) using 1 mol% of ligand 112. According to the general protocol, 500 mg (1.93 mmol) of zirconocene hydrochloride, 175 μL (1.52 mmol) of 1-hexyne, 650 μL (1.29 mmol) of Me_2Zn (2.0 M solution in toluene), 2.8 mg (0.013 mmol) of ligand **17**, and 134 μL (1.29 mmol) of freshly distilled benzaldehyde provided 185 mg (75%) of **27** with an ee of 66%. The numerical value of each data point is listed below (Table 1.13).

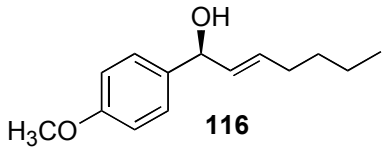
Table 1.13. Enantioselective formation of **27** using ligand **112**.

ligand loading (mol%) of **(*S*)-112**	ee[73] (%) of **(*S*)-27**
1	66
2.5	90
5	93
10	94
15	94



115

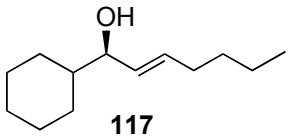
(*R*)-1-Phenylnon-4-en-1-ol (115) using 5 mol% of ligand 112.[46] According to the general protocol, 500 mg (1.93 mmol) of zirconocene hydrochloride, 175 μL (1.52 mmol) of 1-hexyne, 650 μL (1.29 mmol) of Me_2Zn (2.0 M solution in toluene), 14 mg (0.065 mmol) of ligand **112**, and 170 μL (1.29 mmol) of freshly distilled hydrocinnamaldehyde provided 220 mg (79%) of **115** with an ee of 84%: ^{1}H NMR δ 5.70-5.39 (m, 2 H), 3.76 (sx, 1 H, J = 3.4 Hz), 2.04 (q, 2 H, J = 6.8 Hz), 1.78-1.76 (m, 1 H), 1.76-1.63 (m, 4 H), 1.45-1.05 (m, 10 H), 1.05-0.80 (m, 2 H), 0.90 (t, 3 H, J = 6.9 Hz).



116

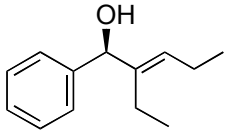
(*R*)-1-(4-Methoxyphenyl)-pent-2-en-1-ol (116) using 10 mol% of ligand 112.[46] According to the general protocol, 500 mg (1.93 mmol) of zirconocene hydrochloride, 175 μL (1.52 mmol) of

1-hexyne, 650 μL (1.29 mmol) of Me_2Zn (2.0 M solution in toluene), 28 mg (0.129 mmol) of ligand **112**, and 156 μL (1.29 mmol) of freshly distilled *p*-anisaldehyde provided 185 mg (65%) of **116** with an ee of 42%: ^{1}H NMR δ 7.30 (d, 2 H, *J* = 8.7 Hz), 6.90 (d, 2 H, *J* = 8.5 Hz), 5.82-5.60 (m, 2 H), 5.13 (dd, 1 H, *J* = 3.7, 5.9 Hz), 3.82 (s, 3 H), 2.07 (q, 2 H, *J* = 6.8 Hz), 1.80 (d, 1 H, *J* = 3.5 Hz), 1.45-1.25 (m, 4 H), 0.90 (t, 3 H, *J* = 7.1 Hz).



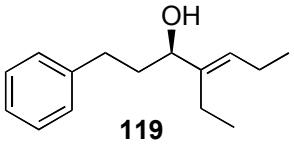
117

(*R*)-1-Phenylnon-4-en-1-ol (117) using 5 mol% of ligand 112.[46] According to the general protocol, 500 mg (1.93 mmol) of zirconocene hydrochloride, 175 μL (1.52 mmol) of 1-hexyne, 650 μL (1.29 mmol) of Me_2Zn (2.0 M solution in toluene), 14 mg (0.065 mmol) of ligand **117**, and 156 μL (1.29 mmol) of freshly distilled cyclohexanecarbaldehyde provided 177 mg (70%) of **27** with an ee of 73%: ^{1}H NMR δ 7.35-7.15 (m, 5 H), 5.78-5.42 (m, 2 H), 4.15-4.00 (m, 2 H), 2.80-2.60 (m, 2 H), 2.04 (q, 2 H, *J* = 6.3 Hz), 1.95-1.70 (m, 2 H), 1.43 (d, 1 H, *J* = 3.8 Hz), 1.41-1.25 (m, 3 H), 0.91 (t, 3 H, *J* = 7.0 Hz).



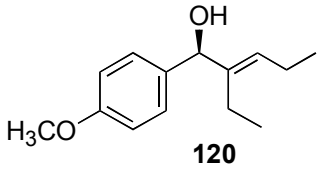
118

(*R*)-2-Ethyl-1-phenylpent-2-en-1-ol (118) using 10 mol% of ligand 112.[46] According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 86 μL (0.76 mmol) of 3-hexyne, 323 μL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 14 mg (0.065 mmol) of ligand **112**, and 78 μL (0.645 mmol) of freshly distilled benzaldehyde provided 110 mg (89%) of **118** with an ee of 90%: ^{1}H NMR δ 7.43-7.28 (m, 5 H), 5.60 (t, 1 H, *J* = 7.8 Hz), 5.18 (s, 1 H), 2.20-1.96 (m, 4 H), 1.96-1.85 (m, 1 H), 1.78 (bs, 1 H), 1.51 (d, 1 H), 1.03 (t, 3 H, *J* =7.5 Hz), 0.84 (t, 3 H, *J* = 7.5 Hz); ^{13}C NMR δ 142.7, 142.1, 128.6, 128.2, 127.3, 126.5, 78.1, 20.7, 20.5, 14.4, 14.2; MS (EI) *m/z* (rel intensity) 190 (M^+, 33), 172 (15), 161 (100), 157 (13), 143 (82), 128 (44), 105 (45).



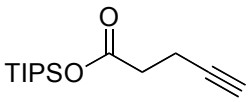
119

(*R*)-4-Ethyl-1-phenylhept-4-en-3-ol (119) using 10 mol% of ligand 112.[46] According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 86 μL (0.76 mmol) of 3-hexyne, 323 μL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 14 mg (0.065 mmol) of ligand **112**, and 95 μL (0.645 mmol) of freshly distilled hydrocinnamaldehyde provided 91 mg (65%) of **119** with an ee of 53%: ^{1}H NMR δ 7.34-7.14 (m, 5 H), 5.39 (t, 1 H, *J* = 7.2 Hz), 4.06 (ddd, 1 H, *J* = 2.4, 3.9, 6.3 Hz), 2.81-2.57 (m, 2 H), 2.20-1.98 (m, 4 H), 1.88 (q, 2 H, *J* = 8.1 Hz), 1.41 (d, 1 H, *J* = 3.0 Hz), 1.03 (t, 3 H, *J* = 7.5 Hz), 1.00 (t, 3 H, *J* = 7.5 Hz); ^{13}C NMR δ 142.53, 142.18, 128.54, 128.42, 128.31, 125.71, 76.23, 37.26, 32.30, 20.66, 20.13, 14.64, 14.37; MS (EI) *m/z* (rel intensity) 218 (M^+, 56), 200 (45), 189 (74), 171 (47), 126 (62), 113 (83), 109 (100).



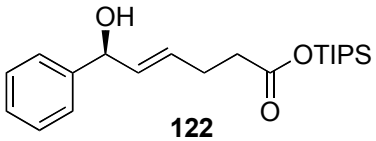
120

(*R*)-2-Ethyl-1-(4-methoxyphenyl)pent-2-en-1-ol (120) using 10 mol% of ligand 112.[46] According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 86 μL (0.76 mmol) of 3-hexyne, 323 μL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 14 mg (0.065 mmol) of ligand **112**, and 78 μL (0.645 mmol) of freshly distilled *p*-anisaldehyde provided 90 mg (63%) of **120** with an ee of 87%: ^{1}H NMR δ 7.29 (d, 2 H, *J* = 9.9 Hz), 6.87 (d, 2 H, *J* = 8.7 Hz), 5.59 (t, 1 H, *J* = 7.2 Hz), 5.12 (d, 1 H, *J* = 2.4 Hz), 2.11 (p, 2 H, *J* = 7.5 Hz), 2.02 (dq, 1 H, *J* = 7.8 Hz, 15.3 Hz), 1.88 (dq, 1 H, *J* = 7.5, 15.0 Hz), 1.79 (d, 1 H, *J* = 3.3 Hz), 1.03 (t, 3 H, *J* = 7.5 Hz), 0.85 (t, 3 H, *J* = 7.5 Hz); ^{13}C NMR δ 158.9, 142.2, 134.9, 127.9, 127.8, 113.6, 77.4, 55.2, 20.7, 20.7, 14.4, 14.1; MS (EI) *m/z* (rel intensity) 220 (M^+, 20), 202 (47), 191 (65), 173 (79), 158 (43), 137 (100), 121 (48), 115 (30), 109 (24).



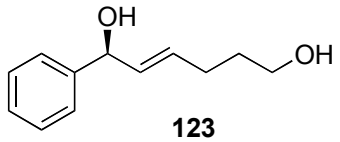
121

Pent-4-ynoic acid triisopropyl silyl ester (121).[46] To a solution of 1.00 g (10.2 mmol) of 4-pentynoic acid and 2.18 mL (10.2 mmol) of TIPSCl in 60 mL of CH_2Cl_2 was added 694 mg (10.2 mmol) of imidazole. The reaction was stirred for 5 h, quenched with H_2O, extracted with CH_2Cl_2, dried($MgSO_4$), and concentrated *in vacuo*. . The resulting crude residue was purified by chromatography on SiO_2 (25% EtOAc/Hexanes) to yield 2.20 g (85%) of **121** as a colorless oil. ^{1}H NMR 2.65-2.55 (m, 2 H), 2.54-2.44 (m, 2H), 2.10-1.93 (m, 1 H), 1.30 (sx, 3 H, J = 7.2 Hz), 1.08 (d, 18 H, J = 7.2 Hz); MS (EI) *m/z* (rel intensity) 295 (20), 271 (20), 257 (13), 211 ([M-*i*-Pr]$^+$, 100), 155 (5), 131 (14), 103 (21), 75 (37), 61 (37).



122

(*S*)-6-Hydroxy-6-phenylhex-4-enoic acid triisopropyl silylester (122) using 10 mol% of ligand 112.[46] According to the general protocol, 250 mg (0.820 mmol) of zirconocene hydrochloride, 193 mg (0.76 mmol) of TIPS alkyne, 323 μL (0.645 mmol) of Me_2Zn (2.0 M solution in toluene), 14 mg (0.065 mmol) of ligand **112**, and 65 μL (0.645 mmol) of freshly distilled benzaldehyde provided 168 mg (72%) of **122** with an ee of 71%: ^{1}H NMR δ 7.43-7.27 (m, 5 H), 5.87-5.68 (m, 2 H), 5.17 (t, 1 H, J = 4.8 Hz), 2.51-2.34 (m, 4 H), 1.86 (d, 1 H, J = 3.6 Hz), 1.27 (sp, 3 H, J = 7.5 Hz), 1.06 (d, 18 h, J = 7.2 Hz); MS (EI) *m/z* (rel intensity) 344 ([M-C_3H_7]$^+$, 65), 317 (68), 301 (100), 157 (7), 141 (5), 131 (11), 103 (14), 75 (20), 61 (11).



123

(*S*)-1-Phenylhex-2-ene-1,6-diol (123). To 80 mg (2.21 mmol) of $LiAlH_4$ in 4 mL of Et_2O at 0 °C was added 80 mg (0.22mmol) of **122** in 2 mL of Et_2O. The resulting reaction was heated at reflux for 3 h, quenched with $NaSO_4 \bullet H_2O$, filtered through celite, and concentrated in vacuo. The resulting crude residue was purified by chromatography on SiO_2 (100% Hexanes) to yield 36 mg g (86%) of **123** as colorless oil: ^{1}H NMR δ 7.44-7.28 (m, 5 H), 5.86-5.67 (m, 2 H), 5.20 (dd, 1 H, *J* = 3.0, 3.6 Hz), 3.66 (q, 2 H, *J* = 6.3 Hz), 2.17 (q, 2 H, *J* = 6.9 Hz), 1.90 (d, 1 H, *J* = 3.3 Hz), 1.69 (p, 2 H, *J* = 6.6 Hz), 1.26 (t, 1 H, *J* = 5.1 Hz); MS (EI) *m/z* (rel intensity) 174 (M+, 30), 143 (5), 131 (17), 104 (17), 86 (64), 84 (100).

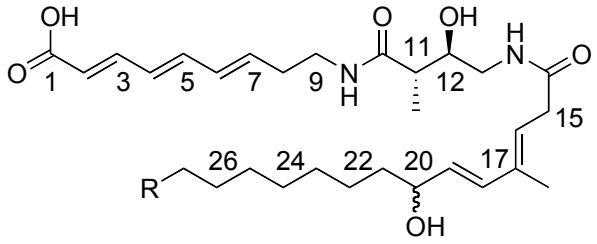
2.0 Pseudotrienic Acid

2.1 Introduction

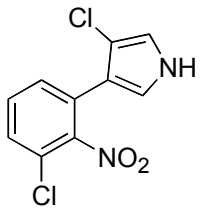
Figure 2.1. Flowers of *Brassica rapa* subsp. *Rapa L.* (Brassicaceae).[103]

Pseudotrienic acids A and B, differing only in the length of their side chains, are secondary metabolites isolated in 2005 using bioassay-guided fractionation of a liquid culture broth of *Pseudomonas* sp. isolate MF381-IODS by Pohanka *et al*.[104] The *Pseudomonas* sp. was isolated from the roots of a *Brassica rapa* subsp. *Rapa L.* (Brassicaceae) plant specimen collected in Switzerland (Figure 2.1).[105] Pseudotrienic acids were isolated using a combination of solid phase extraction and preparative HPLC. During the chromatography, the activity of the fractions was monitored by an *in vitro* bioassay based on inhibition of growth of cells or spore germination of the organisms *Fusarium culmorum, Drechslera sorokiniana* and *Staphylococcus aureus*.[106] Along with pseudotrienic acids A and B, 2,3-deepoxy-2,3-didehydrorhizoxin(DDR) and pyrrolnitrin were also isolated from the broth (Figure 2.2).

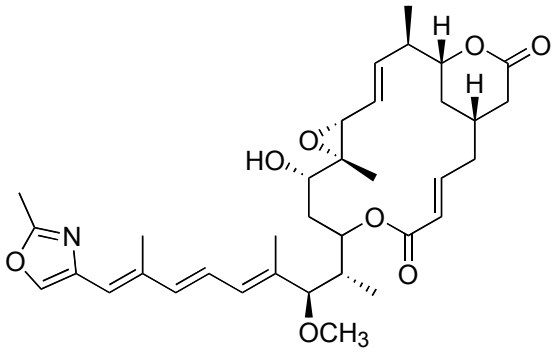
Minimum inhibitory concentrations of the pseudotrienic acids were determined for human and agricultural pathogens as well as bacteria. Both acids inhibited the growth of *Staphylococcus aureus* and *Pseudomonas syringae* pv. *Syringae* at a MIC of 70 μg/mL and were not selective towards the inhibition of *Aspergillus fumigatus*, and *Candida albicans* at concentrations of up to 100 μg/mL.



130: R = CH_2CH_3 Pseudotrienic Acid A
131: R = H Pseudotrienic Acid B



132: Pyrrolnitrin

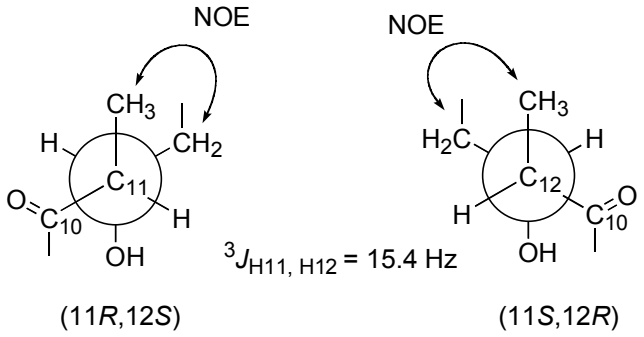


133: 2,3-Deepoxy-2,3-didehydrorhizoxin (DDR)

Figure 2.2. Antimicrobial compounds isolated from *Pseudomonas* sp. MF381-IODS.

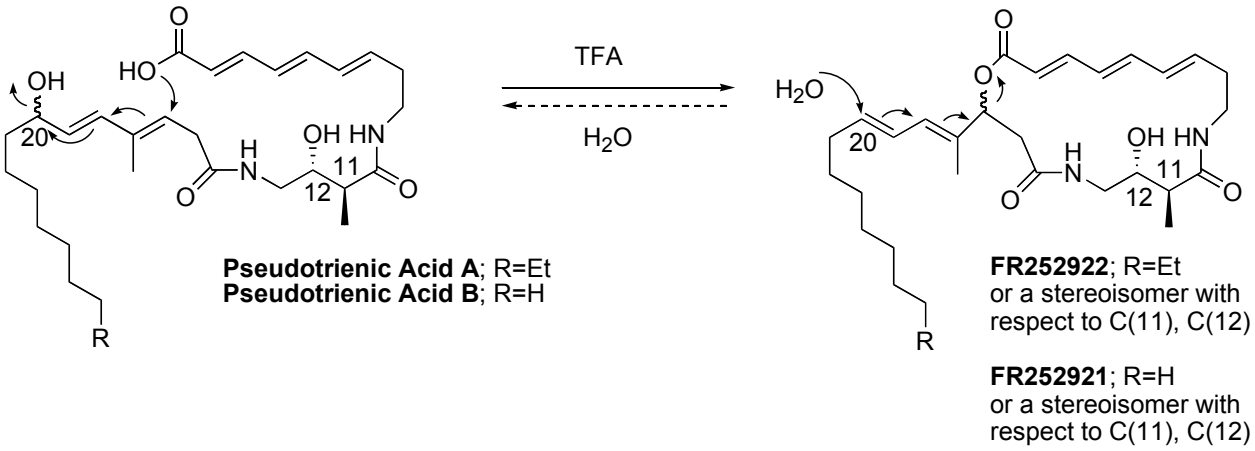
The structural features of pseudotrienic acids include an (*E,E,E*)-trienic acid segment and a trisubstituted conjugated (*E,E*)-diene at C(16)-C(19). The alkene portions of the molecule are connected by two amide linkages to a γ-amino-β-hydroxy acid with (11*S*,12*R*)-configuration. The carbon skeleton of the pseudotrienic acids was assigned based on ^{1}H NMR, ^{13}C NMR, and MS. The *trans*-configuration of all double bonds was established using NOE experiments and determined further by the magnitude of the three bond coupling constants ($^{3}J_{HH}$ = 14.8–16.0 Hz). The relative configurations at C(11) and C(12) were assigned using NOE (Figure 2.3). The absolute configuration was determined by a chiral resolution method. A resolution is achieved

by derivatizing a chiral compound of interest with an enantiomerically pure reagent.[107] In this case, the natural product was degraded through chemical transformations into smaller segments that were analyzed using chiral resolution. The absolute stereochemistry of the γ-amino β-hydroxy acid was determined to be (11*S*,12*R*) in comparison to bistramide A which also contains a γ-amino β-hydroxy acid moiety with a (*S*,*R*)-configuration.[108] The stereochemistry at C(20) was concluded to be a 1:1 mixture of epimers after degradation and GC-MS experiments.



F**igure 2.3.** Elucidation of configuration at C(11) and C(12) of pseudotrienic acids by NOE and $^{3}J_{HH}$ analysis**.**

The biosynthetic origin of the pseudotrienic acids is uncertain. They may be derived from a ring opening of a macrolactone. In the presence of 0.1% TFA, pseudotrienic acids are converted readily to the lactone form (Scheme 2.1). The isolated lactones have the same bonding pattern as macrolides FR252922 and FR252921 which were previously described by Fujine *et al.*[109] The macrolides were isolated from a *Pseudomonas fluorescence* strain and demonstrate immunosuppressive activity.[110] The absolute configurations of the three stereogenic carbons in FR2529922 and FR252921 have yet to be assigned. However, it is suspected that FR252922 and FR252921 possess configurations at C(11) and C(12) identical to those present in pseudotrienic acids. Biosynthetically, pseudotrienic acids may be derived from ring opening of the lactone by nucleophilic attack of H_2O at C(20), leading to a mixture of epimers. This proposed mechanism is in agreement with the formation of epimers at C(20) of the pseudotrienic acids. However, this is contrary to the usually very stereospecific biosynthesis of polyketides.[111] Thus, the epimerization at the C(20) stereogenic carbon could have occured during the isolation of the natural product.

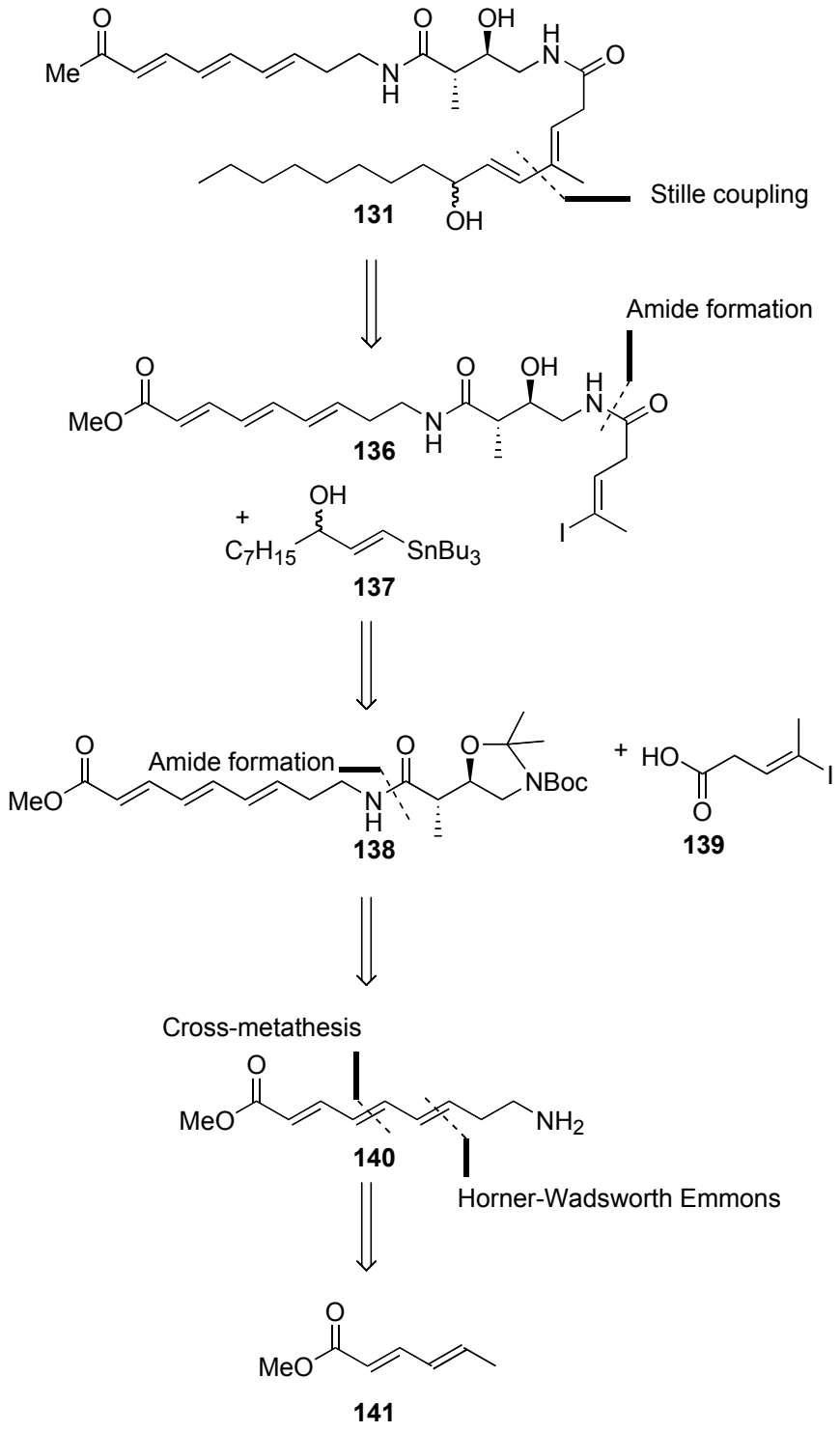


Scheme 2.1. Lactone formation under acidic conditions.

The intrinsic structure as well as the ambiguous biosynthetic pathway makes the pseudotrienic acids an attractive synthetic target. By synthesizing a single enantiomer at C(20), the origin of the mixture of diastereomers isolated can be further investigated. A single diastereomer could be resubjected to isolation conditions to determine if epimerization of the C(20) center is as a result of isolation conditions. The synthesis of pseudotrienic acid can also provide valuable insights that could be relayed to establish the absolute configurations of FR252922 and FR252921 and obtain clues for their biosynthesis.

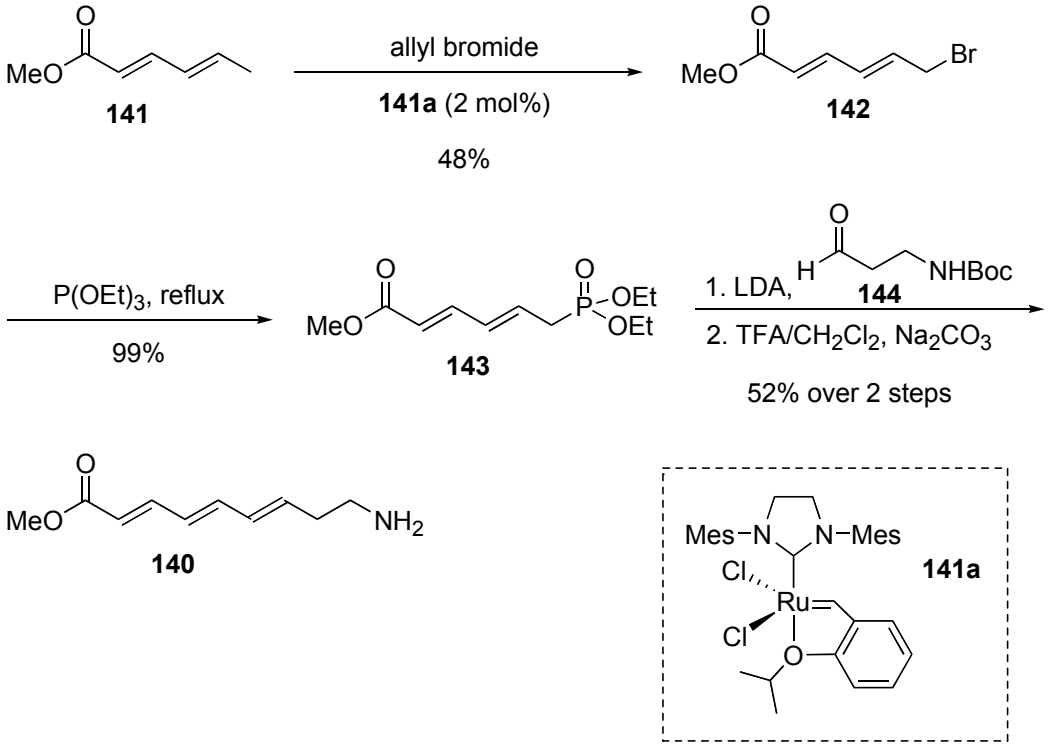
2.1.1 Previous Synthesis of Pseudotrienic Acid B

To date, one total synthesis of pseudotrienic acid B has been reported by Cossy *et al*., affording pseudotrienic acid B as a mixture of epimers at C(20).[112] Their retrosynthetic strategy is depicted in Scheme 2.2. The analysis requires a late stage palladium catalyzed Stille coupling between a vinyl iodide and vinyl stannane to generate the (*E,E*)-diene. The vinyl iodide stems from amide formation between a trienic protected amine and carboxylic acid. The trienic ester portion was synthesized based on a cross metathesis and a Horner-Wadsworth-Emmons reaction sequence.



Scheme 2.2. Cossy's retrosynthetic analysis of pseudotrienic acid B.

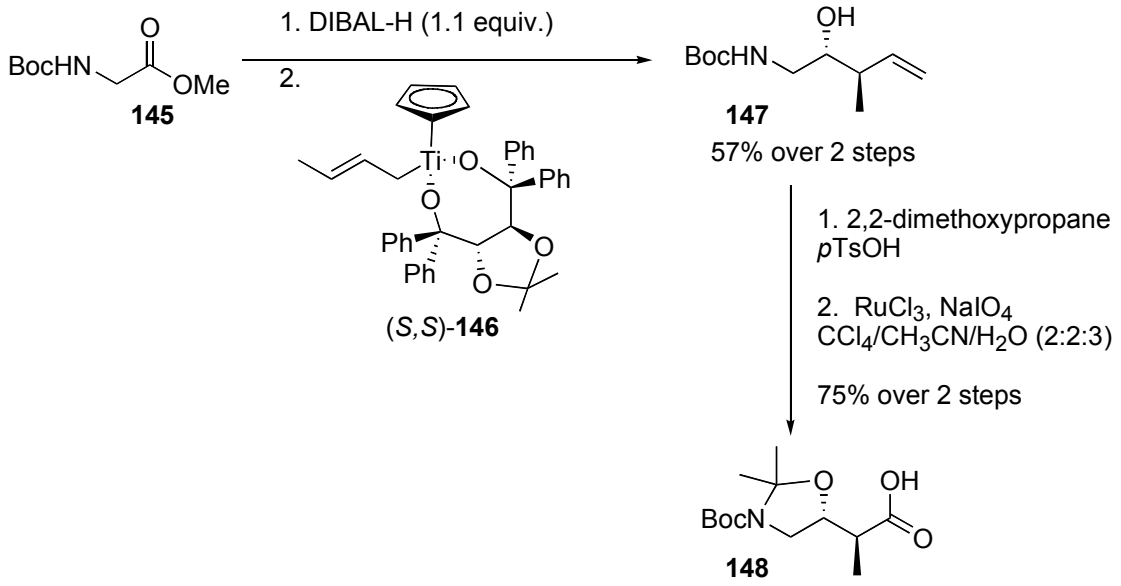
The synthesis of the trienic acid segment was initiated by the metathesis of methyl sorbate with allyl bromide in the presence of 5 mol% of Grubbs-Hoveyda catalyst[113] to afford **142** in 48% yield with good stereoselectivity (*E,E*/*E,Z* > 95:5) (Scheme 2.3). Phosphonation of allylic bromide **142** under Michaelis-Arbuzov conditions employing $P(OEt)_3$ led to the formation of **143** in 99% yield. Diethylphosphonate **143** was coupled with Boc-protected amino aldehyde **144** in a Horner-Wadsworth-Emmons olefination followed by subsequent deprotection to provide the trienic ester fragment **140** in 52% yield over 2 steps and 25% overall yield.



Scheme 2.3. Synthesis of the trienic acid fragment **140**.

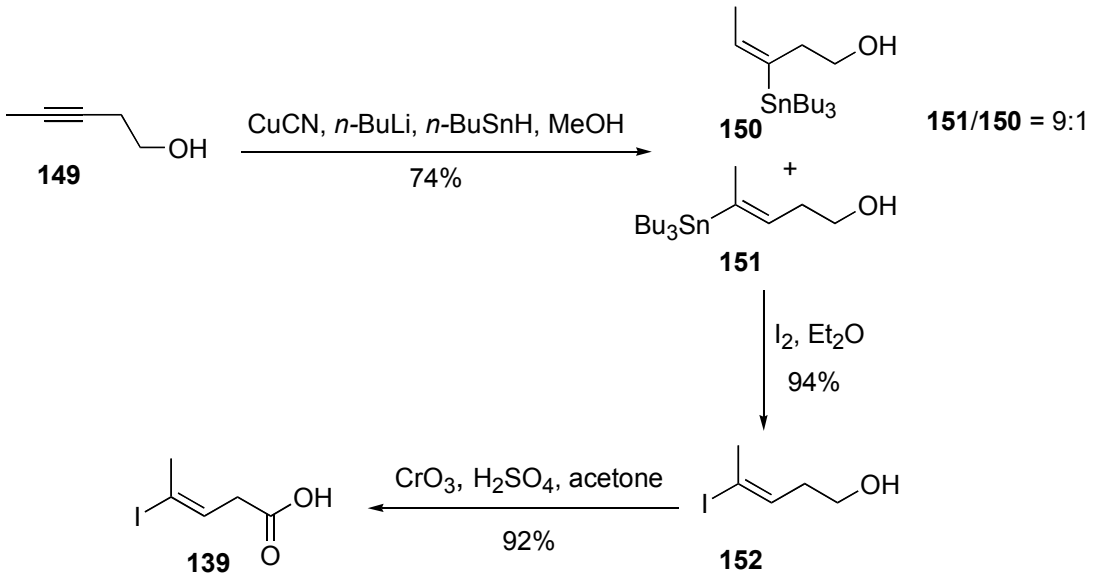
The contiguous stereocenters of the γ-amino acid segment were installed using Hafner-Duthaler crotylation methodology.[114] Initial reduction of methylester **145** with DIBAL-H resulted in the formation of the requisite aldehyde. The aldehyde underwent reaction with crotyltitanocene to afford the homoallylic amino alcohol, **147**, in 57% yield with a diastereomeric ratio of 95:5 and an enantiometric excess of 95% (Scheme 2.4). The amino alcohol was protected as an N,O-acetonide followed by oxidative cleavage of the terminal alkene

under Sharpless conditions, using catalytic $RuCl_3$ and $NaIO_4$, to afford **148** in 75% yield over 2 steps.



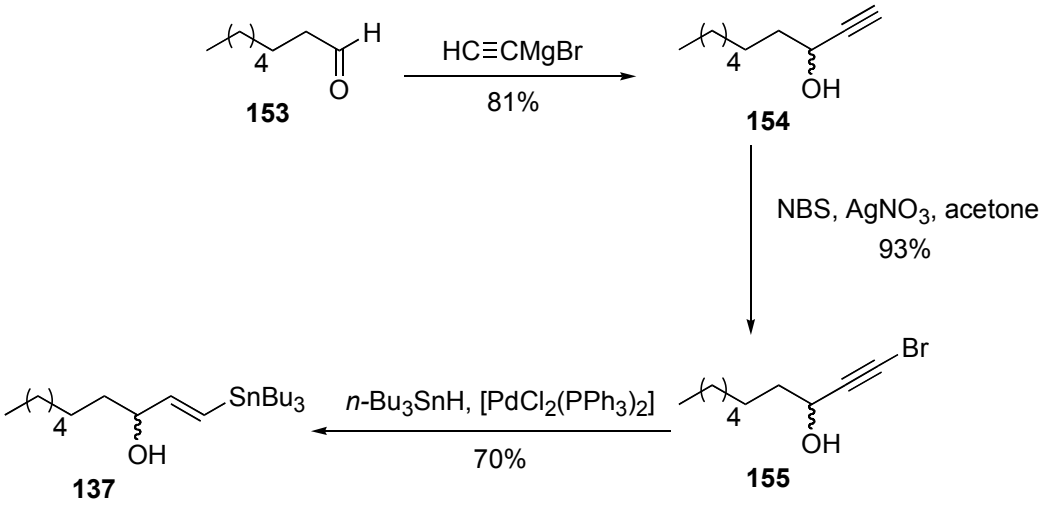
Scheme 2.4. Utililization of crotyltitanocene in the synthesis of fragment **148**.

Vinyl iodide fragment **139** was synthesized via stannylcupration of pent-3-yn-1-ol to give a mixture of vinyl stannane regioisomers favoring the desired regioisomer (9:1) in a combined yield of 74% (Scheme 2.5). The desired isomer was subject to iododestannylation, resulting in iodide **152**. Lastly, oxidation with Jones' reagent afforded the desired carboxylic acid **139** in 92% yield.



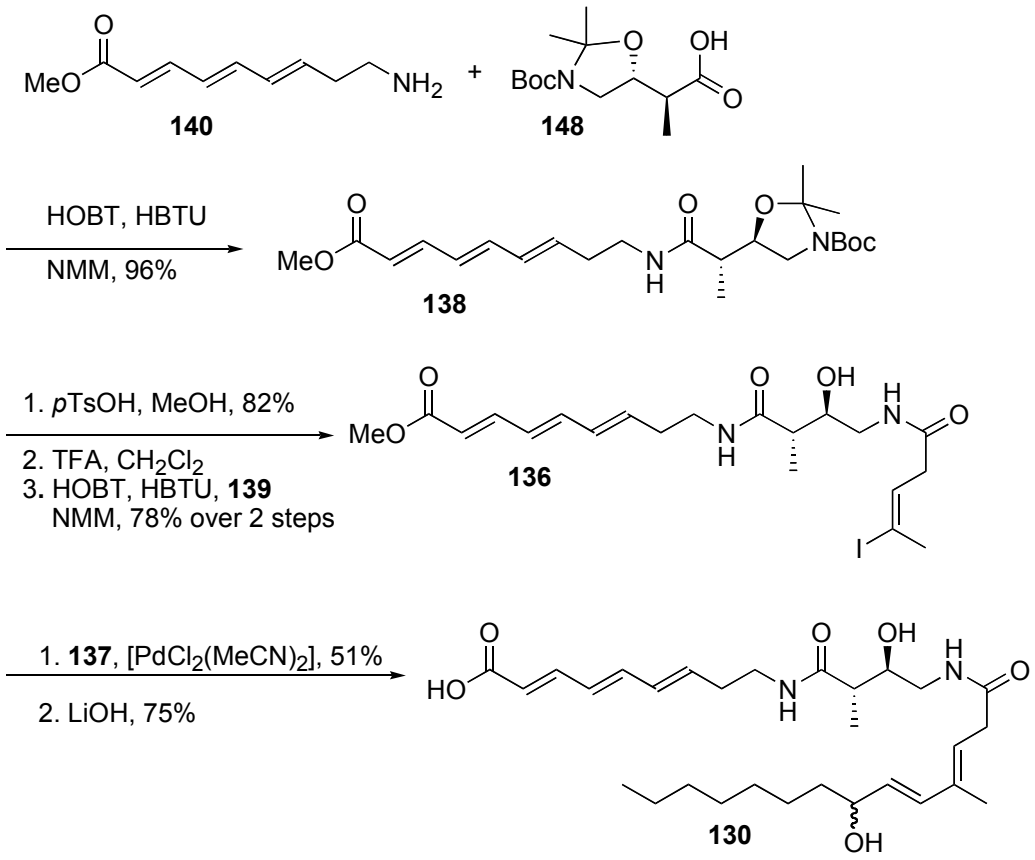
Scheme 2.5. Synthesis of vinyl iodide **139**.

Vinyl stannane **137** was synthesized from octanal following a synthetic sequence beginning with ethynyl magnesium bromide addition to give **154** in 81% yield (Scheme 2.6). Conversion of the alkyne to the bromoalkyne in the presence of NBS and $AgNO_3$ resulted in 93% yield of **155** followed by hydrostannylation to afford the desired (*E*)-vinyl stannane **137** in 70% yield.



Scheme 2.6. Synthesis of vinyl stannane **137**.

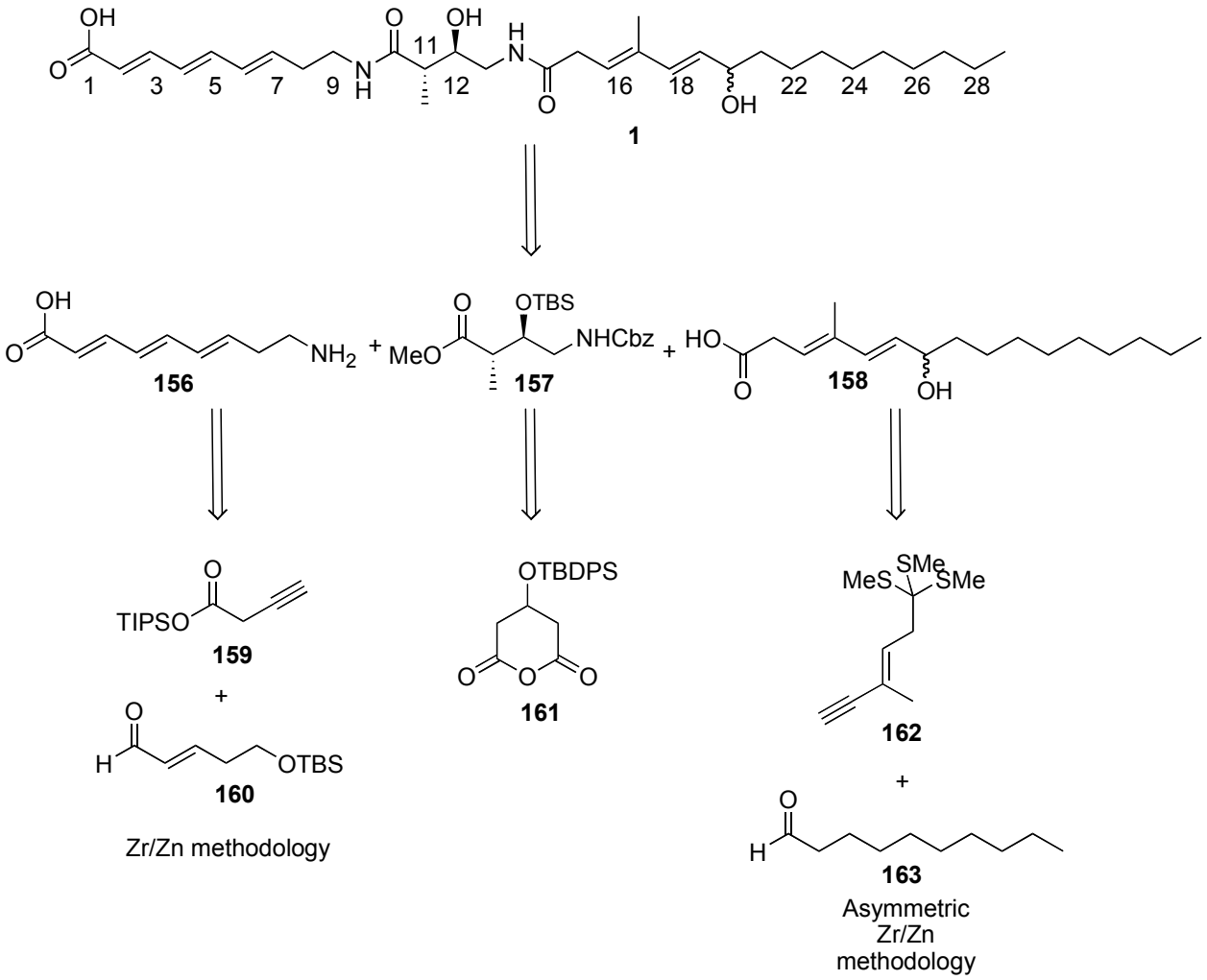
With the desired fragments in hand, elaboration toward pseudotrienic acid B began with a standard HOBT-coupling of carboxylic acid **148** with trienic amine **140**, affording the desired product in 96% yield (Scheme 2.7). Removal of the the acetonide using TFA, deprotection of the *t*-butyloxycarbonyl group using *p*TsOH and MeOH, followed by HOBT-coupling of the resulting amine with acid **139** afforded the C(1)-C(19) segment of the natural product in 78% yield over 2 steps. The resulting vinyl iodide underwent a $[PdCl_2(MeCN)_2]$-catalyzed Stille cross-coupling followed by saponification of the methylester to furnish pseudotrienic acid B in 75% yield. The Cossy synthesis of pseudotrienic acid B is highly convergent with the longest linear sequence consisting of 10 steps from methyl sorbate proceeding in 5.8% overall yield.



Scheme 2.7. Coupling of fragments towards the synthesis of pseudotrienic acid B.

2.2 Pseudotrienic Acid A: Retrosynthesis

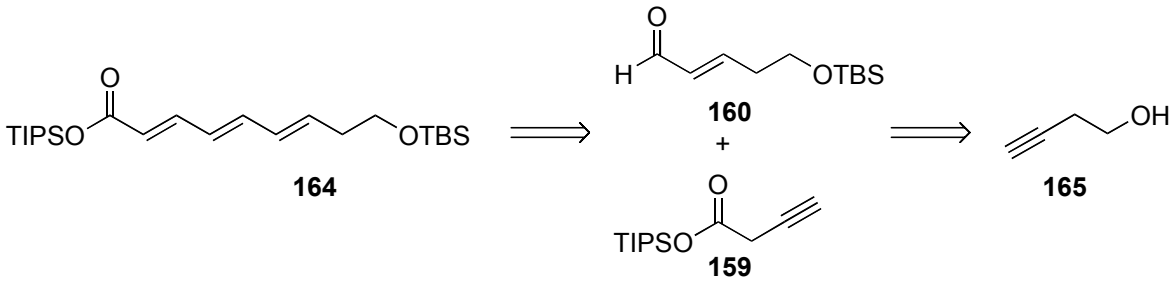
The unassigned hydroxy-bearing stereogenic carbon C(20) is a salient feature of this molecule, which provides an incentive to test the asymmetric alkenylzirconium/zinc methodology, utilizing the ligands synthesized in Chapter 1. Using the asymmetric methodology, both enantiomers at C(20) can be synthesized easily by using both enantiomers of the ligand. The retrosynthetic disassembly is depicted in Scheme 2.8. Pseudotrienic acid A originates from three distinct segments. The trienic acid portion **156** would arise from an alkenyl zirconocene/zinc addition to the α,β-unsaturated aldehyde **160** followed by base-induced 1,4-elimination.[120] Formation of the C(10)-C(14) fragment would arise form desymmetrization of cyclic anhydride **161** followed by Frater-Seebach alkylation, providing the desired (*S,R*)-configuration at C(11) and C(12).[133] As mentioned earlier, the C(20) stereocenter would be formed using an asymmetric zirconocene/zinc addition of eneyne **162** to decyl aldehyde.



Scheme 2.8. Retrosynthetic analysis of pseudotrienic acid A.

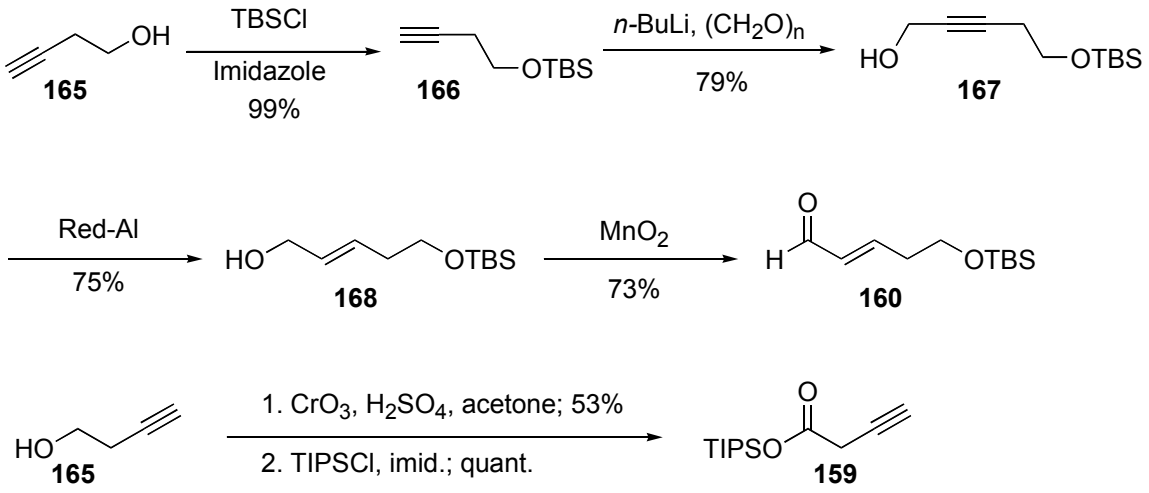
2.3 Synthesis of the Trienic Acid Segment

Retrosynthetically, the C(1)-C(9) segment **156** was envisioned to arise from intermediate **164**. Fragment **164** would arise from an alkenylzirconocene/zinc addition followed by base-induced 1,4-elimination (Scheme 2.9). Fragment **164** can be simplified into α,β-unsaturated aldehyde **160** and alkyne **159**. Both of these intermediates conveniently originate from 3-butyn-1-ol.



Scheme 2.9. Retrosynthetic analysis of trienic acid **164**.

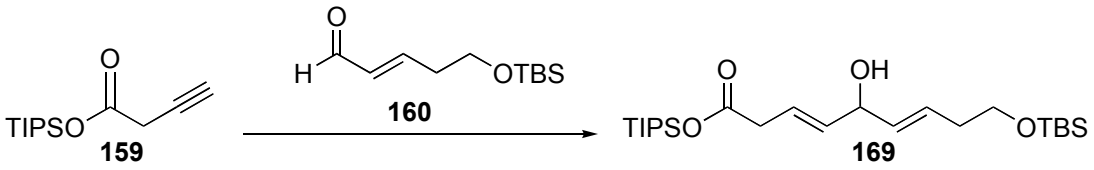
The total synthesis of pseudotrienic acid A commenced with the synthesis of trienic acid **164**. Synthesis of **163** was initiated by TBS protection of 3-butyn-1-ol followed by hydroxymethylation of the resulting alkyne to afford propargyl alcohol **167** in 79% yield (Scheme 2.10).[115] Red-Al reduction of the alkyne generated the desired *trans*-allylic alcohol in 75% yield.[116] $LiAlH_4$ was also tested in the reduction but resulted in concurrent desilylation of the TBS ether along with the desired reduction of the internal alkyne.[117] Lastly, oxidation of the allylic alcohol using MnO_2 gave α,β-unsaturated aldehyde **160** in 73% yield.[118] In contrast, use of Dess-Martin periodane for the ensuing alcohol to aldehyde conversion resulted in only 50% yield of the α,β-unsaturated aldehyde.[119] The alkyne partner was synthesized *via* Jones oxdiation of 3-butyn-1-ol followed by TIPS protection of the resultant acid to afford ester **159** in 53% yield over 2 steps.[120]



Scheme 2.10. Preparation of aldehyde and alkyne for coupling.

With both aldehyde **160** and alkyne **159** in hand, the feasibility of the alkenyl zirconium/zinc addition to form the desired bisallylic alcohol was investigated (Table 2.1).[121] Investigation of the desired hydrozirconation of alkyne **159**, followed by transmetalation and aldehyde addition revealed that 1.1 equivalents of Schwartz reagent[122] did not result in full conversion of the aldehyde. Increasing the amount of Schwartz reagent to 2 equivalents and also employing a different solvent, toluene, in place of dichloromethane after the initial hydrozirconation resulted in 100% conversion and 36% yield (entry 2). In an effort to improve the yield, methods employing carbonyl activation utilizing cationic zirconocene were also explored.[123] Suzuki *et al*. reported a remarkable rate enhancement by employing a catalytic amount of $AgClO_4$ in alkenylzirconium additions to carbonyl compounds. The *in situ* generated cationic species is hypothesized to be responsible for the observed enhancement of rate.[124] Analogously, silver hexafluoroarsenate ($AgAsF_6$) is reported as a safe alternative to $AgClO_4$ and works effectively in both alkyl and alkenylzirconocene additions.[125] The use of both $AgClO_4$ and the more reactive $AgAsF_6$ in catalytic amounts resulted in isolation of 37-38% of the desired product **169** (entries 3-5). While both alkenyl zirconium/zinc addition and cationic zirconocene addition provided similarly low yields, the ^{1}H NMR spectra of all reaction mixtures were quite clean and the mass balance before purification was quite high. It is conceivable that the bisallylic alcohol **169** could be somewhat unstable under the slightly acid chromatography conditions and could partly decompose to give lower yields. To avoid this decomposition pathway, the mixture was used without purification and tested in the ensuing activation-elimination reaction sequence.

Table 2.1. Formation of bisallylic alcohol **169**.

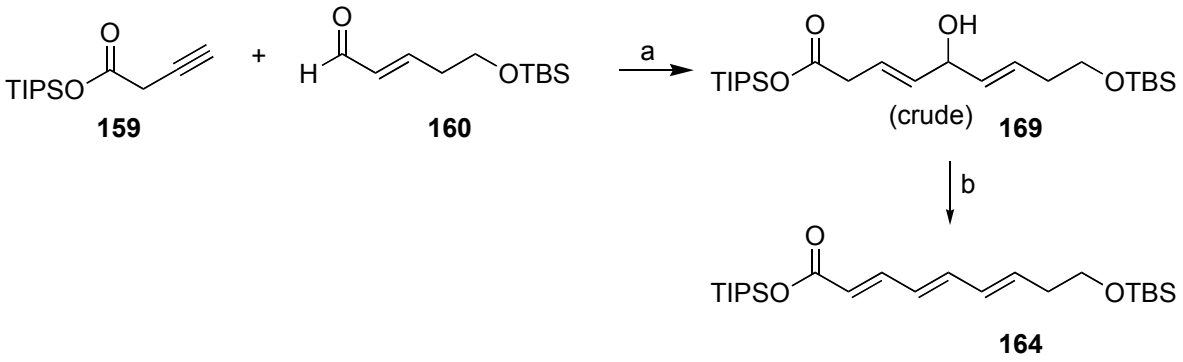


Entry	Conditions	Conversion of **160**[a]	Yield (%) of **169**
1	Cp_2ZrHCl (1.1 equiv), Me_2Zn, CH_2Cl_2, rt, 15 h	incomplete	messy
2	Cp_2ZrHCl (2 equiv), Me_2Zn, Toluene, rt, 15 h	100%	36%
3	Cp_2ZrHCl (2 equiv), $AgClO_4$ (5 mol%), 3 h	100%	38%
4	Cp_2ZrHCl (2 equiv), $AgClO_4$ (25 mol%), 30 min	100%	37%
5	Cp_2ZrHCl (1.8 equiv), $AgAsF_6$ (10 mol%), 30 min	100%	38%

[a]conversion of **160** measured by ^1H NMR.

Initially, trifluoroacetic anhydride was used to activate the alcohol. In the presence of diisopropylethyl amine, the resulting trifluoracetate underwent a 1,4-elimination to give the desired all-*trans* trienyl ester **164** as a single stereoisomer in 39% yield over 2 steps (Table 2.2, entry 1).[126] We were pleased to note that switching to 1-(trifluoroacteyl)imidazole as the activating agent resulted in a respectable yield of 60% over 2 steps (entry 3). When employing TFAA, the lower yield could be attributed to the formation of trifluoracetic acid as the byproduct, whereas benign imidazole is generated as the byproduct from 1-(trifluoroacteyl)imidazole. We thus obtained the trienic acid fragment **164** in 6 steps and 26% overall yield.

Table 2.2. Formation of **164** via a 2-step protocol.

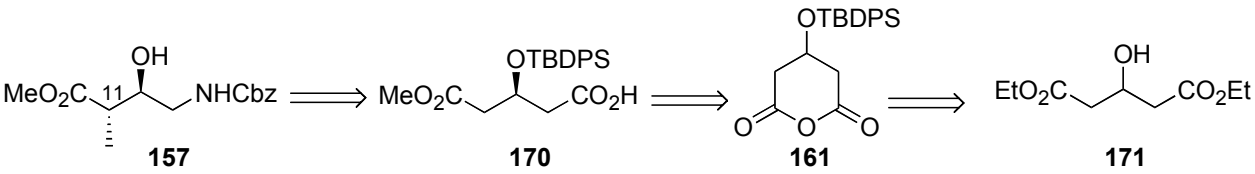


Entry	Conditions	Yield (%) of **164**
1	a) Cp_2ZrHCl, $AgClO_4$ (5 mol%), 3 h; b) i.TFAA, pyridine, ii. *i*-Pr_2NEt	39%
2	a) Cp_2ZrHCl, $AgClO_4$ (10 mol%), 30 min; b) i.TFAA, pyridine, ii. *i*-Pr_2NEt	36%
3	a) Cp_2ZrHCl, $AgClO_4$ (10 mol%), 30 min; b) i.CF_3CO-imid., pyridine, ii. *i*-Pr_2NEt	60%

2.4 Synthesis of the γ-Amino-β-Hydroxy Acid Segment

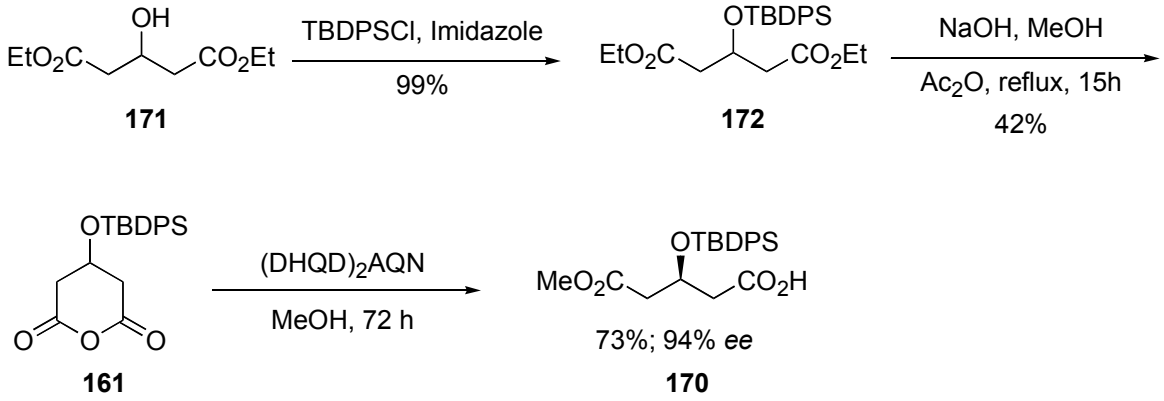
2.4.1 Desymmetrization/Alkylation Approach

At the outset, synthesis of the C(10)-C(13) segment was envisioned based on the desymmetrization of cyclic anhydride **161** to form the enantiomerically enriched hemiester **170** (Scheme 2.11). Utilization of a Frater-Seebach alkylation would install the correct configuration of the methyl substituent at C(11).



Scheme 2.11. Initial retrosynthesis of the γ-amino-β-hydroxy segment.

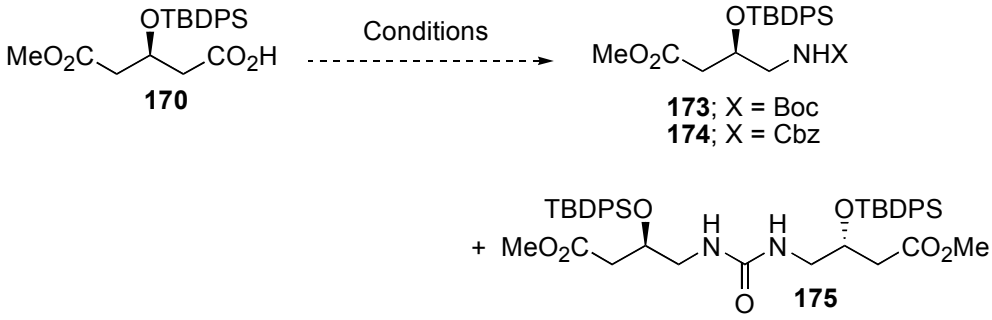
The pursuit of this strategy was initiated by silyl protection of diethyl 3-hydroxyglutarate followed by ester saponification and dehydration to afford the cyclic anhydride **161** (Scheme 2.12).[127] A catalytic desymmetrization using a modified cinchona alkaloid, $(DHQD)_2AQN$, in the presence of methanol produced the optically active methyl ester **170** in 73% yield and in 94% *ee*.[128]



Scheme 2.12. Synthesis of enantiomerically enriched hemiester **170**.

Initial attempts to convert **170** to the Boc-protected amine *via* a Curtius rearrangment[129] using *t*-BuOH as the nucleophile afforded dimer **175** as the major product (Table 2.3, entries 1-3). The formation of **175** can be attributed to the hydrolysis of the intermediate isocyanate by residual water, decarboxylation of the carbamic acid and attack of the resulting amine onto the isocyanate. Alternatively, utilizing the more nucleophilic BnOH (1.5 equiv) to trap the intermediate isocyanate resulted in the desired product **174** in 66% yield along with an unidentified byproduct (entry 4).[130] Gratifyingly, increasing the amount of BnOH to 3 equivalents resulted in the exclusive formation of **174** in 80% yield (entry 5).

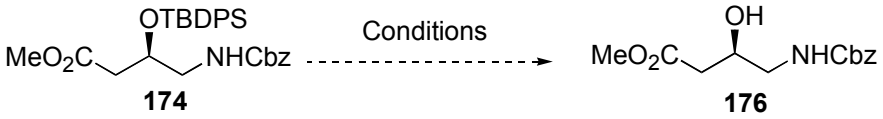
Table 2.3. Curtius rearrangement of **170**.



Entry	Conditions	Product and Isolated Yields
1	DPPA, Et_3N, *t*-BuOH, 1 h at rt, 18 h, reflux	**175**
2	DPPA, Et_3N, *t*-BuOH(distilled), 1 h at rt, 18 h, reflux	**175**
3	DPPA, Et_3N, 1 h at rt, 3 h at reflux, *t*-BuOH (distilled), 18 h, reflux	**175**
4	DPPA, Et_3N, 1 h at rt, 3 h at reflux, BnOH (1.5 equiv), 18 h, reflux	**174**; 66%
5	DPPA, Et_3N, 1 h at rt, 3 h at reflux, BnOH (3.0 equiv), 18 h, reflux	**174**; 80%[131]

A brief survey of deprotection conditions for the removal of the TBDPS group was conducted (Table 2.4).[132] Optimal yields were obtained with HF-pyridine in THF, affording the desired secondary alcohol **176** in 80% yield (entry 1).

Table 2.4. Deprotection of TBDPS ether **174** to afford alcohol **176**.

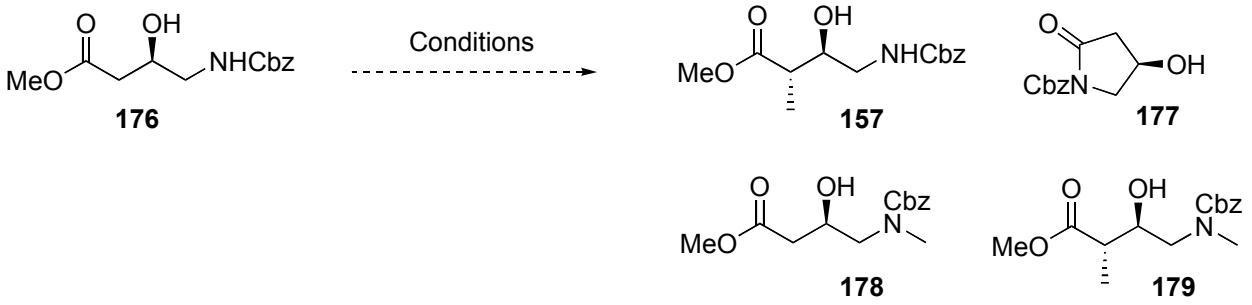


174 **176**

Entry	Conditions	Yield (%) of **176**
1	HF-pyridine/THF, 3 d	80%
2	TBAF, 3 h	44%
3	AcCl, MeOH	66%

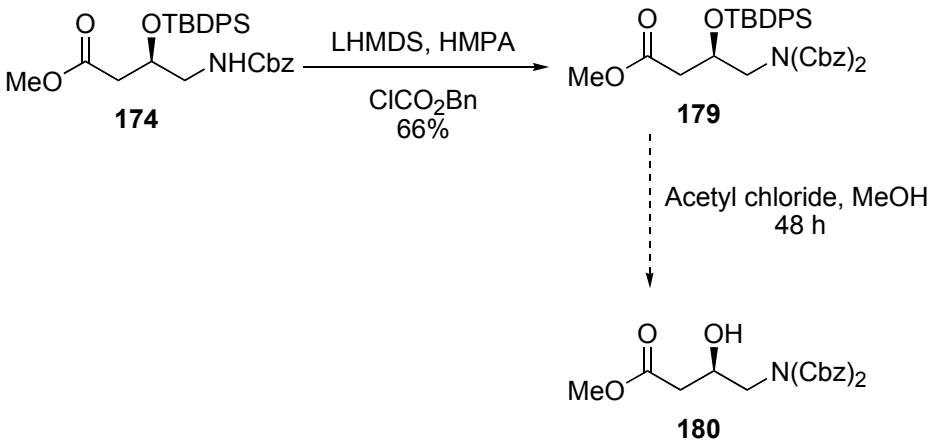
It was envisioned that α-methylation using Frater-Seebach conditions would lead to the desired product **157** in a highly diastereoselective fashion (Table 2.5).[133] However, under the standard conditions none of the desired product **157** was formed, only cyclic amide **177** could be isolated in 46% yield (entry 1). At elevated temperatures, using 2.3 equiv. of freshly prepared LDA and 2.2 equiv. of HMPA, methylation occurred at the amine to give **178** in 55% yield. This result suggested the formation of the dianion at the alcohol and amine sites. Increasing the amount of LDA to 3.3 equivalents in order to facilitate the formation of the trianion afforded methylation of the amine as well as the desired C(11), resulting in a 35% yield of **179** (entry 3). Switching the base to LHMDS and KHMDS resulted in the alkylation of the amine to afford **178**. According to these results, the least acidic site is C(11) and in theory this should be the site of alkylation, but in the majority of these reactions the dianion predominates and alkylation occurs at the amine.

Table 2.5. Attempted Frater-Seebach alkylation.



Entry	Conditions	Isolated Yields
1	LDA (3 equiv); **176**, -78 ºC to -20 ºC; CH_3I, -78 ºC to rt	**177**; 46%
2	LDA (2.3 equiv); **176**, -50 ºC; CH_3I, HMPA; reflux, 45 min	**178**; 55%
3	LDA (3.3 equiv); **176**, -50 ºC; CH_3I, HMPA; reflux, 45 min	**179**; 35%
4	LHMDS (3.3 equiv); **176**, -78 ºC; CH_3I, HMPA; -78 ºC to rt, 1.5 h	**178**; 46%
5	KHMDS (3.3 equiv); **176**, -78 ºC; CH_3I, HMPA; -78 ºC to rt, 1.5 h	**178**; 32%

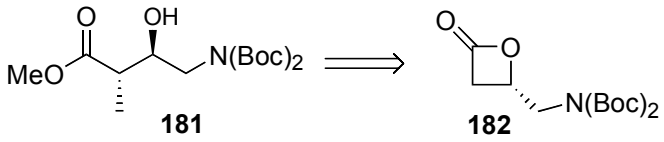
To prevent the formation of the anion on the secondary amine, the bis-CBZ protected amine **179** was synthesized (Scheme 2.13). Attempted deprotection of **179** using acetyl chloride/MeOH or HF•pyridine was unsuccessful and resulted in migration of the Cbz group to the alcohol.



Scheme 2.13. Attempted deprotection of TBDPS-ether **179**.

2.4.2 Acyl Halide-Aldehyde Cyclocondensation Approach

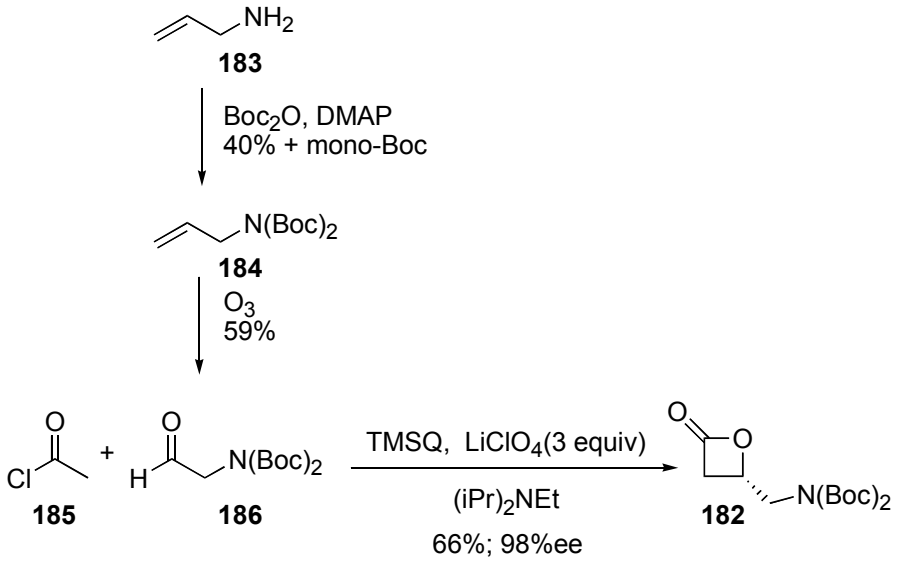
The Acyl Halide-Aldehyde Cyclocondensation (AAC) reaction was also examined as a way to gain direct access to this segment.[134] The AAC reaction offers a convenient tool by which enantioenriched β-lactone can be accessed. Retrosynthetically, this segment could arise from a nucleophilic ring opening of a β-lactone, which in turn could be synthesized under AAC reaction conditions (Scheme 2.14).



Scheme 2.14. Retrosynthesis of γ-amino-β-hydroxy ester via an AAC reaction.

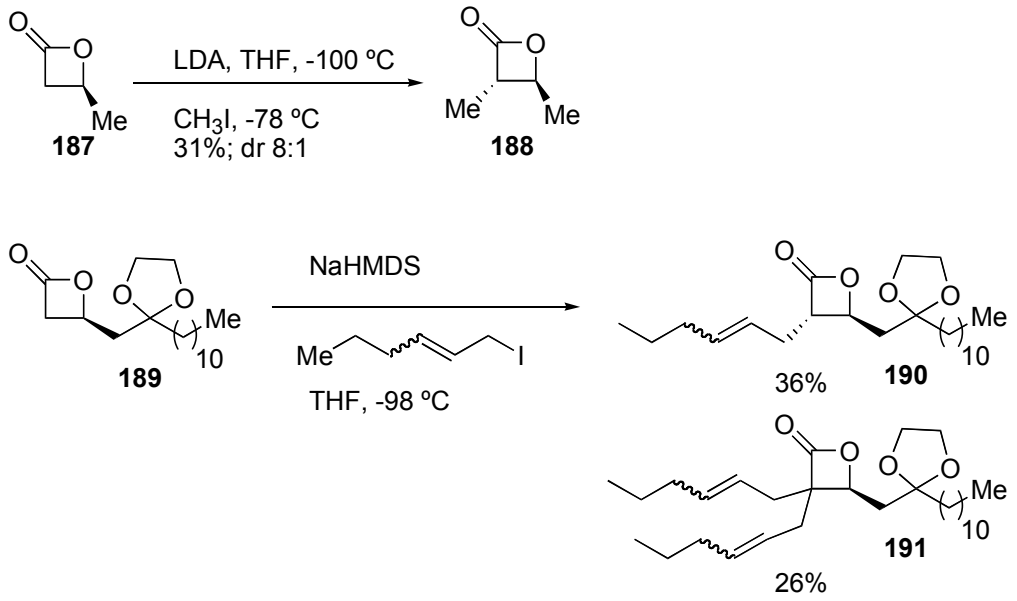
The aldehyde necessary to probe the feasibility of the AAC reaction was synthesized from allyl amine (Scheme 2.15). Allyl amine was bis-Boc protected followed by ozonolysis to give the desired aldehyde **186**. The AAC reaction between acetyl chloride and aldehyde **186** employing a Lewis base catalyst, TMS-quinidine (TMSQ), and $LiClO_4$ afforded the desired β-lactone **182** in 66% yield with 98% ee.[135] The high enantiomeric excess was encouraging, as

aldehyde substrates containing amine functionalities have not been previously reported by the Nelson group.



Scheme 2.15. Application of AAC-reaction to the formation of **182**.

With β-lactone **182** in hand, conditions for enolization and subsequent methylation were explored. Seebach *et al.* disclosed the first example of alkylation at C(3) of a β-lactone to afford the *trans*-3,4-disubstituted lactone **188** in low yield (31%) but with good levels of diasteroselectivity (Scheme 2.16).[136] Another example has been reported more recently by Parsons *et al.* in the total synthesis of (-)tetrahydrolipstatin.[137] In this report, enolization utilizing NaHMDS in the presence of the alkylating agent, 1-iodohex-2-ene, resulted in 36% of the desired monoalkylated product **190** along with 26% of the dialkylated β-lactone **191**.

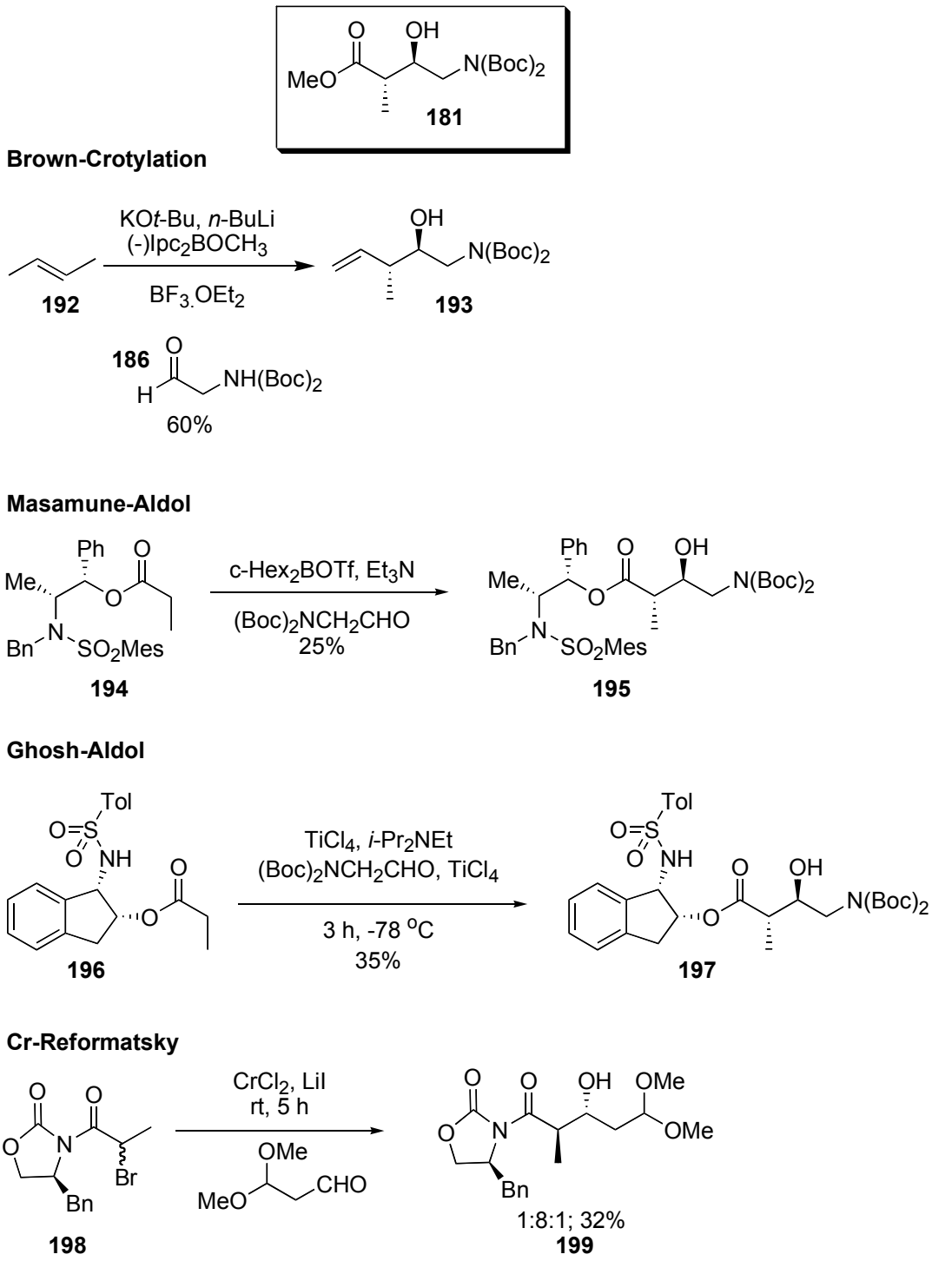


Scheme 2.16. Previously reported enolization-alkylation reactions of β-lactones.

Attempts at enolization in conjunction with methylation using LDA or NaHMDS as bases resulted in no reaction. Alternatively, the use of LHMDS and KHMDS resulted in the recovery of starting material along with an unidentified byproduct.

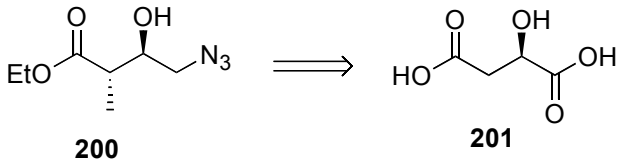
2.4.3 Alternate Approaches Towards the Synthesis of the γ-Amino-β–Hydroxy Acid Segment

Alternative routes to the α-amino-β-hydroxy acid segment were subsequently investigated. Standard Brown[138] crotylation of **186** gave the desired product **193** in 60% yield but with low diastereoselectivity (Scheme 2.17). Asymmetric aldol[139] reactions are convenient methods for introducing two-stereocenters in high enantioselectivity. Retrosynthetically, the stereochemistry inherent in the γ-amino-β-hydroxy acid fragment could arise from an *anti*-aldol. Currently, there are very few general approaches for *anti*-aldol reaction of aliphatic aldehyde substrates. *Anti*-aldol reactions using chiral auxillaries reported by Ghosh[140] and Masamune[141] were considered as viable approached to this fragment, but unfortunately these protocols were low yielding. The chromium-Reformatsky[142] reaction was also considered as a possible option, but low yield and low diastereoselectivity deterred from further exploration.



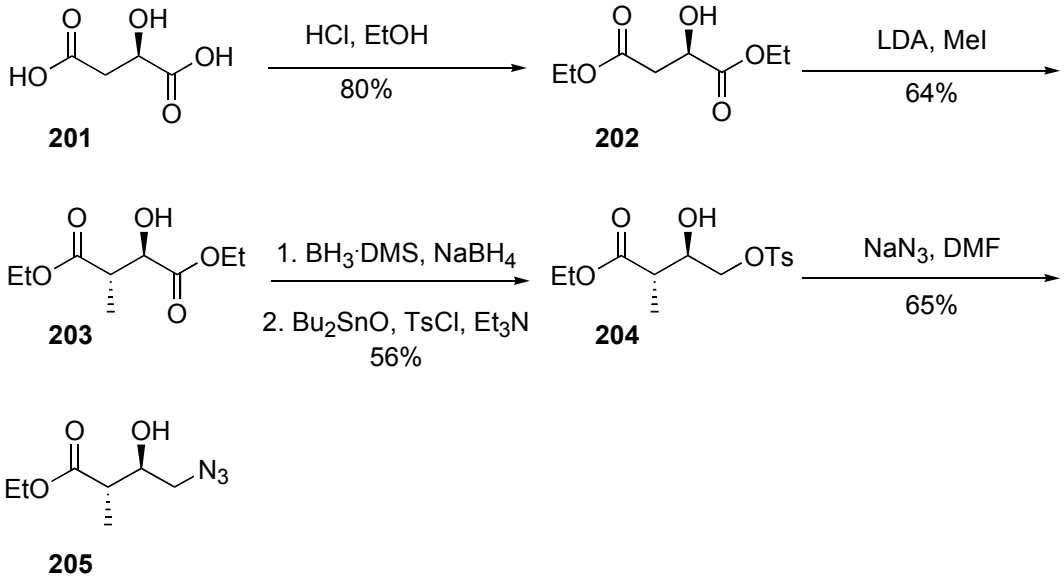
Scheme 2.17. Alternative approaches towards the synthesis of the γ-amino-β–hydroxy acid segment.

2.4.4 Revised Alkylation Approach



Scheme 2.18. Frater-Seebach alkylation of malic acid derivative.

An alternative approach was initiated by a Fischer esterification of (*D*)-malic acid to give the corresponding ethyl diester **202** in 80% yield (Scheme 2.19). A diastereoselective methylation employing Frater-Seebach conditions gave **203** in 64% yield with a dr of 6:1 (*trans*:*cis*). A combination of BH_3•DMS and catalytic $NaBH_4$ affected the chemoselective reduction of the vicinal hydroxy-ester to the desired 1,2-diol.[143] This selective reduction is proposed to occur through a 5-membered boron chelate between the neighboring hydroxy group and the ethyl ester. The resulting crude diol was converted to tosylate **204** employing catalytic Bu_2SnO-mediated sulfonylation conditions, proceeding *via* formation of the tin acetal intermediate to afford 56% of **204** over 2 steps.[144] The tin acetal plays the dual role of activating the primary alcohol while temporarily protecting the secondary alcohol. Lastly, displacement of the tosylate by sodium azide gave the desired fragment **200** in 65% yield.

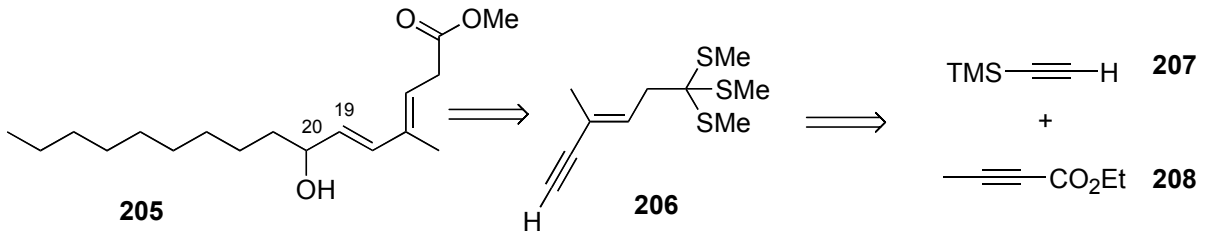


Scheme 2.19. Synthesis of the amino acid fragment **200**.

2.5 Synthesis of the Hydroxy-Diene Segment

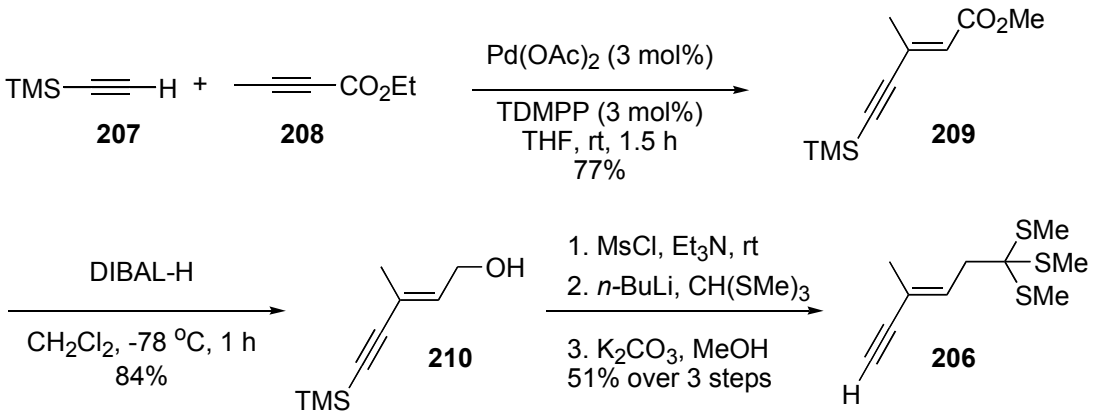
2.5.1 Alkenylzirconium/zinc Addition Approach

The retrosynthetic disconnection of this fragment at the C(19)-C(20) bond **205** gives **206** and decylaldehyde as precursors (Scheme 2.20). Enyne **206** can be conveniently synthesized *via* a palladium coupling.



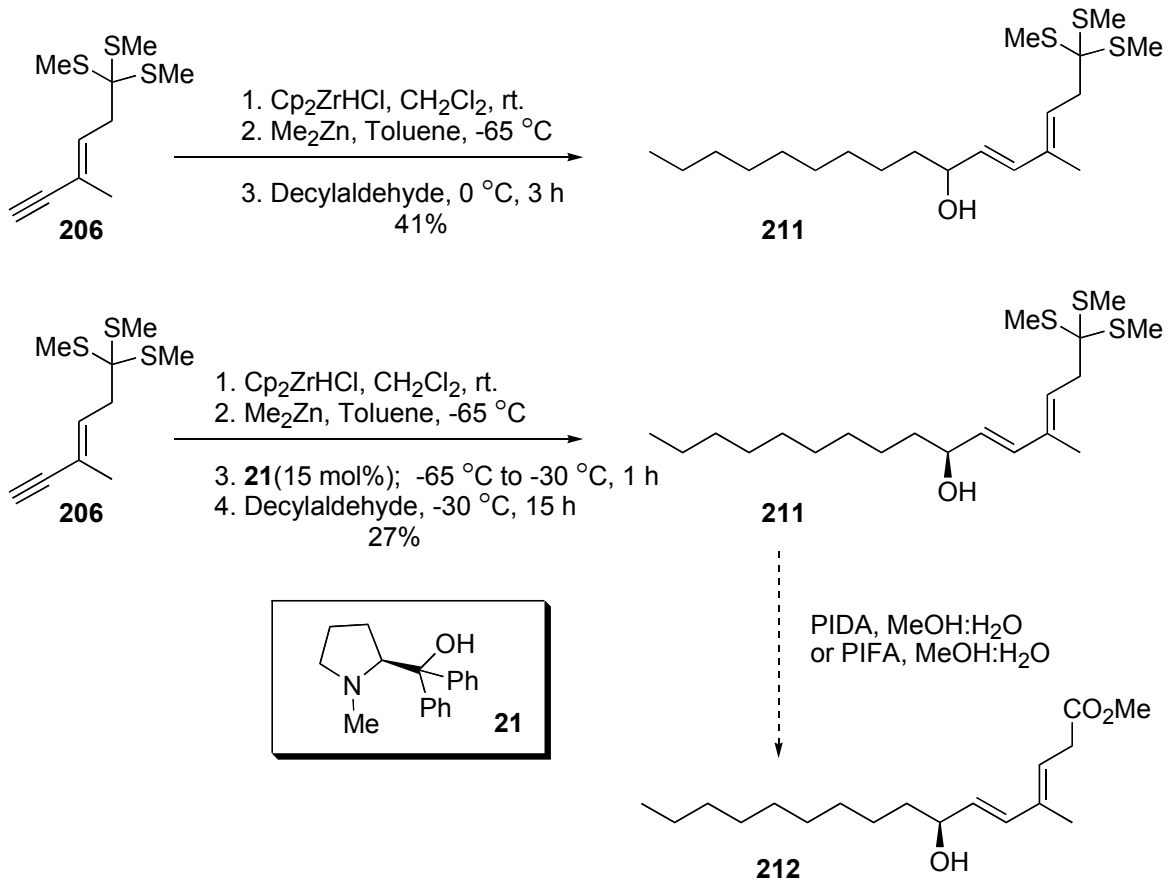
Scheme 2.20. Retrosynthetic analysis of the hydroxy diene segment.

Construction of **205** begins with utilization of a palladium-catalyzed cross coupling method developed by Trost *et al.,* in which 3-methylbutynoate (the activated internal alkyne acceptor) is cross-coupled to TMS-acetylene (donor alkyne) (Scheme 2.21). The reaction proceeded smoothly in the presence of 3% $Pd(OAc)_2$ and 3% tris(2,6-dimethoxyphenyl)phosphine to afford the cross-coupled product **209** in 77% yield (Scheme 5).[145] The resulting methylester was reduced using DIBAL-H to afford the corresponding alcohol **210** in 84% yield. Alcohol **210** was then converted to the mesylate[146] followed by displacement with the carbanion of tris(methylthio)methane.[147] Seebach *et al*. has widely researched the umpolung reactivity of carbonyl compounds through these and other sulfur-containing reagents.[148] The Umpolung reactivity of tris(methylthio)methane can be harnessed by reaction with *n*-BuLi to affect formation of the carbanion.[149] Tris(methylthio)methane is used in synthesis as a masked acid derivative.[150] It provides essentially a route by which homologation and oxidation take place concurrently by introduction of tris(methylthio)methane. The TMS-group is hydrolyzed using K_2CO_3 and MeOH to provide **206** in 51% yield over 3 steps.[151]



Scheme 2.21. Synthesis of enyne **210**.

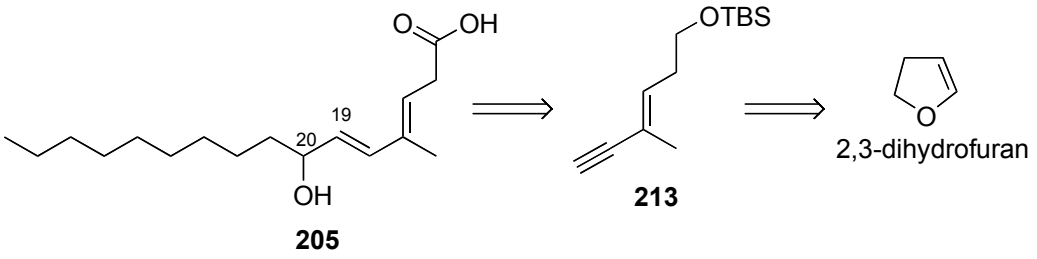
Application of the alkenylzirconocene/zinc methodology in the addition of **206** to decylaldehyde gave the desired allylic alcohol **211** in an unoptimized yield of 41% (Scheme 2.22). The asymmetric reaction was also tested briefly using 15 mol% of **21** to produce 27% of the allylic alcohol **211** in 15% *ee*. The reaction conditions were not optimized due to the problems encountered in the ensuing step. Attempted hydrolysis of the trithioorthoester under the Stork protocol utilizing PIFA or PIDA was unsuccessful.[152] Hydrolysis conditions using PIFA and PIDA were also tested on the shorter fragment **206,** but these also resulted in no product formation. Not many alternatives exist for the hydrolysis of the trithioorthoester, and thus this route was abandoned in favor of an alternate process.



Scheme 2.22. Alkenylzirconocene/zinc addition and subsequent attempted hydrolysis of trithioester **206**.

2.5.2 Alternate Alkenylzirconium/zinc Addition Approach

Retrosynthetic scission of the C(19)-C(20) bond of **205** in hopes of utilizing the alkenylzirconocen/zinc methodology furnishes decyl aldehyde and enyne **213** as precursors (Scheme 2.23). Enyne **213** can be readily obtained from 2,3-dihydrofuran by employing a 1,2-metallate rearrangement. Enyne **213** was used in attempts to avoid the problem encountered with deprotection of trithioorthoester **211**; the requisite carbons are already contained within this alkyne.



Scheme 2.23. Retrosynthetic analysis for the C(14)-C(29) segment.

The vinyl iodide **216** was synthesized in a straightforward manner by utilizing the 1,2-metallate rearrangment strategy described by Kocienski *et al.*[153] 2,3-Dihydrofuran has been shown to undergo a facile 1,2 metallate rearrangement in the presence of a higher order cuprate to afford upon alkylation of the alkenyl cuprate the trisubstituted alkene **215** (Figure 2.4). The alcohol of the vinyl stannane is readily protected, followed by subsequent iododestannylation to afford vinyl iodide **216** in 73% yield over 3 steps (Scheme 2.24).

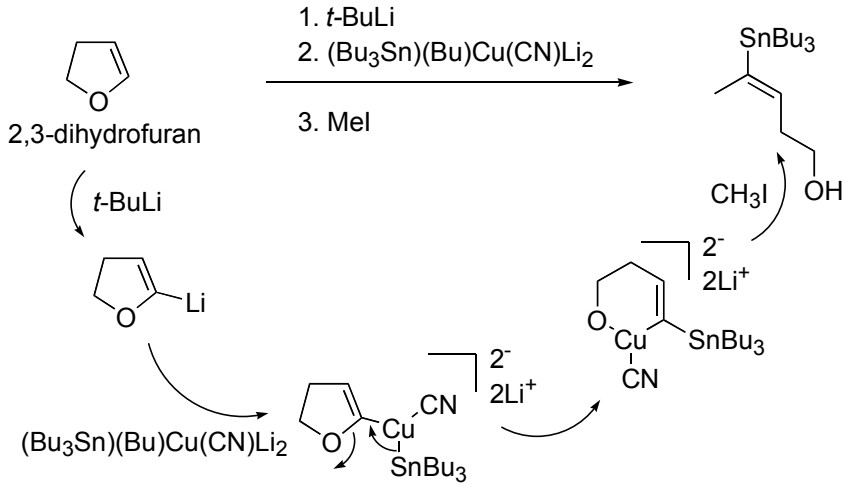
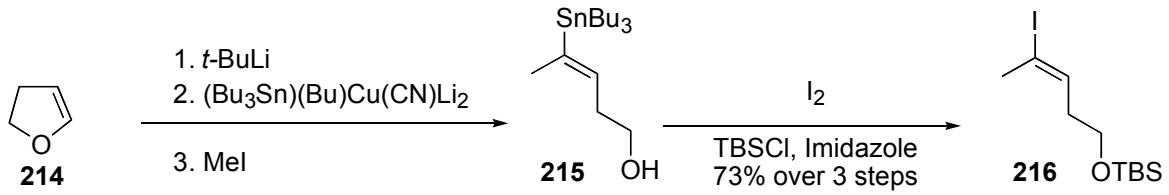
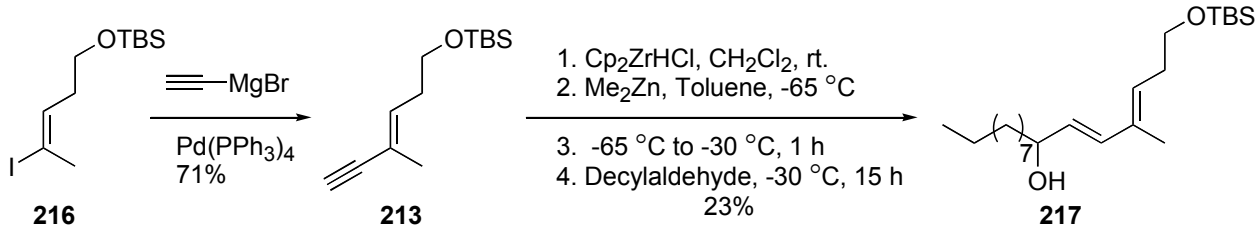


Figure 2.4. Proposed mechanism for the 1,2-metallate rearrangement.

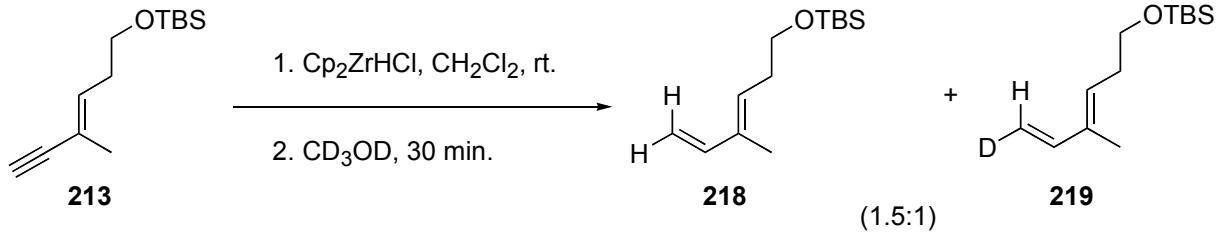


Scheme 2.24. Synthesis of vinyliodide **216** using a 1,2-metallate rearrangement.

Vinyliodide **216** was coupled with ethynyl magnesium chloride in the presence of $Pd(Ph_3P)_4$ to furnish **213** in 71% yield. Use of alkenylzirconocene/zinc methodology in the addition of **213** to decylaldehyde resulted in formation of the allylic alcohol **217** in 23% yield (Scheme 2.25). The major isolated byproduct was the reduced alkyne. Deuterium studies revealed that the low yield was due to protonation of the alkenylzirconium intermediate prior to the transmetallation step. When the hydrozirconation product of **213** was quenched with an excess of CD_3OD, a ratio of 1.5:1 (H:D) of the alkenyl product was observed by ^1H NMR (Scheme 2.26).



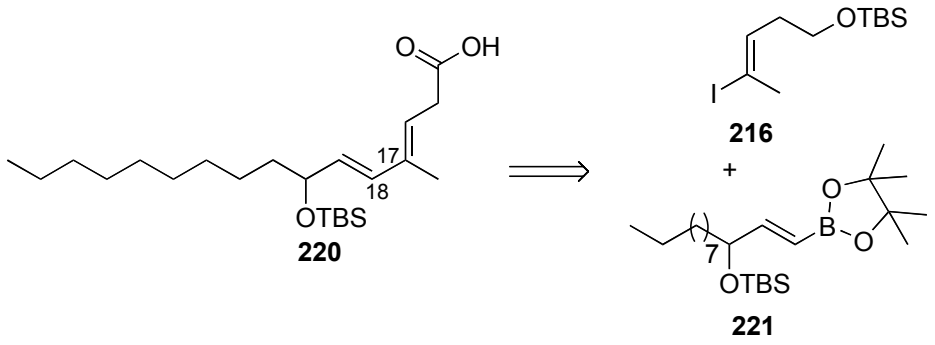
Scheme 2.25. Synthesis of **217**.



Scheme 2.26. Deuterium quenching studies.

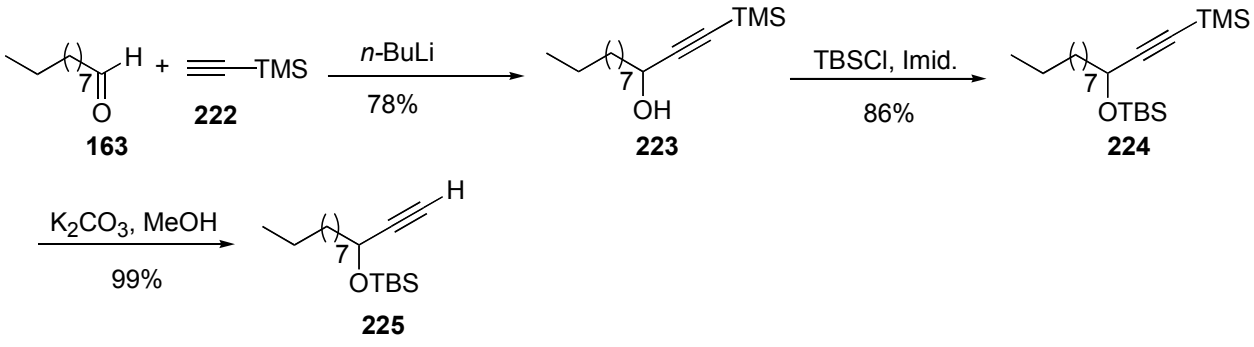
Unfortunately, the low yield in the alkenylzirconocene/zinc addition as a consequence of the inability to inhibit the formation of the diene byproduct **219** did not enable the use of our methodology as a viable approach to this fragment.

2.5.3 Suzuki Approach



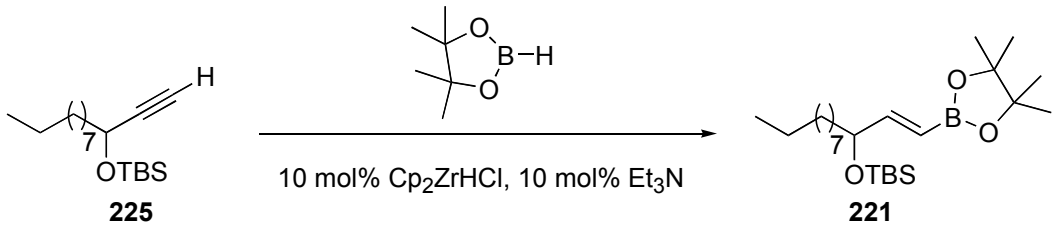
Scheme 2.27. Pd-mediated approach to the C(14)-C(29) segment.

The requisite bond formation at C(17)-C(18) could conceivably be derived from a Suzuki reaction between vinyl iodide **216** and alkenyl borane intermediate **221** (Scheme 2.27). Addition of the lithium anion of TMS-acetylene to decyl aldehyde gave the corresponding alcohol **223** in 78% yield (Scheme 2.28).[154] The resulting alcohol was protected with TBSCl, and subsequent hydrolysis of the TMS group provided **225** in 99% yield.[155]



Scheme 2.28. Synthesis of propargyl alcohol **225**.

Hydroboration of **225** using pinacolborane in the presence of 10 mol% Cp_2ZrHCl and 10 mol% Et_3N gave exclusively the (*E*)-vinylboronic ester (Scheme 2.29).[156] In hydroboration reactions of alkynes containing oxygen atoms, it is speculated that intramolecular chelation between zirconium and oxygen favors the formation of the pseudo-(*Z*)-intermediate, which in turn leads to the (*Z*)-vinylboronic esters.[157] However, the equilibrium can be shifted with the use of a catalytic amount of Et_3N. Et_3N acts to distrupt the intramolecular Zr-O interaction, yielding the (*E*)-vinylboronic ester (Figure 2.4).



Scheme 2.29. Hydroboration of propargyl alcohol **225**.

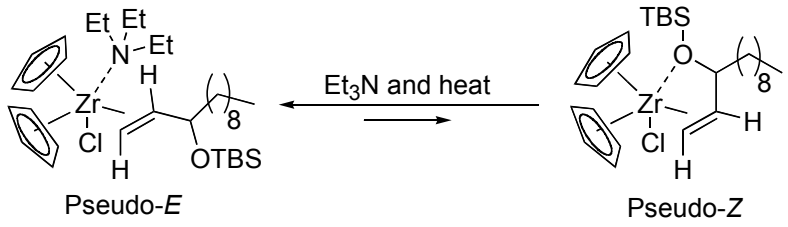
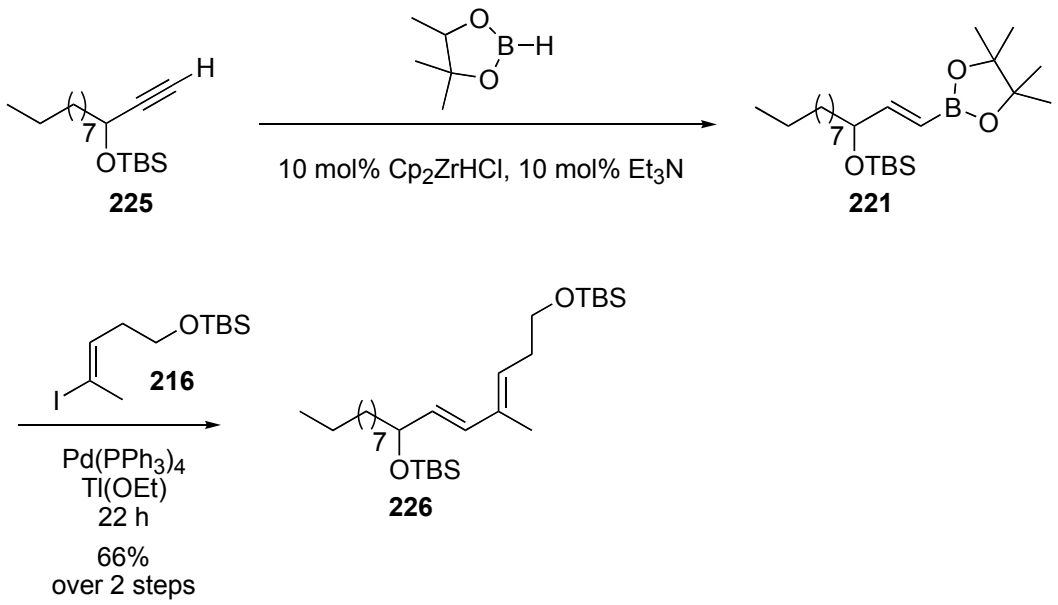


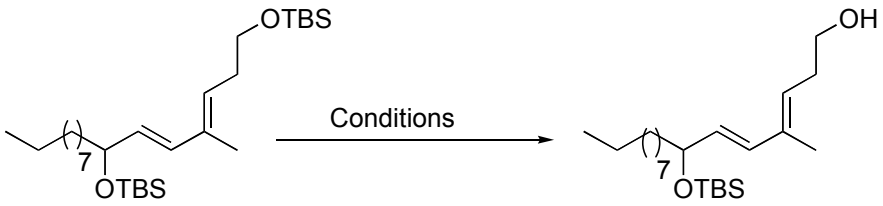
Figure 2.5. Stereoselectivity of the initial hydrozirconation in the presence of Et_3N and temperature.

With the (*E*)-vinylboronic ester in hand, the requisite vinyl iodide coupling partner **216** was synthesized as mentioned above. The (*E*)-vinylboronic ester was coupled via a Suzuki reaction[158] with vinyl iodide **216** in the presence of thallium ethoxide and $Pd(PPh_3)_4$ to furnish the conjugated diene **226** in 66% yield over 2 steps (Scheme 2.30). TlOEt is an alternative base to TlOH, and has been shown by Kishi *et al.* to significantly enhance rates of Suzuki reactions.[159] TlOEt has the advantages over TlOH in terms of commercial availability, stability, and ease of use.[160] Deprotection of the primary alcohol using TBAF while maintaining the temperature between 5 ºC and 15 ºC resulted in a 83% yield of **227** (Table 2.6, entry 3).



Scheme 2.30. Synthesis of fragment **226**.

Table 2.6. Deprotection of **226**.

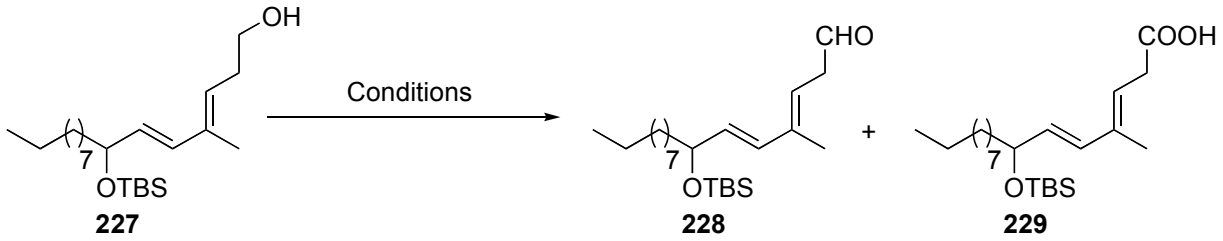


Entry	Conditions	Yield (%) of **227**
1	TBAF, 0 ºC, 1.5 h	66% conversion[a]
2	TBAF, rt, 2.5 h	37%
3	TBAF, rt, 20 h	37% +bisdeprotection
4	TBAF, 5 ºC to 15 ºC, 2.5 h	83%
5	HF/pyridine, 0 ºC to rt, 12 h	45% + bisdeprotection

[a]conversion of **226** measured by ^{1}H NMR.

A variety of conditions for oxidation of the homoallylic alcohol, **227**, were investigated to complete the synthesis of this fragment (Table 2.7). Disappointingly, attempts at oxidation *via* a two-step sequence or a one-step procedure directly to the acid led to none of the desired acid **229**. It is conceivable that **228** and **229** are unstable while isomerization of the diene into conjugation with the newly formed carbonyl group can occur. Partial or total migration of the double bond to the corresponding more stable α,β-unsaturated aldehyde has been reported in the oxidation of β,γ-unsaturated alcohols.[161]

Table 2.7. Oxidation of **227**.

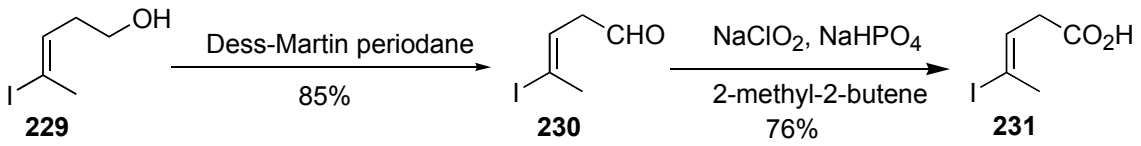


227 **228** **229**

Entry	Conditions	Result[a]
1	PDC, DMF[162]	no reaction
2	DMP, pyridine[163]	many aldehyde peaks
3	TEMPO, PIDA[164]	aldehyde, messy
4	$NaClO_2$, NaOCl, TEMPO[165]	sm
5	CrO_3 (1.2 mol%), H_5IO_6, wet CH_3CN[166]	messy
6	CrO_3, H_2SO_4, acetone[167]	decomposition
7	trichloroisocyanuric acid, TEMPO (0.01 equiv), NaBr (0.05 equiv)[168]	many aldehyde peaks

[a]by ^1H NMR of crude material

It is, however, possible to take a slightly different approach in order to circumvent the problematic oxidation. Initial oxidation of the alcohol **229** to the aldehyde **230** using Dess-Martin reagent followed by subsequent oxidation resulted in formation of the desired acid **231** (Scheme 2.31).



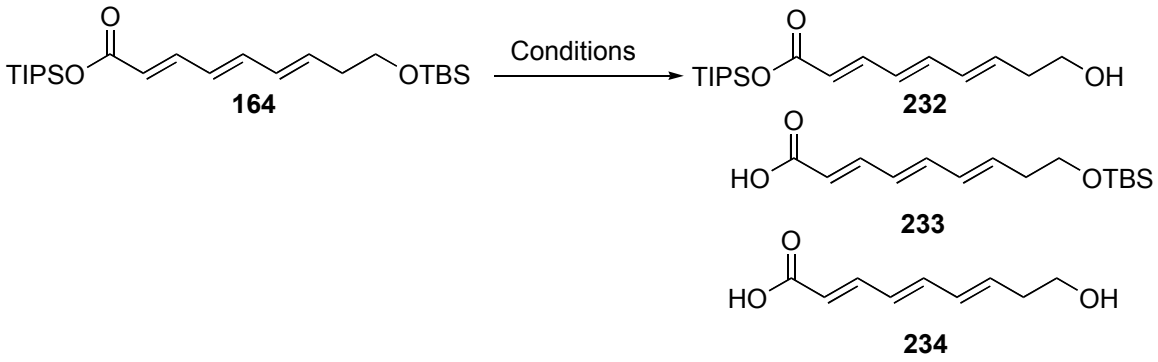
Scheme 2.31. 2-Step oxidation of **229**.

2.6 Fragment Coupling

2.6.1 Coupling of Segments 156 and 157

Preparation of the trienic acid segement **164** for peptide coupling necessitated a deprotection of the TBS-ether in the presence of the TIPS-ester.[169] Conditions were examined using mild acid (Table 2.8). In the presence of 5 equivalents of PPTS, facile deprotection of both TBS-ether along with the TIPS-ester occurred (entry 3). Lowering the amount of PPTS to 2 equivalents and carrying out the reaction at room temperature led to a facile deprotection of the TIPS-ester to give **233** in 75% yield. Use of Cs_2CO_3 and $BiBr_3$ also resulted in cleavage of the TIPS-ester (entry 5 and 6). These results are indicative of the higher lability of the TIPS-ester in comparison to the TBS-ether under acid conditions.

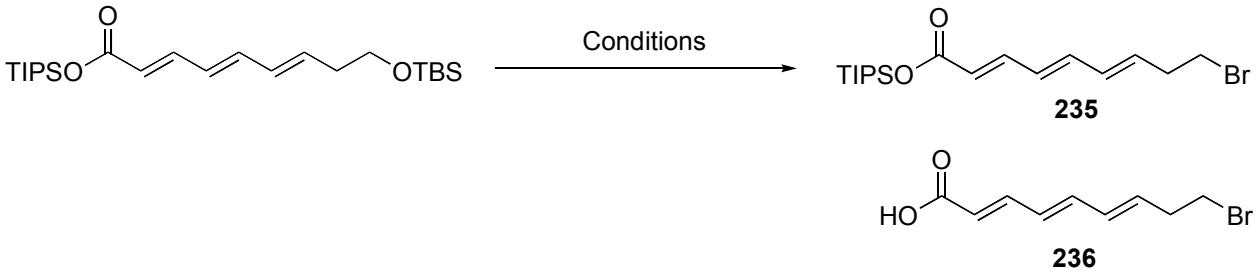
Table 2.8. Deprotection of TBS-ether in the presence of TIPS-ester of **164**.



Entry	Conditions	Products and Isolated Yields
1	PPTS (2 equiv), EtOH, 0 ºC, 3h	SM + **232**
2	PPTS (2 equiv), EtOH, rt, 4.5h	**233**; 75%
3	PPTS (5 equiv), EtOH, rt, 2.5h[170]	**234**; 82%
4	HOAc (1 equiv), THF, H_2O, μW, 125 ºC, 5 min.[171]	**234**; 84%
5	Cs_2CO_3, DMF:H_2O (10:1)[172]	**233**; 71%
6	$BiBr_3$, CH_3CN, H_2O[173]	**233**; 78%

Alternatively, conversion of the TBS-ester to the alkyl bromide was examined as a possible solution to this problem.[174] Treatment of **164** with Ph_3PBr_2 resulted in the formation of the desired product **235** along with acid **236**.

Table 2.9. Conversion of TBS-ether to the bromide in the presence of TIPS-ester of **164**.



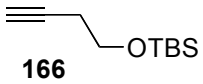
Entry	Conditions	Products and Isolated Yields
1	Ph_3PBr_2 (1.1 equiv), rt, 10 min	**235**(10%) + **236**(24%)
2	Ph_3PBr_2 (1.1 equiv), 0 °C, 10 min	**235** + sm
3	Ph_3PBr_2 (1.1 equiv), 0 °C, 5 h	**235** + sm
4	Ph_3PBr_2 (3.1 equiv), 0 °C, 30 min	**236**(57%) + **235**(5%)

2.7 Conclusions

In summary, the synthesis of the 3 major fragments of pseudotrienic acid A was achieved. The trienic acid fragment was synthesized *via* a cationic zirconocene addition followed by a base induced 1,4-elimination. The synthesis of the γ-amino-β-hydroxy acid segment was accomplished *via* a Frater-Seebach alkylation. The C(17)-C(18) bond was readily made utilizing a Suzuki coupling reaction. Coupling of these fragments remains to be investigated and might ultimately lead to the synthesis of pseudotrienic acid A. Further investigation must also focus on formation of the C(20) hydroxy moiety in an enantioselective fashion.

2.8 Experimental

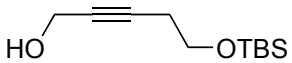
General: All moisture-sensitive reactions were performed under an atmosphere of N_2. Glassware was dried in an oven at 140 ºC prior to use. THF and Et_2O were dried by distillation over Na/benzophenone. CH_2Cl_2 was purified by filtration through activated alumina. Me_2Zn was purchased from the Aldrich Chemical Company and Cp_2ZrHCl was prepared according to a modification of a literature protocol.[175] Unless otherwise stated, solvents and reagents were used as received. Analytical thin layer choromatography was performed on pre-coated silica gel 60 F-254 plates (particle size 0.040-0.055 mm, 230-400 mesh) and visualization was accomplished with a 254 nm UV light or by staining with an anisaldehyde solution (7.5 mL of *p*-anisaldehyde, 25 mL of concentrated H_2SO_4 and 7.5 mL of glacial acetic acid in 675 mL of 95% ethanol) or a $KMnO_4$ solution (1.5 g of $KMnO_4$, 10 g of potassium carbonate and 2.5 mL of 5% aqueous NaOH in 150 mL of H_2O). Flash chromatography on SiO_2 was used to separate and purify the crude reaction mixtures. IR spectra obtained on a Nicolet AVATAR 360 FT-IR E.S.P. Spectrometer. NMR spectra were recorded at 300 MHz/75 MHz (^{1}H NMR/^{13}C NMR) at 21 ºC in $CDCl_3$ unless otherwise noted. Chemical shifts (δ) are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, sx=sextet, sp=septet, o=octet, dt=doublet of triplet, dq=doublet of quartet, m=multiplet, b=broad), integration, and coupling constants. Mass spectra were obtained on a double focusing instrument.



166

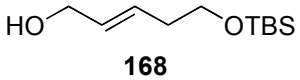
***tert*-Butylbut-3-ynyloxydimethylsilane (166).**[176] To a solution of 1.00 g (14.3 mmol) of 3-butyn-1-ol, 2.39 mL (17.1 mmol) of Et_3N, and 174 mg (1.43 mmol) of DMAP in 45 mL of CH_2Cl_2 was added 2.36 g (15.7 mmol) of TBSCl. The reaction mixture was stirred under N_2 for 3 h, diluted with Et_2O, and extracted with NH_4Cl. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (10% EtOAc/Hexanes) to yield 2.66 g (99%) of **166** as a colorless oil: ^{1}H NMR δ 3.74 (t, 2 H, J = 7.2 Hz), 2.39 (td, 2 H, J = 2.4, 6.9 Hz), 1.95 (t, 1 H, J = 2.4 Hz), 0.90

(s, 9 H), 0.07 (s, 6 H); ^{13}C NMR δ 81.45, 69.28, 61.72, 25.86, 22.83, 18.30, -5.33; MS (EI) *m/z* (rel intensity) 127 ([M-C_4H_9]$^+$, 13), 84 (8), 74 (62), 59 (100).



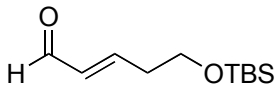
167

5-(*tert*-Butyl-dimethyl-silanyloxy)-pent-2-yn-1-ol (167).[176] A solution of 3.37 mL (5.40 mmol) of *n*-BuLi (1.6 M in hexanes) was added dropwise to a solution of 1.00 g (5.40 mmol) of **166** in 11 mL of THF at –40 ºC. The resulting mixure was stirred for 15 min and then added to a solution of 486 mg (16.2 mmol) of paraformaldehyde in 6 mL of THF at –45 ºC. The reaction mixture was further stirred at –45 ºC for 1 h followed by 1 h at room temperature, diluted with H_2O, washed with NaCl, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (20% EtOAc/Hexanes) to yield 913 mg (79%) of **167** as a colorless oil: ^{1}H NMR δ 4.25 (dt, 2H, *J* = 2.1, 6.0 Hz), 3.73 (t, 2 H, *J* = 7.2 Hz), 2.44 (tt, 2 H, *J* = 2.1, 7.2 Hz), 1.58 (t, 1 H, *J* = 6.3 Hz), 0.91 (s, 9 H), 0.08 (s, 6 H), 0.88 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR δ 83.4, 79.5, 61.8, 51.3, 25.9, 23.1, 18.3, -5.3; MS (EI) *m/z* (rel intensity) 157 ([M-C_4H_9]$^+$, 29), 139 (37), 125 (15), 105 (87), 89 (21), 75 (100), 59 (10); HRMS (EI) Calcd for $C_{11}H_{22}OSi$-C_4H_9 157.0684, found 157.0678.



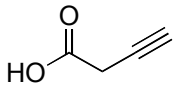
168

5-(*tert*-Butyldimethylsilanyloxy)-pent-2-en-1-ol (168).[177] To a solution of 4.31 g (20.1 mmol) of **167** in 175 mL of Et_2O at 0 ºC was added 12.5 mL (40.2 mmol) of Red-Al (65 wt%). The resulting reaction mixture was stirred for 4 h and quenched with NH_4Cl at 0 ºC. The layers were extracted with EtOAc, washed with NaCl, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (100% Hexanes) to yield 3.25 g (75%) of **168** as a colorless oil: IR (neat) 3352, 1675, 835 cm^{-1}; ^{1}H NMR δ 5.71-5.65 (m, 2 H), 4.12-4.05 (m, 2 H), 3.65 (t, 2 H, *J* = 6.6 Hz), 2.26 (qd, 2 H, *J* = 1.2, 4.2 Hz), 1.65 (t, 2 H, *J* = 5.7 Hz), 0.89 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR δ 130.9, 129.3, 63.6, 62.8, 35.8, 25.9, 18.3, -5.3; MS (EI) *m/z* (rel intensity) 215 (M$^+$, 15), 199 (13), 159 (18), 145 (22), 129 (10), 115 (27), 105 (100); HRMS (EI) Calcd for $C_{11}H_{23}OSi$ 199.1518, found 199.1515.



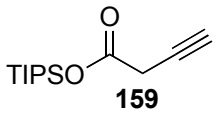
160

5-(*tert*-Butyldimethylsilanyloxy)-pent-2-enal (160).[177] To a suspension of 63.9 g (734 mmol) of MnO_2 in 150 mL of CH_2Cl_2 was added 3.18 g (14.7 mmol) of **168** in 50 mL of CH_2Cl_2. The solution was stirred at rt for 4 h, filtered through celite, and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (5% EtOAc/Hexanes) to yield 2.29 g (73%) of **160** as a colorless oil: ^{1}H NMR δ 9.52 (d, 1 H, *J* = 7.9 Hz), 6.90 (dt, 1 H, *J* = 6.9, 15.7 Hz), 6.18 (qt, 1 H, *J* = 1.4, 7.9 Hz), 3.80 (t, 2 H, *J* = 6.2 Hz), 2.55 (qd, 2 H, *J* = 1.4, 6.2 Hz), 0.90 (s, 9H), 0.07 (s, 6 H); ^{13}C NMR δ 193.9, 155.5, 134.2, 61.1, 36.0, 25.8, 18.2, -5.4; MS (EI) *m/z* (rel intensity) 214 (M^+, 25), 212 (20), 172 (45), 155 (33), 125 (40), 103 (55), 73 (100).



159a

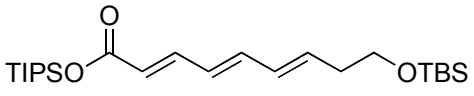
But-3-ynoic acid (159a).[120] To a solution of 14.0 g (139 mmol) of CrO_3 and 96 mL of H_2SO_4 in 360 mL of distilled H_2O was added *via* addition funnel a solution of 5.00 g (71.3 mmol) of 3-butyn-1-ol in 70 mL of acetone over a period of 1.5 h. The reaction mixture was stirred for 3.5 h at 0 ºC, extracted with Et_2O (6x), washed with H_2O, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give 3.41 g (57%) of **159a** as an off-white solid: ^{1}H NMR δ 3.39 (t, 1 H, *J* = 2.6 Hz), 3.39 (d, 2 H, *J* = 2.7 Hz); MS (EI) *m/z* (rel intensity) 122 (7), 121 (50), 91 (9), 84 (M^+, 33), 74 (62), 59 (100).



159

Triisopropylsilyl 3-butynoate (159).[120] To a solution of 223 mg (2.65 mmol) of **159a** and 0.56 mL (2.65 mmol) of TIPSCl in 13 mL of CH_2Cl_2 at rt was added 180 mg (2.65 mmol) of imidazole. The resulting reaction mixture was stirred for 1.5 h and diluted with H_2O and CH_2Cl_2. The organic layer was washed with H_2O and NaCl, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give 636 mg (100%) of **159** as a colorless oil: ^{1}H NMR δ 3.27 (d, 2 H, *J*

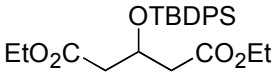
= 2.7 Hz), 2.15 (t, 2 H, *J* = 2.7 Hz), 1.37-1.19 (m, 3 H), 1.05 (d, 18 H, *J* = 7.5 Hz), MS (EI) *m/z* (rel intensity) 197 ([M-C_3H_7]$^+$, 100); 157 (126), 153 (64), 125 (22), 111 (60), 97 (23), 83 (63), 75 (53), 61 (47), 59 (45).



164

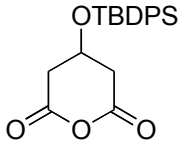
9-(*tert*-Butyldimethylsilanyloxy)-nona-2*E*,4*E*,6*E*-trienoic acid triisopropylsilylester (164). To a solution of 241 mg (0.93 mmol) of Cp_2ZrHCl in 3 mL of CH_2Cl_2 was added 224 mg (0.93 mmol) of **159** in 1 mL of CH_2Cl_2. The mixture was stirred for 15 min followed by the addition of 100 mg (0.46 mmol) of **160** in 1 mL of CH_2Cl_2 and 9.6 mg (0.046 mmol) of $AgClO_4$. The reaction mixture was stirred for 30 min, filtered through florisil, and washed with EtOAc. The filtrate was concentrated *in vacuo* to give **169** as an orange oil which was used without further purification.

To a −10 ºC solution of **169** in 5 mL of THF was added 0.16 mL (1.40 mmol) of 1-(trifluoroacteyl)imidazole followed by 0.13 mL (1.63 mmol) of pyridine. The mixture was allowed to warm to 5 ºC over 1 h, treated with 0.41 mL (2.33 mmol) of DIEA, and allowed to warm to 15 ºC over 3.5 h. The solution was poured into a separatory funnel containing H_2O and Et_2O. The layers were separated and the organic layer was washed with NH_4Cl, H_2O, and NaCl. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was titurated with hexanes and the soluble material was used for chromatography. The resulting crude residue was purified by chromatography on SiO_2 (100% Hexanes) to yield 122 mg (60%) over 2 steps of **164** as a colorless oil: IR (neat) 2930, 1695, 1620, 1006, 976, 835 cm^{-1}; ^{1}H NMR δ 7.27 (dd, 1 H, *J* = 11.5, 15.1 Hz), 6.53 (dd, 1 H, *J* = 10.3, 14.9 Hz), 6.23 (dd, 1 H, *J* = 10.8 Hz), 6.17 (d, 1 H, *J* = 15 Hz), 6.00-5.82 (m, 2 H), 3.68 (t, 2 H, *J* = 6.5 Hz), 2.37 (q, 2 H, *J* = 6.6 Hz), 1.42-1.23 (m, 3 H), 1.09 (d, 18 H, *J* = 7.3 Hz), 0.09 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR δ 166.7, 145.1, 140.7, 136.4, 131.6, 128.3, 122.2. 62.5, 36.6, 25.9, 18.3, 17.8, 12.1, -5.3; MS (EI) *m/z* (rel intensity) 395 ([M-C_3H_7]$^+$,100), 381 (17), 169 (13), 133 (7), 115 (13), 89 (26), 73 (49), 59 (20); HRMS (EI) Calcd for $C_{24}H_{47}O_3Si_2$ 439.3064, found 439.3060.



172

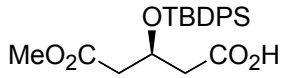
3-((*tert*-Butyldiphenylsilyl)oxy)pentanedioic acid, diethylester (172).[178] To a solution of 16.7 mL (245 mmol) of imidazole in 250 mL of CH_2Cl_2 was added 30.2 mL (116 mmol) of TBDPSCl. After stirring for 10 min at rt, a solution of 25.0 g (122 mmol) of diethyl 3-hydroxyglutarate in 100 mL of CH_2Cl_2 was added. The reaction mixture was stirred at rt for 16 h and diluted with H_2O and Et_2O. The combined organic layers were washed with NaCl. The aqueous layers were combined and re-extracted with Et_2O. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield 51.0 g (99%) of **172** as a yellow solid: Mp 44-46 °C; ^{1}H NMR δ 7.72-7.63 (m, 4 H), 7.43-7.26 (m, 6 H), 4.55 (p, 1 H, J = 6.0 Hz), 4.10-3.93 (m, 4 H), 2.58 (A of ABX, 2 H, J = 6.3, 15.0 Hz), 2.57 (B of ABX, 2 H, J = 6.0, 15.0 Hz), 1.19 (t, 6 H, J = 6.9 Hz), 1.03 (s, 9 H); MS (EI) m/z (rel intensity) 467 (10), 466 (30), 465 ($[M-Na]^+$, 74); HRMS (EI) Calcd for $C_{25}H_{34}O_5Si$ (M+Na) 465.2073, found 465.2083.



161

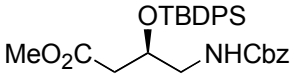
3-[(*tert*-Butyldiphenylsilyl)oxy)]pentanedioic anhydride (161).[178] To a solution of 8.85 g (20.0 mmol) of **172** in 30 mL of MeOH was added 2.00 g (50.5 mmol) of NaOH pellets and the mixture was stirred at rt for 36 h. The resulting suspension was concentrated *in vacuo*. The crude residue was crushed into fine particles and suspended in 40 mL of benzene and 30 mL of Ac_2O. The mixture was heated at reflux for 1.5 h, quenched with NaCl, and extracted with $CHCl_3$. The organic layers were washed with $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (100% Hexanes containing 1% Ac_2O to 20% EtOAc/Hexanes containing 1% Ac_2O) to yield 3.79 g (61%) of **161** as peach-colored oil: ^{1}H NMR δ 7.71-7.52 (m, 4 H), 7.51-7.31 (m, 6 H), 4.30-4.70 (m, 1 H), 2.83 (A of ABX, 2 H, J = 3.6, 16.2 Hz), 2.60 (B of ABX, 2 H, J = 2.7, 16.0 Hz),

1.05 (s, 9 H); MS (EI) *m/z* (rel intensity) 311 ([M-C_4H_9]$^+$, 74), 291 (21), 240 (17), 225 (74), 199 (100), 183 (27), 105 (8), 78 (31).



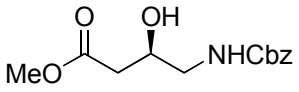
170

(*S*)-((3-*tert*-Butyldiphenylsilyl)oxy)pentanedioic acid, monomethylester (170).[178] To a solution of 1.09 g (2.96 mmol) of **161** in 100 mL of Et_2O at –40 ºC was added 760 mg (0.887 mmol) of $(DHQD)_2AQN$. The mixture was stirred for 20 min, treated with 1.20 mL (29.6 mmol) of MeOH and stirred for 72 h at –40 ºC. The reaction mixture was quenched with 10% aq. HCl at –40 ºC, warmed to rt, and extracted with EtOAc. The aqueous layer was reextracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield 865 mg (73%) of **170** as a colorless oil: ^{1}H NMR δ 7.75-7.60 (m, 4 H), 7.50-7.35 (m, 6 H), 4.51 (p, 1 H, *J* = 6.3 Hz), 3.56 (s, 3 H), 2.71-2.50 (m, 4 H), 1.03 (s, 9H); MS (EI) *m/z* (rel intensity) 357 ([M-CO_2H]$^+$, 5), 343 (58), 265 (66), 225 (15), 199 (100), 179 (32), 78 (30).



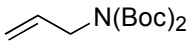
174

(*R*)-4-Benzyloxycarbonylamino-3-(*tert*-butyldiphenylsilyloxy)-butyric acid methyl ester (174). To 600 mg (1.50 mmol) of **170** in 10 mL of toluene was added 0.39 mL (1.80 mmol) of DPPA and 0.25 mL (1.80 mmol) of Et_3N. The solution was stirred at rt for 30 min and further heated at reflux for 3.5 h. At rt, 0.47 mL (4.50 mmol) of BnOH was added. The resulting reaction mixture was heated at reflux for 18 h, quenched with $NaHCO_3$, extracted with Et_2O, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (3% EtOAc/Hexanes) to yield 596 mg (80%) of **174** a colorless oil: IR (neat) 3004, 2866, 1745, 1645, 1525, 1260, 993 cm^{-1}; ^{1}H NMR δ 7.62 (t, 5 H, *J* = 7.0 Hz), 7.42-7.23 (m, 10 H), 4.97 (s, 2 H), 4.84 (t, 1 H, *J* = 5.2 Hz), 3.49 (s, 3 H), 3.30-3.15 (m, 2 H), 2.54-2.36 (m, 2 H), 1.00 (s, 9 H); ^{13}C NMR δ 171.0, 156.2, 136.4, 135.7, 135.6,133.3, 133.0, 129.9, 129.8, 128.4, 128.0, 127.9, 127.7, 127.6, 127.7, 69.2, 66.5, 51.5, 46.1, 39.6, 26.8, 19.2; MS (EI) *m/z* (rel intensity) 449 (M$^+$, 6), 448 (15), 340 (10), 319 (13), 283 (6), 236 (10), 199 (14), 135 (11), 105 (8), 91 (100); HRMS (EI) Calcd for $C_{25}H_{26}NOSi$ 448.1580, found 448.1580.



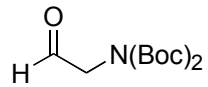
176

(*R*)-4-Benzyloxycarbonylamino-3-hydroxybutyric acid methyl ester (176). To a solution of 50 mg (0.10 mmol) of **174** in 2 mL THF in a polyethylene vial at rt was added 0.13 mL (4.94 mmol) of 70% HF·pyr. The reaction mixture was stirred for 4 d, quenched with $NaHCO_3$, extracted with Et_2O, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (20% EtOAc/Hexanes) to yield 20 mg (80%) of **176** a colorless oil: ^{1}H NMR δ 7.43-7.29 (m, 5 H), 5.20 (bs, 1 H), 5.12 (s, 2 H), 4.20-4.10 (m, 1 H, *J* = 3.5 Hz), 3.72 (s, 3 H), 3.47-3.35 (m, 1 H, *J* = 3.5 Hz), 3.27-3.12 (m, 1 H, *J* = 1.3 Hz), 2.59-2.42 (m, 2 H); MS (EI) *m/z* (rel intensity) 267 (M^+, 25), 263 (4), 249 (5), 236 (6), 165 (5), 108 (11), 104 (15), 91 (100); HRMS (EI) Calcd for $C_{13}H_{17}NO5$ 267.1096, found 267.1107.



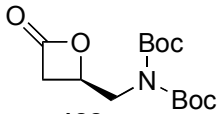
184

Bis-*tert*-butoxycarbonyl allylamine (184).[179] To 0.75 mL (10 mmol) of allyl amine and 12 mg (0.1 mmol) of DMAP in 25 mL of CH_3CN was added 2.18 g (10 mmol) of Boc_2O in 20 mL of CH_3CN. The reaction mixture was stirred at rt for 6 h, diluted with 10 mL of toluene and concentrated *in vacuo*. The resulting solid was redissolved in 25 mL of CH_3CN followed by addition of 12 mg (0.1 mmol) of DMAP and 2.18 g (10 mmol) of Boc_2O. The solution was heated to 60 ºC for 14 h and concentrated *in vacuo*. The resulting oil was washed with $NaHCO_3$, extracted with CH_2Cl_2, washed with NaCl, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (5% EtOAc/Hexanes) to yield 1.03 g (40%) of **184** a white solid: Mp 43-44 ° C (EtOAc/Hexanes); lit. 43-44 ° C; ^{1}H NMR δ 5.92-5.78 (m, 1 H), 5.16 (dq, 1 H, *J* = 1.5, 26.8 Hz), 5.15-5.12 (m, 1 H), 4.18 (dt, 2 H, *J* = 1.5, 5.5 Hz), 1.51 (s, 9 H); MS (EI) *m/z* (rel intensity) 280 (M^+, 82), 224 (53), 168 (100), 140 (13), 124 (90).



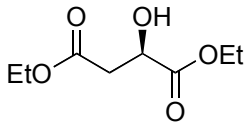
186

1-(Bis-*tert*-butoxycarbonyl amino)-2-ethanal (186). To solution of 1.66 g (6.45 mmol) of **184** in 70 mL of CH_2Cl_2 at –78 ºC was introduced O_3 for 30 min until blue color persisted. The reaction mixture was purged with N_2 for 30 min followed by quenching with 4 mL of DMS and stirred for 16 h at rt. The reaction mixture was poured into dilute NaCl, extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (5% EtOAc/Hexanes) to yield 1.67 g (59%) of **186** a colorless oil: ^{1}H NMR δ 9.54 (s, 1 H), 4.37 (s, 2 H), 9.54 (s, 1 H); ^{13}C NMR 196.7, 151.8, 83.4, 55.2, 27.9; HRMS (EI) Calcd for $C_{12}H_{21}NO_5$ 282.1317, found 282.1311.



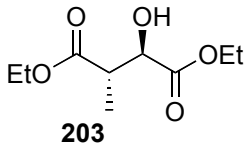
182

(*R*)-4-(Dicarbamic acid-*t*-butylester)-oxetane-2-one (39). To a solution of 20 mg (0.05 mmol) of TMSQ and 160 mg (1.5 mmol) of $LiClO_4$ in 0.5 mL of diethyl ether was added 1.0 mL of CH_2Cl_2. The reaction mixture was cooled to –78 ºC, and treated with 0.21 ml (1.3 mmol) of *N*,*N*-diisopropylethylamine followed by the addition of 130 mg (0.5 mmol) of **186**. A solution of 72 μL (0.5 mmol) of acetyl chloride in 0.3 mL CH_2Cl_2 was then added over 1 h by syringe pump. The reaction mixture was stirred for 16 h at –78 ºC and was quenched at –78 ºC by adding 5 mL of Et_2O, filtered through silica gel, washed with Et_2O, and concentrated *in vacuo*. The crude material was triturated with hexanes to remove impurities to yield 100 mg (66%) of **182** as a white solid: ^{1}H NMR δ 4.71 (p, 1 H, J = 5.5 Hz), 4.07 (A of AB, 1 H, J = 5.5, 14.9 Hz), 4.01 (B of AB, 1 H, J = 5.4, 14.9), 3.52 (A of AB, 1 H, J = 5.9, 16.5 Hz), 3.34 (B of AB, 1 H, J = 4.3, 16.6 Hz), 1.52 (s, 18 H).



202

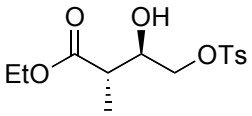
(*R*)-Diethyl malate (202).[180] To a solution of 5.00 g (37.3 g) of (*D*)-malic acid in 32 mL of EtOH was added 120 μL of HCl. The resulting solution was stirred at reflux for 15 h, concentrated *in vacuo*, purified by chromatography on SiO_2 (20% EtOAc/Hexanes) to yield 5.68 g (80%) of **202** as a colorless oil: ^{1}H NMR δ 4.48 (q, 1 H, *J* = 5.7 Hz), 4.28 (qd, 2 H, *J* = 1.2, 7.2 Hz), 4.18 (q, 2 H, *J* = 7.2 Hz), 3.21 (d, 2 H, *J* = 5.4 Hz), 2.83 (A of ABX, 1 H, *J* = 4.5, 16.2 Hz), 2.82 (B of ABX, 1 H, *J* = 6.0, 16.2 Hz), 1.31 (t, 3 H, *J* = 6.9 Hz), 1.28 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR δ 173.1, 170.3, 67.0, 61.6, 60.6, 38.5, 13.8.



203

Diethyl (2*R*, 3*S*)-3-methylmalate (203).[180] To a solution of 6.38 mL (45.8 mmol) of diisopropylamine in 21 mL of THF was added 26.3 mL (42.1 mmol) of *n*-BuLi dropwise via an addition funnel at 0 ºC. The solution was stirred at 0 ºC for 30 min and further cooled to -78 ºC. A solution of 3.48 g (18.3 mmol) of **202** in 5 mL of THF was added slowly to the LDA solution. The resulting solution was stirred for 50 min at -78 ºC, warmed to -20 ºC over 2 h, stirred at -20 ºC for 20 min, and recooled to -78 ºC. At -78 ºC, 1.71 mL (27.5 mmol) of MeI was added, and the mixture was stirred for 30 min and warmed to -30 ºC over 1 h. After 1 h at 0 ºC, the reaction mixture was warmed to rt during a 1 h period and stirred at rt for 1 h. The mixture was quenched with 1.0 M citric acid and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (5% EtOAc/Hexanes) to yield 2.40 g (64%) of **203** as a yellow oil in a 6:1 ratio of diastereomers based on integration of ^{1}H NMR signals at 3.03 ppm (major) and 2.92 ppm (minor): ^{1}H NMR δ 4.36-4.21 (m, 3 H), 4.15 (qd, 2 H, *J* = 1.5, 7.2 Hz), 3.14 (bd, 1 H, *J* = 5.4 Hz), 3.03 (qd, 1 H, *J* = 3.6, 7.2 Hz), 1.32 (d, 3 H, *J* = 7.2 Hz), 1.31 (t, 3 H, *J* = 6.9 Hz), 1.26 (t, 3

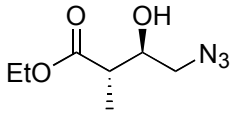
H, J = 7.2 Hz); Major isomer: ^{13}C NMR δ 173.0, 172.6, 72.2, 61.7, 60.7, 42.9, 13.9, 12.6, 10.4. Minor isomer: ^{13}C NMR δ 173.0, 172.6, 71.2, 61.6, 60.6, 42.8, 13.8, 12.6, 10.4.



204

(2*S*,3*R*)-3-Hydroxy-2-methyl-4-(toluene-4-sulfonyloxy)-butyric acid ethyl ester (204).[180] To a solution of 400 mg (1.96 mmol) of **203** in 4 mL of THF was added 1.01 mL (2.20 mmol) of BH_3·DMS over 15 min. The resulting solution was stirred for 20 min at rt and cooled to 0 ºC. At 0 ^{o}C, 3.7 mg (0.098 mmol) of $NaBH_4$ was added. The mixture was stirred for 2 h, quenched with 1 mL of EtOH and 18.6 mg of *p*-TsOH, stirred for 30 min at rt, and concentrated *in vacuo*. The resulting residue was dissolved in 4 mL of 1:1 mixture of EtOH: benzene and concentrated *in vacuo* (repeated three times). The crude **204a** was used in the next step without further purification.

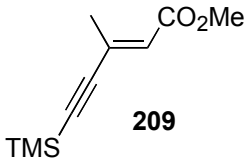
To a solution of crude **204a** in 6 mL of CH_2Cl_2 at rt was added 25 mg (0.099 mmol) of dibutyltin oxide, 0.27 mL (1.96 mmol) of Et_3N, and 374 mg (1.96 mmol) of TsCl. The reaction mixture was stirred for 15 h at rt, filtered, and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (25% EtOAc/Hexanes) to yield 348 mg (56% over 2 steps) of **204** as a colorless oil: ^{1}H NMR δ 7.80 (d, 2 H, J = 8.4 Hz), 7.36 (d, 2 H, J = 8.1 Hz), 4.15 (q, 2 H, J = 7.2 Hz), 4.09 (d, 2 H, J = 4.8 Hz), 3.89 (q, 1 H, J = 5.7 Hz), 2.69 (p, 1 H, J = 6.6 Hz), 2.46 (s, 3 H), 2.09 (s, 1 H), 1.26 (t, 3 H, J = 7.2 Hz), 1.21 (d, 3 H, J = 7.2 Hz).



205

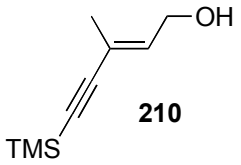
(2*S*,3*R*)-4-Azido-3-hydroxy-2-methylbutyric acid ethyl ester (205).[180] To 110 mg (0.35 mmol) of **204** in 2 mL of DMF was added 45 mg (0.70 mmol) of NaN_3. The reaction mixture was heated at reflux for 5.5 h, cooled to rt, and diluted with EtOAc. The solution was washed with H_2O and NaCl, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield 39 mg of **204** (65%) as a colorless oil: ^{1}H NMR δ 4.16 (q, 2 H, J = 7.2 Hz), 3.85 (ddd, 1 H, J = 6.3, 10.2, 12.6

Hz), 3.38 (A of ABX, 1 H, J = 3.6, 12.6 Hz), 3.36 (B of ABX, 1 H, J = 6.0, 12.3 Hz), 3.30 (d, 1 H, J = 6.3 Hz), 2.65 (p, 1 H, J = 7.2 Hz), 1.26 (t, 3 H, J = 11.1 Hz), 1.19 (d, 3 H, J = 7.2 Hz); ^{13}C NMR δ 175.2, 72.5, 60.9, 54.3, 42.6, 14.0, 13.9; Major isomer: ^{13}C NMR δ 175.2, 72.5, 60.9, 54.3, 42.6, 14.0, 13.9. Minor isomer: ^{13}C NMR δ 175.2, 70.5, 60.9, 54.0, 42.4, 14.0, 13.9.



209

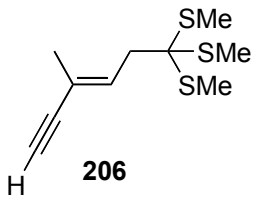
3-Methyl-5-(trimethyl-silanyl)-pent-2-en-4-ynoic acid methyl ester (209).[145] A solution of 132 mg (0.30 mmol) of TDMPP and 136 mg (0.30 mmol) of $Pd(OAc)_2$ in 10 mL of THF was stirred for 15 min, followed by the addition of 1.00 mL (10 mmol) of 3-methylbutynoate. The resulting solution was stirred for 5 min, followed by the addition of 1.41 mL (10 mmol) of trimethylsilylacetylene. The reaction mixture was stirred for 75 min at rt and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (100% Hexanes) to yield 1.51 g (77%) of **209** as an orange oil: ^{1}H NMR δ 6.07 (s, 1 H), 3.69 (s, 3 H), 2.26 (s, 3 H), 0.18 (s, 9 H); ^{13}C NMR δ 166.4, 137.8, 124.4, 106.4, 99.3, 51.1, 19.6, -0.4; MS (EI) *m/z* (rel intensity) 196 (M^+, 20), 181 (100), 165 (27), 151 (60), 122 (100), 113 (47); HRMS (EI) Calcd for $C_{10}H_{16}NO_2Si$ 196.0920, found 196.0914.



210

3-Methyl-5-(trimethyl-silanyl)-pent-2-en-4-yn-1-ol (210). To a solution of 1.80 g (9.18 mmol) of **209** in 48 mL of CH_2Cl_2 at –78 ºC was added 20.2 mL (20.2 mmol) of diisobutylaluminum hydride (1 M in hexanes). The resulting reaction mixture was stirred for 1 h, quenched with aqueous sodium potassium tartrate, and stirred for 2 h at rt. The mixture was diluted with CH_2Cl_2, washed with NaCl, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (25% EtOAc/Hexanes) to yield 1.30 g (84%) of **210** as an orange oil: IR (neat) 3345, 2959, 2900, 2144, 1680, 1250 cm^{-1}; ^{1}H NMR δ 6.01 (td, 1 H, J = 1.2, 6.6 Hz), 4.21 (dd, 2 H, J = 0.6, 6.6 Hz), 1.82 (s, 3 H), 1.60 (s, 1 H), 0.18 (s, 9 H); ^{13}C NMR

δ 136.5, 120.7, 107.3, 92.1, 59.1, 17.4, -0.1; MS (EI) *m/z* (rel intensity) 181 (7), 168 (M^+, 14), 153 (28), 141 (20), 125 (48), 109 (16), 99 (27), 83 (55), 75 (84), 73 (100); HRMS (EI) Calcd for $C_9H_{16}NOSi$ 168.0970, found 198.0964.



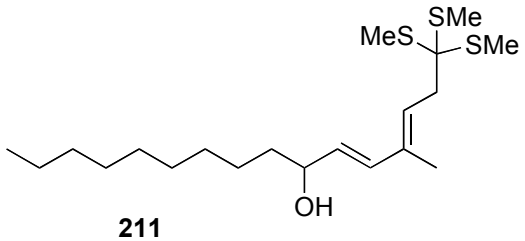
206

3-Methyl-6,6,6-trismethylsulfanyl-hex-3-en-1-ynyl (206). To a solution of 1.90 g (11.3 mmol) of **210** and 2.67 mL (19.2 mmol) of Et_3N in 40 mL of CH_2Cl_2 at –10 ºC was added 0.95 mL (12.4 mmol) of methanesulfonylchloride. The reaction mixture was stirred for 30 min at –10 ºC, 1 h at 0 ºC, and 15 h at rt. The mixture was washed with cold H_2O, 10% HCl, $NaHCO_3$, NaCl, dried ($MgSO_4$), and concentrated *in vacuo* to yield the mesylate. The mesylate was immediately used in the next step without further purification.

To 2.53 mL (19.0 mmol) of tris(methylthio)methane in 40 mL of THF at –78 ºC was added 12.3 mL (18.4 mmol) of *n*-BuLi (1.5 M/Hexanes). The resulting solution was stirred at –78 ºC for 15 min followed by the addition of the above prepared mesylate in 5 mL of THF. The reaction mixture was stirred at –78 ºC for 1 h, warmed to –40 ºC and quenched with ether. The organic layer was washed with $NaHCO_3$, NaCl, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (100% hexanes) to yield 3.27 g of **206a** and excess tris(methylthio)methane as an yellow/orange oil. This material was used in the next step.

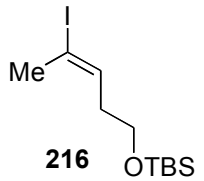
To a solution of 3.27 g (10.7 mmol) of **206a** in 40 mL of distilled MeOH at rt was added 1.63 g (11.8 mmol) of K_2CO_3. The reaction mixture was stirred at rt for 15 h, quenched with NH_4Cl, washed with H_2O, extracted with CH_2Cl_2, washed with NaCl, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (100% Hexanes) to yield 1.27 g (51% over 3 steps) of **206** as a yellow oil: IR (neat) 3287, 2982, 2916, 2093, 1403, 962, 754 cm^{-1}; ^1H NMR δ 6.29-6.20 (m, 1 H), 2.83 (s, 1 H), 2.83 (s, 1 H), 2.74 (d, 2 H, J = 6.7 Hz), 2.12 (s, 9 H), 1.85 (s, 3 H); ^{13}C NMR δ 133.2, 118.8, 86.1, 74.6, 69.5, 37.2, 17.6, 13.0; MS (EI) *m/z* (rel intensity) 249 (10), 217 (67), 201 (15), 184 ($[M\text{-}SMe]^+$, 100), 153 (50),

138 (30), 123 (30), 112 (28); HRMS (EI) Calcd for $C_9H_{13}S_2$ (M-SCH_3) 185.0459, found 185.0456.



211

4-Methyl-1,1,1-trismethylsulfanylhexadeca-3,5-dien-7-ol (211). To a suspension of 126 mg (0.49 mmol) of zirconocene hydrochloride in 2 mL of CH_2Cl_2 under N_2 was added 100 mg (0.43 mmol) of **206** at room temperature. The reaction mixture was stirred for 15 min, cooled to -65 ºC, and was treated with 0.21 mL (0.43 mmol) of Me_2Zn (2.0 M solution in toluene). After 5 min, the mixture was warmed to 0 ºC, stirred for 30 min, treated with 74 µL (0.39 mmol) of decylaldehyde, stirred for 3 h at 0 ºC, quenched by addition of $NaHCO_3$ solution, filtered through a plug of florisil and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (10% EtOAc/Hexanes) to yield 62 mg (41%) of **211** as a colorless oil: ^{1}H NMR (CD_3OD) δ 6.14 (d, 1 H, *J* = 15.7 Hz), 5.66 (t, 1 H, *J* = 6.9 Hz), 5.49 (dd, 1 H, *J* = 7.0, 15.7 Hz), 3.96 (q, 1 H, *J* = 6.7 Hz), 2.70 (d, 2 H, *J* = 6.8 Hz), 1.99 (s, 9 H), 1.69 (s, 3 H), 1.50-1.30 (m, 2 H), 1.30-1.20 (bs, 14 H), 0.80 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR (CD_3OD) δ 136.1, 135.8, 131.8, 127.5, 73.8, 71.5, 38.6, 38.0, 33.1, 30.8, 30.7, 30.7, 30.5, 26.7, 23.8, 14.5, 13.4, 13.2; MS (EI) *m/z* (rel intensity) 803 (38), 621 (22), 524 (38), 413 ([M+Na]$^+$, 100), 381 (28), 325 (23); HRMS (EI) Calcd for $C_{20}H_{38}OS_3Na$ 413.1983, found 413.2002.

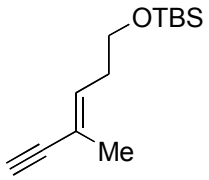


216

***tert*-Butyl-(4-iodopent-3-enyloxy)dimethylsilane (216).**[181] To a solution of 448 mg (5 mmol) of CuCN in 10 mL of a 1:1 solution of THF:ether at –40 ºC was added 7.1 mL (10 mmol) of *n*-BuLi (1.4M/hexanes). After 5 min, the solution was stirred at rt for 15 min, cooled to –40 ºC, treated with 2.69 mL (10 mmol) of Bu_3SnH, and stirred for 70 min at –40 ºC. In a separate flask,

to a solution of 0.38 mL (5 mmol) of 2,3-dihydrofuran in 5 mL of THF was added 7.06 mL (12 mmol) of *t*-BuLi (1.7 M/Hexanes). The mixture was stirred at –60 ºC for 10 min and at 0 ºC for 55 min before it was added via cannula to the above reaction mixture. The resulting solution was then stirred at 0 ºC for 1.5 h, treated with 2.18 mL (35 mmol) of MeI, allowed to warm to rt during a period of 1 h and stirred at rt for another 3 h. The mixture was poured into an aqueous mixture of NH_4Cl and NH_3-H_2O at 0 ºC and stirred for 30 min. The aqueous layer was extracted with ether, dried ($MgSO_4$), filtered, and concentrated *in vacuo*.

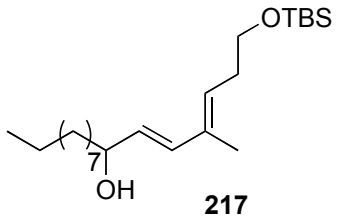
To a solution of the resulting oil in 45 mL of CH_2Cl_2 at 0 ºC was added a solution of 1.4 g (5 mmol) of I_2 in CH_2Cl_2 until the brown color persisted. The mixture was treated with 1.0 g (15 mmol) of imidazole followed by the addition of 2.23 g (15 mmol) of TBSCl. The resulting reaction mixture was stirred at 0 ºC for 20 min, quenched with aqueous solution of $Na_2S_2O_3$, extracted with Et_2O, dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (100% Hexanes) to yield 1.22 g (76%) of **216** a colorless oil: ^{1}H NMR δ 6.17 (td, 1 H, *J* = 1.5, 7.8 Hz), 3.62 (t, 2 H, *J* = 6.6 Hz), 2.39 (s, 3 H), 2.24 (q, 2 H, *J* = 6.9 Hz), 0.90 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR δ 137.7, 95.3, 61.7, 34.2, 27.7, 25.9, 18.3, -5.3; MS (EI) *m/z* (rel intensity) 325 (M^+, 10), 311 (33), 269 (100), 215 (5), 185 (20), 141 (6); HRMS (EI) Calcd for $C_{11}H_{23}OSiI$ (M-CH_3) 311.0328, found 311.0313.



213

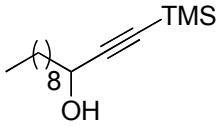
***tert*-Butyldimethyl-(4-methylhex-3-en-5-ynyloxy)silane (213).** To a solution of 199 mg (0.02 mmol) of $Pd(PPh_3)_4$ in 6 mL of THF was added at rt 1.12 g (3.44 mmol) of **216** and 10.3 mL (5.15 mmol) of ethynylmagnesium chloride. The reaction mixture was stirred for 2 h and quenched with NH_4Cl, extracted with pentane, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (100% pet. Et_2O) to yield 550 mg (71%) of **213** a colorless oil: IR (neat) 3351, 2899, 2144, 1250, 1677, 1014, 844 cm^{-1}; ^{1}H NMR δ 5.96 (t, 1 H, *J* = 7.2 Hz), 3.64 (t, 2 H, *J* = 6.9 Hz), 2.77 (s, 1 H), 2.33 (q, 2 H, *J* = 7.2 Hz), 1.82 (s, 3 H), 0.90 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR δ 135.9, 118.5, 86.7, 73.3, 62.0, 32.3,

25.9, 18.3, 17.2, -5.3; MS (EI) *m/z* (rel intensity) 167 ([M-*t*-Bu]$^+$, 73), 132 (12), 89 (43); HRMS (EI) Calcd for $C_{13}H_{24}OSi$ (M-CH_3) 209.1369, found 209.1362.



217

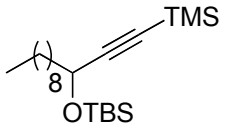
1-(*tert*-Butyldimethylsilanyloxy)-4-methylhexadeca-3,5-dien-7-ol (217). To a suspension of 125 mg (0.49 mmol) of zirconocene hydrochloride in 2 mL of CH_2Cl_2 under N_2 was added 100 mg (0.45 mmol) of **213** at room temperature. The reaction mixture was stirred for 10 min, cooled to -65 ºC, and treated with 0.21 mL (0.43 mmol) of Me_2Zn (2.0 M solution in toluene). After 5 min, the mixture was warmed to 0 ºC, stirred for 30 min, treated with 74 μL (0.41 mmol) of decylaldehyde, and stirred for 4 h at 0 ºC. The solution was quenched by addition of sat. $NaHCO_3$ solution, filtered through a plug of florisil and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (10% EtOAc/Hexanes) to yield 35 mg (23%) of **217** as a colorless oil: IR (neat) 3312, 2928, 1682, 1005, 1361, 938, 776 cm^{-1}; ^{1}H NMR δ 6.23 (d, 1 H, *J* = 15.6 Hz), 5.58 (dd, 1 H, *J* = 7.3, 15.7 Hz), 5.40 (t, 1 H, *J* = 7.4 Hz), 4.10-4.25 (m, 1 H), 3.64 (t, 2 H, *J* = 6.9 Hz) 2.38 (q, 2 H, *J* = 7.1 Hz), 1.84 (s, 3 H), 1.49-1.42 (m, 2 H), 1.40-1.20 (bs, 14 H), 0.95-0.83 (t, 3 H), 0.91 (s, 9 H), 0.07 (s, 6 H).



223

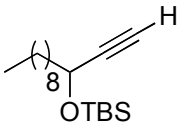
1-(Trimethylsilanyl)dodec-1-yn-3-ol (223). To a solution of 1.41 mL (10 mmol) of trimethylsilylacetylene in 4 mL of THF at –12 ºC was added 6.67 mL (10 mmol) of *n*-BuLi (1.5 M/hexanes). After stirring for 1 h at –12 ºC, a pre-cooled solution of 1.88 mL (10 mmol) of decylaldehyde in 4 mL of THF was added. The reaction mixture was stirred at –78 ºC for 30 min, and at -12 ºC for 1 h, quenched with NH_4Cl and extracted with Et_2O. The combined organic layers were washed with NaCl, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The

resulting crude residue was purified by chromatography on SiO_2 (10% EtoAc/Hexanes) to yield 1.98 g (78%) of **223** as a colorless oil: ^{1}H NMR δ 4.36 (bs, 1 H), 1.80-1.60 (m, 2 H), 1.57 (s, 1 H), 1.50-1.40 (m, 2 H), 1.28 (bs, 12 H), 0.89 (t, 3 H, *J* = 6.3 Hz), 0.17 (s, 9 H); ^{13}C NMR δ 107.0, 89.3, 62.9, 37.7, 31.9, 29.5, 29.3, 29.2, 25.1, 22.7, 14.1, -0.1; MS (EI) *m/z* (rel intensity) 275 ([M+Na]$^+$, 5), 249 (28), 239 (7), 221 (8), 181 (25), 153 (12), 127 (95), 99 (91), 78 (65), 72 (100); HRMS (EI) Calcd for $C_{15}H_{30}OSi$ (M-CH_3) 239.1831, found 239.1841.



224

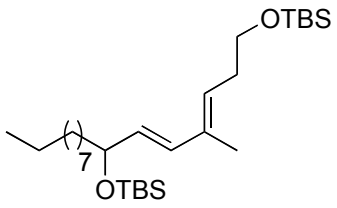
3-(*tert*-Butyldimethylsilanyloxy)-1-(trimethylsilanyl)dodec-1-yne (224). To a solution of 1.98 g (7.78 mmol) of **224** in 21 mL of CH_2Cl_2 at 0 ºC was added 1.59 g (23.3 mmol) of imidazole and 1.76 g (11.7 mmol) of TBSCl. The resulting reaction mixture was stirred at rt for 20 h, quenched with sat. NH_4Cl, and extracted with Et_2O. The combined organic layers were washed with NaCl, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (100% Hexanes) to yield 2.47 g (86%) of **224** a colorless oil: IR (neat) 3333, 2925, 2855, 2171, 1464, 1250, 1017, 844 cm^{-1}; ^{1}H NMR δ 4.32 (t, 1 H, *J* = 6.3 Hz), 1.72-1.60 (m, 2 H), 1.48-1.20 (m, 14 H), 0.92 (s, 9 H), 0.93-0.82 (m, 3 H), 0.16 (s, 9 H), 0.13 (d, 6 H, *J* = 6.3 Hz); ^{13}C NMR δ 108.1, 88.3, 63.4, 38.5, 31.9, 29.5, 29.3, 29.2, 25.9, 25.3, 22.7, 18.3, 14.1, -0.1, -4.4, -4.9; MS (EI) *m/z* (rel intensity) 354 ([M-CH_3]$^+$,13), 353 (35), 311 (100), 241 (76), 213 (72), 185 (78), 155 (98), 147 (89), 133 (77), 109 (57); HRMS (EI) Calcd for $C_{21}H_{44}OSi_2$ (M-CH_3) 353.2696, found 353.27.



225

3-(*tert*-Butyldimethylsilanyloxy)-1-(trimethylsilanyl)dodec-1-yne (225). To a solution of 2.74 g (7.43 mmol) of **224** in 30 mL of dry MeOH was added 1.13 g (8.17 mmol) of K_2CO_3. The reaction mixture was stirred for 16 h at rt, quenched with NH_4Cl, extracted with CH_2Cl_2, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by

chromatography on SiO_2 (100% Hexanes) to yield 2.20 g (99%) of **225** a colorless oil: IR (neat) 3312, 2927, 2856, 1713, 1466, 1254, 1095, 838 778 cm^{-1}; ^1H NMR δ 4.34 (td, 1 H, *J* = 1.8, 6.6 Hz), 2.37 (d, 1 H, *J* = 1.8 Hz), 1.72-1.62 (m, 2 H), 1.50-1.22 (m, 14 H), 0.92 (s, 9 H), 0.90 (t, 3 H, *J* = 7.2 Hz), 0.13 (d, 6 H, *J* = 7.2 Hz); ^{13}C NMR δ 85.5, 71.8, 62.8, 38.6, 31.9, 29.6, 29.3, 29.3, 25.8, 25.1, 22.7, 18.2, 14.1, -4.6, -5.1; MS (EI) *m/z* (rel intensity) 296 (M^+, 10), 239 (38), 221 (24), 169 (27), 113 (100); HRMS (EI) Calcd for $C_{18}H_{36}OSi$ 296.56, found 296.25.

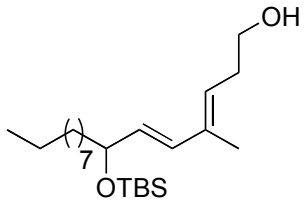


226

1,7-Bis-(*tert*-butyldimethylsilanyloxy)-4-methylhexadeca-3,5-diene (216). To a mixture of 500 mg (1.69 mmol) of **225** and 0.26 mL (1.77 mmol) of 4,4,5,5-tetramethyl-[1,3,2]dioxaborolane was added 44 mg (0.169 mmol) of Cp_2ZrHCl and 24 μL (0.169 mmol) of Et_3N. The resulting mixture was heated for 16 h and diluted with EtOAc. The resulting precipitate was filtered through a plug of celite and washed with EtOAc. The filtrate was concentrated *in vacuo* to yield 756 mg of **221** as a light yellow oil that was used in the next step without further purification.

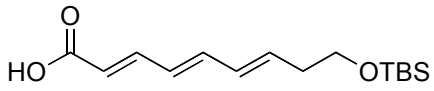
A solution of the crude boronic ester (717 mg, 1.69 mmol) prepared above and 799 mg (2.45 mmol) of **216** in THF-H_2O (32 mL:15 mL) was degassed using freeze-pump-thaw(3x), treated with 195 mg (0.169 mmol) of $Pd(PPh_3)_4$ and stirred for 5 min in the dark. The resulting mixture was treated with 0.181 mL (2.54 mmol) of TlOEt, stirred for 20 h in the dark, filtered through a plug of celite and separated from the aqueous layer. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (100% Hexanes) to yield 551 mg (66% over 2 steps) of **226** as a yellow oil: IR (neat) 3011, 2985, 1683, 1245, 1003, 910, 845 cm^{-1}; ^1H NMR δ 6.11 (d, 1 H, *J* = 15.6 Hz), 5.52 (dd, 1 H, *J* = 6.9, 15.9 Hz), 5.43 (t, 1 H, *J* = 6.9 Hz), 4.12 (q, 1 H, *J* = 6.0 Hz), 3.64 (t, 2 H, *J* = 7.2 Hz), 2.36 (q, 2 H, *J* = 6.9 Hz), 1.74 (s, 3 H), 1.56-1.36 (m, 2 H), 1.26 (s, 14 H), 0.89 (s, 18 H), 0.88 (t, 3 H), 0.05 (s, 6 H), 0.04 (d, 6 H, *J* = 8.1 Hz); ^{13}C NMR δ 134.8, 133.8, 130.9, 127.8, 73.9, 62.8, 38.7, 32.1, 31.9, 29.6, 29.6, 29.3, 26.0, 25.4, 22.7, 18.4, 18.3, 14.1, 12.6, -4.2, -4.7, -5.3; MS (EI)

m/z (rel intensity) 497 (M^+, 50), 439 (40), 369 (40), 307 (87), 271 (10), 237 (65), 89 (29), 75 (100); HRMS (EI) Calcd for $C_{29}H_{60}O_2Si_2$ 496.957, found 496.4124.



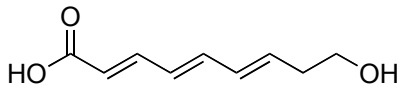
227

7-(*tert*-Butyldimethylsilanyloxy)-4-methylhexadeca-3,5-dien-1-ol (227). To a solution of 551 mg (1.11 mmol) of **226** in 10 mL of THF was added 0 ºC 1.11 mL (1.11 mmol) of TBAF (1 M/THF). The reaction mixture was slowly warmed from 0 ºC to 20 ºC over a period of 3.5 h, quenched with NH_4Cl, extracted with Et_2O, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (10% EtOAc/Hexanes) to yield 354 mg (83%) of **227** a yellow oil: ^{1}H NMR δ 6.17 (d, 1 H, *J* = 15.7 Hz), 5.56 (dd, 1 H, *J* = 6.7, 15.6 Hz), 5.43 (t, 1 H, *J* = 7.5 Hz), 4.13 (q, 1 H, *J* = 6.0 Hz), 3.70 (t, 2 H, *J* = 6.5 Hz), 2.43 (q, 2 H, *J* = 6.7 Hz), 1.77 (s, 3 H), 1.52-1.30 (m, 2 H), 1.26 (s, 14 H), 0.92-0.83 (t, 3H), 0.90 (s, 9 H), 0.04 (d, 6 H, *J* = 7.9 Hz); ^{13}C NMR δ 135.8, 133.5, 131.3, 127.0, 73.8, 62.2, 38.6, 31.9, 31.8, 29.6, 29.6, 29.3, 25.9, 25.3, 22.7, 18.2, 14.1, 12.7, -4.2, -4.8; MS (EI) *m/z* (rel intensity) 382 (M^+, 13), 325 (20), 255 (40), 199 (23), 151 (15), 135 (37), 123 (45), 107 (75), 93 (100); HRMS (EI) Calcd for $C_{23}H_{46}O_2Si$ 382.3267, found 382.3271.



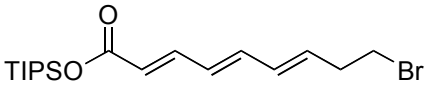
233

9-(*tert*-Butyldimethylsilanyloxy)-nona-2*E*,4*E*,6*E*-trienoic acid (233). To a solution of 50 mg (0.114 mmol) of **164** in MeOH was added 57 mg (0.228 mmol) of PPTS. The resulting mixture was stirred at rt for 4.5 h and concentrated *in vacuo*. The residue was redissolved in EtOAc, washed with NaCl, H_2O, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (100% CH_2Cl_2 to 10% MeOH/CH_2Cl_2) to yield 32 mg (75%) of **233** a white solid: IR (KBr) 3010, 2837, 1634, 1590, 1345 cm^{-1}; ^{1}H NMR δ 7.17 (dd, 1 H, *J* = 11.1, 15.0 Hz), 6.49 (dd, 1 H, *J* = 10.8, 14.4 Hz), 6.17 (td, 2 H, *J* = 11.4, 15.6 Hz), 5.92-5.78 (m, 1 H), 5.74 (d, 1 H, *J* = 15.3 Hz), 3.60 (t, 2 H, *J* = 6.6 Hz), 2.25 (q, 2 H, *J* = 6.6 Hz).



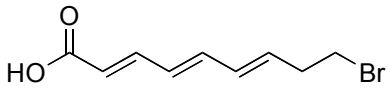
234

9-Hydroxynona-2*E*,4*E*,6*E*-trienoic acid (234). To a solution of 50 mg (0.114 mmol) of **164** in MeOH was added 142 mg (0.570 mmol) of PPTS. The resulting mixture was stirred at rt for 4.5 h and concentrated *in vacuo*. The residue was redissolved in EtOAc, washed with NaCl and H_2O, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (100% CH_2Cl_2 to 10% MeOH/CH_2Cl_2) to yield 30 mg (82%) of **233** a white solid: IR (KBr) 3104, 2967, 1620, 1520, 945, 735 cm^{-1}; ^1H NMR δ 7.29 (dd, 1 H, *J* = 11.1, 15.3 Hz), 6.61 (dd, 1 H, *J* = 10.8, 15.0 Hz), 6.38-6.21 (m, 2 H), 6.06-5.91 (m, 1 H), 5.84 (d, 1 H, *J* = 15.0 Hz), 3.62 (t, 2 H, *J* = 6.3 Hz), 2.37 (q, 2 H, *J* = 6.6 Hz); ^{13}C NMR δ 169.0, 146.8, 142.5, 137.7, 133.1, 129.7, 121.6, 62.4, 37.4.



235

9-Bromonona-2*E*,4*E*,6*E*-trienoic acid triisopropylsilylester (235). To a suspension of 126 mg (0.30 mmol) of PPh_3Br_2 in 1 mL of CH_2Cl_2 was added a solution of 119 mg (0.27 mmol) of **164** in 0.5 mL of CH_2Cl_2. The reaction mixture was stirred for 10 min, diluted with CH_2Cl_2, washed with H_2O, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting crude residue was purified by chromatography on SiO_2 (100% CH_2Cl_2 to 10% MeOH/CH_2Cl_2) to yield 10 mg (10%) of **235** as a white solid and 25 mg (24%) of **236** as a white solid: IR (KBr) 3082, 2960, 1622, 1301, 1090, 980, 625 cm^{-1}; ^1H NMR δ 7.35-7.20 (m, 1 H), 6.52 (dd, 1 H, *J* = 14.4 Hz), 6.27 (td, 2 H, *J* = 14.4 Hz), 5.90-5.60 (m, 2 H), 3.43 (t, 2 H, *J* = 6.9 Hz), 2.73 (q, 2 H, *J* = 6.6 Hz), 1.50-1.20 (m, 3 H), 1.07 (d, 9 H, *J* = 7.5 Hz); ^{13}C NMR δ 166.6, 144.7, 139.9, 135.1, 132.4, 129.5, 122.9, 36.0, 31.6, 17.8, 12.0.



236

9-Bromonona-2*E*,4*E*,6*E*-trienoic acid (236). ^{1}H NMR δ 7.39 (dd, 1 H, *J* = 11.4, 15.0 Hz), 7.65-6.50 (m, 1 H), 6.45-6.20 (m, 2 H), 6.05-5.80 (m, 2 H), 3.44 (t, 2 H, *J* = 6.9 Hz), 2.74 (q, 2 H, *J* = 6.6 Hz); ^{13}C NMR δ 172.1, 146.7, 141.2, 136.1, 132.2, 129.1, 119.9, 36.0, 31.4.

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