Asymmetric Synthesis using 3,3′-Disubstituted Binaphthol-modified Boronates

by

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Abstract

A number of 3,3′-disubstituted binaphthol-modified allylboronates (**2.42a-m**) were prepared from the reaction between triallylborane and the corresponding 3,3′-disubstituted binaphthols. These chiral allylboronates could allylate carbonyl compounds to produce chiral homoallylic alcohols in high chemical and optical yields. Chiral ligands were readily recycled through simple acid-base extraction. Among all allylboronates tested, 3,3′-$(CF_3)_2$-BINOL-modified allylboronate (**2.42b**) is an especially effective reagent that allows for allylborations of both aldehydes and ketones in high enantioselectivities (up to 98% yield and >99% *ee*). Reagent **2.42b** represents one of the best allylation reagents for carbonyl compounds developed thus far.

Allylations of cyclic imines using 3,3′-disubstituted binaphthol-modified allylboronates (**2.42a-j**) were carried out at low temperature. 3,3′-Bis[3,5-$(CF_3)_2$-C_6H_3]-binaphthol-modified allylboronate (**2.42j**) gave the best enantioselectivities (91% *ee* to >99% *ee*) in the allylation of a variety of cyclic imines. This methodology represents the first successful enantioselective allylboration of cyclic imines. The versatility of the allylation products (chiral α-allyl cyclic amines) was demonstrated through efficient total syntheses of several naturally occurring alkaloids such as coniine, crispine A and corynantheidol.

3,3′-Disubstituted binaphthol-modified alkynylboronates (**4.47a-g**) were synthesized according to a reported procedure. It was found that these chiral alkynylboronates add to *N*-acylaldimines in an enantioselective manner to produce chiral propargylamides in excellent yields and enantioselectivities. Up to >99% *ee* could be obtained with 3,3′-diphenyl binaphthol-modified alkynylboronates (**4.47f**). This represents the first direct asymmetric synthesis of chiral propargylamides. Using this

methodology, an antitubulin agent (-)-*N*-acetylcolchinol (AstraZeneca® ZD6126 phenol) was synthesized in 4 steps from commercially available 3-hydroxybenzaldehyde.

During a study of the asymmetric conjugate alkynylation of enones *via* chiral alkynylboronates, it was found that achiral dialkyl alkynylboronates could add to enones enantioselectively in the presence of catalytic amounts of chiral bidentate ligands (such as 3,3′-disubstituted binaphthols, diisopropyl tartrate and activated chiral amino acids). A catalytic cycle driven by "ligand-exchange" processes was proposed to rationalize this asymmetric induction. This is the first reported example of an asymmetric reaction that is promoted by a catalytic amount of an exchangeable chiral ligand on the boron reagent. More importantly, we have demonstrated a proof of principle that ligand exchange with boronates can be sufficiently fast that catalytic amounts of chiral ligands can be used to effect high levels of stereoselectivity. This catalytic protocol can potentially be applied to other asymmetric reactions providing the following three requirements are met: (1) the starting achiral boronate does not react with the electrophile (no background reaction); (2) the chiral boronate reacts with the electrophile and (3) ligand exchange or transesterification occurs under the reaction conditions. Potential applications of this principle include asymmetric allylboration, hydroboration, aldol reaction and reduction, just to name a few.

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Finally, I want to give a special acknowledgement to my wife Grace, who has been supporting me with love, encouragement, compassion and most importantly, delicious food.

To my wife Grace and my parents who have given me so much…

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List of Abbreviations

Ac	acetyl
All	allyl
anal	analysis
aq	aqueous
Ar	aryl
9-BBN	9-borabicyclo[3.3.1]nonane
BINAL-H	2,2′-(1,1′-binaphthoxy)aluminum hydride
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	2,2′-dihydroxy-1,1′-binaphthyl
Bn	benzyl
Boc	*t*-butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
Bz	benzoyl
c	cyclo
c	concentration (g per 100 mL)
CAL	*Candida antarctica* Lipase
Calcd	calculated
cat	catalytic
compd no.	compound number
d	doublet
DCC	*N*,*N*′-dicyclohexyl carbodiimide
de	diastereomeric excess
DEAD	Diethyl azodicarboxylate

DIPT	diisopropyl tartrate
DMAP	4-*N*,*N*-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
E^+	electrophile
ee	enantiomeric excess
EI	electron impact
ent	enantiomeric
equiv	equivalent(s)
Et	ethyl
ether	diethyl ether
Fc	ferrocenyl
FT-IR	Fourier transform infrared spectroscopy
GABA	*γ*-aminobutyric acid
GC	gas chromatography
GC-MS	gas chromatography and mass spectroscopy
h	hour
Hex	hexyl
hfc	3-(heptafluoropropylhydroxymethylene)-(+)-camphorate
HMDS	hexamethyldisilylazide
HMPA	hexamethylphosphoric amide
HPLC	high performance liquid chromatography
Hz	Hertz
i	iso
imid	imidazole
Ipc	isopinocampheyl
J	spin coupling constant

L	ligand
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
lit	literature
m	multiplet
Met	metal
M	molar
M	metal
max	maximum
MCPBA	*meta*-chloroperbenzoic acid
Me	methyl
min	minute
mL	millilitre
mmol	millimole
mol	mole
MOM	methoxymethyl
mp	melting point
MS	mass spectrometry
MTPA-amide	α-methoxy-α-trifluoromethylphenylacetamide
m/z	mass/charge
n	normal
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
nM	nanomolar
NMM	*N*-methylmorpholine
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Np	naphthyl

Nu	nucleophile
o	ortho
Ph	phenyl
pin	pinacol
PLE	pig liver esterase
PMB	*para*-methoxybenzyl
ppm	parts per million
Pr	propyl
q	quartet
quant	quantitative
quint	quintet
R	alkyl group
rac	racemic
R_f	retention factor
t_R	retention time
rt	room temperature
s	singlet
s	secondary
S_N2	substitution nucleophilic bimolecular
t	triplet
t	tertiary
TBS or TBDMS	*t*-butyldimethylsilyl
THF	tetrahydrofuran
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TLC	thin-layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine

TMS	trimethylsilyl
Tol	tolyl
Ts	*p*-toluenesulfonyl
triflate	trifluoromethanesulfonate
UV	ultraviolet spectroscopy

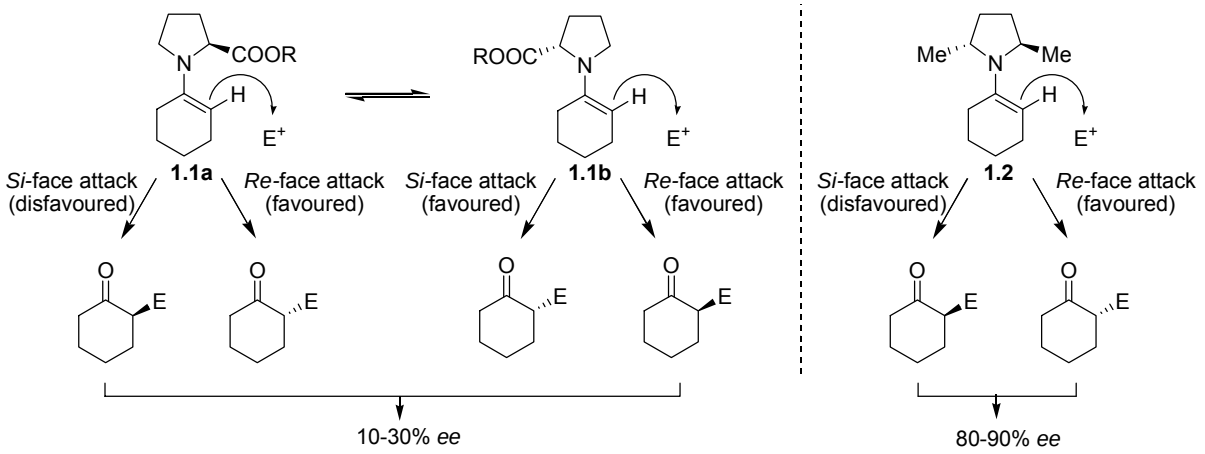
Chapter 1. Introduction

1.1 C_2 Symmetry and Binaphthols in Asymmetric Synthesis

1.1.1 C_2 Symmetry

"C_2 symmetry", by definition, means that 180^o rotation about an axis through the molecule results in a geometry equivalent to the starting geometry. When compared to chiral reagents with other symmetries, the presence of a C_2 symmetry axis within the auxiliary often offers unique advantages in achieving asymmetric induction for given chemical transformations. Indeed the primary benefit of a C_2-symmetric auxiliary is that the number of competing diastereomeric transition states is greatly reduced, making system and protocol design more rational.[1] For example, Yamada has reported the enantioselective alkylation of cyclohexanone enamines using proline esters as chiral auxiliaries giving alkylation products in low *ee*'s (10-30% *ee*),[2-4] while Whitesell applied a C_2-symmetrical 2,5-dimethylpyrrolidine in the same reaction and achieved much higher enantioselectivities (80-90% *ee*, Scheme 1.1).[5,6] It was reasoned that when an enamine (**1.1**) is formed from cyclohexanone and (*S*)-methyl proline, there are two possible distinct conformations (**1.1a** and **1.1b**) which result in four possible diastereomeric transition states in the alkylation reaction and only one of them is disfavoured due to steric hindrance. The three favoured transition states then lead to the formation of the final product in both *R* and *S* forms and low enantioselectivities are observed accordingly. On the other hand, when 2,5-dimethylpyrrolidine is adopted, only two diastereomeric transition states are possible

and one of them is disfavoured. Therefore the only favoured diastereomeric transition state gives the alkylated product in high enantioselectivity (Scheme 1.1).



Scheme 1.1

In the past few decades, C_2-symmetric reagents have received increasing attention in asymmetric synthesis as a result of the generally high selectivities that are obtained with them. To date, a large number of molecules possessing C_2 symmetry have been synthesized and utilized as chiral auxiliaries and catalysts in asymmetric synthesis. Some of the common ones are illustrated in Figure 1.1.[7-12]

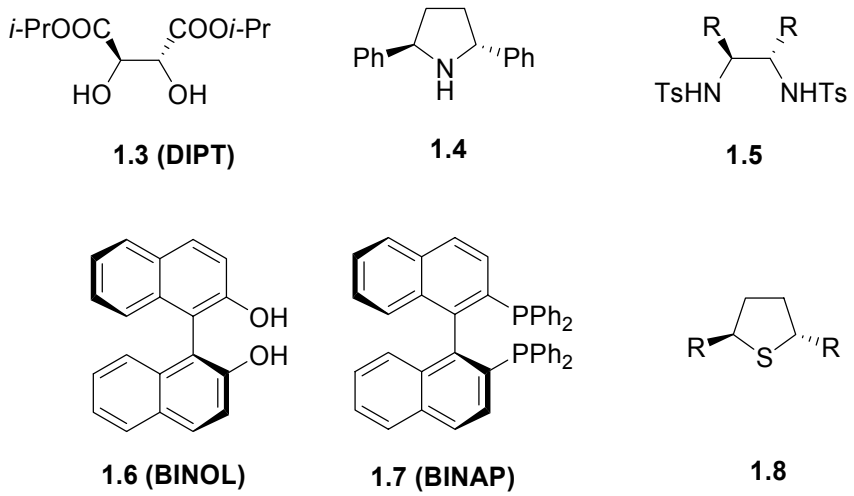
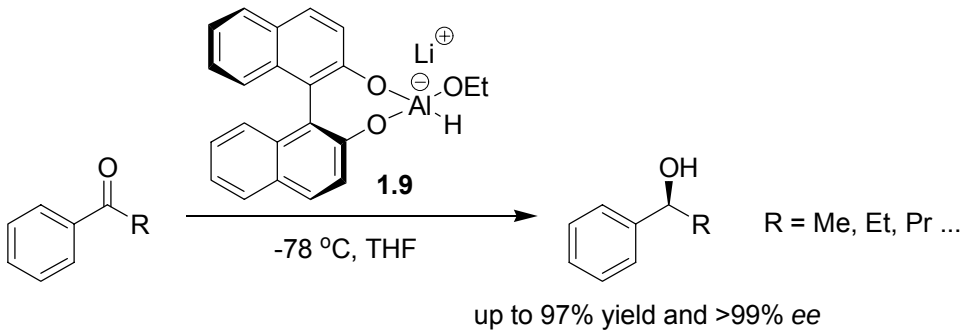


Figure 1.1 Examples of commonly used C_2-symmetric reagents.

1.1.2 Binaphthols in Asymmetric Synthesis

2,2′-Dihydroxy-1,1′-binaphthyl (BINOL), the two enantiomers of which are stable at high temperature and under various experimental conditions, is undoubtedly one of the most successful C_2-symmetrical molecules that have been applied in asymmetric synthesis. Although it was first synthesized in 1926, its application in asymmetric induction was only recognized in 1979 by Noyori in the reduction of aromatic ketones and aldehydes (Scheme 1.2).[12]



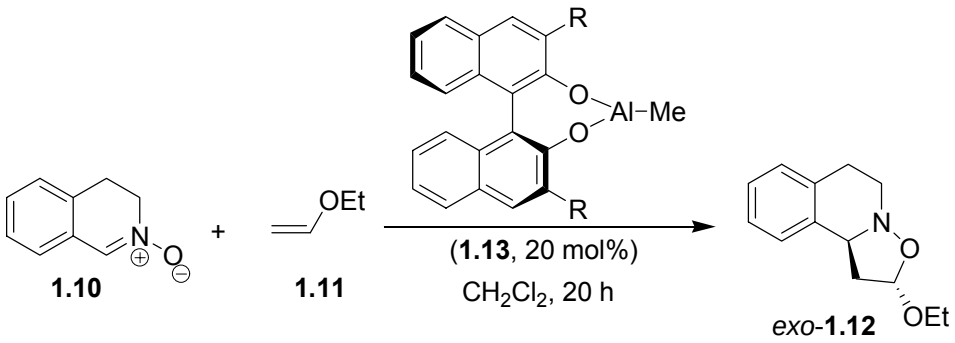
Scheme 1.2

Since Noyori's discovery, BINOL has been applied in numerous metal catalyzed asymmetric reactions such as asymmetric aldol reactions, allylations, Diels-Alder reactions and epoxidations. In some rare cases, BINOL was also used as a chiral auxiliary. There is no need to describe those processes individually since a comprehensive review has been published concerning recent advances in asymmetric synthesis involving BINOL as chiral reagent or ligand.[13]

Although great success in asymmetric synthesis has been achieved with BINOL, it does not always give satisfactory results. Thus there has been an increasing interest in modified BINOL's. Substitution on BINOL-based metal complexes affects not only the steric environment around the metal center but also the electronic properties of the metal complexes, which may induce asymmetric reactions with enhanced stereoselectivities. For instance, in an enantioselective 1,3-dipolar

cycloaddition of nitrones **1.10** with ethyl vinyl ether (**1.11**), BINOL modified aluminum catalyst (Table 1.1, entry 1) gave poor conversion (11%) and enantioselectivity (24% *ee* for the *exo* product). However, introduction of bulkier substituents on BINOL led to remarkable increases in yield, exo/endo selectivity and enantioselectivity of the reaction (Table 1.1, entries 2 and 3).[14]

Table 1.1 Enantioselective 1,3-dipolar cycloaddition of nitrones catalyzed by **1.13**.



entry	R	conversion (%)	*exo*/*endo*	*ee* (%, for *exo*)
1	H	11	85/15	24
2	2-naphthyl	78	87/13	67
3	2,5-$(OMe)_2$-C_6H_3-	74	98/2	82

During the last decade, a huge collection of modified binaphthols has been successfully prepared and applied to a wide range of asymmetric transformations. Some typical examples are shown in Figure 1.2. Details of preparations and applications of these modified BINOLs are presented in a review article published by Yudin and co-workers recently.[15]

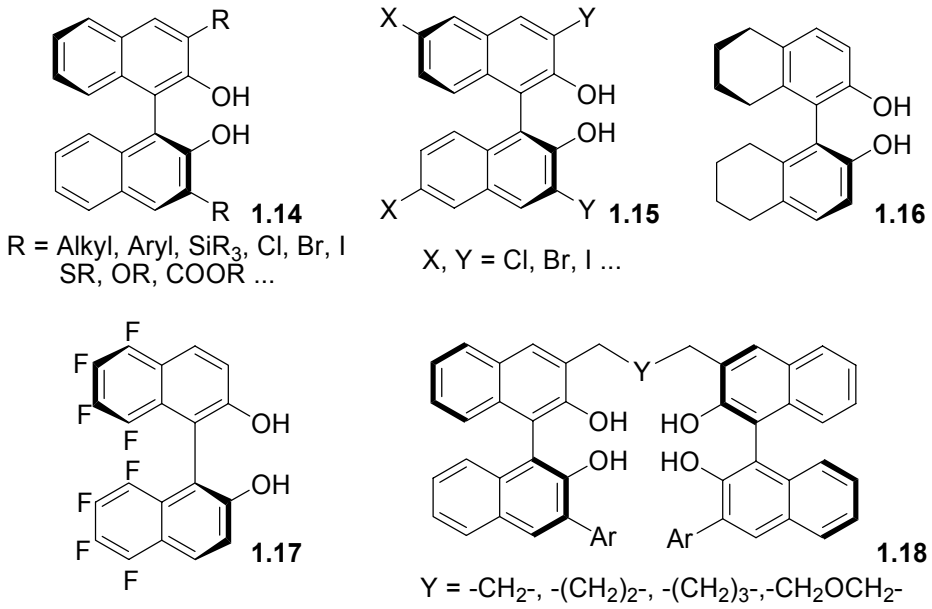


Figure 1.2 Examples of modified binaphthols.

1.2 Boron in Asymmetric Synthesis

Chirally modified boron reagents have proven to be effective in many asymmetric processes. In fact, the first non-enzymatic asymmetric synthesis with high enantioselectivity was the hydroboration of alkenes with $(Ipc)_2BH$.[16] Since then, many asymmetric reactions such as the reduction of ketones, aldol reactions, the allylation of carbonyls, and Diels-Alder reactions have been successfully conducted using chirally modified boron reagents. Several reviews have been published regarding the application of chiral boron reagents in asymmetric synthesis.[17-22]

There are several factors that contribute to the popularity of chiral boron reagents. Firstly, the boron atom is small (atomic radius: 82 pm), which may result in strong interactions between adjacent groups and lead to highly stereoselective reactions (Figure 1.3). Secondly, due to the electron configuration of boron ($1s^2 2s^2 2p^1$), only a maximum of four bonds can be formed around a boron atom (Scheme 1.3). The simplicity of the bond patterns around boron makes the stereochemistry of

boron-induced asymmetric reactions easily rationalized. Thirdly, the boron atom forms relatively strong covalent bonds with heteroatoms such as C, N, O and halogens. This allows one to modify chiral auxiliaries on boron easily, given that there are a huge number of carbon-, nitrogen- or oxygen-based chiral auxiliaries available. Some classical chiral controllers on boron are shown in Figure 1.4.[9,10,23-26] Finally, the low cost and low toxicity of boron allow for scaling up those methodologies in the pharmaceutical industry.

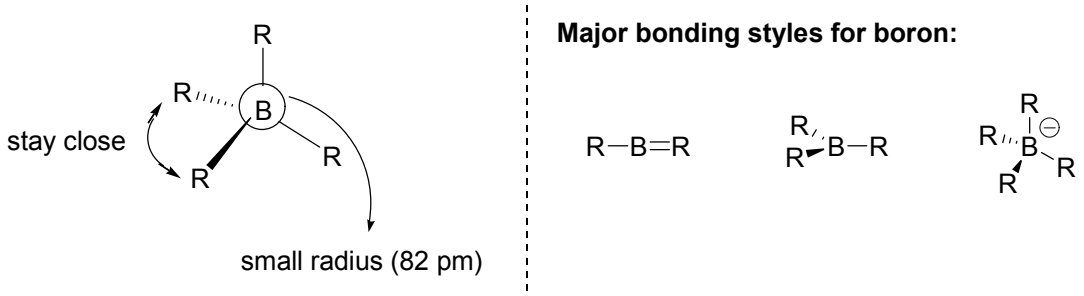


Figure 1.3 Bonding of boron atom.

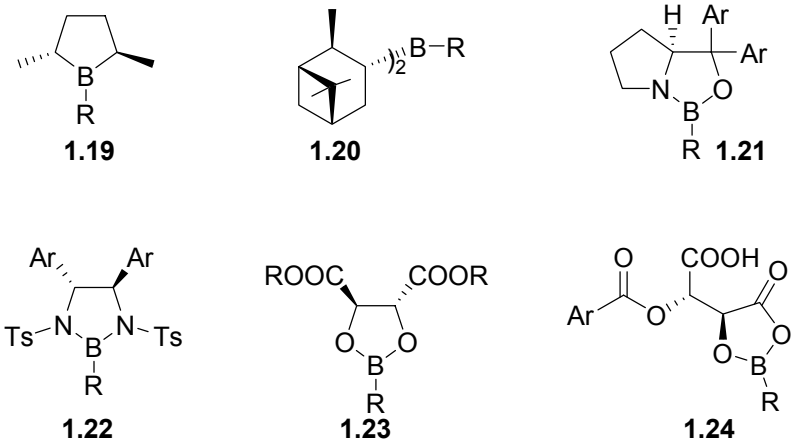
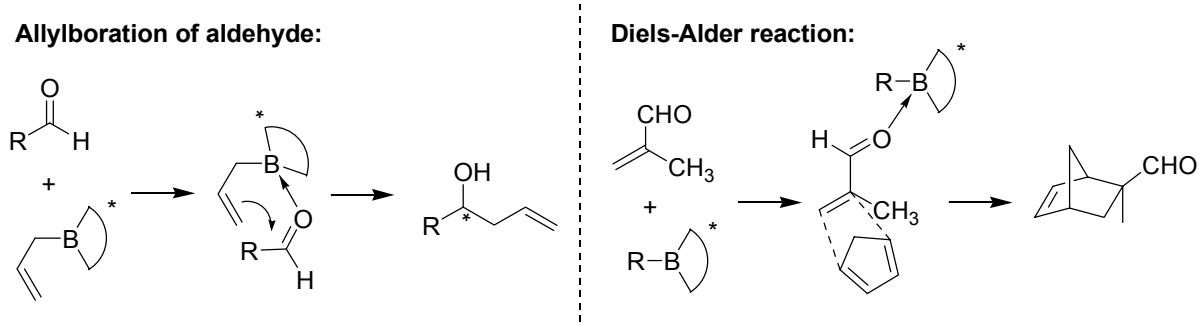


Figure 1.4 Examples of chirally modified boron reagents**.**

1.3 Boron and Binaphthol

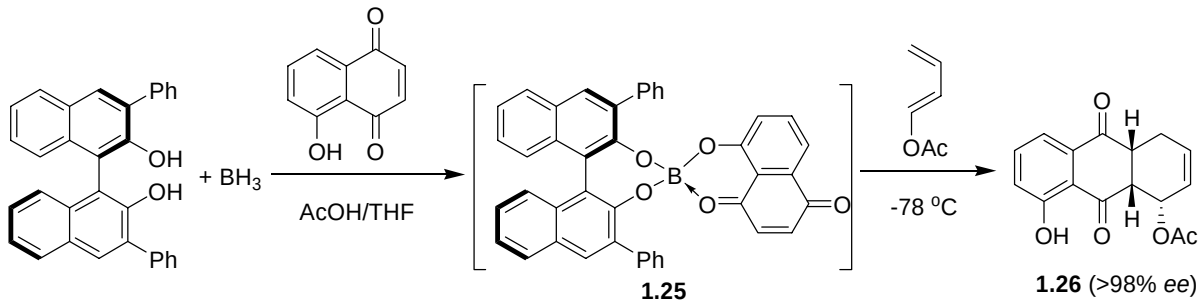
In most boron-induced asymmetric reactions, the initial step involves the coordination of the boron atom and one of the reactants. For example, in a typical allylboration reaction, the oxygen on the aldehyde coordinates with the allylborane. The allyl group is then delivered to afford the final product (Scheme 1.3).[10] Another example is chiral borane catalyzed Diels-Alder reaction, in which the dienophile coordinates with the boron atom before reacting with the diene (Scheme 1.3).[9]



Scheme 1.3

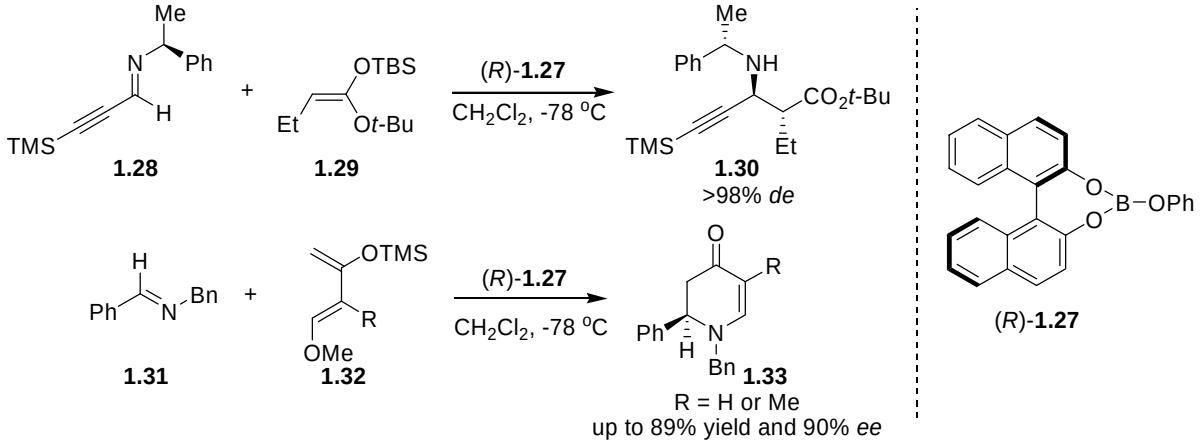
Since the coordination step is crucial, increasing the Lewis acidity of the chiral boron reagent would lead to a stronger coordination between the boron and reactants, which may in turn enhance the reaction rate. In other words, electron deficient ligands could be excellent candidates for modifying chiral boron reagents.

Given that BINOL and its derivatives are non-basic alcohols, they should be suitable chiral ligands for boron-induced asymmetric reactions. However, to our knowledge, there are only limited examples of asymmetric processes induced by binaphthol-modified boron reagents. For example, Kelly reported a Diels-Alder reaction induced by a binaphthol-boron complex **1.25** (Scheme 1.4).[27]



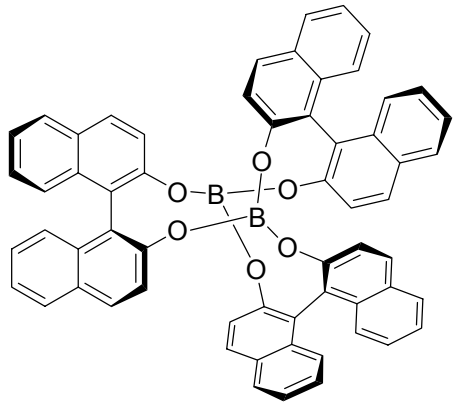
Scheme 1.4

Binaphthol-borane complexes such as **1.27** could also be used to catalyze Mannich reactions between chiral imine **1.28** and ketene acetals **1.29**.[28,29] or a hetero-Diels-Alder reaction (Scheme 1.5).[30]

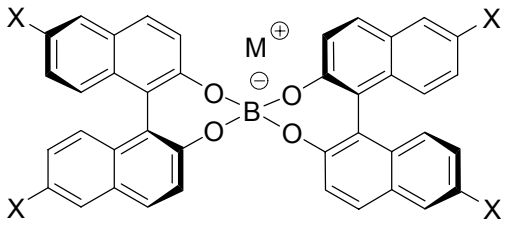


Scheme 1.5

In addition, several "propeller-shaped" and spiro binaphthol-borane complexes (Figure 1.5) have also been applied in asymmetric inductions such as catalytic Diels-Alder reactions,[31] Mannich reactions,[32] Pictet-Spengler reactions[33,34] and cyclopropanations.[35]



1.34



1.35

M = H, Ag, Cu
X = H or Br

Figure 1.5 "Propeller-shaped" and spiro binaphthol-boron complexes.

1.4 Purpose and Scope of the Thesis

As was mentioned in previous sections, both boron reagents and binaphthols have been utilized successfully in asymmetric synthesis. However, asymmetric reactions that take advantage of both boron and binaphthols are rare. This thesis mainly focuses on the development of asymmetric inductions involving binaphthol-modified boron reagents.

Several highly effective methodologies are presented in this thesis. These include the asymmetric allylboration of carbonyl compounds and cyclic imines, the enantioselective synthesis of propargylamides and the catalytic conjugate alkynylation of enones accelerated by "exchangeable" ligands on boron. These methodologies were applied to the synthesis of several naturally occurring alkaloids such as coniine, crispine A and corynantheidol as well as a pre-clinical antivascular agent *N*-acetylcolchinol (AstraZeneca ZD6126 phenol), the details of which are also discussed.

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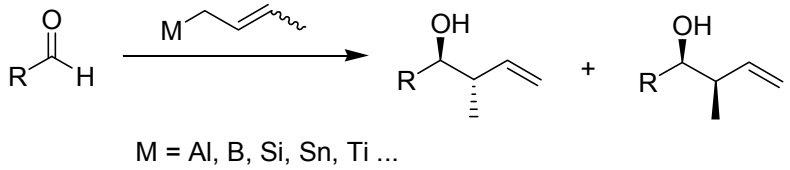
Chapter 2. Asymmetric Allylboration of Aldehydes and Ketones using 3,3′-Disubstituted Binaphthol-modified Boronates

2.1 Introduction

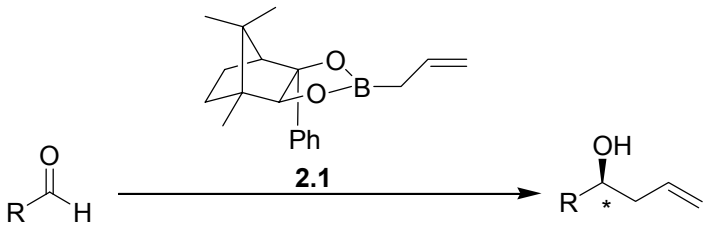
Asymmetric allylation of aldehydes and ketones has been one of the most useful reactions in organic chemistry not only because the chiral homoallylic alcohol products occur in many natural products, but also because these alcohols can be easily transformed into many other functionalities such as β- and γ-hydroxyaldehydes, γ- or δ-lactones, 1,3-diol and 1,3-aminoalcohols. Over the past two decades, efforts have been constantly made towards the development of new allylmetallic reagents that can generate chiral homoallylic alcohols with high stereoselectivities.[1]



Scheme 2.1

Many metal reagents such as Al-, B-, Cr-, Mg-, Sn-, Si-, Ti-based allylmetallics have been applied successfully in the allylation of carbonyls (Scheme 2.1).[1] Among those, allylboron reagents have been extensively studied and utilized due to their high efficiency in inducing excellent stereoselectivities. The low cost and low toxicity of boron also makes allylboron reagents more popular.

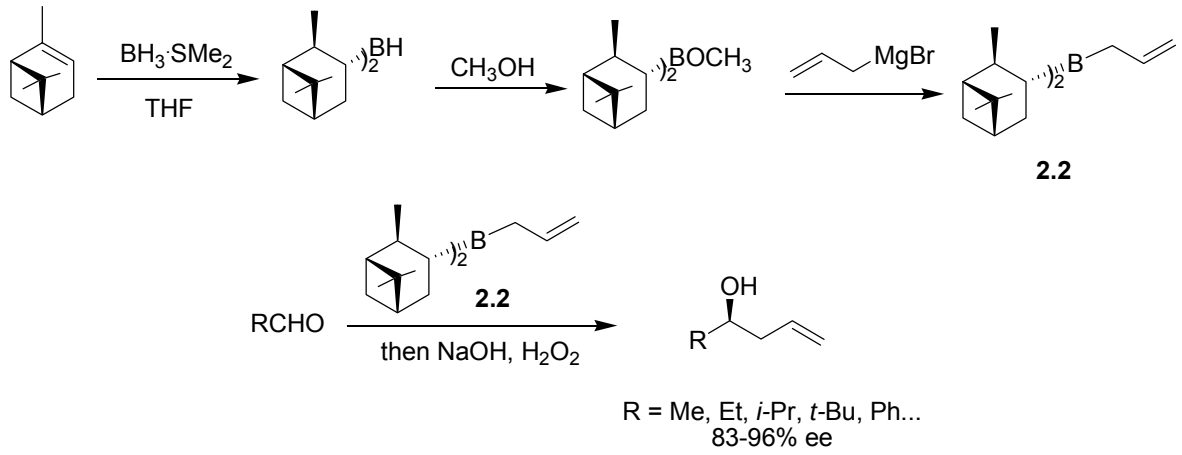
One of the first studies in the allylboration of carbonyls was done by Hoffmann, who developed the first chiral allylboron reagents from camphor glycols in 1978.[2,3] Upon treatment of aliphatic aldehydes with borolane **2.1**, homoallylic alcohols were obtained in excellent yields with moderate enantiomeric excesses (Scheme 2.2). However, unsaturated aldehydes gave only poor *ee*'s (24-54%).



R	yield (%)	*ee* (%)
Me	92	65
Et	91	77
i-Pr	88	70
t-Bu	85	45

Scheme 2.2

It was not until 1983 that H. C. Brown discovered the first practical allylboron reagent for the asymmetric allylation of aldehydes.[4] Chiral *B*-allyldiisopinocampheylborane **2.2** can be easily prepared from naturally occurring (+) or (-)-α-pinene in both enantiomeric forms (Scheme 2.3). It allylates a variety of aldehydes (both aliphatic and aromatic ones) to furnish homoallylic alcohols in 83-96% *ee*.



Scheme 2.3

The allylboration is believed to proceed through a six-membered chair (*Zimmerman-Traxler*) transition state (Figure 2.1). Of the two possible transition states, B is disfavoured due to the repulsion between the methyl group on the pinene ring and methylene protons of the allyl group. [5]

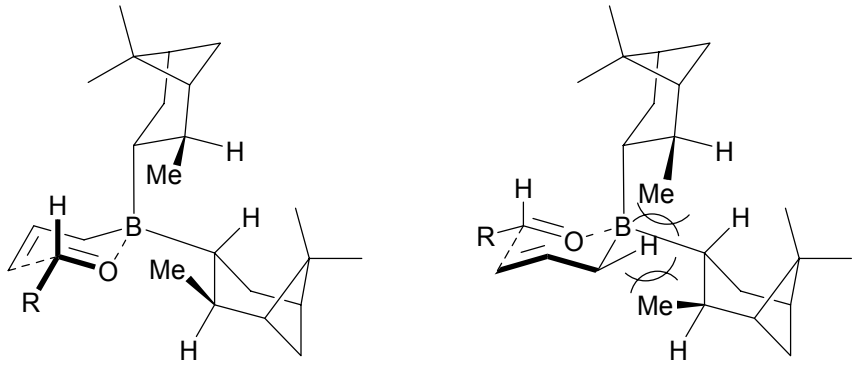
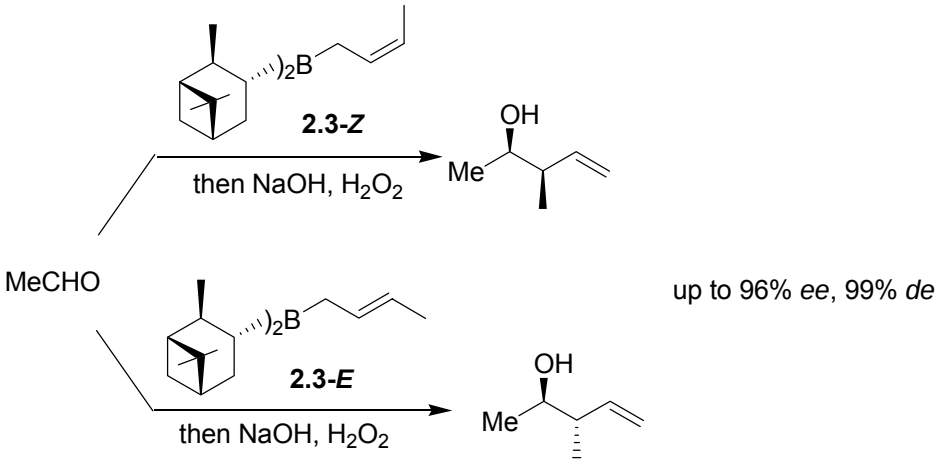


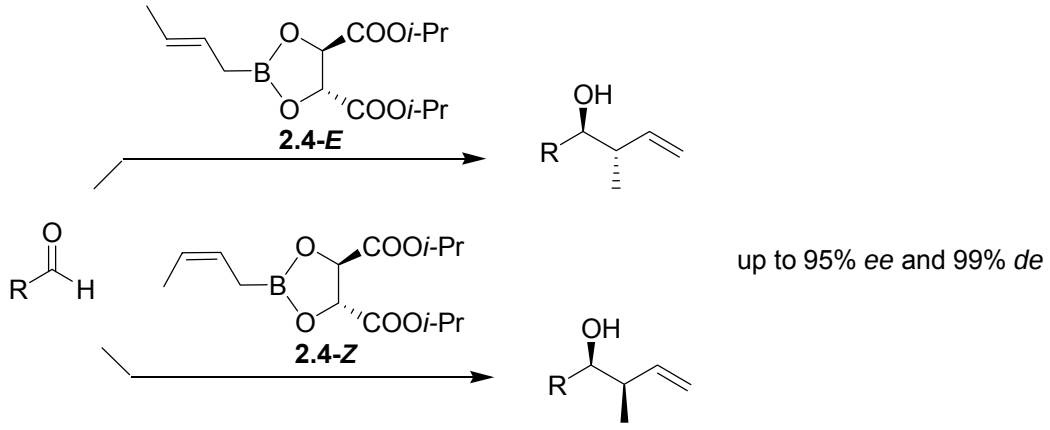
Figure 2.1 Transition states for allylboration of aldehydes using $(Ipc)_2BAll$.

Crotylation using **2.3** also proceeded with excellent diastereo- and enantioselectivities (*E*-allylborane gives *anti*- products while *Z*-allylborane gives *syn*- products).[6]



Scheme 2.4

Later, Roush reported that good yields and enantioselectivities (up to 95% *ee*) could be obtained in reactions of tartrate-modified allylboronates with aldehydes.[7] The auxiliary system was also applied to the (*E*) and (*Z*)-crotyl cases to give *anti*- or *syn*- allylboration products, respectively, with excellent *ee* and more than 99% *de* (Scheme 2.5).[8]



Scheme 2.5

Interestingly, different from the allylborations developed by Brown or Hoffmann mentioned above, this asymmetric induction cannot be explained simply by steric interactions since the R group in the aldehyde is far too remote to interact with the tartrate ester. It has thus been proposed that the

stereoelectronic interaction may play an important role (Figure 2.2).[8] Of the two possible chair transition states of the reaction, transition state A is favoured over transition state B, in which an *n*-*n* electronic repulsive interaction involving the aldehydic oxygen atom and the *β*-face ester group is the cause of destabilization.

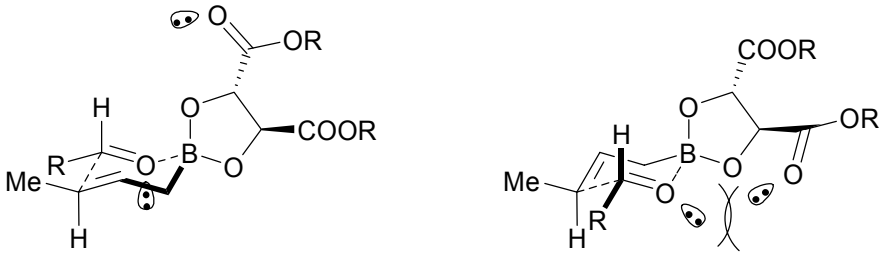
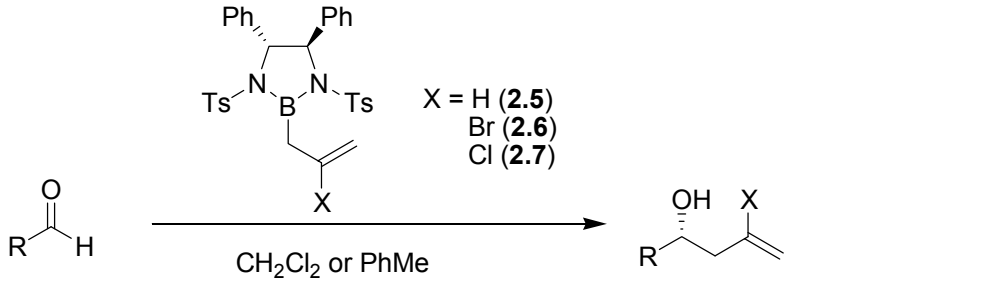


Figure 2.2 Transition states for allylboration of aldehydes using tartrate modified allylboranes.

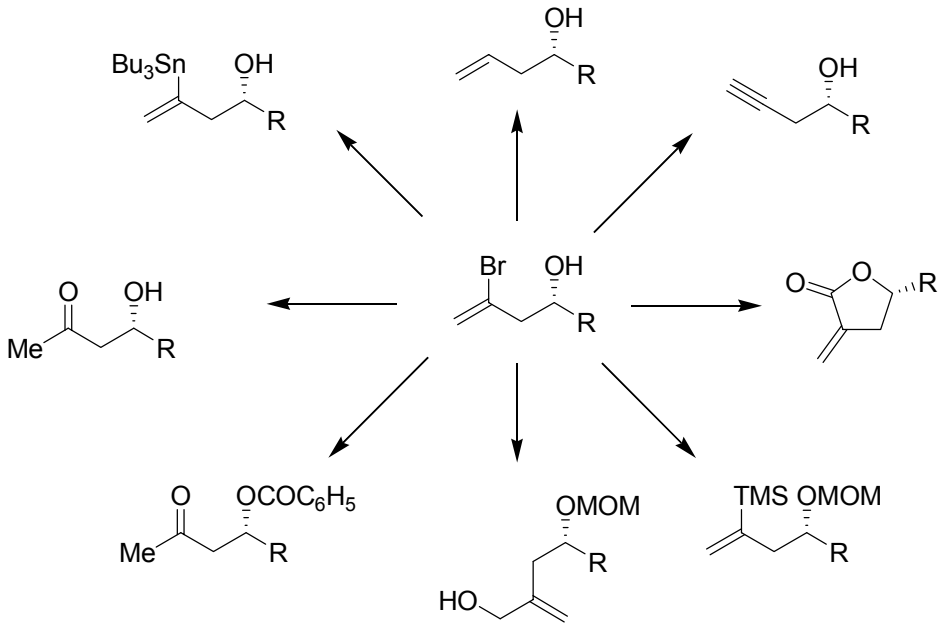
In 1989, Corey developed another effective chiral boron reagent for aldehyde allylation using 1,2-diamino-1,2-diphenylethane as the controller group (Scheme 2.6). Allylborane **2.5** exhibited excellent enantioselectivities towards a number of aldehydes (90-98% *ee*).



Scheme 2.6

In addition to unsubstituted borane **2.5**, two special 2-haloallyl reagents **2.6** and **2.7** were also successfully prepared. Allylations of aldehydes using **2.6** and **2.7** also showed high stereoselectivity (79-99% *ee*). The synthetic utility of their allylboration products has been demonstrated through a

number of transformations (Scheme 2.7). The outstanding enantioselectivity and the versatility of the adducts make this methodology one of the most popular allylboration reactions.



Scheme 2.7

As asymmetric allylboration of aldehydes became more and more popular, several other allylboron reagents have been synthesized and used for allylation of aldehydes in the past two decades. Some of them exhibited excellent stereoselectivities and were also utilized in natural product syntheses (Figure 2.3).[2,4,8-14]

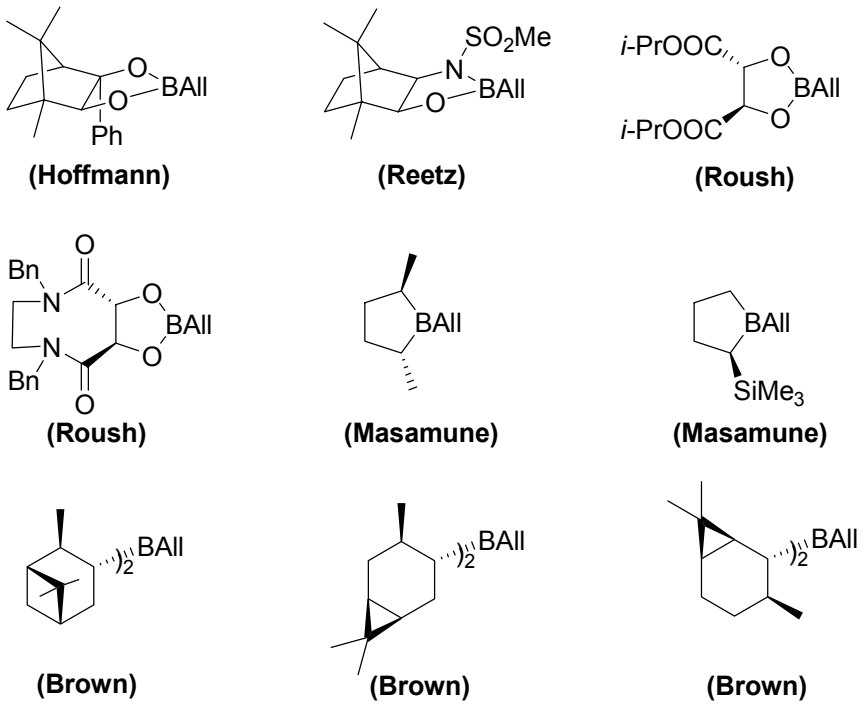
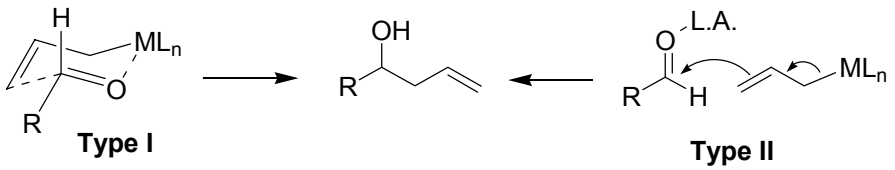


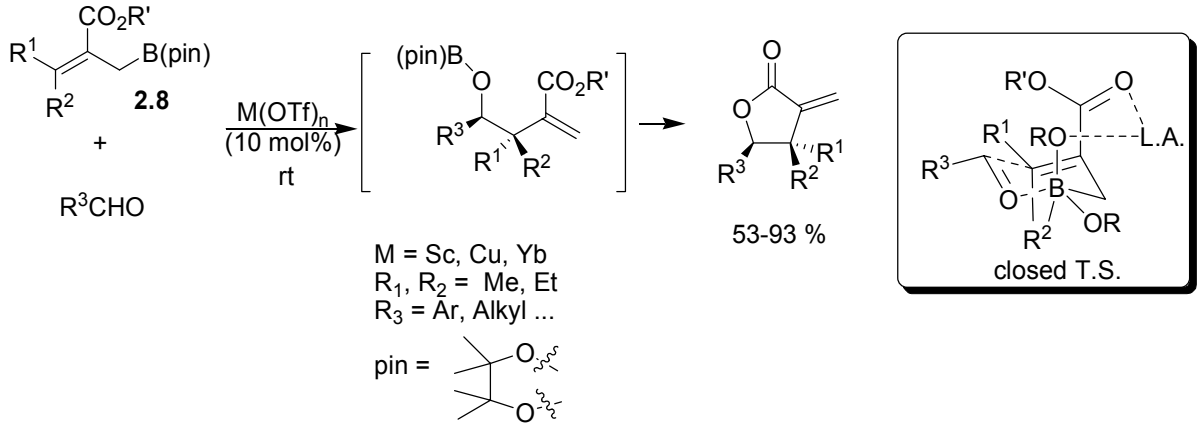
Figure 2.3 Common chiral allylboranes for the allylation of aldehydes (All = allyl).

It is generally accepted that the addition of an allylboronate onto an aldehyde occurs *via* six-membered ring transition states (Type I) where the aldehyde is activated by the internal boron atom (Scheme 2.8).[1] Accordingly, it was believed that the addition of an external Lewis acid would not help to accelerate the reaction, and that the use of Lewis acids might change the closed six-membered ring transition state to an open chain transition state (Type II) and possibly change the reaction's stereoselectivity. Therefore, there has been a perception that the allylboration of aldehydes is not suited to Lewis acid catalysis. In other words, it was believed that induction of asymmetric allylborations would always require a stoichiometric amount of "chiral source". This has been the major drawback of allylboration over other methodologies such as allylsilations and allylstannations which can be induced by catalytic amounts of chiral Lewis acids.



Scheme 2.8

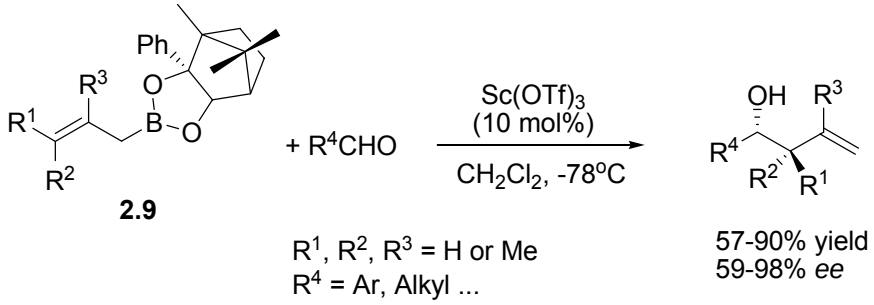
However this perception was challenged in 2002 by Hall who discovered that under the catalysis of some metal salts, tetrasubstituted allylboronates **2.8** add to aldehydes at temperatures almost 100 ^{o}C lower than the corresponding uncatalyzed reactions (Scheme 2.9).[15] It was proposed that the catalyzed reaction proceeds through a closed transition state similar to that of the uncatalyzed reaction. Since the allylboronates and metal salts he used were all racemic, there were no enantioselectivities involved in this allylboration reaction. However, his discovery raised the hope that one might be able to utilize only catalytic amounts of chiral Lewis acids to induce an asymmetric allylboration of carbonyls.



Scheme 2.9

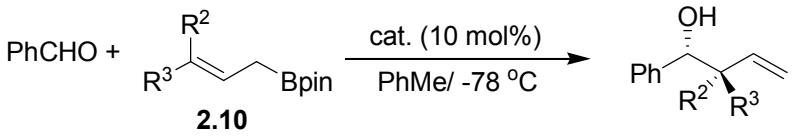
Later on, Hall also developed a practical aldehyde allylboration methodology based on the Sc(OTf)$_3$-catalyzed reaction of camphor-based allylboronates (Scheme 2.10).[16] Chiral allylboronate **2.9** (R^1, R^2, R^3 = H) reacted with both aliphatic and aromatic aldehydes to give excellent yields and

enantioselectivities (up to 98% *ee*). Crotylboration (R^1 or R^2 = Me) also gave comparably high levels of enantioselectivities (94-97% *ee*) and very high diastereoselectivities (>98% *de*). Unlike other chiral allylboron reagents, allylboronates **2.9** are "bench-stable" compounds which can be purified by chromatography and conveniently stored for a long period of time without any special precautions.



Scheme 2.10

Almost at the same time as Hall found the Lewis acid catalyzed allylboration reactions, Ishiyama also realized that Lewis acids such as $AlCl_3$ and $Sc(OTf)_3$ can catalyze the addition of achiral allylboronates **2.10** to aldehydes.[17] More importantly, enantioselective crotylborations catalyzed by (*S*)-binaphthol-modified Lewis acids were attempted and yielded the desired adducts in up to 51% *ee*. Although the stereoselectivities are not very high, this methodology is nevertheless the first asymmetric allylboration/crotylboration of aldehyde using only a catalytic amount of chiral source (Lewis acids).



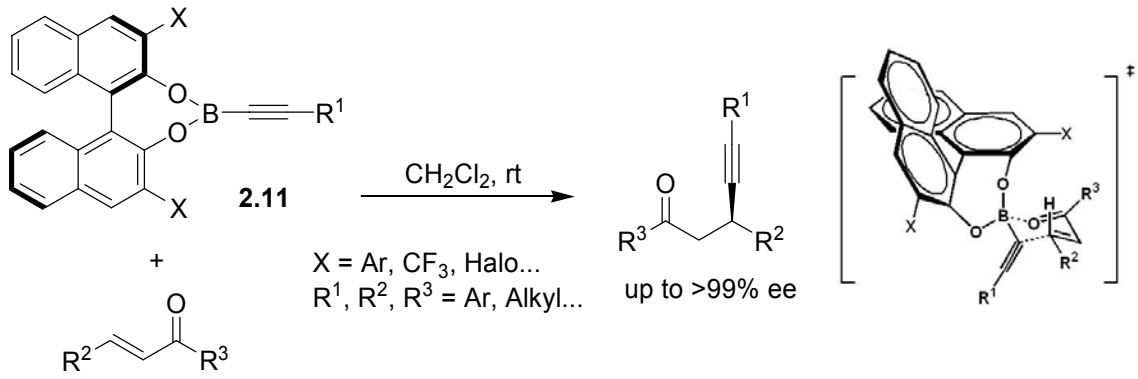
2.10

catalyst	***E*-Crotylboration**
$AlCl_3$/(*S*)-BINOL	92% yield, 39% *ee*, 98% *de*
Et_2AlCl/(*S*)-BINOL	92% yield, 39% *ee*, 98% *de*
$Sc(OTf)_3$/(*S*)-BINOL	Trace
	***Z*-Crotylboration**
Et_2AlCl/(*S*)-BINOL	19% yield, 8% *ee*, 96% *de*

Scheme 2.11

2.2 Proposal

Recently, our group discovered that 3,3′-disubstituted binaphthol-modified alkynylboronates **2.11** could deliver alkynyl groups onto enones in a conjugate fashion with excellent yields (up to 99%) and enantioselectivities (up to >99% *ee*).[18] The stereochemical result may be explained using a closed six-membered chair transition state model (Scheme 2.12).



Scheme 2.12

Similar to the six-membered chair transition state for the allylboration of aldehyde (A), the six-membered chair transition state for the alkynylboration (B) also possesses one boron, one oxygen, four consecutive carbons and two double bonds (Figure 2.4). Since 3,3′-disubstituted binaphthols are able to take good control of the enantioselectivities in the alkynylboration reactions, we thought that they may also have potential for inducing good stereoselectivity in the allylboration of carbonyls. Thus it seemed worthwhile to investigate the allylboration of carbonyls using 3,3′-disubstituted binaphthol-modified allylboronates.

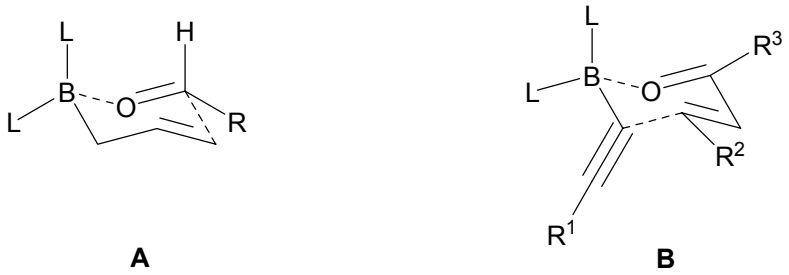


Figure 2.4 Transition states for allylboration of aldehydes (A) and alkynylation of enones (B).

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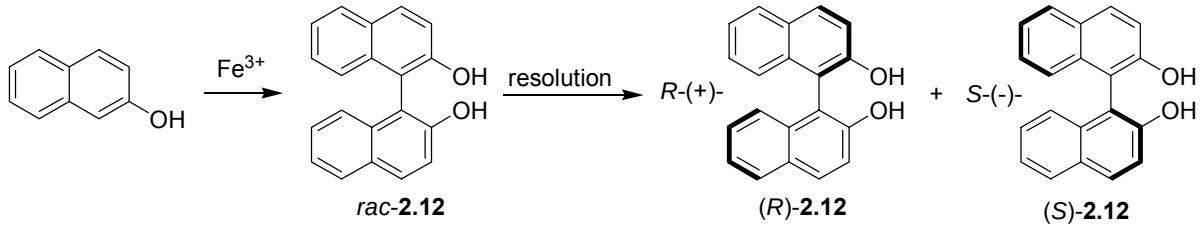
2.3 Results and Discussions

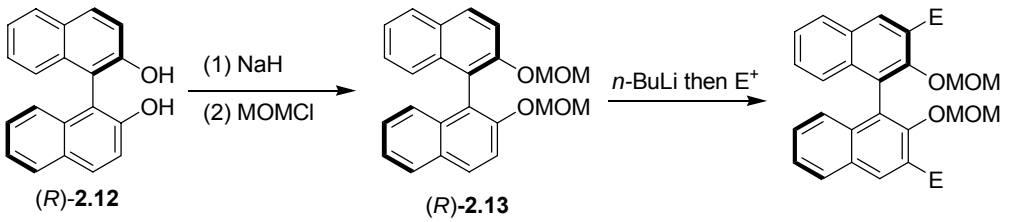
2.3.1 Preparation of 3,3′-Disubstituted Binaphthols

(±)-BINOL (*rac*-**2.12**) was prepared *via* the oxidative coupling of 2-naphthol in aqueous $Fe_2(SO_4)_3$ solution.[22] A resolution of *rac*-**2.12** using (8*S*, 9*R*)-(-)-*N*-benzylcinchonidinium chloride provided enantiomerically pure (*R*)-**2.12** and (*S*)-**2.12** according to the literature.[23,24]



Scheme 2.13

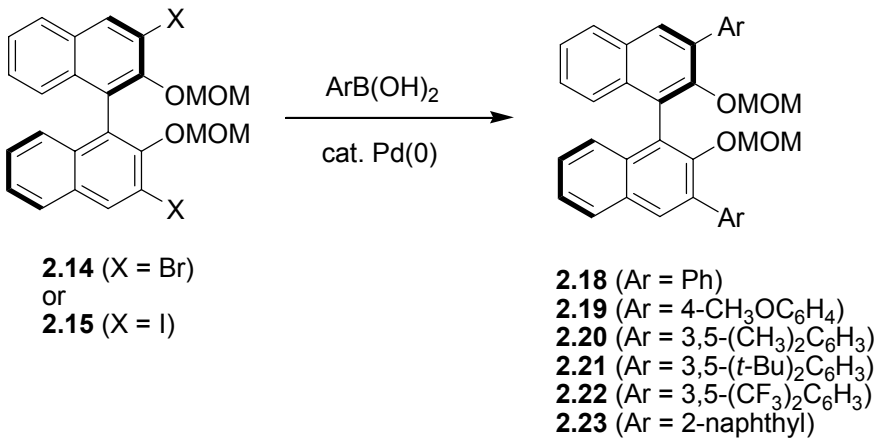
3,3′-Disubstituted BINOLs were then easily prepared from the MOM derivative of **2.12**. Thus, protection of the two hydroxy groups of **2.12** using MOMCl and NaH gave **2.13** in quantitative yield. Ortho-lithiation of **2.13** using *n*-butyllithium followed by trapping the anion with the appropriate electrophiles gave **2.14-2.17**. [25]



(*R*)-**2.14** (E^+ = $BrCCl_2CCl_2Br$, E = Br)
(*R*)-**2.15** (E^+ = I_2, E = I)
(*R*)-**2.16** (E^+ = MeI, E = Me)
(*R*)-**2.17** (E^+ = TMSCl, E = TMS)

Scheme 2.14

Dibromide **2.14** or diiodide **2.15** underwent Suzuki cross-coupling with various arylboronic acids to yield the corresponding diaryl compounds **2.18**~**2.23** uneventfully.

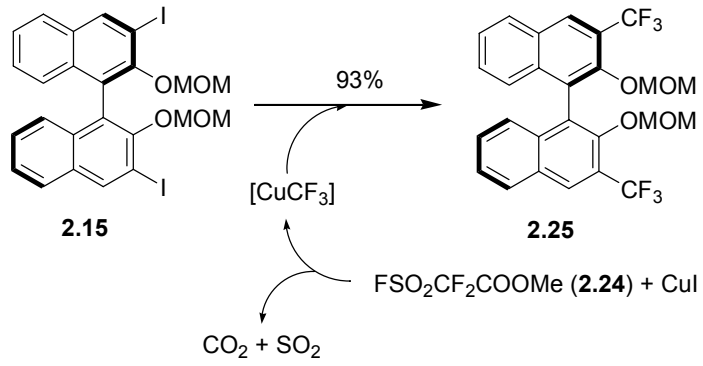


2.14 (X = Br)
or
2.15 (X = I)

2.18 (Ar = Ph)
2.19 (Ar = 4-$CH_3OC_6H_4$)
2.20 (Ar = 3,5-$(CH_3)_2C_6H_3$)
2.21 (Ar = 3,5-(t-Bu)$_2C_6H_3$)
2.22 (Ar = 3,5-$(CF_3)_2C_6H_3$)
2.23 (Ar = 2-naphthyl)

Scheme 2.15

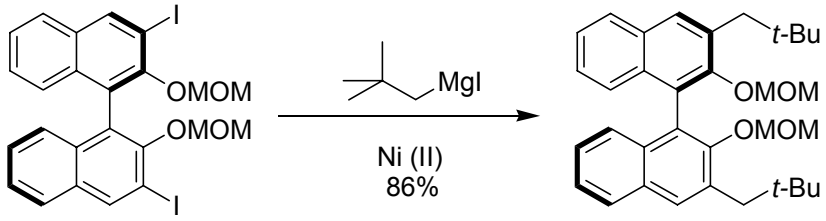
A trifluoromethyl derivative (**2.25**) was obtained in excellent yield through a Cu mediated cross-coupling reaction between diiodide **2.15** and methyl fluorosulfonyldifluoroacetate (**2.24**).[26] The reaction is believed to involve a [$CuCF_3$] intermediate. Coincidently, a similar preparation of **2.25** using CBr_2F_2/Cd/CuI was reported by Kobayashi after we developed this methodology. In comparison to Kobayashi's method, this heavy metal free method is more practical in terms of both manipulation and toxicity.



2.15 **2.25**

Scheme 2.16

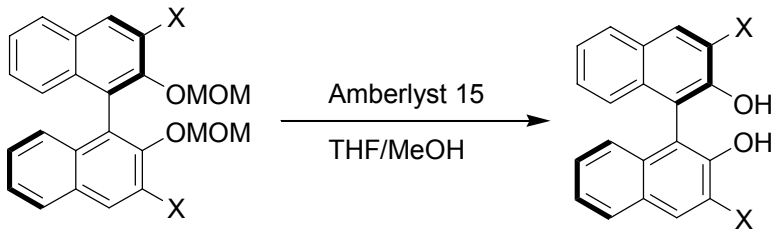
The installation of neopentyl groups on the 3 and 3′ positions of BINOL was accomplished *via* nickel catalyzed Kumada cross-coupling between **2.15** and neopentyl magnesium iodide.



2.15 **2.26**

Scheme 2.17

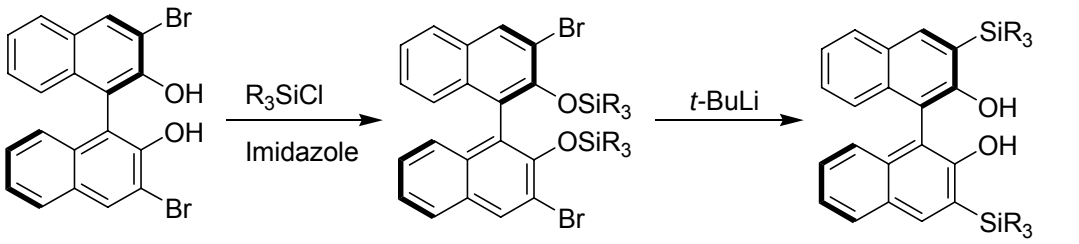
Finally, the MOM derivatives were deprotected under mildly acidic conditions to afford the desired 3,3′-disubstituted BINOL (**2.27**~**2.37**) in nearly quantitative yields except for disilyl compound **2.17**.[25] In this case, a desilylation product was obtained instead.



2.27 (X = Br)
2.28 (X = I)
2.29 (X = Me)
2.30 (X = neopentyl)
2.31 (X = CF_3)
2.32 (X = Ph)
2.33 (X = 4-$CH_3OC_6H_4$)
2.34 (X = 3,5-$(CH_3)_2C_6H_3$)
2.35 (X = 3,5-$(t\text{-Bu})_2C_6H_3$)
2.36 (X = 3,5-$(CF_3)_2C_6H_3$)
2.37 (X = 2-naphthyl)

Scheme 2.18

In order to obtain 3,3′-disilyl BINOL, Yamamoto's procedure was followed.[27] Protection of the hydroxyl groups on dibromo BINOL **2.27** followed by an intramolecular 1,3-silyl rearrangement induced by *t*-BuLi afforded the desired disilyl BINOLs **2.38** and **2.39** in good yields.



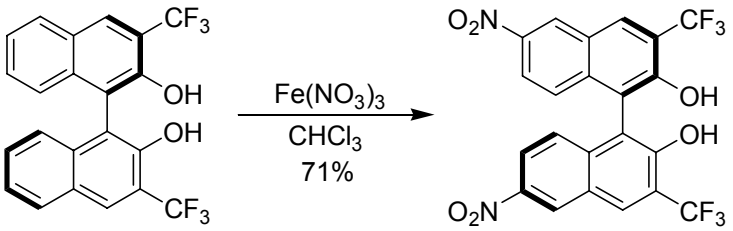
2.15

2.38a: SiR_3 = TMS
2.38b: SiR_3 = TBDMS

2.39 (SiR_3 = TMS)
2.40 (SiR_3 = TBDMS)

Scheme 2.19

In 1989, Poirier and coworkers developed a mild method for the nitration of phenols using $Fe(NO_3)_3$.[28] Following his procedure, treatment of 3,3′-$(CF_3)_2$-BINOL **2.31** with $Fe(NO_3)_3$ in hot chloroform led to the selective nitration of the molecule on the 6 and 6′ positions. This turned out to be a novel way of derivatizing BINOLs.



2.31

2.41

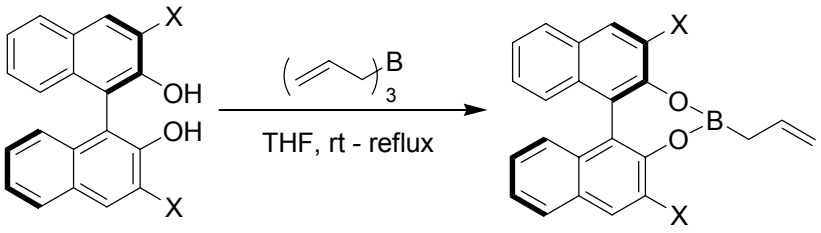
Scheme 2.20

2.3.2 Allylboration of Aldehydes using 3,3′-Disubstituted Binaphthyl-modified Allylboronates

2.3.2.1 Optimization of Reaction Conditions

With a variety of 3,3′-disubstituted BINOLs in hand, the preparation of binaphthol-modified allylboronates was pursued. It has been reported by several groups that treatment of triallylborane with bidentate ligands such as diols or some acidic diamines has led to the formation of allylboronates

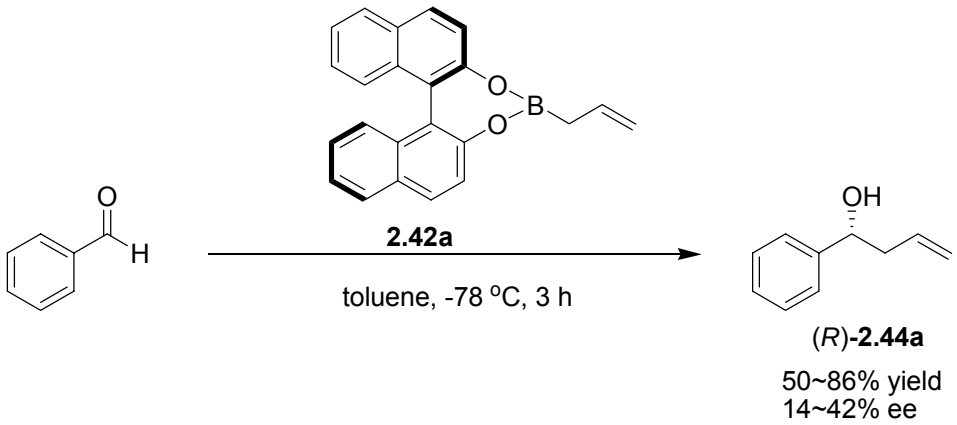
in good yields.[2,29] Therefore triallylborane was reacted with stoichiometric amounts of 3,3′-disubstituted BINOLs in THF to afford 3,3′-disubstituted binaphthol-modified allylboronates. Allylboronates are very sensitive to moisture and were therefore used without further purification or characterization. In addition, since triallylborane is a pyrophoric liquid, it was prepared and stored with great caution.[30]



2.42

Scheme 2.21

The allylboration of benzaldehyde using binaphthol-modified allylboronate (*R*)-**2.42a** (X = H) was first attempted. As expected, the reaction occurred readily at -78 ^{o}C to give the desired (*R*)-homoallylic alcohol. However the reaction gave highly variable yields and enantioselectivities from time to time.

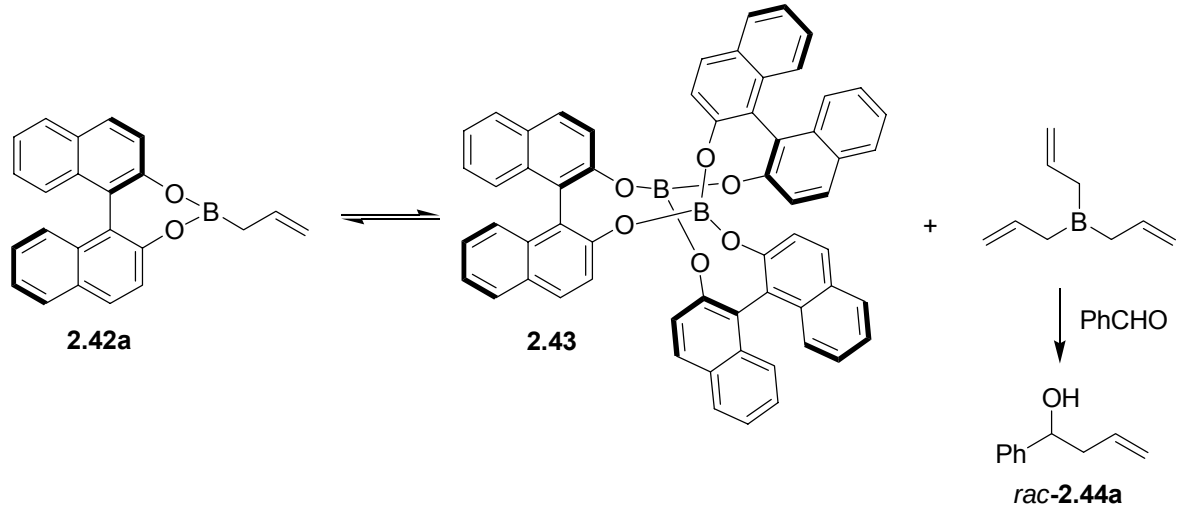


(*R*)-**2.44a**

50~86% yield
14~42% ee

Scheme 2.22

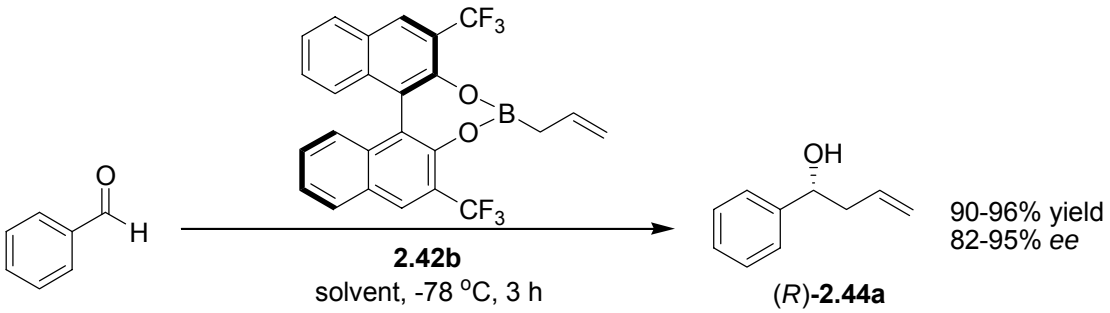
This problem could be explained by proposing that allylboronate **2.42a** can undergo disproportionation to give a thermodynamically stable compound **2.43**, the formation of which has been documented by others (Scheme 2.23).[31] Another byproduct of this process would be triallylborane which induces a non-stereoselective allylation, leading to low enantioselectivity.



Scheme 2.23

In order to avoid this problem, all one needs to do is introduce substituents on the 3 and 3′ positions of the parent BINOL. The steric hindrance provided by those substituents appears to make the formation of the trimer **2.43** highly disfavoured. Therefore, another modified allylboronate **2.42b** (X = CF_3) was tested. In addition, the strongly electron-withdrawing CF_3 groups on the BINOL rings should also make the allylboronate more electrophilic and hence more reactive toward carbonyl compounds. The allylboration of benzaldehyde using **2.42b** was carried out in several solvents at low temperature. In all solvents tested, the allylation was complete in less than 5 minutes (indicated by TLC of the reaction mixture). The best result was obtained in THF at -78 ^{o}C with 90% yield and 95%

ee. Other solvents (toluene, methylene chloride, acetonitrile, diethyl ether, DME) gave respectable but slightly lower enantioselectivities (82-90% *ee*).

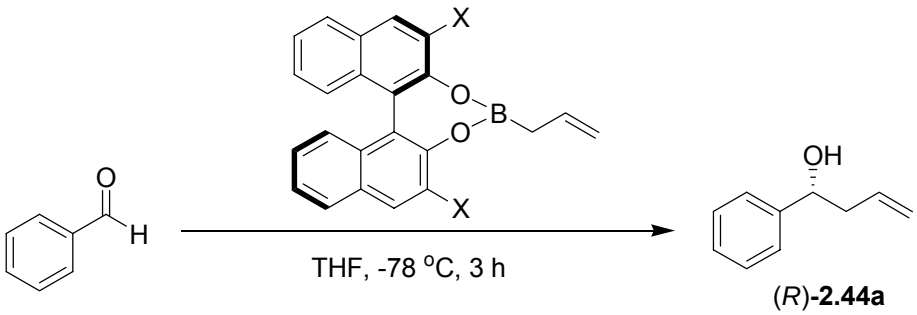


Scheme 2.24

Similar to other asymmetric allylborations, this allylboration chemistry also requires a stoichiometric amount of chiral ligand 3,3′-$(CF_3)_2$-BINOL (**2.31**). However, the 3,3′-$(CF_3)_2$-BINOL (**2.31**) is easily recovered from the reaction mixture with no detectable racemization by simple extraction with aqueous base (1 M NaOH). Actually, **2.31** seems to be extremely resistant to racemization even under strongly acidic (10% HCl, H_2O/THF, reflux, 24 hours) or basic (0.1 M KOH, *n*-BuOH, 60 °C, 48 hours) conditions which cause complete racemization of the parent BINOL.

Given the fact that THF provides the best result for the allylboration of benzaldehyde using boronate **2.42b,** allylations of benzaldehyde with other boronates were examined in THF. The results were summarized in Table 2.2.

Table 2.1 Reactions of allylboronates **2.42b-j** with benzaldehyde.



(*R*)-**2.44a**

entry	X	yield (%)	*ee* (%)[a]
1	H (**2.42a**)	50	42
2	CF_3 (**2.42b**)	90	95
3	Me (**2.42c**)	91	75
4	neopentyl (**2.42d**)	>95[b]	69
5	I (**2.42e**)	91	74
6	Ph (**2.42f**)	90	45
7	4-$CH_3OC_6H_4$ (**2.42g**)	89	62
8	3,5-$(CH_3)_2C_6H_3$ (**2.42h**)	94	60
9	3,5-(*t*-Bu)$_2C_6H_3$ (**2.42i**)	92	66
10	3,5-$(CF_3)_2C_6H_3$ (**2.42j**)	92	70
11	2-naphthyl (**2.42k**)	90	50
12	TMS (**2.42l**)	>95 [b]	12
13	TBDMS (**2.42m**)	>95 [b]	0.3

[a] Enantiomeric excesses were determined by chiral HPLC analysis on a Chiralcel OD column. The absolute configuration of the product was determined by the comparison of rotation value with reported value.[32] [b] Conversion determined by ^{1}H NMR.

In all cases, allylboronates (*R*)-**2.42** gave homoallylic alcohol **2.44a** with *R* configuration. Upon comparison of the parent compound **2.42a** (X = H, Table 2.2, entry 1), **2.42c** (X = Me, Table 2.2,

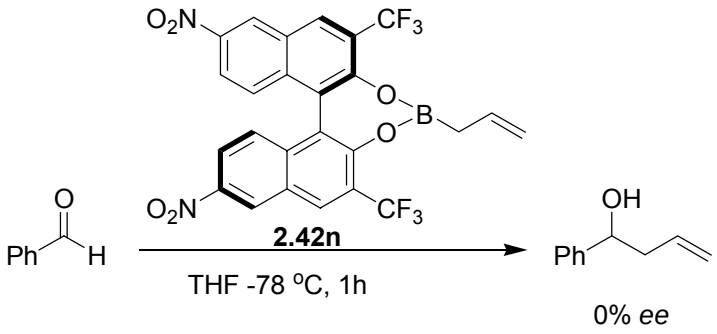
entry 3) or **2.42d** (X = neopentyl, Table 2.2, entry 4) gave much better enantioselectivities (Table 2.2, entries 3 and 4). It means that the size of 3 and 3′ substituents does have some effect on the enantioselectivity of this reaction. On the other hand, although a CF_3 group is only slightly larger than a methyl group (based upon the A values of those two groups), CF_3-reagent **2.42b** (Table 2.2, entry 2) gave much better enantioselectivity than did CH_3-reagent **2.42c** (Table 2.2, entry 3). Also, **2.42e** (X = I, Table 2.2, entry 5) and **2.42c** (X = Me, Table 2.2, entry 3) gave comparable stereoselectivities (74% *ee* vs. 75% *ee*), even though an iodo group is much smaller than a methyl group (based on A values). This indicates that steric bulkiness of the 3 and 3′ substituents is not the only factor that affects the enantioselectivity in this reaction. Electronic effects must also play an important role; however this is not fully understood.

Various 3,3′-diaryl BINOLs were also examined (Table 2.2, entries 6-11) because those ligands induced the best stereoselectivities in the alkynylations of enones. However, for the allylation of benzaldehyde, 3,3′-diaryl BINOLs only gave enantiomeric excesses from 45% to 70% depending on the structures of the aryl groups. Increasing the size of the aryl groups resulted in a slight increase of selectivities. Again, **2.42j** bearing four electron-withdrawing CF_3 groups gave the best result (70% *ee*, Table 2.2, entry 10).

The disilyl-BINOLs were also used for allylborations. It was thought that the bulkiness of silyl groups could have more of an impact on the transition state of the reaction and increase the stereoselectivity. However, for TMS-BINOL, only 12% *ee* was observed (Table 2.2, entry 12). On replacement of the TMS substituents with larger TBDMS groups, the enantioselectivity dropped to 0.3% *ee* (Table 2.2, entry 13). These results show that increasing the size of the 3 and 3′ substituents

does not always result in better stereoselectivity. Also the electron-donating nature of the silyl groups might be another reason for the low *ee*'s.

In an effort to determine whether the electron-withdrawing nature of the substituents in **2.42b** was the most important factor, nitro-substituted BINOL derivative **2.42n** was applied to the allylboration of benzaldehyde. Provided that electron-withdrawing groups on the BINOL ring are good for enantioselectivities, allylboronate **2.42n** which bears four electron-withdrawing groups was expected to give improved results. Surprisingly, the allylboration of benzaldehyde using **2.42n** gave 0% *ee*, the reason for which is not clear. One possible explanation is that the reaction might proceed through other types of mechanisms, such as an open chain transition state or a radical process, although no work has been done to elucidate the reasons for the formation of racemic product with this nitrated reagent.



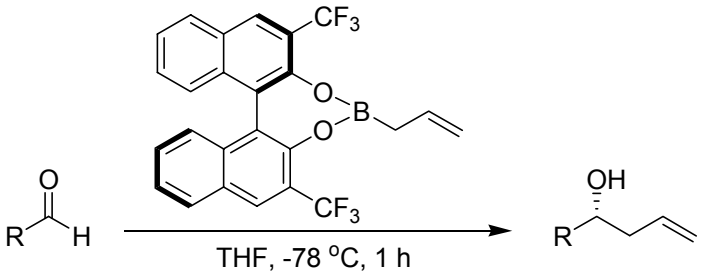
Scheme 2.25

In summary, among all the 3,3′-disubstituted binaphthol-modified allylboronates tested, **2.42b** (X = CF_3) showed the best enantioselectivity. The capacity of **2.42b** for inducing high enantioselectivity in the allylboration of benzaldehyde seems to be the result of a delicate combination of steric and electronic effects.

2.3.2.2 Allylboration of Aldehydes using 3,3′-$(CF_3)_2$-Binaphthol-modified Allylboronates (**2.42b**)

In order to examine the scope and limitations of the allylboration reaction, several other aldehydes were subjected to the allylation with **2.42b** (Table 2.3). In all cases, the reactions proceeded smoothly at -78 ^oC to give products in high yields. High enantioselectivities were obtained for all the aromatic aldehydes, regardless of substitution. In cases involving non-aromatic aldehydes (Table 2.3, entries 6 and 7), high yields but slightly lower selectivities were observed. Similar observations were reported by our group in the alkynylation of enones using 3,3′-disubstituted BINOL modified boronates where only enones bearing β-aryl groups gave high enantioselectivities.[18]

Table 2.2 Reactions of allylboronates **2.42b** with aldehydes.



(*R*)-**2.45**

entry	R	yield (%)	*ee* (%)[a]
1	Ph (**2.45a**)	90	95
2	4-$CH_3OC_6H_4$(**2.45b**)	93	94
3	4-ClC_6H_4(**2.45c**)	93	94
4	4-$O_2NC_6H_4$(**2.45d**)	96	92
5	4-$CF_3C_6H_4$(**2.45e**)	94	94
6	PhCH=CH(**2.45f**)	98	75
7	*c*-C_6H_{11}(**2.45g**)	90	75

[a] Enantiomeric excesses were determined by chiral HPLC analysis on a Chiralcel OD column. The absolute configuration of the products was determined by the comparison of rotation values with reported values (see experimental section).

2.3.2.3 Working Model for the Allylboration of Aldehydes

Based on the observation that (*R*)-boronates **2.42** afforded (*R*)-homoallylic alcohols **2.44a**, a six-membered chair transition state model similar to that of other allylborations was proposed to explain the sense of asymmetric induction. For the allylation of aromatic aldehydes, the aryl group on the aldehyde is forced into the equatorial position in order to prevent a repulsive *n*-π electron interaction between the lone pair of a boronate oxygen and the aryl group (Figure 2.5).[33]

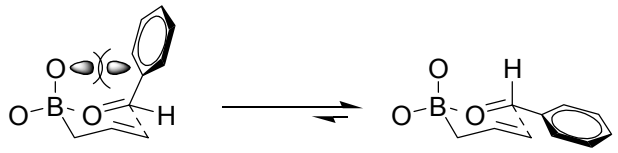
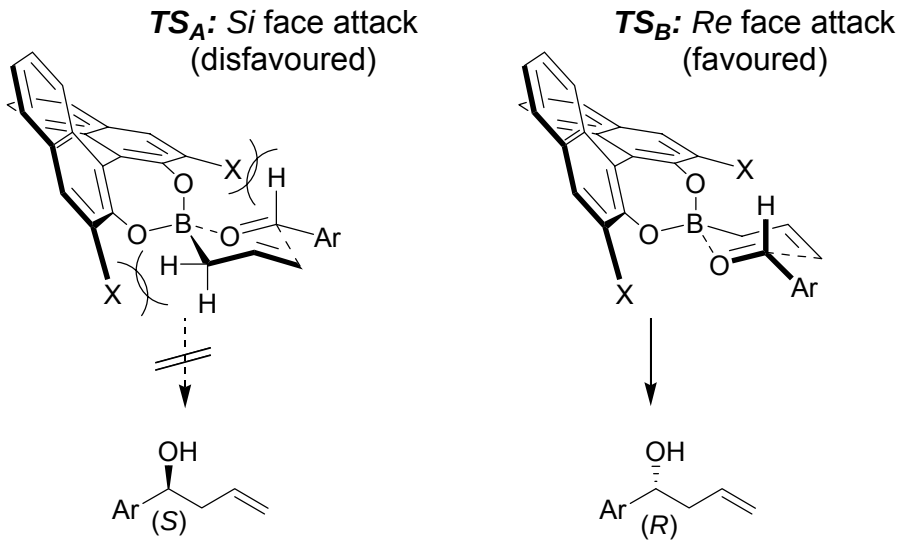


Figure 2.5 *n*-π Interaction between the lone pair on oxygen and the aromatic ring on the aldehyde.

The 3 and 3′ substituents on the BINOL play an important role in destabilizing one of the two possible transition states (Scheme 2.26). In transition state **A**, there seems to be a strong interaction between a CF_3 group and the aldehydic H. In addition, the other CF_3 group has an interaction with one of the methylene proton on the allyl group. The accumulation of the two interactions appears to sufficiently destabilize transition state **A**, such that transition state **B** is favoured and the *R* enantiomer is produced.



Scheme 2.26

In the cases of non-aromatic aldehydes, in comparison to aromatic aldehydes, the chance for the alkyl (or alkenyl) group occupying an axial position is slightly higher due to the lack of the *n*-π electron interaction with the boronate oxygen. This results in lower enantioselectivities although transition state **B** is still favoured.

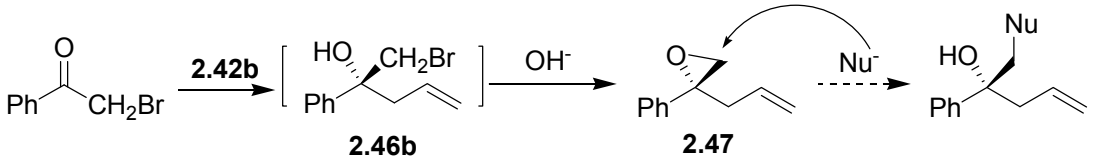
2.3.3 Allylboration of Ketones using 3,3′-$(CF_3)_2$-Binaphthol-modified Allylboronate (2.42b)

According to the proposed model for the allylation of aldehydes discussed above, the interaction of one of the CF_3 group with aldehydic proton contributes to the high enantioselectivities observed. It prompted us to expect that replacement of the aldehydic proton with a larger group would result in a stronger destabilization of transition state **A** (Scheme 2.26) and accordingly better enantioselectivity. In other words, the allylboration of ketones using **2.42b** would be expected to also give high enantioselectivities based on the proposed model. In terms of the reactivity of the

allylboration of ketones, it is clear that the carbonyl group in a ketone is more hindered than the one in an aldehyde and the alkyl group on a ketone is more electron-donating than a proton to make the ketone carbonyl group less electrophilic. Accordingly, we expected that the allylboration of ketones would be more difficult than the allylboration of aldehydes.

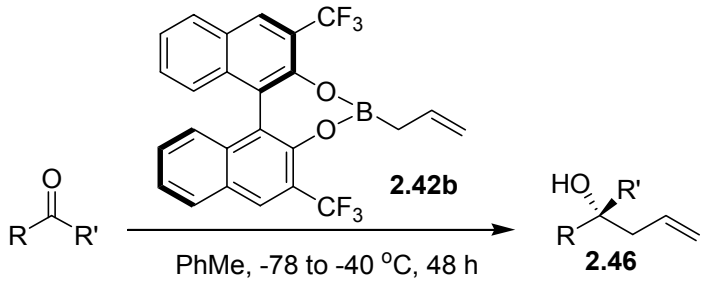
To our delight, allylboronate **2.42b** did in fact react with ketones, albeit much more slowly than with aldehydes. As was mentioned above, **2.42b** usually gave complete reactions with aldehydes in THF within 5 minutes at -78 ^{o}C. However, acetophenone was only partially consumed giving the corresponding adduct in 60% yield even after 6 hours at -78 ^{o}C (Table 2.4, entry 1). Despite the low yield, the enantioselectivity of the reaction was excellent (96% *ee*) as expected. Allowing the reaction to warm up to -40 ^{o}C gave a complete reaction. The *ee* of the product dropped slightly to 92% but was still acceptable (Table 2.4, entry 2).

Other alkyl aryl ketones were examined under the same conditions. The desired adducts were obtained in excellent yields and enantioselectivities (Table 2.4, entries 3-5). It is worthwhile to point out that in the allylation of α-bromoacetophenone (Table 2.4, entry 3), an epoxide **2.47** could be obtained from the allylation product **2.46b** in one pot by simply basifying the reaction mixture during workup (Table 2.4, Scheme 2.27). The resulting epoxide **2.47** is a potentially useful compound since it could be converted into other chiral tertiary alcohols using known chemistry.



Scheme 2.27

Table 2.3 Reactions of allylboronates **2.42b** with ketones.



entry	R	R′	compd no.	yield (%)[c]	*ee* (%)[d]
1	Ph	CH_3	**2.46a**	60[b]	96
2	Ph	CH_3	**2.46a**	88	92
3	Ph	CH_2Br	**2.46b**	87[e]	94
4	4-$CH_3OC_6H_4$	CH_3	**2.46c**	95	98
5	4-ClC_6H_4	CH_3	**2.46d**	94	>99[f]
6	PhCH=CH	CH_3	**2.46e**	91	75
7	*t*-Bu	CH_3	**2.46f**	75	90[g]
8	$PhCH_2CH_2$	CH_3	**2.46g**	98	50
9	HC≡C	CH_3	**2.46h**	71	10[g]

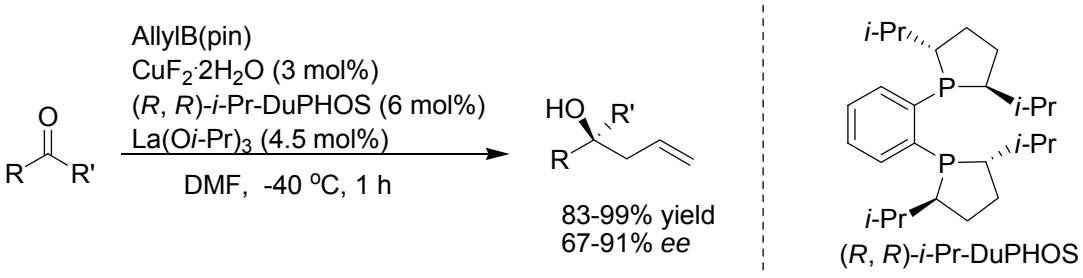
[a] Reactions were run in toluene at -78 to -40 °C, 48 h. [b] The reaction was performed at -78 °C for 6 h. [c] Isolated yields of chromatographed products. [d] Determined by HPLC analysis with a Chiralcel OD column. [e] Isolated yield of 1-phenyl-1- (2-propenyl)oxirane **2.47** after workup with 1 M NaOH. [f] The minor enantiomer was not detected by HPLC analysis. [g] Determined by the ^{1}H NMR analysis in the presence of Eu(hfc)$_3$.

Similar to aldehyde allylations, allylboration of a non-aromatic *α,β*-unsaturated ketone, benzalacetone, gave lower but still respectable enantioselectivity (Table 2.4, entry 6). Allylboration of a dialkyl ketone, pinacolone, also gave decent enantioselectivity (90% *ee*, Table 2.4, entry 7). However, low enantioselectivity was observed for the allylation of a ketone bearing two sterically similar alkyl groups (Table 2.4, entry 8). Even lower enantioselectivity (10% *ee*) was obtained in the

allylation of an alkynyl methyl ketone (Table 2.4, entry 9) and the absolute configuration of the allylation product **2.46h** was not determined.

Asymmetric allylboration of ketones in general has been a very difficult reaction. To our knowledge, there had been only one example for the allylboration of acetophenone using Brown's $Ipc_2BCH_2CH{=}CH_2$ to gave adduct **2.46a** in only 5% *ee*.[32] The high enantioselectivities obtained with **2.42b** are also comparable with other methods for the asymmetric allylation of ketones (such as allylstannations and allylsilations).[1,34-36] In fact, **2.42b** is one of the best enantioselective allylation reagents for alkyl aryl ketones thus far developed.

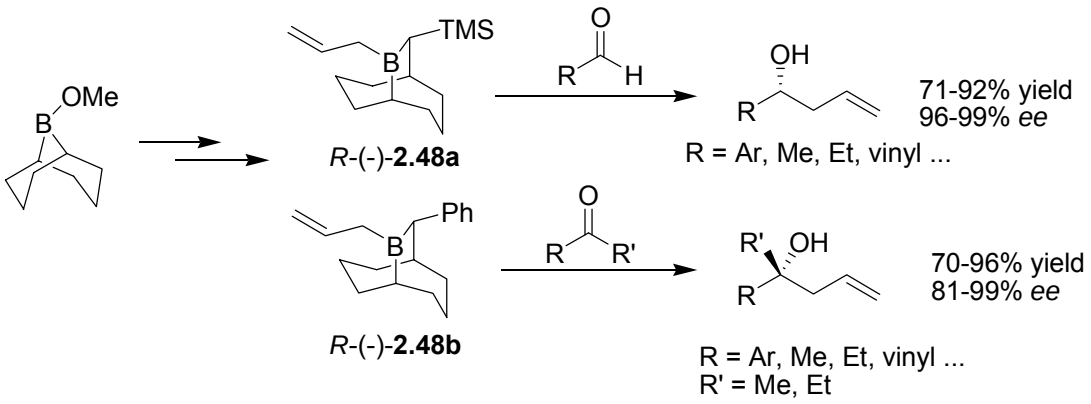
During the course of this work, Shibasaki reported the first catalytic asymmetric allylboration of ketones with allylB(pin) catalyzed by CuF_2/*i*-Pr-DuPHOS/La(O*i*-Pr)$_3$. However, this allylboration chemistry seems to work only for ketones (no corresponding aldehyde allylation was reported) and the enantioselectivities of this reactions are not as high as those of our allylboration chemistry.[37]



Scheme 2.28

Also, very recently, Soderquist reported another aldehyde/ketone allylboration using chiral boranes derived from 9-BBN. *R*-(-)-**2.48a** exhibited high enantioselectivities in the allylboration of aldehydes while *R*-(-)-**2.48b** worked well specifically for ketone allylations. It is particularly noteworthy that *R*-(-)-**2.48b** induced high levels of enantioselectivity even in some very demanding

cases where the groups on the ketone are similar in size (for instance, methyl ethyl ketone gave 87% *ee*).[38,39]



Scheme 2.29

The new concept of a "chiral pocket" was proposed to explain the sense of enantioselectivities in this allylation. The allyl group and the 10-substituent clearly define a chiral pocket which controls the facial discrimination during the allylation (Figure 2.6). The size of the pocket could be adjusted by changing the 10-substituent of the borane.

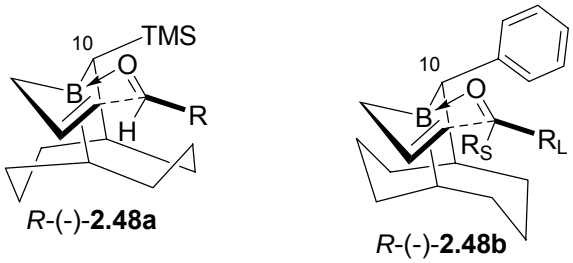
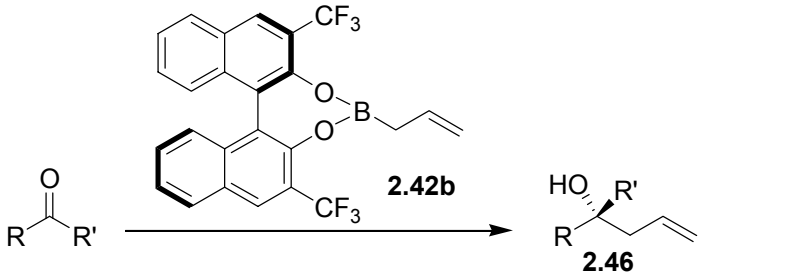


Figure 2.6 "Chiral pocket" model.

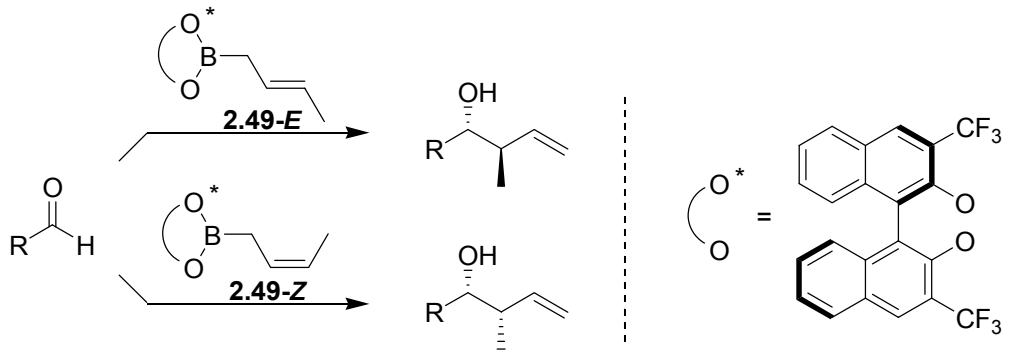
2.4 Summary and Future Work

In summary, we have shown that 3,3′-disubstituted-BINOL modified allylboronates can be used to allylate carbonyl compounds. The easily prepared 3,3′-$(CF_3)_2$-BINOL (**2.31**) (4 steps from BINOL) was the best ligand among all the ligands tested. It is highly effective in inducing the asymmetric allylboration of both aldehydes and ketones in high enantioselectivities (Scheme 2.30). Also it is readily recycled and reused without loss of enantiomeric purity. Some part of this work has been published in *Organic Letters* (Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett.* **2004**, *6*, 2701-2704).[40] Considering all the merits mentioned above, we anticipate that other applications of ligand **2.31** as well as this allylboration reaction in asymmetric synthesis will be found in the near future.



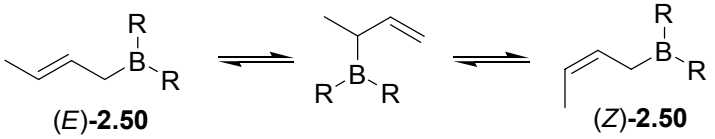
Scheme 2.30

Since 3,3′-$(CF_3)_2$-binaphthol-modified allylboronate **2.42b** induces excellent enantioselectivities in the allylboration of carbonyls, crotylboration of carbonyls using crotylboronate **2.49** (*Z* or *E*) which proceeds through the same closed six-membered transition state as that of the allylboration might give the same level of enantioselectivity as well as good diastereoselectivity (Scheme 2.31).



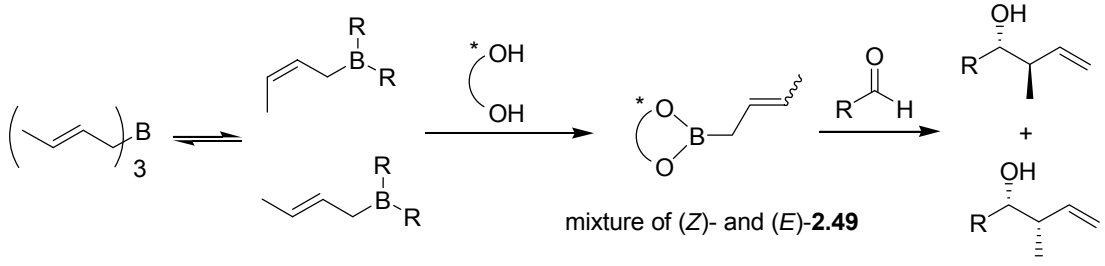
Scheme 2.31

However, some possible problems need to be taken into consideration. Brown and coworkers have reported that a diastereomerically pure (*Z*) or (*E*)-*B*-crotyl borane **2.50** isomerizes quickly to the other diastereomer *via* a simple borotropic rearrangement (Scheme 2.32). The rate of the isomerization of *B*-crotyl boranes varies greatly with the nature of other groups on boron: allyldialkylborane > allylalkylborinate > allylboronate.[5]



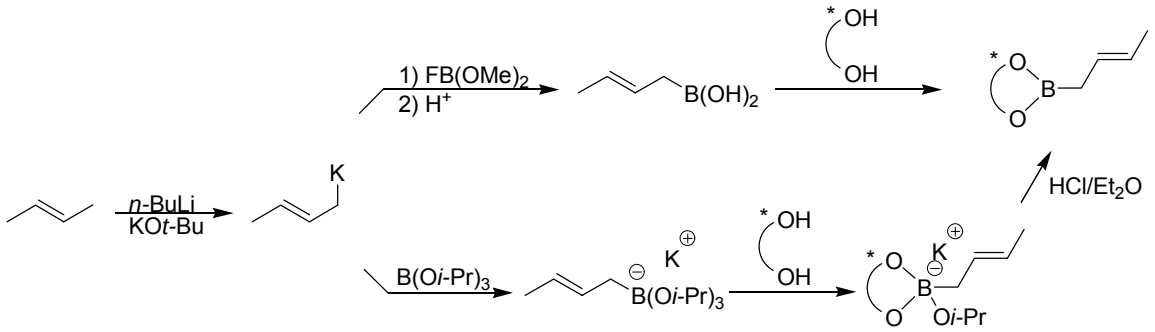
Scheme 2.32

According to this study, it is impossible to prepare diastereomerically pure chiral crotylboronate **2.49** from tricrotylborane due to its fast isomerization (Scheme 2.33).



Scheme 2.33

Diastereomerically pure 3,3′-$(CF_3)_2$-binaphthol-modified crotylboronate **2.49** may be synthesized using Roush's route[8] or a method similar to the preparation of binaphthol-modified alkynylboronates developed by our group (Scheme 2.34).[18]



Scheme 2.34

A potential application of the asymmetric allylboration of ketones would be the total synthesis of antifungal agents Sch56592 and Sch51048 which have shown promising activities against a variety of systemic fungal infections in normal and immunocompromised infection models.[41-43]

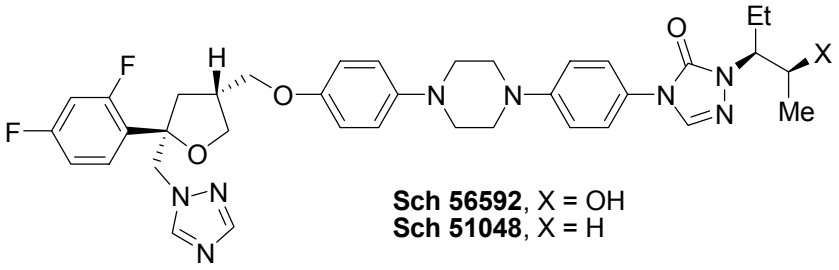
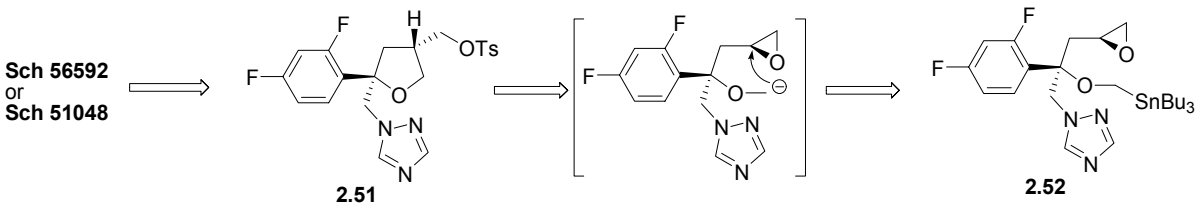


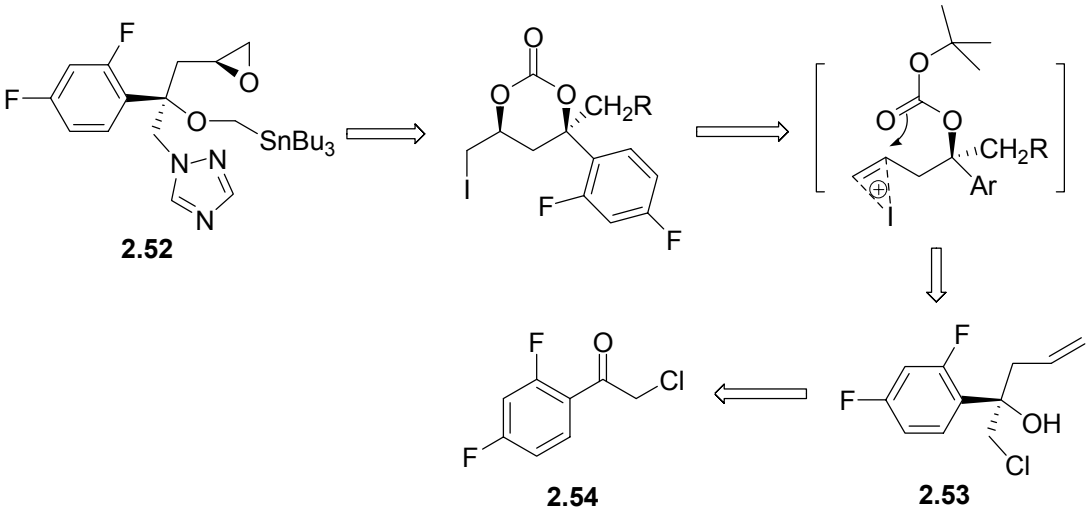
Figure 2.7 Structures of antifungal agents Sch56592 and Sch51048.

Sch56592 and Sch51048 might be synthesized from a common intermediate **2.51**. The chiral tetrahydrofuran core of **2.51** could be obtained through an intramolecular epoxide ring opening reaction of **2.52** (Scheme 2.35).



Scheme 2.35

The epoxide **2.52** might be prepared using a known strategy[44] from a homoallylic alcohol **2.53** which could be generated using our asymmetric allylboration method.



Scheme 2.36

2.5 Experimental

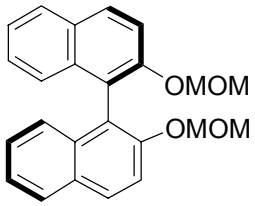
2.5.1 General Experimental

IR spectra were recorded on a Bomem MB-100 infrared spectrophotometer. ^{1}H (250 and 300 MHz), ^{13}C (63 and 75 MHz), and ^{19}F (188 and 282 MHz) NMR spectra were recorded on Bruker AM250 or AVANCE 300 spectrometers unless otherwise noted. Chemical shifts are given in parts per million (ppm) downfield from tetramethylsilane (TMS). The ^{1}H NMR samples were run in deuteriochloroform containing ca. 0.01% TMS as an internal standard (δ = 0.0). The spectral reference for ^{13}C NMR spectra was $CDCl_3$ (δ = 77.0). The spectral reference for ^{19}F NMR spectra was CF_3COOH (δ = 76.53 upfield of $CFCl_3$). Elemental analyses were conducted by M-H-W Laboratories, Phoenix, Arizona. Mass spectra were recorded on a GC-MS (Hewlett Packard G 1800A GCD System) or a Kratos MA890 mass spectrometer using electron impact (EI, 70 eV) ionization if the mass was over 430. Optical rotations were recorded in cells with 10 cm path length on a Perkin-Elmer 241 digital polarimeter.

All reactions involving air or moisture sensitive reagents were performed under an argon or nitrogen atmosphere on the bench using standard Schlenk techniques. Solvents were dried prior to use. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were dried by distillation from sodium/benzophenone. Dichloromethane (CH_2Cl_2), DMF, HMPA and *n*-pentane were dried by distillation from calcium hydride. Chloromethyl methyl ether was prepared according to the literature.[45] $BrCl_2CCCl_2Br$ was prepared in 85% yield from the reaction of tetrachloroethene and bromine in dichloromethane under reflux condition for 3 days, followed by the removal of organic solvent.[25] Triallylborane was prepared as reported by Brown and was distilled prior to use.[30] BINOL

(**2.12**) was prepared following a literature procedure[22] and was resolved using the Merck method.[24,46] Methyl fluorosulfonyldifluoroacetate was purchased from SynQuest Laboratories, Alachua, FL and used without further purification. Unless otherwise noted, other chemicals were purchased from Aldrich Chemical Company.

2.5.2 Preparation of (±)- and (*R*)-2,2′-Bis(methoxymethoxy)-1,1′-binaphthyl (2.13)



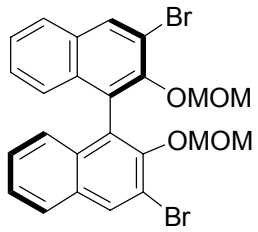
The preparation followed literature procedures[47] with some modifications. NaH (2.92 g, 60% in oil, 73.0 mmol) was mixed in dry THF (150 mL) in a 500 mL round bottom flask at 0 ^{o}C under an argon atmosphere. To the mixture with stirring, was added a solution of (±)-2,2′-dihydroxy-1,1′-binaphthyl (**2.12**) (9.50 g, 33.2 mmol) in THF (50 mL) in a dropping funnel. After the addition, the mixture was stirred at 0 ^{o}C for 1 hour, then allowed to warm up to room temperature for 15 minutes. After the mixture was re-cooled to 0 ^{o}C, chloromethyl methyl ether (5.54 mL, 73.0 mmol) was slowly added from the dropping funnel. After the addition, the reaction mixture was warmed to room temperature and stirred for 4.5 hours. Saturated aqueous NH_4Cl (50 mL) was added to the flask, and then the solvent was removed *in vacuo*. The residue was extracted with CH_2Cl_2 (50 mL x 3). The organic layers were combined, washed with brine (50 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography (EtOAc/hexanes: 1/10) and crystallized from CH_2Cl_2/hexanes to give a white crystalline product (±)-**2.13** in quantitative yield. mp 89-92 ^{o}C (lit.[5] mp 88-91 ^{o}C); IR (KBr): υ(max) 1236, 1144, 1028 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.88-8.14 (H_{Ar}, 2H, m),

7.76-7.84 (H_{Ar}, 2H, m), 7.10-7.62 (H_{Ar}, 8H, m), 4.97 (OCH_2O, 2H, d, J = 8.5 Hz), 5.08 (OCH_2O, 2H, d, J = 8.5 Hz), 3.10 (OCH_3, 6H, s); ^{13}C NMR ($CDCl_3$): δ 152.6 (C_{Ar}), 130.0 (C_{Ar}), 129.9 (C_{Ar}), 129.3 (C_{Ar}), 127.8 (C_{Ar}), 126.3 (C_{Ar}), 125.5 (C_{Ar}), 124.0 (C_{Ar}), 121.3 (C_{Ar}), 117.3 (C_{Ar}), 95.2 ($O\underline{C}H_2O$), 55.7 ($O\underline{C}H_3$); MS *m/e* (relative intensity): 374 (M^+, 100), 298 (90), 270 (71), 239 (23); Anal. Calcd for $C_{24}H_{22}O_4$: C, 76.99; H, 5.92. Found: C, 77.02; H, 5.94. (*R*)-2,2′-Dihydroxy-1,1′-binaphthyl was used to afford (*R*)-**2.13** in quantitative yield. mp 98-100 °C. The sample showed $[\alpha]_D^{25}$ +95.0 (c = 1.0, THF).

2.5.3 General Procedure A: Preparation of 3,3′-Disubstituted-2,2′-bis(methoxymethoxy) -1,1′-binaphthyls 2.14-2.17

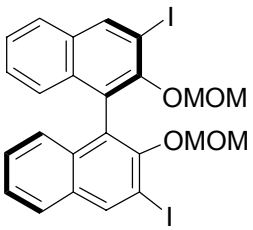
The preparation of 3,3′-disubstituted binaphthyl compounds followed literature procedures[47] with some modifications. (±)- or (*R*)-2,2′-Bis(methoxymethoxy)-1,1′-binaphthyl (**2.13)** (1.0 equiv.) was dissolved in dry Et_2O (17 mL/1 mmol of **2.13**) in a round bottom flask under an argon atmosphere. To the mixture with stirring, was added *n*-BuLi (3.0 equiv.) at room temperature by syringe injection. After the reaction mixture was stirred for 3 hours, THF (11 mL/1 mmol of **2.13**) was injected into the flask and then the mixture was stirred for 1 hour. After the flask was cooled in an ice water bath for 5 minutes, the appropriate electrophile (3.0 equiv.) was added quickly in one portion. The reaction mixture was stirred for 15 minutes, quenched with saturated aqueous NH_4Cl and diluted with water. The two phases were separated. The aqueous layer was extracted with Et_2O twice. All organic solutions were combined, washed with brine, dried over Na_2SO_4 and concentrated. Subsequent work-up gave the product.

2.5.3.1 (±)- and (*R*)-3,3′-Dibromo-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.14**)



(±)-2,2′-Bis(methoxymethoxy)-1,1′-binaphthyl (**2.13**) (8.80 g, 23.5 mmol) was treated with *n*-BuLi (44.10 mL of a 1.6 M solution in hexane, 70.5 mmol) at room temperature and the resulting mixture was quenched with dibromotetrachloroethane (23.0 g, 70.5 mmol). The crude product was purified by column chromatography (EtOAc/hexanes: 1/10) and crystallized from Et_2O/hexanes to give a white crystalline product (±)-**2.14** (10.60 g) in 85% yield. mp 125-126 ^oC (lit.[47] mp 124-126 ^oC); IR (KBr): υ(max) 1235, 1157, 1026 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.25-8.30 (H_{Ar}, 2H, m), 7.78-7.82 (H_{Ar}, 2H, m), 7.18-7.48 (H_{Ar}, 6H, m), 4.81 (OCH_2O, 2H, d, J = 6.0 Hz), 4.82 (OCH_2O, 2H, d, J = 6.0 Hz), 2.56 (OCH_3, 6H, s); Anal. Calcd for $C_{24}H_{20}Br_2O_4$: C, 54.16; H, 3.79. Found: C, 54.10; H, 3.87. (*R*)-2,2′-Bis(methoxymethoxy)-1,1′- binaphthyl was used to afford (*R*)-**2.14** in 84% yield. mp 123-124 ^oC. The sample showed $[\alpha]_D^{25}$ +28.3 (c = 1.0, THF).

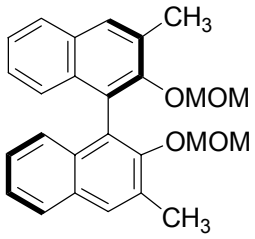
2.5.3.2 (±)- and (*R*)-3,3′-Diiodo-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.15**)



(±)-2,2′-Bis(methoxymethoxy)-1,1′-binaphthyl (**2.13**) (6.50 g, 17.3 mmol) was treated with *n*-BuLi (33.0 mL of a 1.6 M solution in hexane, 52.8 mmol) at room temperature and the resulting

mixture was quenched with iodine (13.2 g, 52.0 mmol). The crude product was purified by column chromatography (EtOAc/hexanes: 1/10) and crystallized from CH_2Cl_2/hexanes to give a white crystalline product (**2.15**) (9.60 g) in 88% yield. mp 45-47 ^oC.; IR (KBr): υ (max) 1232, 1156, 1026 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.50-8.62 (H_{Ar}, 2H, m), 7.70-7.85 (H_{Ar}, 2H, m), 7.10-7.54 (H_{Ar}, 6H, m), 4.81 (OCH_2O, 2H, d, J = 5.7 Hz), 4.69 (OCH_2O, 2H, d, J = 5.7 Hz), 2.59 (OCH_3, 6H, s); MS *m/e* (relative intensity): 626 (M^+, 35), 550 (20), 549 (100), 422 (60), 268 (45), 239 (46), 237 (28), 226 (37), 224 (45); Anal. Calcd for $C_{24}H_{20}I_2O_4$: C, 46.03; H, 3.22. Found: C, 46.05; H, 3.20. The *R* enantiomer showed $[\alpha]_D^{25}$ -5.3 (c = 1.0, THF).

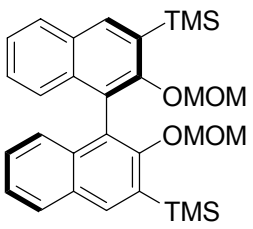
2.5.3.3 (*R*)-3,3′-Dimethyl-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.16**)



(*R*)-2,2′-Bis(methoxymethoxy)-1,1′-binaphthyl [(*R*)-**2.13**] (2.0 g, 5.34 mmol) was treated with *n*-BuLi (10.0 mL of a 1.6 M solution in hexane, 16.0 mmol) at room temperature and the resulting mixture was quenched with iodomethane (1.0 mL, 16.0 mmol). The crude product was purified by column chromatography (EtOAc/hexanes: 1/10) and crystallized from CH_2Cl_2/hexanes to give a white crystalline product (*R*)-**2.16** (2.1 g) in 96% yield. mp 91-92 ^oC (lit.[47] (*S*)-**2.16** mp 90.5-91.5 ^oC); IR (KBr): υ (max) 1238, 1155, 1035 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.72-7.80 (H_{Ar}, 4H, m), 7.26-7.38 (H_{Ar}, 2H, m), 7.14-7.20 (H_{Ar}, 4H, m), 4.46 (OCH_2O, 2H, d, J = 5.8 Hz), 4.58 (OCH_2O, 2H, d, J = 5.8 Hz), 2.83 (OCH_3, 6H, s), 2.57 ($ArCH_3$, 6H, s); ^{13}C NMR ($CDCl_3$): δ 153.1 (C_{Ar}), 133.0 (C_{Ar}), 131.6 (C_{Ar}), 131.0 (C_{Ar}), 129.6 (C_{Ar}), 127.1 (C_{Ar}), 126.1 (C_{Ar}), 125.5 (C_{Ar}), 125.4 (C_{Ar}), 124.7 (C_{Ar}), 98.5

(O<u>C</u>H_2O), 56.4 (O<u>C</u>H_3), 17.8 (Ar<u>C</u>H_3); MS *m/e* (relative intensity): 402 (M^+, 30), 327 (29), 326 (100), 309 (26), 298 (36), 297 (50), 296 (45), 283 (29), 252 (20), 239 (30), 119 (27), 111 (25); Anal. Calcd for $C_{26}H_{26}O_4$: C, 77.59; H, 6.51. Found: C, 77.55; H, 6.47. The sample showed $[\alpha]_D^{25}$ -86.6 (c = 1.0, THF).

2.5.3.4 (*R*)-2,2′-Bis(methoxymethoxy)-3,3′-bis(trimethylsilyl)-1,1′-binaphthyl (**2.17**)[47]



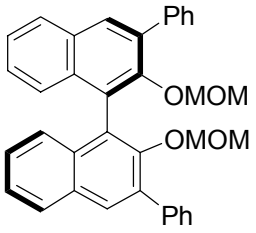
(*R*)-2,2′-Bis(methoxymethoxy)-1,1′-binaphthyl [(*R*)-**2.13**] (2.07 g, 5.53 mmol) was treated with *n*-BuLi (10.5 mL of a 1.6 M solution in hexane, 16.6 mmol) at room temperature and the resulting mixture was quenched with chlorotrimethylsilane (1.8 g, 16.6 mmol). The crude product was purified by column chromatography (EtOAc/hexanes: 1/20) and crystallized from CH_2Cl_2/hexanes to give an off-white foamy product (*R*)-**2.17** (2.80 g) in 98% yield. ^{1}H NMR ($CDCl_3$): δ 8.04 (H_{Ar}, 2H, s), 7.85 (H_{Ar}, 2H, d, J = 8.1 Hz,), 7.36 (H_{Ar}, 2H, m), 7.18-7.26 (H_{Ar}, 4H, m), 4.43 (OCH_2O, 2H, d, J = 4.4 Hz), 4.08 (OCH_2O, 2H, d, J = 4.4 Hz), 2.90 (OCH_3, 6H, s), 0.40 ($SiMe_3$, 18H, s).

2.5.4 General Procedure B: Preparation of 3,3′-Diaryl-2,2′-bis(methoxymethoxy)-1,1′-binaphthyls 2.18-2.23

The preparation of 3,3′-disubstituted binaphthyl compounds followed literature procedures[47] with some modifications. (*R*)-3,3′-Dibromo-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.14**) or (*R*)-3,3′-diiodo-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.15**) (1.0 equiv.) and $Pd(PPh_3)_4$ (10 mol%) were mixed in THF or DME in a round bottom flask at room temperature under an argon

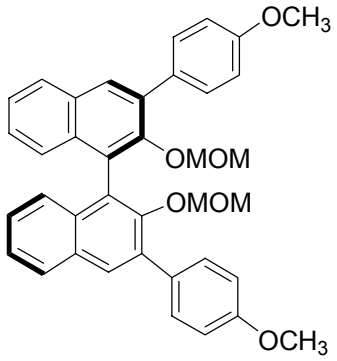
atmosphere. To the mixture, with stirring, were added arylboronic acid (2.5-3.5 equiv.) and 1-2 M aqueous degassed K_2CO_3 (or Na_2CO_3) solution. The resulting mixture was stirred and heated to reflux for 24-48 hours, cooled to room temperature, and passed through a pad of Celite. The organic solution was evaporated to give a residue. The residue was dissolved in CH_2Cl_2, washed with saturated aqueous NH_4Cl, water, brine, dried over Na_2SO_4, and concentrated to give a crude product. Subsequent purification gave the product.

2.5.4.1 (*R*)-3,3′-Diphenyl-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.18**)



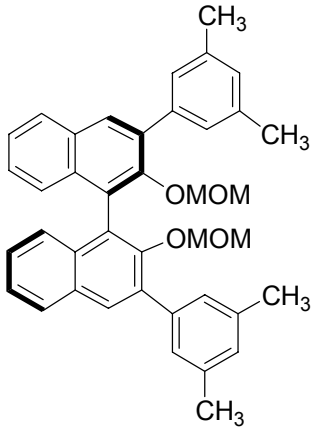
Following General Procedure B, (*R*)-3,3′-diiodo-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.15**) (4.70 g, 7.5 mmol) was treated with $Pd(PPh_3)_4$ (0.87 g, 0.75 mmol), phenylboronic acid (2.31 g, 18.8 mmol) and 1 M aqueous K_2CO_3 solution (38 mL) in THF (75 mL). Purification was carried out by column chromatography (EtOAc/hexanes: 1/10) to give a foamy product (*R*)-**2.18** (3.55 g) in 90% yield. The product was directly used for the deprotection of MOM group with only ^{1}H NMR and ^{13}C NMR being examined. ^{1}H NMR ($CDCl_3$): δ 7.65-8.05 (H_{Ar}, 8H, m), 7.22-7.55 (H_{Ar}, 12H, m), 4.40 (OCH_2O, 2H, d, J = 5.8 Hz), 4.37 (OCH_2O, 2H, d, J = 5.8 Hz), 2.34 (OCH_3, 6H, s); ^{13}C NMR ($CDCl_3$): δ 139.0 (C_{Ar}), 135.5 (C_{Ar}), 133.6 (C_{Ar}), 130.9 (C_{Ar}), 130.6 (C_{Ar}), 129.6 (C_{Ar}), 128.3 (C_{Ar}), 127.9 (C_{Ar}), 127.3 (C_{Ar}), 126.5 (C_{Ar}), 126.4 (C_{Ar}), 126.3 (C_{Ar}), 125.2 (C_{Ar}), 98.5 ($O\underline{C}H_2O$), 55.8 ($O\underline{C}H_3$).

2.5.4.2 (±)- and (*R*)-3,3′-Bis(4-methoxyphenyl)-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.19**)



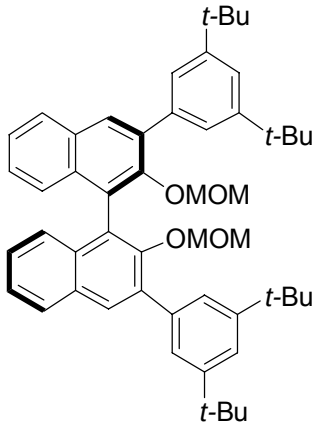
Following General Procedure B, (±)-3,3′-diiodo-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.15**) (3.13 g, 5 mmol) was treated with $Pd(PPh_3)_4$ (0.58 g, 0.5 mmol), 4-methoxyphenylboronic acid (1.90 g, 12.5 mmol) and 1 M aqueous K_2CO_3 solution (25 mL) in THF (50 mL). Purification was carried out by column chromatography (EtOAc/hexanes: 1/10) (**2.19**) (2.73 g) in 93% yield; IR (KBr): υ (max) 1608, 1513, 1247 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.82-7.96 (H_{Ar}, 4H, m), 7.63-7.78 (H_{Ar}, 4H, m), 7.18-7.47 (H_{Ar}, 6H, m), 6.90-7.08 (H_{Ar}, 4H, m), 4.42 (OCH_2O, 2H, d, J = 5.7 Hz), 4.37 (OCH_2O, 2H, d, J = 5.7 Hz), 3.87 (OCH_3, 6H, s), 2.35 (OCH_3, 6H, s); ^{13}C NMR ($CDCl_3$): δ 159.0 (C_{Ar}), 151.3 (C_{Ar}), 135.0 (C_{Ar}), 133.4 (C_{Ar}), 131.4 (C_{Ar}), 130.9 (C_{Ar}), 130.7 (C_{Ar}), 130.2 (C_{Ar}), 127.7 (C_{Ar}), 126.6 (C_{Ar}), 126.4 (C_{Ar}), 126.1 (C_{Ar}), 125.1 (C_{Ar}), 113.8 (C_{Ar}), 98.3 ($O\underline{C}H_2O$), 55.9 ($O\underline{C}H_3$), 55.3 ($O\underline{C}H_3$); Anal. Calcd for $C_{38}H_{34}O_6$: C, 77.80; H, 5.84. Found: C, 77.68; H, 5.78. (*R*)-3,3′-Dibromo-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl was used to afford (*R*)-**2.19**. mp 68-70 ^oC. The sample showed $[\alpha]_{578}^{25}$ -109.6 (c = 1.0, THF).

2.5.4.3 (±)- and (*R*)-3,3′-Bis(3,5-dimethylphenyl)-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.20**)



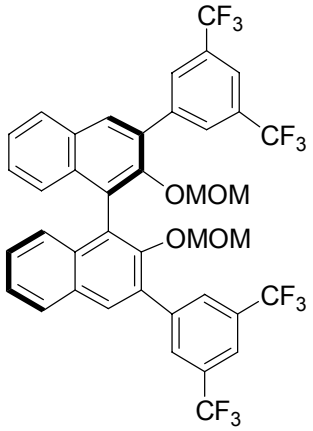
Following General Procedure B, (±)-3,3′-dibromo-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.20**) (2.0 g, 3.76 mmol) was treated with $Pd(PPh_3)_4$ (0.43 g, 0.372 mmol), 3,5-dimethylphenylboronic acid (2.0 g, 13.34 mmol) and 2 M aqueous Na_2CO_3 solution (10 mL) in DME (40 mL) in a 100 mL round bottom flask. Purification was carried out by column chromatography (CH_2Cl_2/hexanes: 1/1) and crystallization from CH_2Cl_2/hexanes to give colorless crystals (**2.20**) (2.25 g) in 93% yield. mp 84-85 ^oC; IR (KBr): υ (max) 1600, 1389, 1233, 1157 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.80-7.97 (H_{Ar}, 4H, m), 7.18-7.48 (H_{Ar}, 10H, m), 7.02-7.08 (H_{Ar}, 2H, m), 4.69 (OCH_2O, 2H, d, J = 5.8 Hz), 4.44 (OCH_2O, 2H, d, J = 5.8 Hz), 2.40 ($ArCH_3$, 12H, s), 2.36 (OCH_3, 6H, s); ^{13}C NMR ($CDCl_3$): δ 151.4 (C_{Ar}), 139.0 (C_{Ar}), 137.7 (C_{Ar}), 135.7 (C_{Ar}), 133.6 (C_{Ar}), 130.8 (C_{Ar}), 130.5 (C_{Ar}), 128.9 (C_{Ar}), 127.7 (C_{Ar}), 127.4 (C_{Ar}), 126.4 (C_{Ar}), 126.1 (C_{Ar}), 125.0 (C_{Ar}), 98.5 ($O\underline{C}H_2O$), 55.8 ($O\underline{C}H_3$), 21.4 ($Ar\underline{C}H_3$); MS *m/e* (relative intensity): 582 (M^+, 35), 518 (12), 507 (41), 506 (100), 478 (28); Anal. Calcd for $C_{40}H_{38}O_4$: C, 82.44; H, 6.57. Found: C, 82.55; H, 6.50. (*R*)-3,3′-Dibromo-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl was used to afford (*R*)-**2.20**. mp 81-83 ^oC. The sample showed $[\alpha]_{578}^{25}$ -36.8 (c = 1.1, THF).

2.5.4.4 (*R*)-3,3′-Bis[3,5-di(*tert*-butyl)phenyl]-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.21**)



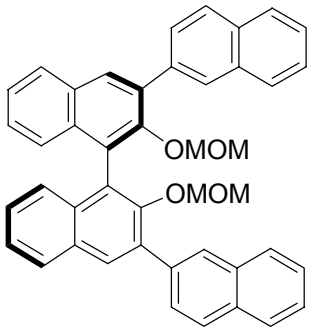
Following general procedure B, (*R*)-3,3'-dibromo-2,2'-bis(methoxymethoxy-1,1'-binaphthyl (**2.14**) (2.50 g, 4.70 mmol) was treated with $Pd(PPh_3)_4$ (0.54 g, 0.470 mmol), 3,5-di(*tert*-butyl)phenylboronic acid (3.85 g, 16.40 mmol) and 2 M aqueous Na_2CO_3 solution (12.5 mL) in DME (50 mL) in a 100 mL round bottom flask. Purification was carried out by column chromatography (CH_2Cl_2/hexanes: 1/1) and crystallization from CH_2Cl_2/hexanes to give colorless crystals (**2.21**) (3.5 g) in 99% yield. mp 97-99 ^oC; IR (KBr): υ (max) 1595, 1390, 1244, 1157 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.84-8.02 (H_{Ar}, 4H, m), 7.54-7.64 (H_{Ar}, 4H, m), 7.20-7.50 (H_{Ar}, 8H, m), 4.42 (OCH_2O, 2H, d, J = 5.7 Hz), 4.40 (OCH_2O, 2H, d, J = 5.7 Hz), 2.37 (OCH_3, 6H, s), 1.39 (CMe_3, 18H, s); ^{13}C NMR ($CDCl_3$): δ 151.6 (C_{Ar}), 150.6 (C_{Ar}), 138.2 (C_{Ar}), 136.4 (C_{Ar}), 133.5 (C_{Ar}), 130.8 (C_{Ar}), 130.2 (C_{Ar}), 127.8 (C_{Ar}), 126.5 (C_{Ar}), 126.4 (C_{Ar}), 126.0 (C_{Ar}), 124.9 (C_{Ar}), 123.9 (C_{Ar}), 121.0 (C_{Ar}), 98.3 ($O\underline{C}H_2O$), 55.7 ($O\underline{C}H_3$), 34.9 ($\underline{C}Me_3$), 31.5 ($C\underline{Me}_3$); Anal. Calcd for $C_{52}H_{62}O_4$: C, 83.16; H, 8.32. Found: C, 82.96; H, 8.19. The sample showed $[\alpha]_{578}^{25}$ -73.8 (c = 1.1, THF).

2.5.4.5 (*R*)-3,3′-Bis[3,5-bis(trifluoromethyl)phenyl]-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.22**)



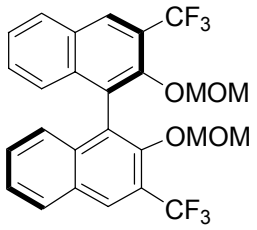
Following General Procedure B, (*R*)-3,3′-dibromo-2,2′-*bis*(methoxymethoxy-1,1′-binaphthyl (**2.14**) (2.36 g, 4.43 mmol) was treated with $Pd(PPh_3)_4$ (0.512 g, 0.443 mmol), 3,5-bis(trifluoromethyl)phenylboronic acid (4.0 g, 15.5 mmol) and 2 M aqueous Na_2CO_3 solution (11.7 mL) in DME (50 mL) in a 100 mL round bottom flask. Purification was carried out by column chromatography (CH_2Cl_2/hexanes: 2/3) and crystallization from CH_2Cl_2/hexanes to give slightly yellow crystals (*R*)-**2.22** (3.0 g) in 85% yield. mp 69-71 ^oC; IR (KBr): υ (max) 1621, 1377, 1281, 1153 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.20-8.32 (H_{Ar}, 4H, m), 7.86-8.08 (H_{Ar}, 6H, m), 7.20-7.56 (H_{Ar}, 6H, m), 4.43 (OCH_2O, 2H, d, J = 6.0 Hz), 4.37 (OCH_2O, 2H, d, J = 6.0 Hz), 2.50 (OCH_3, 6H, s); ^{13}C NMR ($CDCl_3$): δ 151.3 (C_{Ar}), 141.2(C_{Ar}), 134.2(C_{Ar}), 132.8(C_{Ar}), 132.0(C_{Ar}), 131.5(C_{Ar}), 131.1(C_{Ar}), 130.7(C_{Ar}), 130.0(C_{Ar}), 128.3(C_{Ar}), 127.5(C_{Ar}), 126.4(C_{Ar}), 126.3(C_{Ar}), 125.9(C_{Ar}), 125.6(C_{Ar}), 121.1(CF_3), 99.2 ($O\underline{C}H_2O$), 56.2 ($O\underline{C}H_3$); ^{19}F NMR ($CDCl_3$): δ -63.43; Anal. Calcd for $C_{40}H_{26}F_{12}O_4$: C, 60.16; H, 3.28. Found: C, 60.35; H, 3.17. The sample showed $[\alpha]_{578}^{25}$ -83.6 (c = 1.1, THF).

2.5.4.6 (±)- and (*R*)-3,3′-Bis(2-naphthyl)-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.23**)



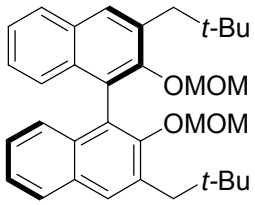
Following General Procedure B, (±)-3,3′-dibromo-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.14**) (1.2 g, 2.25 mmol) was treated with $Pd(PPh_3)_4$ (0.26 g, 0.225 mmol), 2-naphthylboronic acid (2.02 g, 11.76 mmol) and 2 M aqueous Na_2CO_3 solution (5.9 mL) in DME (25 mL) in a 100 mL round bottom flask. Purification was carried out by column chromatography (CH_2Cl_2/hexanes: 1/1) and crystallization from CH_2Cl_2/hexanes to give colorless crystals (**2.14**) (1.4 g) in 85% yield. mp 103-104 ^oC; IR (KBr): υ (max) 1597, 1154 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.14-8.28 (H_{Ar}, 2H, m), 8.01-8.10 (H_{Ar}, 2H, m), 7.70-8.01 (H_{Ar}, 10H, m), 7.22-7.66 (H_{Ar}, 10H, m), 4.45 (OCH_2O, 2H, d, J = 5.9 Hz), 4.44 (OCH_2O, 2H, d, J = 5.9 Hz), 2.32 (OCH_3, 6H, s); ^{13}C NMR ($CDCl_3$): δ 151.5 (C_{Ar}), 136.7 (C_{Ar}), 135.3 (C_{Ar}), 133.7 (C_{Ar}), 133.5 (C_{Ar}), 132.5 (C_{Ar}), 130.9 (C_{Ar}), 128.1 (C_{Ar}), 128.0 (C_{Ar}), 127.9 (C_{Ar}), 127.7 (C_{Ar}), 127.6 (C_{Ar}), 126.6 (C_{Ar}), 126.5 (C_{Ar}), 126.4 (C_{Ar}), 126.1 (C_{Ar}), 126.0 (C_{Ar}), 125.2 (C_{Ar}), 98.6 ($O\underline{C}H_2O$), 55.9 ($O\underline{C}H_3$); MS *m/e* (relative intensity): 627 (M^+, 1), 271 (22), 270 (100), 269 (30), 268 (15), 239 (22); Anal. Calcd for $C_{44}H_{34}O_4$: C, 84.32; H, 5.47. Found: C, 84.23; H, 5.38. (*R*)-3,3′-Dibromo-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl was used to afford (*R*)-**2.14** as a yellowish syrup. The sample showed $[\alpha]_{578}^{25}$ -110 (c = 1.1, THF).

2.5.5 Preparation of (*R*)-3,3′-Bis(trifluoromethyl)-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (2.25)



A mixture of $FSO_2CF_2CO_2Me$ (1.63 mL, 12.78 mmol), CuI (1.46 g, 7.67 mmol), HMPA (2.22 mL, 12.78 mmol) and (*R*)-3,3′-diiodo-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.15**) (2.0 g, 3.19 mmol) in DMF (40 mL) was stirred under argon atmosphere for 6 hours at 70 ^oC. The reaction mixture was then cooled to room temperature. It was diluted with CH_2Cl_2 (400 mL), the solution washed with water (3 x 200 mL), dried over Na_2SO_4, and concentrated to afford a syrup. Purification was done by column chromatography (EtOAc/hexanes: 1/20) to give 1.51 g of pure product **2.25** (93%). mp 43-45 ^oC; IR (KBr): υ (max) 1230, 1165, 1035 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.22-8.32 (H_{Ar}, 2H, m), 7.85-7.98 (H_{Ar}, 2H, m), 7.25-7.55 (H_{Ar}, 4H, m), 7.08-7.25 (H_{Ar}, 2H, m), 4.68 (OCH_2O, 2H, d, J = 5.5 Hz), 4.44 (OCH_2O, 2H, d, J = 5.5 Hz), 2.63 (OCH_3, 6H, s); ^{13}C NMR ($CDCl_3$): δ 150.8 (C_{Ar}), 140.3 (C_{Ar}), 135.6 (C_{Ar}), 129.2 (C_{Ar}), 129.1 (C_{Ar}), 129.0 (C_{Ar}), 128.9 (C_{Ar}), 126.9 (C_{Ar}), 126.2 (C_{Ar}), 126.0 (C_{Ar}), 123.9 (CF_3-$\underline{C}_{Ar}$, q, J = 30.4 Hz), 123.6 ($\underline{C}F_3$, q, 272.7 Hz), 99.7 ($O\underline{C}H_2O$), 56.2 ($O\underline{C}H_3$); ^{19}F NMR ($CDCl_3$): δ -61.7; Anal. Calcd for $C_{26}H_{20}F_6O_4$: C, 61.18; H, 3.95, F, 22.33. Found: C, 61.10; H, 3.76; F, 22.43. The sample showed $[\alpha]_D^{25}$ –57.0 (c = 1.0, THF).

2.5.6 Preparation of (*R*)-3,3′-Di-neopentyl-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (2.26)

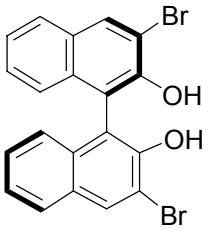


Neopentyl iodide (3.67 g, 18.53 mmol, 11.6 equiv.) was added *via* syringe over 2 hours to Mg turnings (0.26 g, 10.9 mmol, 6.8 equiv.) in 20 mL refluxing diethyl ether. After the addition, the mixture was stirred at room temperature for 1.5 hours. The resulting solution was transferred *via* cannula into a mixture of $NiCl_2$(dppe) (6.1 mg) and (*R*)-3,3′-diiodo-2,2′-bis(methoxy methoxy)-1,1′-binaphthyl **2.15** (1.0 g, 1.6 mmol, 1.0 equiv.) in 20 mL ether at 0 ^oC. The reaction mixture was allowed to reflux for 20 hours then cool to room temperature before quenching with saturated aqueous NH_4Cl. The organic layer was separated and the aqueous layer was extracted with Et_2O twice. The combined organic phases were washed with sodium thiosulfate and brine. The ethereal solution was dried over Na_2SO_4 and concentrated and the crude product was purified by column chromatography (EtOAc/hexanes: 1/30) to give a white foamy product (0.583 g) in 86% yield. ^1H NMR ($CDCl_3$): δ 7.81 (H_{Ar}, 2H, d, J = 8.1 Hz), 7.72 (H_{Ar}, 2H, s), 7.03-7.36 (H_{Ar}, 6 H, m), 4.30 (OCH_2O, 2H, d, J = 5.9 Hz), 4.41 (OCH_2O, 2H, d, J = 5.9 Hz), 3.03 ($C\underline{H_2}t$-Bu, 2H, d, J = 12.8 Hz), 3.01 (OCH_3, 6 H, s), 2.66 ($C\underline{H_2}t$-Bu, 2H, d, J = 12.8 Hz), 0.99 (-CH_3, 18H, s).

2.5.7 General Procedure C: Preparation of 3,3′-Disubstituted-2,2′-dihydroxy-1,1′-binaphthyls 2.27-2.37

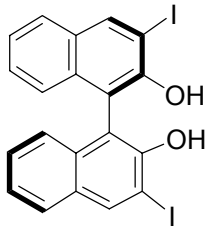
A mixture of 3,3′-disubstituted-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (2.0 mmol) and Amberlyst 15 resin (1.0 g) in THF/MeOH (1:1) was stirred and heated to reflux under an argon atmosphere for 15 hours, then cooled to room temperature. The resin was removed by filtration and the filtrate was concentrated by rotary evaporation. Subsequent purification gave the product.

2.5.7.1 (*R*)-3,3′-Dibromo-2,2′-dihydroxy-1,1′-binaphthyl (**2.27**)



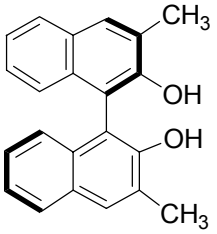
(*R*)-3,3′-Dibromo-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.14**) (2.0 g, 3.76 mmol) was treated with Amberlyst 15 (2.0 g) in THF/MeOH (100 mL, 1:1) as described in general procedure C. Purification was carried out by crystallization (CH_2Cl_2/hexanes) to afford 1.6 g of a white crystalline product (*R*)-**2.27** (96%). mp 256-257 ^oC (lit.[48] mp 243-244 ^oC); IR (KBr): υ (max) 3479, 1616, 1577, 1499, 1448, 1421, 1382, 1359, 1255, 1195, 1138 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.20-8.35 (H_{Ar}, 2H, m), 7.74-7.88 (H_{Ar}, 2H, m), 7.05-7.50 (H_{Ar}, 6H, m), 5.53 (OH, 2 H, s); ^{13}C NMR ($CDCl_3$): δ 148.1, 132.8, 129.8, 127.6, 127.4, 124.9, 124.6, 114.7, 112.3; Anal. Calcd for $C_{20}H_{12}Br_2O_2$: C, 54.09; H, 2.72. Found: C, 54.05; H, 2.68. The sample showed $[\alpha]_D^{25}$ +104.7 (c = 1.0, THF); lit.[48] $[\alpha]_D^{25}$ +43 (c = 0.22, $CHCl_3$)

2.5.7.2 (*R*)-3,3′-Diiodo-2,2′-dihydroxy-1,1′-binaphthyl (**2.28**)



(*R*)-3,3′-Diiodo-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.15**) (3.7 g, 5.91 mmol) was treated with Amberlyst 15 (3.0 g) in THF/MeOH (160 mL, 1:1) as described in general procedure C. Purification was carried out by column chromatography (EtOAc/hexanes: 1:10), and by crystallization (EtOAc/hexanes) to afford 3.0 g of a light yellow crystalline product (*R*)-**2.28** (94%). mp 312-314 ^{o}C; IR (KBr): υ (max) 3483, 1565, 1355, 1177, 1141 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.40-8.60 (H_{Ar}, 2H, m), 7.70-7.90 (H_{Ar}, 2H, m), 7.02-7.50 (H_{Ar}, 6H, m), 5.41 (OH, 2H, s); ^{13}C NMR ($CDCl_3$): δ 152.0, 140.4, 133.4, 130.7, 128.0, 127.3, 126.8, 125.2, 124.8, 124.4; Anal. Calcd for $C_{20}H_{12}I_2O_2$: C, 44.64; H, 2.25. Found: C, 44.58; H, 2.27. The sample showed $[\alpha]_D^{25}$ +102.7 (c = 1.0, THF).

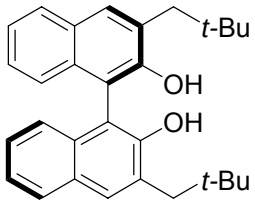
2.5.7.3 (*R*)-3,3′-Dimethyl-2,2′-dihydroxy-1,1′-binaphthyls (**2.29**)



(*R*)-3,3′-Dimethyl-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.16**) (1.80 g, 4.47 mmol) was treated with Amberlyst 15 (2.5 g) in THF/MeOH (80 mL, 1:1) as described in general procedure C. Purification was carried out by column chromatography (EtOAc/hexanes: 1:10), and by crystallization (CH_2Cl_2/hexanes) to afford 1.40 g of a slightly yellow crystalline product (*R*)-**2.29** (100%). mp 201-202 ^{o}C [lit.[49] for (*S*)-**2.29**, mp 200-202 ^{o}C]; IR, ^{1}H NMR, and ^{13}C NMR were

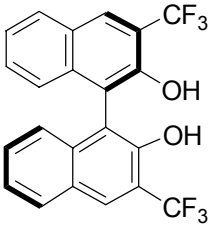
identical with that of (±)-**2.29**.[49] Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 84.01; H, 5.78. The sample showed $[\alpha]_{589}^{25}$ +43.4 (c = 1.0, THF).

2.5.7.4 (*R*)-2,2′-Dihydroxy-3,3′-di-neopentyl-1,1′-binaphthyl (**2.30**)



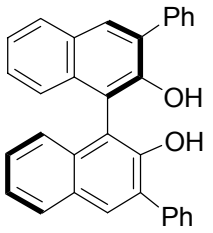
A mixture of (*R*)-**2.26** (2.2 g, 5.16 mmol) and Amberlyst-15 resin (2.58 g) in THF/MeOH (110 mL, 1:1) was heated to reflux under an argon atmosphere for 47 hours. The resin was removed by filtration through Celite and the filtrate was concentrated to dryness. Purification was carried out by column chromatography with silica gel (CH_2Cl_2/hexanes = 1:10) to afford at yellow foam (quantitative yield). ^{1}H NMR ($CDCl_3$): δ 7.84 (H_{Ar}, 2H, d, J = 8.1 Hz), 7.76 (H_{Ar}, 2H, s), 7.05-7.35 (H_{Ar}, 6H, m), 5.36 (OH, 2H, s), 2.88 (CH_2, d, J = 12.8 Hz), 2.77 (CH_2, d, J = 12.8 Hz), 1.01 (-CH_3, 18H, s).^{13}C NMR ($CDCl_3$): δ 152.5 (C_{Ar}), 132.8 (C_{Ar}), 132.4 (C_{Ar}), 129.1 (C_{Ar}), 128.8 (C_{Ar}), 128.0 (C_{Ar}), 126.6 (C_{Ar}), 124.0 (C_{Ar}), 123.9 (C_{Ar}), 110.8 (C_{Ar}), 43.2 ($\underline{C}H_2t$-Bu), 32.9 ($\underline{C}Me_3$), 29.6 ($\underline{C}H_3$). MS *m/e* (relative intensity): 627 (M^+, 1), 271 (22), 270 (100), 269 (30), 268 (15), 239 (22);. The sample showed $[\alpha]_{578}^{25}$ -110 (c = 1.1, THF).

2.5.7.5 (*R*)-3,3′-Bis(trifluoromethyl)-2,2′-dihydroxy-1,1′-binaphthyl (**2.31**)



(*R*)-3,3′-Bis(trifluoromethyl)-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.25**) (1.60 g, 3.13 mmol) was treated with Amberlyst 15 (1.6 g) in THF/MeOH (80 mL, 1:1) as described in General Procedure C. Purification was carried out by column chromatography (EtOAc/hexanes: 1:10), and by crystallization (CH_2Cl_2/hexanes) to afford 1.30 g of a white crystalline product (*R*)-**2.31** (98%). mp 240-242 ^oC; IR (KBr): υ (max) 3490, 1545, 1365, 1179 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.30-8.48 (H_{Ar}, 2H, m), 7.90-8.10 (H_{Ar}, 2H, m), 7.00-7.62 (H_{Ar}, 6H, m), 5.30 (OH, 2H, s); ^{13}C NMR ($CDCl_3$): δ 149.4, 134.6, 130.4 (q, J = 5.5 Hz), 130.0, 129.7, 127.9, 125.5, 123.9, 123.3 ($\underline{C}F_3$, q, J = 272.2 Hz), 118.9 (q, J = 30.9 Hz), 112.2; ^{19}F NMR ($CDCl_3$): δ -63.38; Anal. Calcd for $C_{22}H_{12}F_6O_2$: C, 62.57; H, 2.86; F, 26.99. Found: C, 62.50; H, 2.82; F, 26.88. MS *m/e* (relative intensity): 426 (M^+, 100), 411 (M^+-CH_3, 8), 369 (M^+-*t*-Bu); The sample showed $[\alpha]_{589}^{25}$ +100.3 (c = 1.0, THF).

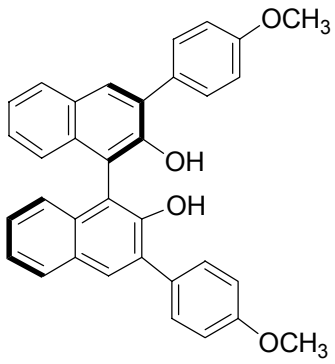
2.5.7.6 (±)- and (*R*)-3,3′-Diphenyl-2,2′-dihydroxy-1,1′-binaphthyl (**2.32**)



(±)-3,3′-Diphenyl-2,2′-bis(methoxymethoxy)-1,1′-binaphthol (**2.18**) (6.4 g, 12.15 mmol) was treated with Amberlyst 15 (6.0 g) in THF/MeOH (200 mL, 1:1)) as described in general procedure C. Purification was carried out by column chromatography (EtOAc/hexanes: 1:10), followed by crystallization (CH_2Cl_2/hexanes) to afford 4.70 g of a white crystalline product (±)-**2.32** (89%). mp 209-210 ^oC [lit.[49] mp 210-211 ^oC]; IR, ^1H NMR, ^{13}C NMR were identical to that of (±)-(**2.32**) in the literature[8]; Anal. Calcd for $C_{32}H_{22}O_2$: C, 87.65; H, 5.06. Found C, 87.55; H, 4.99. (*R*)-3,3′-Diphenyl-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl (**2.18**) was used to afford (*R*)-**2.32**. mp

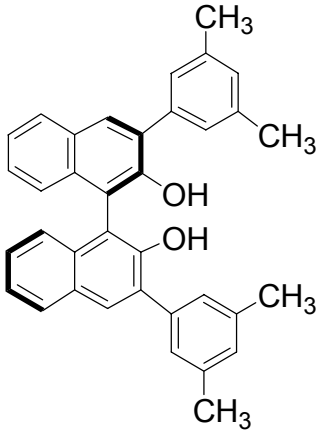
200-202 °C [lit.[50] mp 197-198 °C]; The sample showed $[\alpha]_D^{25}$ +135.0 (c = 1.0, THF) [lit.[50] $[\alpha]^{25}_{546}$ +132.4° (c = 1.0, THF)].

2.5.7.7 (±)- and (*R*)-3,3′-Bis(4-methoxyphenyl)-2,2′-dihydroxy-1,1′-binaphthyl (**2.33**)



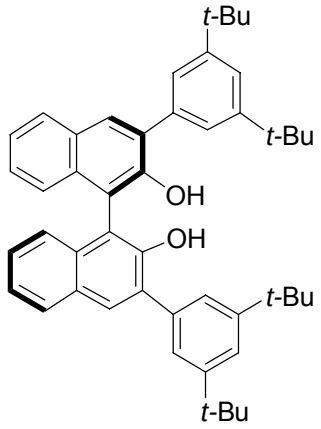
(±)-3,3′-Bis(4-methoxyphenyl)-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.19**) (1.50 g, 2.56 mmol) was treated with Amberlyst 15 (1.3 g) in THF/MeOH (80 mL, 1:1) as described in general procedure C. Purification was carried out by crystallization (EtOAc/hexanes) to afford 1.15 g of a light yellow crystalline product (±)-**2.33** (90%). mp 224-225 °C; IR (KBr): υ (max) 3480, 1606, 1512, 1244, 1177 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.80-8.10 (H_{Ar}, 4H, m), 7.56-7.75 (H_{Ar}, 4H, m), 7.12-7.45 (H_{Ar}, 6H, m), 6.90-7.06 (H_{Ar}, 4H, m), 5.36 (OH, 2H, s), 3.83 (OCH_3, 6H, s); ^{13}C NMR ($CDCl_3$): δ 159.3 (C_{Ar}), 150.2 (C_{Ar}), 132.7 (C_{Ar}), 130.9 (C_{Ar}), 130.7 (C_{Ar}), 130.3 (C_{Ar}), 129.8 (C_{Ar}), 129.5 (C_{Ar}), 128.3 (C_{Ar}), 127.1 (C_{Ar}), 124.2 (C_{Ar}), 113.9 (C_{Ar}), 112.4 (C_{Ar}), 55.3 ($O\underline{C}H_3$); Anal. Calcd for $C_{34}H_{26}O_4$: C, 81.91; H, 5.26. Found: C, 82.02; H, 5.16. (*R*)-3,3′-Bis(4-methoxyphenyl)-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl was used to afford (*R*)-**2.33** mp 109-111 °C. The sample showed $[\alpha]_{578}^{25}$ +50.1 (c = 1.0, THF).

2.5.7.8 (±)- and (*R*)-3,3′-Bis(3,5-dimethylphenyl)-2,2′-dihydroxy-1,1′-binaphthyl (**2.34**)



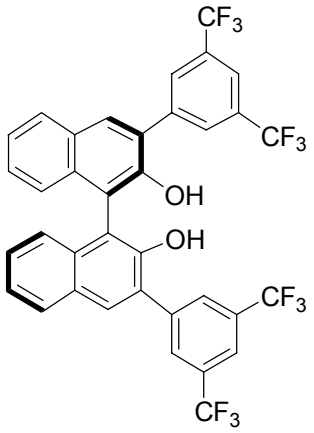
(±)-3,3′-Bis(3,5-dimethylphenyl)-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.20**) (2.20 g, 3.78 mmol) was treated with Amberlyst 15 (2.0 g) in THF/MeOH (100 mL, 1:1) as described in general procedure C. Purification was carried out by crystallization (THF/hexanes) to afford 1.74 g of a light yellow crystalline product (±)-**2.34** (93%). mp 299-301 ^{o}C; IR (KBr): υ (max) 3476, 1600, 1497, 1411, 1252, 1211 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.82-8.08 (H_{Ar}, 4H, m), 7.18-7.48 (H_{Ar}, 10H, m), 6.98-7.15 (H_{Ar}, 2H, m), 5.39 (OH, 2H, s), 2.40 (CH_3, 12H, s); ^{13}C NMR ($CDCl_3$): δ 150.0 (C_{Ar}), 138.1 (C_{Ar}), 137.3 (C_{Ar}), 133.0 (C_{Ar}), 130.9 (C_{Ar}), 129.5 (C_{Ar}), 129.4 (C_{Ar}), 128.3 (C_{Ar}), 127.3 (C_{Ar}), 127.1 (C_{Ar}), 124.4 (C_{Ar}), 124.1 (C_{Ar}), 112.8 (C_{Ar}), 21.4 ($\underline{C}H_3$); Anal. Calcd for $C_{36}H_{30}O_2$: C, 87.42; H, 6.11. Found: C, 87.35; H, 5.98. (*R*)-3,3′-Bis(3,5-dimethylphenyl)-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl was used to afford (*R*)-**2.34**. mp 124-125 ^{o}C. The sample showed $[\alpha]_{578}^{25}$ +53.2 (c = 1.1, THF).

2.5.7.9 (*R*)-3,3′-Bis[3,5-di(*tert*-butyl)phenyl]-2,2′-dihydroxy-1,1′-binaphthyl (**2.35**)



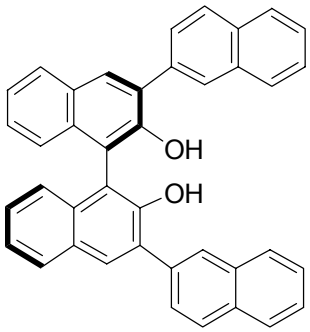
(*R*)-3,3′-Bis[3,5-di(*tert*-butyl)phenyl]-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.21**) (3.0 g, 3.76 mmol) was treated with Amberlyst 15 (2.0 g) in THF/MeOH (100 mL, 1:1) as described in General Procedure C. Purification was carried out by column chromatography (EtOAc/hexanes: 1:10), and by crystallization (EtOAc/hexanes) to afford 2.60 g of a white crystalline product (*R*)-**2.35** (98%). mp 142-144 ^{o}C; IR (KBr): υ (max) 3490, 1601, 1360, 1209 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.85-8.05 (H_{Ar}, 4H, m), 7.15-7.62 (H_{Ar}, 12H, m), 5.47 (OH, 2 H, s), 1.38 ($C(CH_3)_3$, 18H, s); ^{13}C NMR ($CDCl_3$): δ 151.0 (C_{Ar}), 150.1 (C_{Ar}), 136.5 (C_{Ar}), 133.0 (C_{Ar}), 131.6 (C_{Ar}), 130.9 (C_{Ar}), 129.4 (C_{Ar}), 128.3 (C_{Ar}), 127.0 (C_{Ar}), 124.5 (C_{Ar}), 124.1 (C_{Ar}), 123.9 (C_{Ar}), 121.9 (C_{Ar}), 113.0 (C_{Ar}), 35.0 ($\underline{C}Me_3$), 31.5 ($C\underline{Me}_3$); Anal. Calcd for $C_{48}H_{54}O_2$: C, 86.96; H, 8.21. Found: C, 86.86; H, 8.17. The sample showed $[\alpha]_D^{25}$ +27.5 (c = 1.0, THF).

2.5.7.10 (*R*)-3,3′-Bis[3,5-bis(trifluoromethyl)phenyl]-2,2′-dihydroxy-1,1′-binaphthyl (**2.36**)



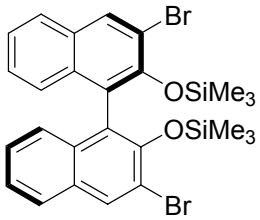
(*R*)-3,3′-Bis[3,5-bis(trifluoromethyl)phenyl]-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.22**) (3.0 g, 3.76 mmol) was treated with Amberlyst 15 (2.0 g) in THF/MeOH (100 mL, 1:1) as described in general procedure C. Purification was carried out by column chromatography (EtOAc/hexanes: 1:10), and by crystallization (EtOAc/hexanes) to afford 2.60 g of a light yellow crystalline product (*R*)-**2.36** (97%). mp 97-99 ^{o}C; IR (KBr): υ (max) 3477, 1603, 1385, 1203, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.80-8.35 (H_{Ar}, 10H, m), 7.10-7.60 (H_{Ar}, 6H, m), 5.37 (OH, 2H, s); ^{13}C NMR ($CDCl_3$): δ 150.0 (C_{Ar}), 139.7 (C_{Ar}), 133.4 (C_{Ar}), 132.4 (C_{Ar}), 131.7 (C_{Ar}, q, J = 33.9 Hz), 129.9 (C_{Ar}), 129.6 (C_{Ar}), 128.9 (C_{Ar}), 128.6 (C_{Ar}), 127.9 (CF_3, q, J = 275.5 Hz), 125.2 (C_{Ar}), 124.1 (C_{Ar}), 121.3 (C_{Ar}), 112.0 (C_{Ar}); ^{19}F NMR ($CDCl_3$): δ -63.49; Anal. Calcd for $C_{36}H_{18}O_2F_{12}$: C, 60.86; H, 2.55; F, 32.09. Found: C, 60.80; H, 2.48; F, 31.99. The sample showed $[\alpha]_D^{25}$ -11.9 (c = 1.1, THF).

2.5.7.11 (±)- and (*R*)-3,3′-Bis(2-naphthyl)-2,2′-dihydroxy-1,1′-binaphthyl (**2.37**)



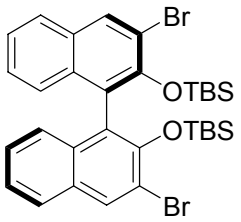
(±)-3,3′-Bis(2-naphthyl)-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.23**) (1.35 g, 2.15 mmol) was treated with Amberlyst 15 (1.1 g) in THF/MeOH (80 mL, 1:1) as described in general procedure C. Purification was carried out by column chromatography (CH_2Cl_2/hexanes: 1:1), then by crystallization (CH_2Cl_2/hexanes) to afford 1.05 g of a light yellow crystalline product (±)-**2.37** (91%). mp 184-185 ^oC; IR (KBr): υ (max) 3478, 1615, 1501, 1384, 1226, 1169, 1118 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.70-8.40 (H_{Ar}, 14H, m), 7.15-7.60 (H_{Ar}, 10H, m), 5.46 (OH, 2H, s); ^{13}C NMR ($CDCl_3$): δ 150.3, 135.0 (C_{Ar}), 133.5 (C_{Ar}), 133.0 (C_{Ar}), 132.8 (C_{Ar}), 131.7 (C_{Ar}), 130.6 (C_{Ar}), 129.6 (C_{Ar}), 128.5 (C_{Ar}), 128.2 (C_{Ar}), 127.9 (C_{Ar}), 127.7 (C_{Ar}), 127.4 (C_{Ar}), 126.3 (C_{Ar}), 124.4 (C_{Ar}), 124.3 (C_{Ar}), 112.5 (C_{Ar}); Anal. Calcd for $C_{40}H_{26}O_2$: C, 89.19; H, 4.86. Found: C, 88.98; H, 5.05. (*R*)-3,3′-Bis(2-naphthyl)-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl was used to afford (*R*)-**2.37**: mp 217-218 ^oC (dec.). The sample showed $[\alpha]_{578}^{25}$ -32.9 (c = 1.0, THF).

2.5.8 (*R*)-3,3′-Dibromo-2,2′-bis(trimethylsiloxy)-1,1′-binaphthyl (2.38a)[27]



(*R*)-**2.27** (1.50 g, 3.38 mmol,) and imidazole (0.70 g, 10.30 mmol, 3.05 equiv.) was dissolved in 23 mL of DMF. Chlorotrimethylsilane (0.93 g, 8.58 mmol, 2.5 equiv.) was syringed into the reaction flask at room temperature and the reaction mixture was stirred overnight. Ether (50 mL) was added to the reaction flask, and the reaction was quenched with 50 mL of 5% sodium bicarbonate solution. The aqueous layer was extracted and washed three times with diethyl ether. The combined organic layers were washed five times with water and dried over sodium sulfate. The desired product (1.20 g, 60% yield) was obtained after flash column chromatography on silca gel (1:15 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$): δ 8.19 (H_{Ar}, 2H, s), 7.75 (H_{Ar}, 2H, d, J = 8.1 Hz), 7.18-7.36 (H_{Ar}, 4H, m), 7.01 (H_{Ar}, 2H, d, J = 8.1 Hz), -0.24 (TMS, 18H, s).

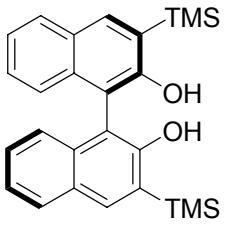
2.5.9 (*R*)-3,3′-Dibromo-2,2′-bis(*tert*-butyl-dimethylsiloxy)-1,1′-binaphthyl (2.38b)[27]



(*R*)-**2.27** (3.00 g, 6.75 mmol) and imidazole (1.86 g, 27.3 mmol, 4.05 equiv.) was dissolved in 50 mL of DMF. *tert*-Butylchlorodimethylsilane (4.07 g, 27.0 mmol, 4.0 equiv.) was syringed into the reaction flask at room temperature. The reaction was stirred at that temperature 70 hours. Ether (100 mL) was added to the reaction flask, and the reaction was quenched with 50 mL of 5% sodium bicarbonate solution. The aqueous layer was extracted and washed three times with diethyl ether. The combined organic layers were washed with water and brine and dried over sodium sulfate. The organic layers were dried over sodium sulfate and concentrated to dryness. The crude product (4.11g) was obtained in 91% yield which was used in the next step without further purification. ^{1}H NMR

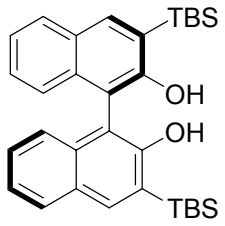
($CDCl_3$): δ 8.19 (H_{Ar}, 2H, s), 7.72 (H_{Ar}, 2H, d, J = 8.1 Hz), 7.19-7.34 (H_{Ar}, 4H, m), 7.07 (H_{Ar}, 2H, d, J = 8.1 Hz), 0.80 ($Me_2SiC\underline{Me}_3$, 18H, s), -0.03 ($\underline{Me}_2SiCMe_3$, 12H, s).

2.5.10 (*R*)-3,3′-Bis(trimethylsilyl)-2,2′-dihydroxy-1,1′-binaphthyl (2.39)[27]



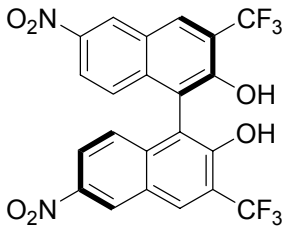
(*R*)-**2.38a** (0.87 g, 1.48 mmol) was dissolved in 30 mL of dry THF. The solution was cooled to 0 ^oC and *tert*-butyllithium (6.19 mL, 1.43 M solution in pentane, 8.86 mmol, 6.0 equiv.) was added dropwise. After the addition, the reaction was warmed to room temperature and stirred overnight. The reaction was quenched by pouring the reaction mixture into 20 mL of saturated aqueous NH_4Cl. The aqueous layer was extracted and washed three times with dichloromethane. Organic layers were combined and dried over sodium sulfate. Crude product was purified by column chromatography (EtOAc/hexanes: 1/20) to give a foam (0.379 g) in 60% yield. ^1H NMR ($CDCl_3$): δ 8.06 (H_{Ar}, 2H, s), 7.87 (H_{Ar}, 2H, d, J = 8.1 Hz), 7.27-7.38 (H_{Ar}, 4H, m), 7.07 (H_{Ar} 2H, d, J = 8.1 Hz), 5.28 (OH, 2H, s) 0.40 (TMS, 18H, s).

2.5.11 (*R*)-3,3′-Bis(*tert*-butyldimethylsilyl)-2,2′-dihydroxy-1,1′-binaphthyl (2.40)[27]



(*R*)-**2.38b** (0.50 g, 0.74 mmol) was dissolved in 20 mL of dry THF. *tert*-Butyllithium (3.1 mL, 1.43 M solution in pentane, 4.46 mmol, 6.0 equiv.) was added dropwise at 0 ^{o}C. After the addition, the reaction warmed to room temperature and stirred overnight. The reaction mixture was poured into 20 mL of saturated aqueous NH_4Cl. The aqueous layer was extracted and washed three times with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated to dryness. The crude product was purified by column chromatography (EtOAc/hexanes: 1/10) to give a white foam (0.362g) in 95% yield. . ^{1}H NMR ($CDCl_3$): δ 8.06 (H_{Ar}, 2 H, s), 7.87 (H_{Ar}, 2 H, d, J = 7.8 Hz), 7.21-7.35 (H_{Ar}, 4H, m), 7.07 (H_{Ar}, 2H, d, J = 7.8 Hz), 5.34 (OH, 2H, s), 0.93 ($Me_2SiC\underline{Me}_3$, 18H, s), 0.41 ($\underline{Me}_2SiCMe_3$, 12H,s).

2.5.12 Preparation of (*R*)-3,3′-Bis(trifluoromethyl)- 2,2′-dihydroxy-6,6′-dinitro-1,1′ -binaphthyl (2.41)



To a solution of (*R*)-3,3′-bis(trifluoromethyl)-2,2′-dihydroxy-1,1′-binaphthyl **2.31** (0.65g, 1.54mmol) in 27 mL of 2:1 THF/$CHCl_3$ was added $Fe(NO_3)_3{\cdot}9H_2O$ (3.08 g, 7.70 mmol, 5.0 equiv.). The resulting brown suspension was heated to reflux for 3 hours. The reaction was quenched with 1 M HCl and was diluted with ether. The organic phase was separated and the aqueous phase was extracted with ether three times. The combined organic layers were then washed with brine and dried over Na_2SO_4. Purification was done by flash column chromatography on silica gel (1:5

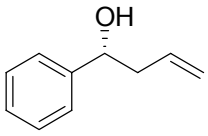
EtOAc/hexanes) yielding the desired product as pale yellow powder (0.66 g, 71%). ^{1}H NMR ($CDCl_3$): δ 8.96 (H_{Ar}, 2H, d, J = 1.9 Hz), 8.58 (H_{Ar}, 2H, s), 8.20 (H_{Ar}, 2H, dd, J = 1.9 Hz, 9.2Hz), 7.15 (H_{Ar}, 2H, d, J = 9.2 Hz), 5.90 (OH, 2H, s); ^{13}C NMR ($CDCl_3$ with a few drops of DMSO, CF_3 signal was not found): δ 154.6 (C_{Ar}), 143.2 (C_{Ar}), 138.2 (C_{Ar}), 131.0 (C_{Ar}, q, J = 5.6 Hz), 125.8 (C_{Ar}), 125.1 (C_{Ar}), 124.6 (C_{Ar}), 121.4 (C_{Ar}), 121.3 (C_{Ar}, q, J = 30.3 Hz), 114.3 (C_{Ar}); ^{19}F NMR ($CDCl_3$ with a few drops of DMSO): δ -62.8; MS *m/e* (relative intensity): 512 (M^+, 100), 493 (M^+-F, 8); HRMS *m/z* Calcd for $C_{22}H_{10}F_6N_2O_6$ (M^+): 512.0443. Found: 512.0440. This sample showed $[\alpha]_D^{25}$ -1.4 (c = 0.94, THF).

2.5.13 General Procedure D: Allylboration of Aldehydes and Ketones using Binaphthol-modified Allylboronates 2.42b

To a solution of triallylborane (0.75 mmol, 1.5 equiv.) in dry THF (4 mL) under argon was added the 3,3′-disubstituted BINOL (0.9 mmol, 1.8 equiv.). This mixture was stirred at room temperature for 2 hours and then was heated at reflux for 1 hour. The solution was cooled to -78 ^{o}C (in ketone cases, THF was evaporated, and 5 mL toluene was added). The aldehyde (or ketone) (0.5 mmol) was dissolved in 1 mL of dry THF (toluene for ketones) and added dropwise to the solution. Upon completion of the addition, the solution was stirred at –78 ^{o}C for 1 hour (-78 ^{o}C - -40 ^{o}C for 48 hours for ketones). The reaction was quenched cold with 1 M NaOH and allowed to warm to room temperature. The mixture was diluted with CH_2Cl_2 (20 mL) and the organic layer washed with 0.1 M NaOH then brine, dried with sodium sulfate. The ligand was recovered by neutralizing the aqueous layer with 1 M HCl and extracting with Et_2O. The organic layer was evaporated under reduced pressure to afford a clear colorless oil, which was purified via flash column chromatography (10:1

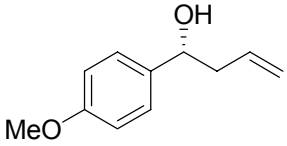
hexanes/EtOAc) to provide the expected homoallylic alcohol in the yields reported in Tables 2.2, 2.3, and 2.4**.** The enantiomeric excesses of most alcohols were determined by HPLC (4.6 x 250 mm Chiralcel OD) using racemic mixtures prepared with triallylborane as standards. While excess binaphthol was typically used to ensure that no free triallylborane remained, control experiments using 1.0:1.0 binaphthol:triallylborane gave essentially identical enantioselectivities.

2.5.13.1 (*R*)-1-Phenyl-3-buten-1-ol (**2.44a**)



$[\alpha]_D^{25}$ = +43.6 (c 1.24, benzene, 86% *ee*), lit.[32] for *S* enantiomer: $[\alpha]_D^{25}$ = -44.92 (c 7.38, benzene, 96% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.60 (H_{Ar}, 5H, m), 5.72-5.86 (C<u>H</u>=CH_2, 1H, m), 5.11-5.17 (CH=C<u>H_2</u>, 2H, m), 4.70 (PhC<u>H</u>, 1H, dd, *J* = 11.6 Hz, 7.0 Hz), 2.34-2.57 (CH_2, 2H, m), 2.06 (OH, 1H, br, s); The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 98/2, flow rate = 1 mL/min), t_R = 15.87 min (*R*), t_R = 18.90 min (*S*).

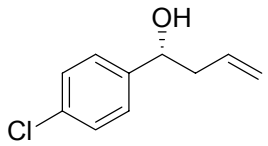
2.5.13.2 (*R*)-1-(4-Methoxyphenyl)-3-buten-1-ol (**2.44b**)



$[\alpha]_D^{25}$ = +62.4 (c 0.75, $CHCl_3$, 93% *ee*), lit.[51]: $[\alpha]_D^{25}$ = +30.5 (c 1.0, benzene, 95% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (H_{Ar}, 2H, d, *J* = 8.7 Hz), 6.82 (H_{Ar}, 2H, d, *J* = 8.7 Hz), 5.53-5.93 (C<u>H</u>=CH_2, 1H, m), 5.08-5.13 (CH=C<u>H_2</u>, 2H, m), 4.59 (ArC<u>H</u>, 1H, d, *J* = 6.6 Hz, 6.6 Hz), 3.74 (OCH_3, 3H, s), 2.48 (CH_2, 2H, t, *J* = 6.6 Hz), 2.06 (OH, 1H, br, s); The enantiomeric excess of the product was

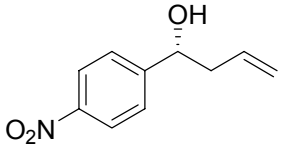
determined by HPLC (hexanes/*i*-PrOH = 98/2, flow rate = 1 mL/min), t_R = 21.09 min (*R*), t_R = 26.12 min (*S*).

2.5.13.3 (*R*)-1-(4-Chlorophenyl)-3-buten-1-ol (**2.44c**)



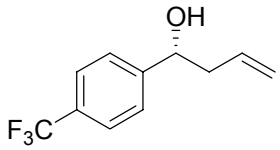
$[\alpha]_D^{25}$ = +61.4 (c 1.17, $CHCl_3$, 94% *ee*), lit.[52]: $[\alpha]_D^{25}$ = +26.4 (c 0.38, C_6H_6, 98% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19-7.31 (H_{Ar}, 4H, m), 5.68-5.83 (C<u>H</u>=CH_2, 1H, m), 5.12-5.17 (CH=C<u>H_2</u>, 2H, m), 4.68 (ArC<u>H</u>, 1H, dd, J = 7.5 Hz, 5.2 Hz), 2.37-2.53 (CH_2, 2H, m), 2.02 (OH, 1H, br, s); The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 98/2, flow rate = 0.6 mL/min), t_R = 23.19 min (*S*), t_R = 25.29 min (*R*).

2.5.13.4 (*R*)-1-(4-Nitrophenyl)-3-buten-1-ol (**2.44d**)



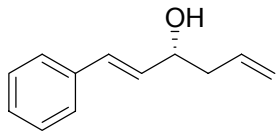
$[\alpha]_D^{25}$ = +58.6 (c 0.5, $CHCl_3$, 91% *ee*), lit.[53]: $[\alpha]_D^{25}$ = +40.1 (c 1.4, $CHCl_3$, 89% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (H_{Ar}, 2H, d, *J* = 8.4 Hz), 7.52 (H_{Ar}, 2H, d, *J* = 8.4 Hz), 5.70-5.84 (C<u>H</u>=CH_2, 1H, m), 5.14-5.20 (CH=C<u>H_2</u>, 2H, m), 4.85 (ArC<u>H</u>, 1H, dd, *J* = 4.8 Hz, 7.6 Hz), 2.38-2.60 (CH_2, 2H, m), 2.22 (OH, 1H, br, s); The enantiomeric excess of the product was determined by ^{19}F NMR of its corresponding *R*-Mosher esters (282 MHz, $CDCl_3$): δ -70.83 (for *RR* diastereomer), -70.96 (for *SR* diastereomer).

2.5.13.5 (*R*)-1-(4-Trifluoromethylphenyl)-3-buten-1-ol (**2.44e**)



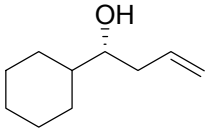
$[\alpha]_D^{25}$ = +53.2 (c 0.82, $CHCl_3$, 93% *ee*), lit.[53]: $[\alpha]_D^{25}$ = +43.1 (c 1.24, $CHCl_3$, 96% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (H_{Ar}, d, *J* = 8.1 Hz), 7.44 (H_{Ar}, 2H, d, *J* = 8.1 Hz), 5.70-5.83 (C<u>H</u>=CH_2, 1H, m), 5.13-5.17 (CH=C<u>H_2</u>, 2H, m), 4.74-4.76 (ArCH, 1H, m), 2.40-2.53 (CH_2, 2H, m), 2.37 (OH, 1H, br, s); The enantiomeric excess of the product was determined by ^{19}F NMR of its corresponding *R*-Mosher esters (282 MHz, $CDCl_3$): δ -70.89 (for *RR* diastereomer), -71.06 (for *SR* diastereomer).

2.5.13.6 (*R*)-1-Phenyl-1,5-hexadien-3-ol (**2.44f**)



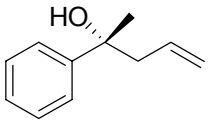
$[\alpha]_D^{25}$ = -6.3 (c 0.8, Et_2O, 75% *ee*), lit.[51]: $[\alpha]_D^{25}$ = -12.3 (c 1.0, Et_2O, 87% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21-7.40 (H_{Ar}, 5H, m), 6.60 (PhC<u>H</u>=CH, 1H, *J* = 16.0 Hz), 6.25 (PhCH=C<u>H</u>,1H, dd, *J* = 6.0 Hz, 16.0 Hz), 5.81-5.87 (C<u>H</u>=CH_2, 1H, m), 5.15-5.21 (CH=C<u>H_2</u>, 2H, m), 4.34-4.38 (PhCH=CH-C<u>H</u>, 1H, m), 2.32-2.49 (CH_2, 2H, m), 1.90 (OH, 1H, br, s); The enantiomeric excess of the product was determined by ^{19}F NMR of its corresponding *R*-Mosher ester (282 MHz, $CDCl_3$): δ -71.04 (for *RR* diastereomer), -71.15 (for *SR* diastereomer).

2.5.13.7 (*R*)-1-Cyclohexyl-3-buten-1-ol (**2.44g**)



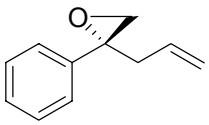
$[\alpha]_D^{25}$ = +1.1 (c 0.53, $CHCl_3$, 75% *ee*), lit.[51]: $[\alpha]_D^{25}$ = +13.7 (c 1.0, Ethanol, 93 %ee); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.74-5.88 (CH_2=C<u>H</u>, 1H, m), 5.08-5.13 (C<u>H_2</u>=CH, 2H, m), 3.33-3.39 (R_2C<u>H</u>OH, 1H, m), 2.06-2.27 (OH and CH_2=CHC<u>H_2</u>, 3H, m), 0.95-1.85 (H_{Cy}, 11H, m),; The enantiomeric excess of the product was determined by HPLC analysis (hexanes/*i*-PrOH = 99.9/0.1, flow rate = 1 mL/min) of its corresponding benzoate ester, t_R = 7.62 min (*R*), t_R = 8.65 min (*S*).

2.5.13.8 (*R*)-2-Phenyl-4-penten-2-ol (**2.46a**)



$[\alpha]_D^{25}$ = +61.7 (c 0.36, $CHCl_3$, 91% *ee*), lit.[54]: $[\alpha]_D$ = +36.3 (c 0.84, $CHCl_3$, 61% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20-2.44 (H_{Ar}, 5H, m), 5.54-5.68 (CH_2=C<u>H</u>, 1H, m), 5.10-5.15 (C<u>H_2</u>=CH, 2H, m), 2.68 (CH_2, 1H, dd, ABX, *J* = 13.7 Hz, 6.9 Hz), 2.49 (CH_2, 1H, dd, ABX, *J* = 8.4 Hz, 13.7 Hz), 1.99 (OH, 1H, br, s), 1.54 (CH_3, 3H, s); The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 99/1, flow rate = 1 mL/min) , t_R = 12.58 min (*R*), t_R = 13.98 min (*S*).

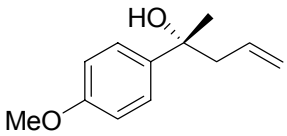
2.5.13.9 (*R*)-1-Phenyl-1-(2-propenyl)-oxirane(**2.47**)[55]



(*R*)-1-Phenyl-1-(2-propenyl)-oxirane was obtained from the allylboration of α-bromoacetophenone after workup with 1 M NaOH. $[\alpha]_D^{25}$ = -29.8 (c 0.84 , $CHCl_3$, 93% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25-7.38 (H_{Ar}, 5H, m), 5.70-5.84 (CH_2=C<u>H</u>, 1H, m), 5.06-5.14 (C<u>H_2</u>=CH, 2H, m), 2.99 (OCH_2, 1H, d, *J* = 5.2 Hz), 2.88 (CH_2=CHC<u>H_2</u>, 1H, dd, ABX, *J* = 6.3 Hz, 15.0 Hz), 2.75 (OCH_2, 1H, d, AB, *J* = 5.2 Hz), 2.64 (CH_2=CHC<u>H_2</u>, 1H, dd, ABX, *J* = 7.8 Hz, 15.0

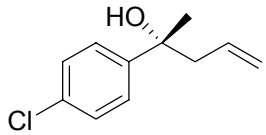
Hz); The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 99.5/0.5, flow rate = 1 mL/min) , t_R = 6.54 min (*R*), t_R = 7.93 min (*S*). This compound has not been previously reported in enantiomerically enriched form; the absolute configuration has been assigned based on correlation with results for acetophenone and the assumption that $-CH_2Br$ (A value = 1.79 kcal mol^{-1})[56] and $-CH_3$ (A value = 1.74) behave similarly in the allylation.

2.5.13.10 (*R*)-2-(4′-Methoxyphenyl)-4-penten-2-ol (**2.46c**).[36]



$[\alpha]_D^{25}$ = +65.2 (c 0.71 , $CHCl_3$, 98% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 (H_{Ar}, 2H, d, *J* = 8.4 Hz), 6.85 (H_{Ar}, 2H, d, *J* = 8.4 Hz), 5.54-5.68 (CH_2=C<u>H</u>, 1H, m), 5.07-5.13 (C<u>H_2</u>=CH, 2H, m), 3.78 (OMe, 3H, s), 2.64 (CH_2=CHC<u>H_2</u>, 1H, dd, ABX, *J* = 6.0 Hz, 13.1 Hz), 2.46 (CH_2=CHC<u>H_2</u>, 1H, dd, ABX, *J* = 8.1 Hz, 13.1 Hz), 2.02 (OH, 1H, br, s), 1.51 (R_3C-C<u>H_3</u>, 3H, s); The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 99.5/0.5, flow rate = 0.6 mL/min) , t_R = 34.0 min (*R*), t_R = 38.0 min (*S*).

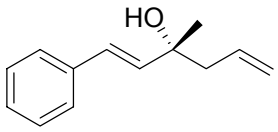
2.5.13.11 (*R*)-2-(4′-Chlorophenyl)-4-penten-2-ol (**2.46d**)[36]



$[\alpha]_D^{25}$ = +63.1 (c 0.58, $CHCl_3$, > 98% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27-7.36 (H_{Ar}, 4H, m), 5.49-5.65 (CH_2=C<u>H</u>, 1H, m), 5.09-5.13 (C<u>H_2</u>=CH, 2H, m), 2.63 (CH_2=CHC<u>H_2</u>, 1H, dd, ABX, *J* = 7.8 Hz, 13.2 Hz), 2.46 (CH_2=CHC<u>H_2</u>, 1H, dd, ABX, *J* = 6.0 Hz, 13.2 Hz), 2.08 (OH, 1H, br, s), 1.50 (CH_3, 3H, s); The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH =

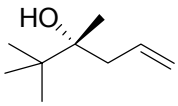
99.5/0.5, flow rate = 0.6 mL/min) , t_R = 33.49 min (*S*), t_R = 35.03 min (*R*). The minor (*S*) isomer was not detected but its retention time was determined using authentic racemate.

2.5.13.12 (*R*)-1-Phenyl-3-hydroxy-3-methyl-1,5-hexandiene (**2.46e**)[36]



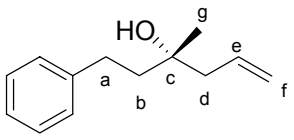
$[\alpha]_D^{25}$ = +65.8 (c 1.1, $CHCl_3$, 75% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21-7.38 (H_{Ar}, 5H, m), 6.59 (ArC<u>H</u>=CH, 1H, d, *J* = 15.9 Hz), 6.29 (ArCH=C<u>H</u>, 1H, d, *J* = 15.9 Hz), 5.69-5.90 (CH_2=C<u>H</u>, 1H, m), 5.12-5.18 (C<u>H_2</u>=CH, 2H, m), 2.31-2.47 (CH_2=CHC<u>H_2</u>, 2H, m), 1.78 (OH, 1H, br, s), 1.38 (CH_3, 3H, s); The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 95/5, flow rate = 1.0 mL/min) , t_R = 11.58 min (*R*), t_R = 13.78 min (*S*).

2.5.13.13 (*R*)-2,2,3-Trimethyl- 5-hexen-3-ol (**2.46f**)[57]



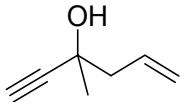
^{1}H NMR (300 MHz, C_6D_6): δ 5.87-6.00 (CH_2=C<u>H</u>, 1H, m), 5.02-5.13 (C<u>H_2</u>=CH, 2H, m), 2.32 (CH_2, 1H, dd, ABX, *J* = 6.9 Hz, 13.5Hz), 2.06 (CH_2, 1H, dd, ABX, *J* = 7.8 Hz, 13.5 Hz), 1.19 (OH, 1H, br, s), 1.03 (Me, 3H, s), 0.97 (CMe_3, 9H, s); The enantiomeric excess of the product was determined by ^{1}H NMR (300 MHz, $CDCl_3$) in the presence of chiral shift reagent, Eu(hfc)$_3$. The optical rotation was not taken due to the volatility of the sample

2.5.13.14 (*R*)-3-Methyl-1-phenyl-5-hexen-3-ol (**2.46g**)



$[\alpha]_D^{25}$ = +6.0 (c 1.1, $CHCl_3$, 51% *ee*), literature value for the *S* enantiomer[58]: $[\alpha]_D^{25}$ = -58.0 (c 1.0, $CHCl_3$, 92% *ee*); ^{1}H NMR (300 MHz, C_6D_6): δ 7.16-7.23 (H_{Ar}, 5H, m), 5.75-5.90 (H_e, 1H, m), 5.02-5.10 (H_f, 2H, m), 2.66-2.70 (H_a, 2H, m), 2.12-2.14 (H_d, 2H, m), 1.64-1.70 (H_b, 2H, m), 1.07 (H_g, 3H, s), 0.97 (OH, 1H, br, s); The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 95/5, flow rate = 0.6 mL/min) , t_R = 16.18 min (*S*), t_R = 17.35 min (*R*).

2.5.13.15 3-Methylhex-5-en-1-yn-3-ol (**2.46h**)[32]



^{1}H NMR (300 MHz, $CDCl_3$): δ 5.87-6.02 (CH_2=C<u>H</u>, 1H, m), 5.15-5.23 (C<u>H_2</u>=CH, 2H, m), 2.48 (CH_2, 1H, dd, ABX, *J* = 6.6 Hz, 13.5 Hz), 2.36 (CH_2, 1H, dd, ABX, *J* = 8.1 Hz, 13.5 Hz), 2.10 (OH, 1H, s, br), 1.49 (CH_3, 3H, s); The enantiomeric excess of the product was determined by ^{1}H NMR (300 MHz, $CDCl_3$) in the presence of chiral shift reagent, $Eu(hfc)_3$ and the absolute configuration of this compound was not determined. The optical rotation was not taken due to the volatility of the sample.

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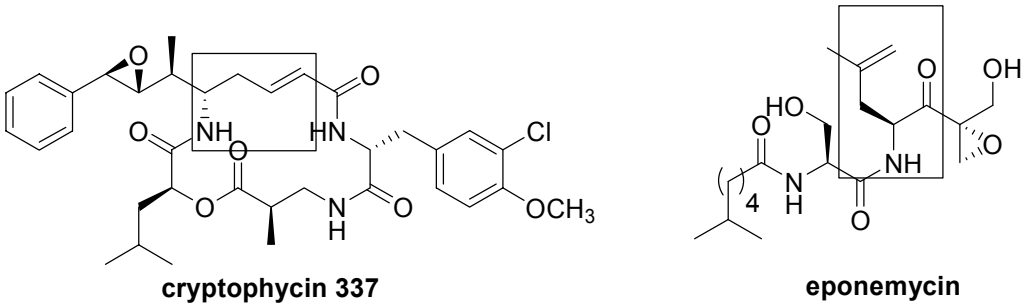
Chapter 3. Asymmetric Allylboration of Cyclic Imines and Applications to Alkaloid Syntheses

3.1 Introduction: Enantioselective Allylation of Imino Compounds

Since Hoffmann reported the first enantioselective allylboration of aldehydes almost thirty years ago,[1] a large number of chiral allylmetallic reagents have been developed for the enantioselective allylation of carbonyl compounds.[2,3] However, an analogous reaction to the allylation of carbonyls, namely the enantioselective allylation of imino compounds (compounds that contain C=N double bonds), has received much less attention. This may be partially due to the lower reactivity of C=N double bonds. Nevertheless, such a reaction is of great synthetic value because the products are optically active homoallylic amines, compounds which are versatile intermediates in total syntheses and are key structural features in many bioactive natural products such as cryptophycin 337 and eponemycin (Figure 3.1).[4]



cryptophycin 337 **eponemycin**

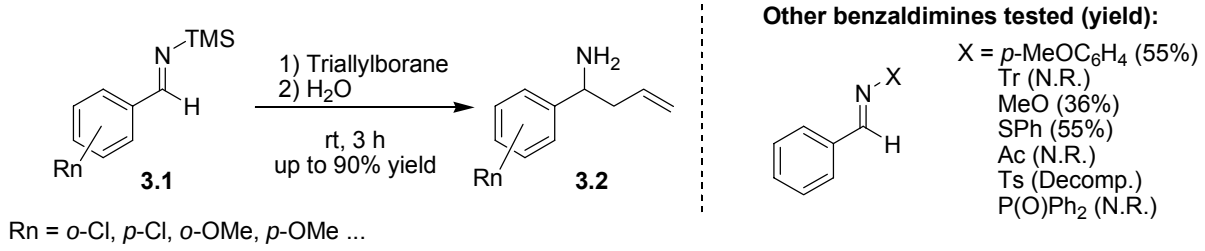
Figure 3.1 Natural products containing homoallylic amine moieties.

Owing to increasing demands for chiral nitrogen-containing compounds from the pharmaceutical industry, the number of methods for the enantioselective allylation of imino compounds has been increasing dramatically in the last few years. Various chiral allylmetallic agents

such as B-, In-, Pd-, Si-, Sn- and Zn-based reagents have been successfully adopted in this type of transformation. Some examples regarding these enantioselective additions of chiral allylmetallics to imino compounds are discussed in the following section.

3.1.1 Boron-based Allylation of Imino Compounds

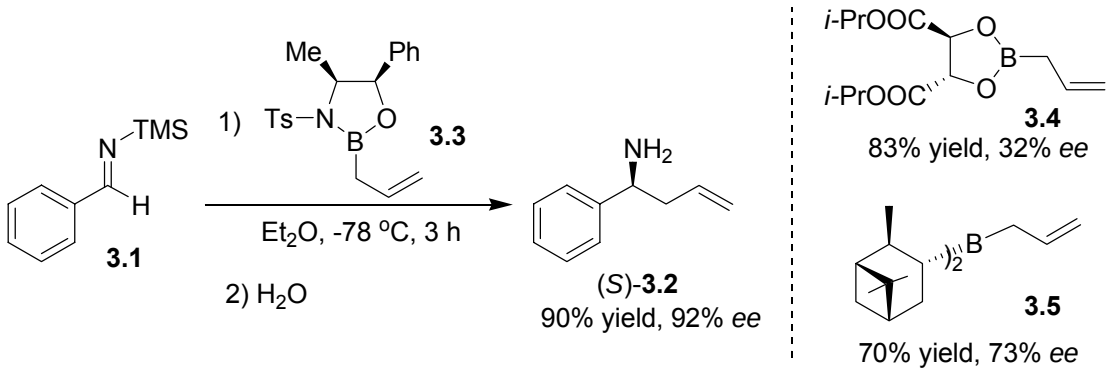
Chiral allylboron reagents have been one of the most popular reagents for the asymmetric allylation of carbonyl compounds in the past two decades. However, these reagents are in general not very reactive toward imino compounds. In 1995, after surveying the reactivities of various imines toward triallylborane, Itsuno found that *N*-trimethylsilylimine **3.1** was relatively reactive toward triallylborane, and gave homoallylamine **3.2** in high yield (Scheme 3.1). [5-7]



Rn = *o*-Cl, *p*-Cl, *o*-OMe, *p*-OMe ...

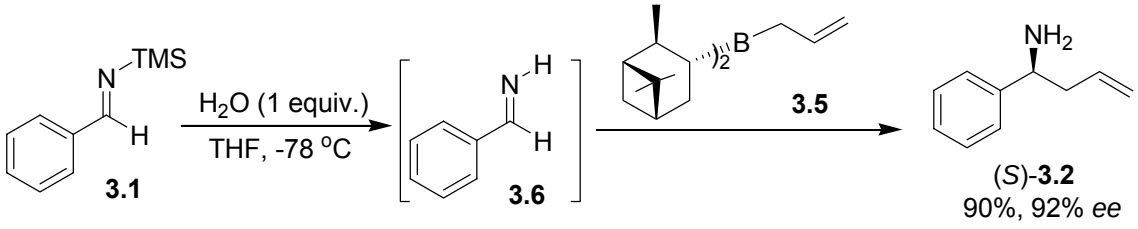
Scheme 3.1

Imine **3.1** was then subjected to the asymmetric allylation with chiral allylboranes. It was found that allyl oxazaborolidine **3.3** gave the highest enantioselectivity (92% *ee*) among a variety of chirally modified reagents including Roush's and Brown's reagents which produced only 32% and 73% *ee*, respectively (Scheme 3.2).



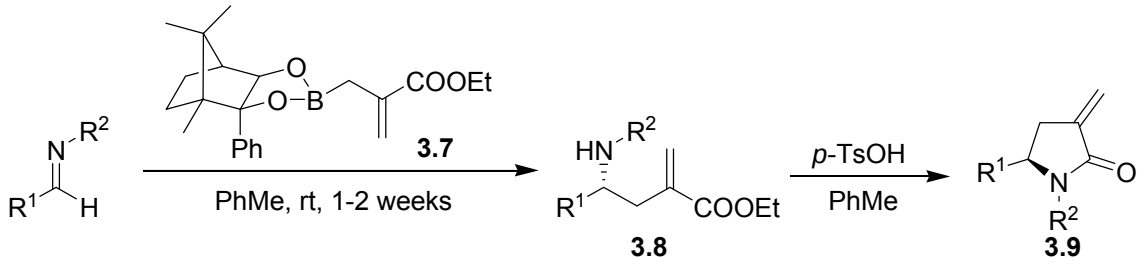
Scheme 3.2

However, a low-temperature ^{11}B NMR study conducted by Brown and coworkers revealed that Brown's chiral borane **3.5** did not react with *N*-TMS imine **3.1** even at room temperature, which is inconsistent with the results obtained by Itsuno (70% yield and 73% *ee*). Instead, they found that a fast allylboration took place during the aqueous work-up to produce homoallylic amine (*S*)-**3.2**. Consequently, they repeated the reaction with dropwise addition of a molar equivalent of water in THF to the solution of imine **3.1** and chiral borane **3.5** at -78 °C. A highly reactive aldimine intermediate **3.6** was released which reacted immediately with borane **3.5** to give the product amine **3.2** in 92% *ee* and 90% yield, which is considerably better than the 73% *ee* and 70% yield realized by Itsuno (Scheme 3.3).[8]



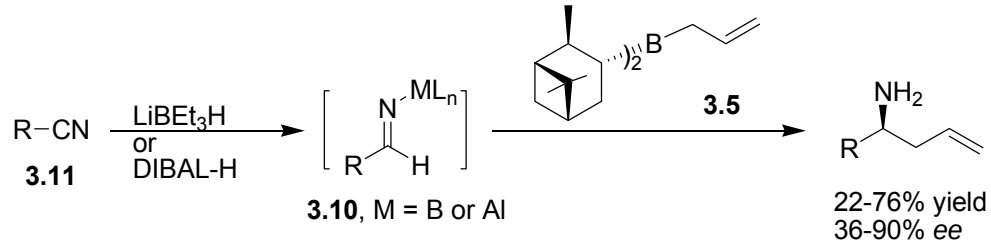
Scheme 3.3

Villiéras and coworkers discovered that chiral *β*-functionalized allylboronate **3.7** could also allylate *N*-silyl and *N*-alkylimines in excellent chemical and optical yields.[9] The resultant chiral amines **3.8** could be converted to *α*-methylene-*γ*-lactams **3.9** readily. However, these allylation reactions need to be carried out at room temperature for 1-2 weeks which is not very practical (Scheme 3.4).



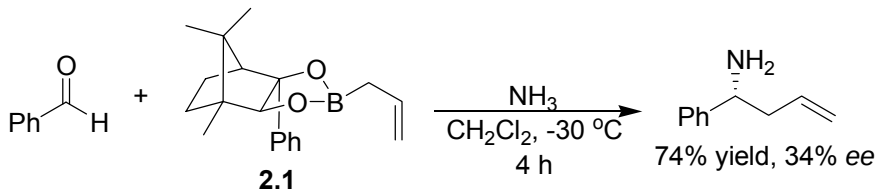
Scheme 3.4

In addition, Itsuno also reported the asymmetric allylboration of *N*-metalloimines **3.10** prepared *in situ* from the corresponding cyano compounds **3.11**. [10,11] However, enantioselectivities and yields obtained were mostly not encouraging (Scheme 3.5).



Scheme 3.5

Recently, Kobayashi developed the first three-component synthesis of homoallylic amines using aldehydes, ammonia and Hoffmann's reagent **2.1**, although the enantioselectivity produced is poor.[12]

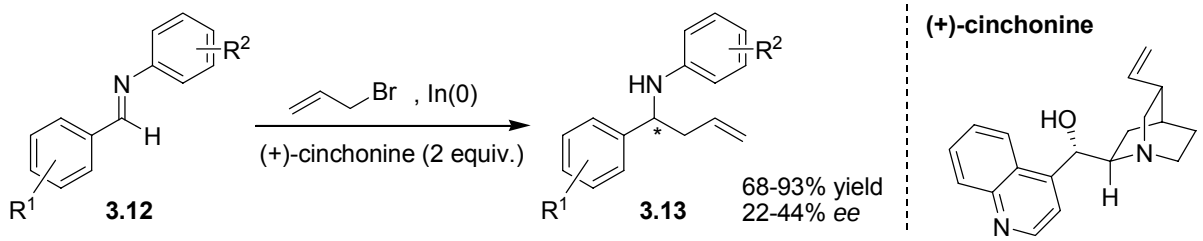


Scheme 3.6

3.1.2 Indium-based Allylation of Imino Compounds

Over the past decade, allylindium complexes have become popular as mild reagents for the allylation of carbonyl compounds.[13-17] However, the application of chiral ligands to indium-mediated allylation of C=N double bonds has been a challenge due to the low heterophilicity of organoindium reagents and the low reactivity of imino compounds. Nevertheless, several examples of the enantioselective allylation of imino compounds utilizing allylindium and chiral inducers have been reported recently.

Cinchona alkaloids, which induce good enantioselectivities in the indium-mediated allylation to aldehydes, were applied to the analogous allylation of imines **3.12**. Although the yields of these reactions were excellent, enantioselectivities obtained were poor (Scheme 3.7).[18]

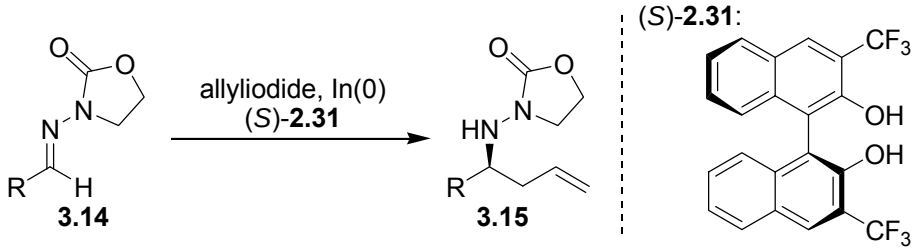


Scheme 3.7

Very recently, another enantioselective allylation of C=N double bonds was reported by Cook and coworkers.[19] (*R*)-3,3′-Bis(trifluoromethyl)-binaphthol **2.31**, which was introduced by our group, was used as chiral additive to induce high enantioselectivity in the allylation of hydrazones **3.14**.

When stoichiometric amounts of chiral ligand **2.31** were applied, excellent enantioselectivities were obtained with aromatic, alkenyl and aliphatic substrates (84-97% *ee*). A catalytic amount (10 mol%) of ligand could be used but gave reduced enantioselectivities. Selected results are listed in Table 3.1.

Table 3.1 Indium-mediated allylation of hydrazones catalyzed by (*S*)-BINOL **2.31**.



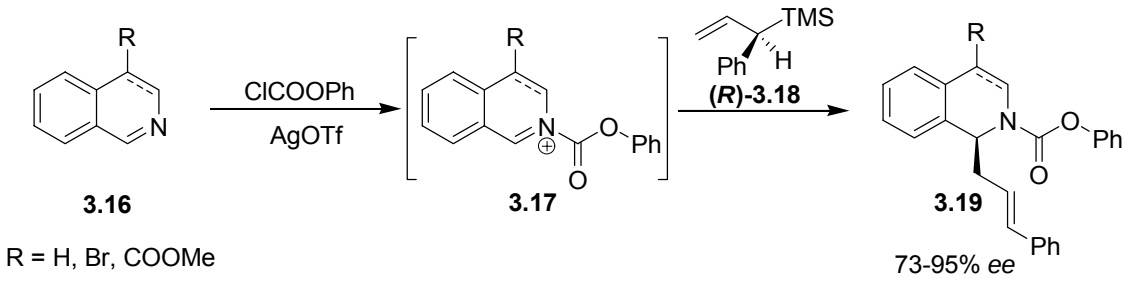
entry	R	100 mol% 2.31		10 mol% 2.31	
		yield (%)	*ee* (%)	yield (%)	*ee* (%)
1	Ph	72	84	77	70
2	4-MeO-C_6H_4	68	92	74	77
3	4-Cl-C_6H_4	61	93	78	82
4	2-Cl-C_6H_4	50	97	67	91
5	PhCH=CH	76	90	79	34
6	$PhCH_2CH_2$	61	92	73	34

3.1.3 Si/Sn-based Allylation of Imino Compounds

Allylsilanes and allylstannanes, which have been widely used in the catalytic asymmetric allylation of carbonyl compounds, can be applied to the asymmetric allylation of imino compounds as well.[3] In general, allylsilane/stannane-induced asymmetric allylations are divided into four types: (1) chiral allylsilane/stannane-induced allylation; (2) chiral Lewis acid-activated allylation; (3) chiral Lewis base-activated allylation and (4) palladium catalyzed allylation.

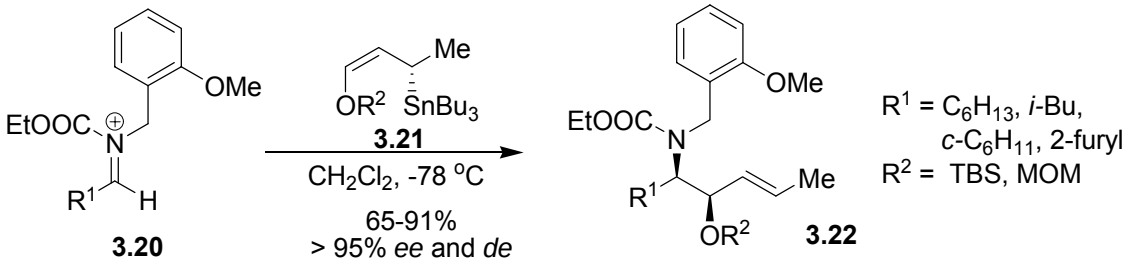
3.1.3.1 Chiral Allylsilane/stannane-induced Allylations

In 1999, Yamaguchi and coworkers reported the first chiral allylsilane-induced enantioselective allylation of *N*-acyliminium ions **3.17** (Scheme 3.8). [20] Activated cyclic *N*-acyliminium ions **3.17** could be allylated by an α-chiral allylsilane (**3.18**) to produce chiral cyclic homoallylic amides in good to excellent *ee*'s.



Scheme 3.8

A similar transformation using chiral allylstannanes was reported by Marshall in 2000, in which *N*-acyliminium ions **3.20** were treated with chiral γ-alkoxy allylstannanes **3.21** to form chiral homoallylic amines **3.22**. Excellent yields and stereoselectivities were observed (Scheme 3.9).[21]

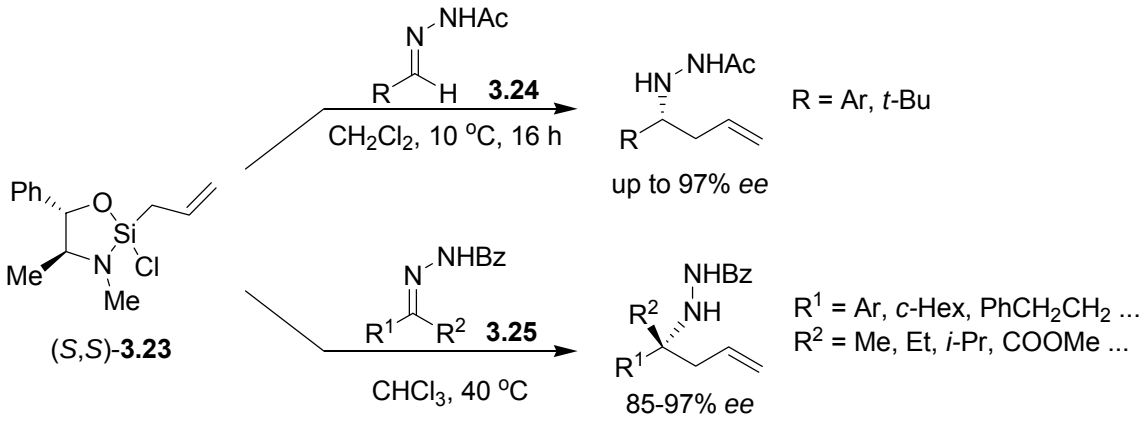


Scheme 3.9

In these cases, since α-chirality on the allylsilane or allylstannane is required for the asymmetric induction, transferring an unsubstituted allyl group is impossible.

A general chiral allylsilane-induced allylation of imino compounds was realized by Leighton and coworkers.[22,23] They found that allylsilane **3.23** bearing a chiral bidentate ligand is a suitable

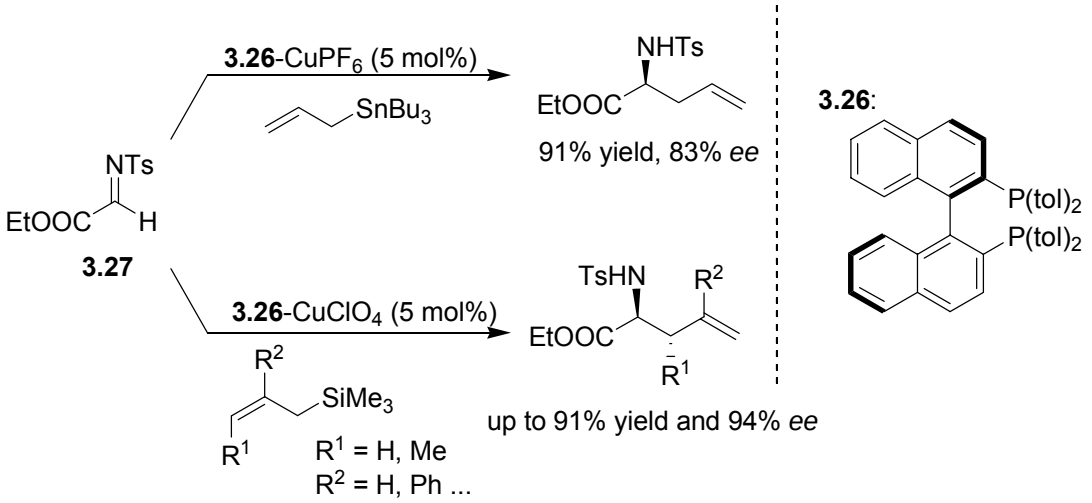
reagent for the asymmetric allylation of aldehyde-derived hydrazones **3.24**. The same chiral allylsilane was also applied to the allylation of ketone-derived hydrazones to produce chiral tertiary carbinamines in excellent enantioselectivities (Scheme 3.10).



Scheme 3.10

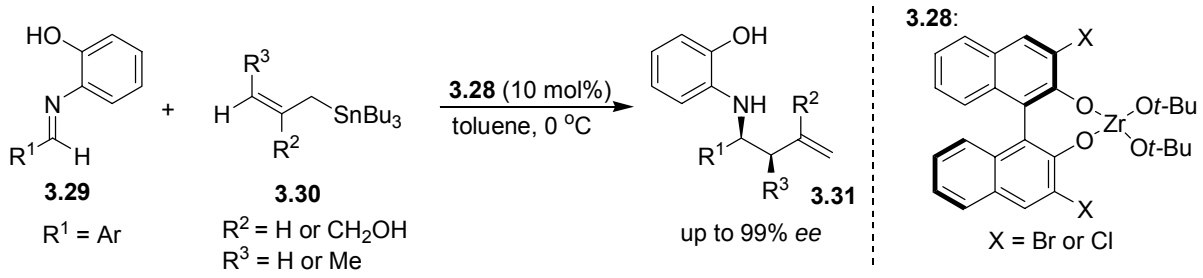
3.1.3.2 Chiral Lewis Acid-activated Allylations

Under the catalysis of chiral Lewis acids, allylsilanes and allylstannanes can transfer an allyl group to imino electrophiles in an enantioselective manner. Several chiral-modified metal catalysts were found to be effective for this type of transformation. For instance, a copper salt ($CuPF_6$) modified with chiral phosphine ligand **3.26** could induce the allylation of *N*-tosyl iminoester **3.27** in moderate enantioselectivity. Allylsilanes could be used in the same reaction but exhibited much lower yields.[24] However, in the presence of another copper salt ($CuClO_4$), allylsilanes allylate imine **3.27** readily to produce chiral homoallylic amines in high yields and enantioselectivities (Scheme 3.11).[25]



Scheme 3.11

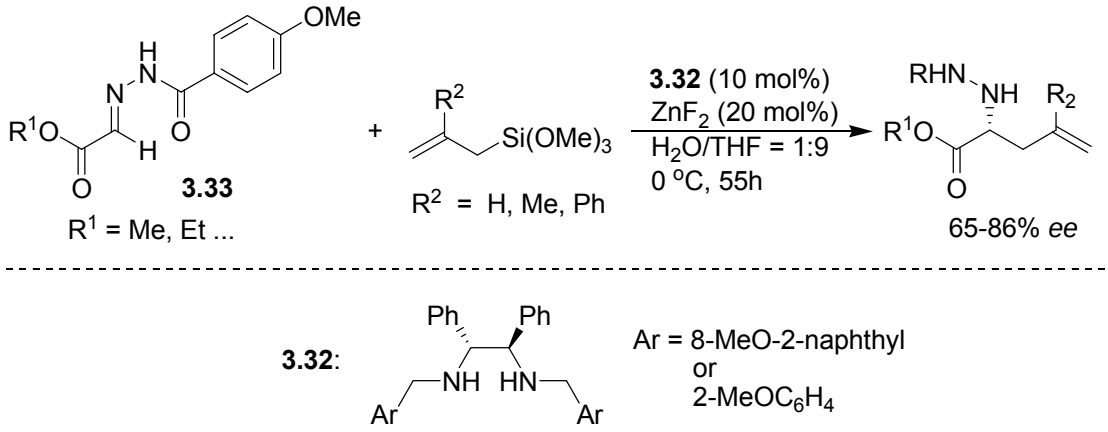
Chiral zirconium reagents also proved efficient in catalyzing the addition of allylstannanes to imines. Kobayashi has developed a very effective procedure to synthesize substituted homoallylic amines **3.31** from imines **3.29** catalyzed by chiral BINOL-modified zirconium reagents **3.28**. High yields and high levels of diastereo- and enantioselectivity were obtained for a variety of substrates (Scheme 3.12).[26]



Scheme 3.12

Chiral Lewis acid-catalyzed reactions are sometimes very sensitive to moisture. For example, in a copper(I) catalyzed asymmetric allylation of *N*-tosylimino ester **3.27**, high enantioselectivities could be obtained only if molecular sieves are present.[27] Nevertheless, a water tolerant asymmetric

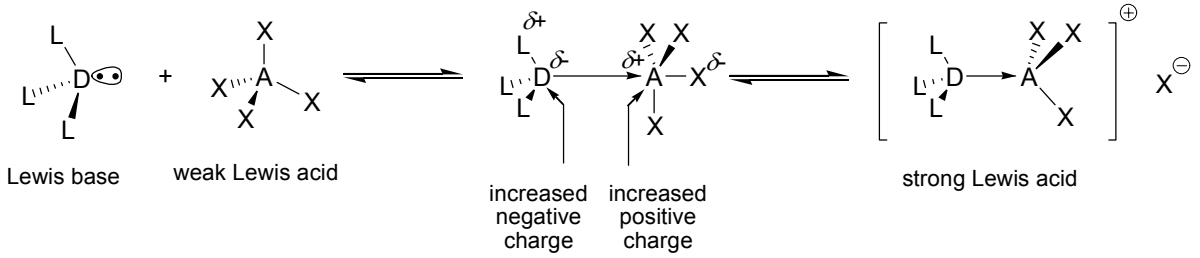
allylation of hydrazones was reported by Kobayashi and coworkers. In the presence of a chiral 1,2-diamine **3.32** and ZnF_2, allyltrimethoxysilanes add to hydrazones **3.33** to give the desired chiral amine products in moderate to good enantioselectivities (Scheme 3.12).[28]



Scheme 3.12

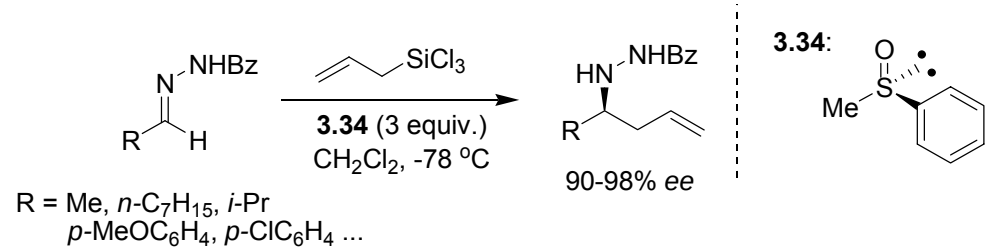
3.1.3.3 Chiral Lewis Base-activated Allylations

Recently, Denmark disclosed that electron-pair donors (Lewis bases) have a counter-intuitive ability of enhancing the electrophilic character of the electron-pair acceptors (Lewis acids, Scheme 3.13). This novel concept was soon applied to asymmetric syntheses such as Lewis base catalyzed enantioselective aldol reactions with trichlorosilyl enolates[29] and allylation of aldehydes using allyl trichlorosilane.[3]



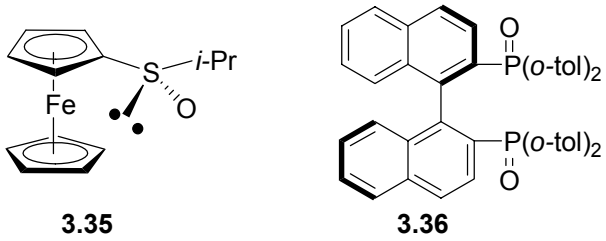
Scheme 3.13

The first Lewis base-activated allylsilane addition to imino compounds was realized by Kobayashi and coworkers.[30] Chiral methyl tolyl sulfoxide **3.34** offered good stereocontrol in the addition of allyltrichlorosilane to various benzoylhydrazones, including those derived from aliphatic aldehydes (Scheme 3.14). Asymmetric crotylations with (*Z*)- and (*E*)-crotyltrichlorosilanes also exhibited excellent enantioselectivities as well as excellent diastereoselectivities[31]



Scheme 3.14

Similar additions activated by other chiral bases such as a ferrocene-based chiral sulfoxide **3.35** and BINAP dioxide (**3.36**) have also been reported very recently (Figure 3.2).[32,33]



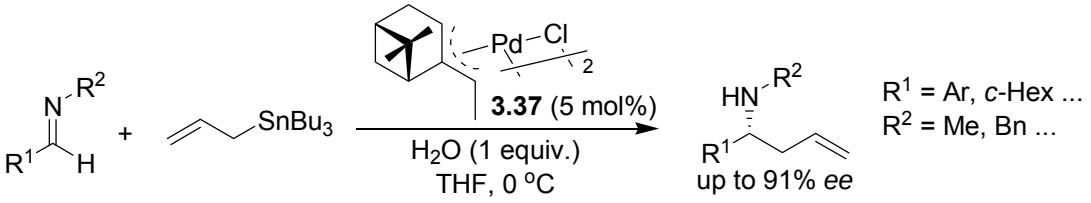
3.35 **3.36**

Figure 3.2 Chiral catalysts for allyltrichlorosilane additions to hydrazones.

3.1.3.4 Palladium Catalyzed Allylations

Yamamoto and co-workers developed chiral bis-π-allylpalladium complexes as catalysts for the asymmetric allylation of imines.[34-37] A π-allyl complex **3.37** derived from β-(-)-pinene proved to be an effective catalyst for the palladium catalyzed asymmetric allyltributylstannane addition to imines. For the allylation of a wide range of substrates, up to 91% *ee* was obtained in the presence of a

stoichiometric amount of water. The role of water is crucial in this reaction as lower enantioselectivities were obtained in the absence of water (Scheme 3.15).[35]



Scheme 3.15

The asymmetric induction is believed to proceed through a transmetalation between the palladium catalyst **3.37** and the allylstannane followed by a nucleophilic addition of the resulting allylpalladium species to imines. A six-membered chair-like transition state model for the addition of the allylpalladium intermediate to imines was proposed to explain the sense of enantioselectivity (Figure 3.3). [35]

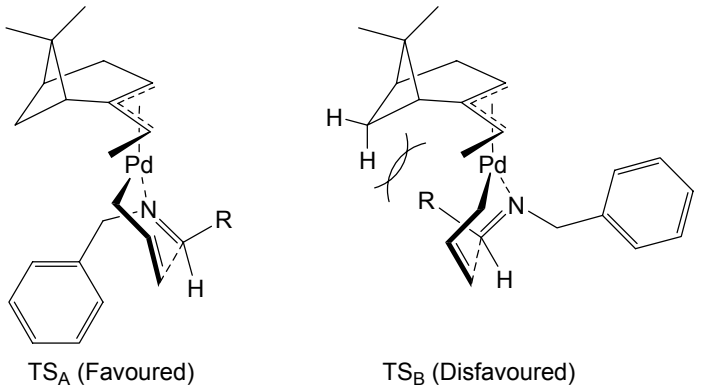
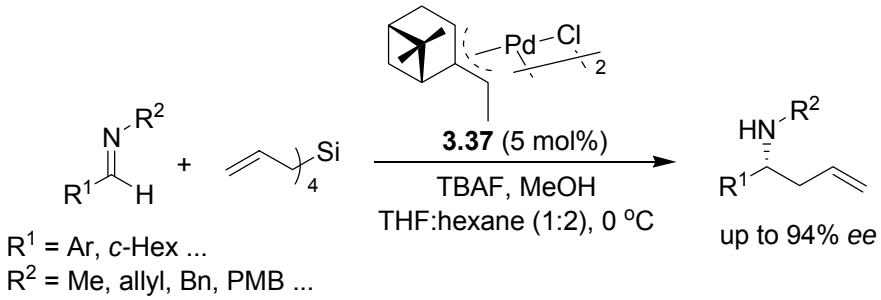


Figure 3.3 Transition state model for palladium catalyzed allylation of imines.

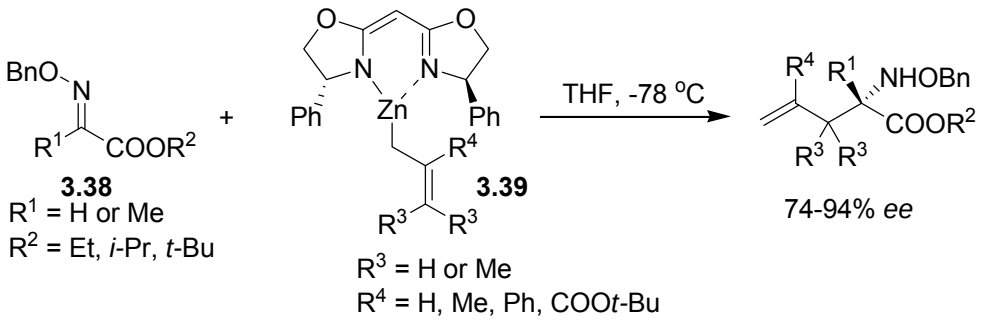
The same palladium catalyst **3.37** could also induce an asymmetric addition of tetraallylsilane to imines in up to 94% *ee* (Scheme 3.16). [37]



Scheme 3.16

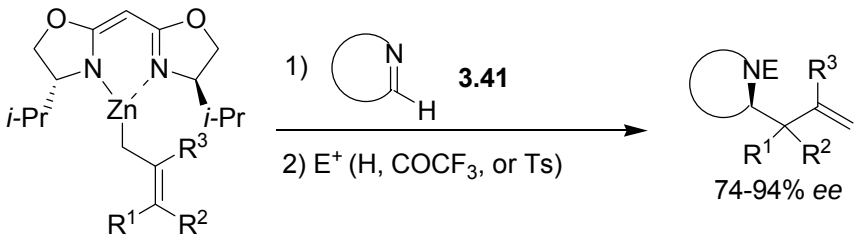
3.1.4 Zn-based Allylations

In 1996, Hanessian developed an effective method for the enantioselective allylation of ketoester oximes **3.38** with phenyl substituted chiral bis(oxazoline)allylzinc reagents **3.39**. This method provides an expedient access to enantiomerically enriched derivatives of allylglycine (Scheme 3.17).[38]



Scheme 3.17

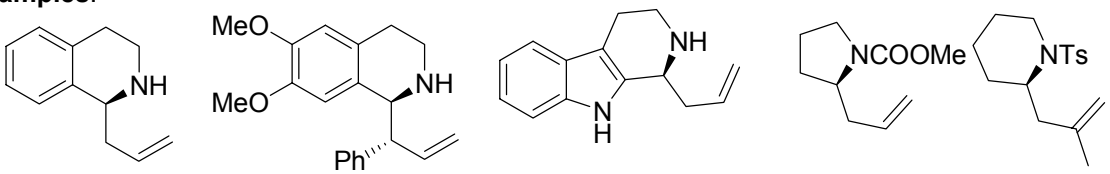
Almost at the same time, Nakamura reported an allylation of cyclic imines using a similar chiral allylzinc reagent **3.40**. Various chiral cyclic homoallylic amines were synthesized in excellent *ee*'s using this method (Scheme 3.18).[39] This also represents the only general method for the enantioselective allylation of cyclic imines to date.



3.40a: $R^1 = R^2 = R^3 = H$; **3.40b**: $R^1 = R^2 = H$, $R^3 = Me$

3.40c: $R^1 = R^2 = H$, $R^3 = SiMe_2Ph$; **3.40d**: $R^1 = Ph$, $R^2 = R^3 = H$

Examples:



72% yield, 95% *ee*

91% yield, 77% *ee*

54% yield, 90% *ee*

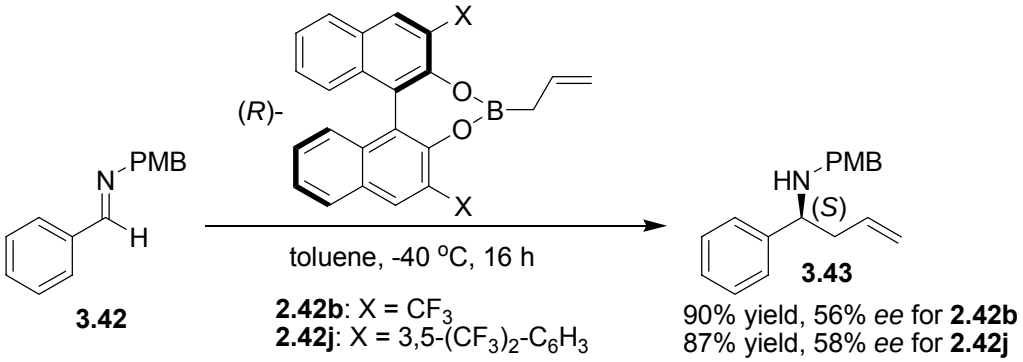
54% yield, 88% *ee*

42% yield, 99% *ee*

Scheme 3.18

3.2 Proposal

In the previous chapter, we have shown that substituted binaphthol-modified allylboronate **2.42b** is an excellent reagent for the allylation of carbonyl compounds in terms of both chemical and optical yields (up to 98% yield and >99% *ee*). Since it was also found that **2.42b** is one of the most reactive chiral allylboron reagents toward carbonyls (complete reaction in less than 5 minutes at -78 ^{o}C for aldehydes), we then turned our interest to the more challenging allylboration of imines, an area in which limited success has been achieved. Thus, chiral allylboronates (*R*)-**2.42b** and (*R*)-**2.42j** were treated with benzaldimine **3.42** at low temperature. To our delight, the reactions proceeded smoothly in both cases to afford the desired homoallylic amine in excellent yields with *S* configuration. However, the enantiomeric excesses obtained were only moderate (Scheme 3.19).



Scheme 3.19

To rationalize this observation, the six-membered transition state model for this imine allylation was evaluated. As is illustrated in Figure 3.4, the phenyl ring of the imine adopts an axial position in each of the two possible transition states. In transition state A, a clear repulsion between the 3-substituent on BINOL ring and the bulky phenyl group of imine **3.42** is present. In transition state B,

the interaction between the 3-substituent on BINOL and the methylene protons α to the imine nitrogen is the major destabilizing factor. Therefore, both transition states are severely destabilized and transition state A appears to be slightly less favoured based on the results obtained from the allylation reactions.

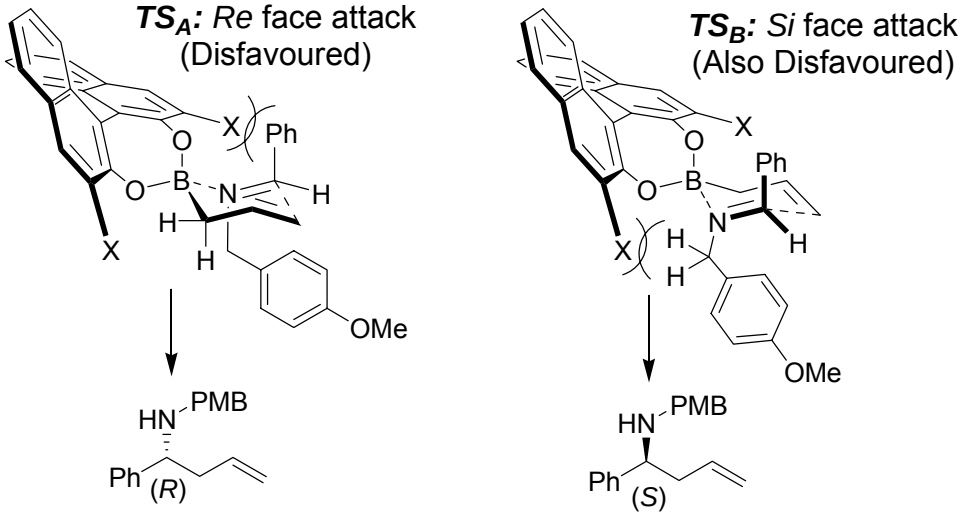


Figure 3.4 Transition state model for the allylboration of acyclic imine **3.42**.

Based on the model above, it was thought that improved enantioselectivity could be obtained if either of the two destabilizing interactions could be removed. For instance, if Ph groups in both transition states are moved to the equatorial position, the repulsion between the 3-substituent on BINOL ring and the Ph group in transition state A would be diminished while transition state B would not be affected. Consequently, this may result in good enantioselectivities. In other words, the allylboration of cyclic (*Z*) imines would be expected to give better results than acyclic (*E*) imines since the bigger substituent on the cyclic imine would be "locked" in an equatorial position in the six-membered transition state (Figure 3.5).

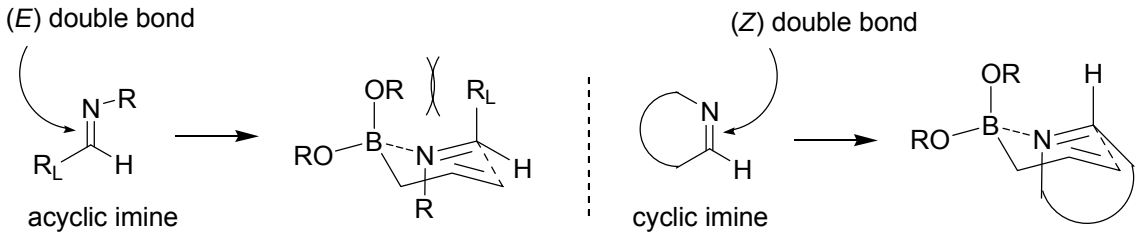


Figure 3.5 Comparison of the allylation of acyclic imine and cyclic imine.

The asymmetric allylation of cyclic imines is potentially of great value because the products, chiral cyclic homoallylic amines, are found in a number of natural products such as angustifoline and are versatile intermediates for total syntheses of various bioactive compounds (Figure 3.6).[4,40-43]

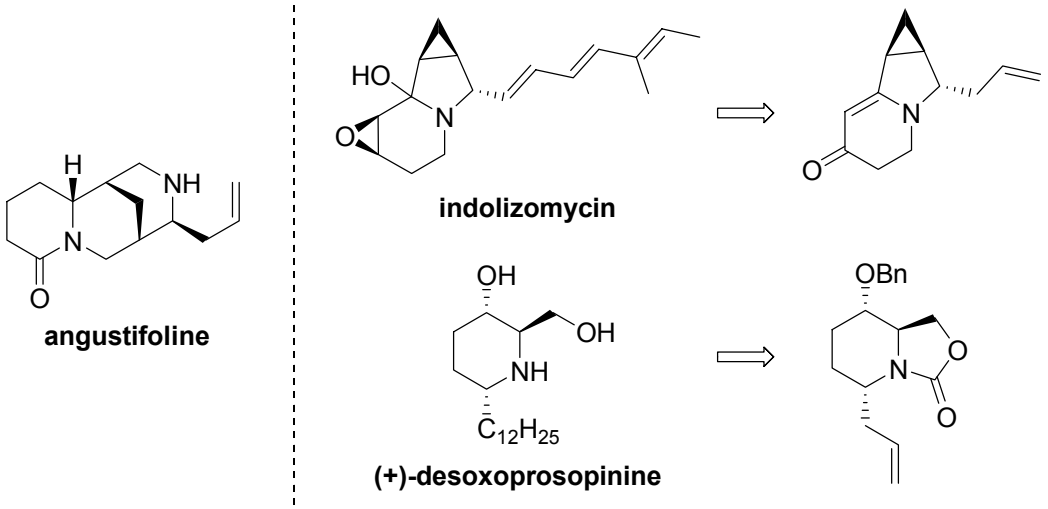


Figure 3.6 Chiral cyclic homoallylic amines in the total synthesis of natural products.

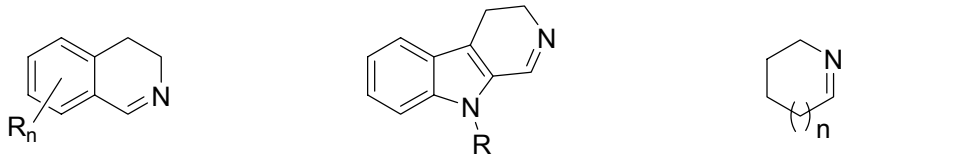
As previously mentioned, the enantioselective allylation of acyclic imino compounds has become one of the most important methods for the preparation of homoallylic amines, and many efficient methodologies have been developed in the past few years. However, the analogous enantioselective allylation of cyclic imines is very rare. To the best of our knowledge, there have been only a few successful enantioselective allylation of cyclic imines using chiral allylzinc[39] or allylsilane reagents[20] (Scheme 3.8 and Scheme 3.18) and there has been no analogous asymmetric allylboration

process known for cyclic imines. In the following section, the asymmetric allylboration of cyclic imines using substituted binaphthol-modified allylboronates is discussed.

3.3 Results and Discussions

3.3.1 Preparation of Substrates

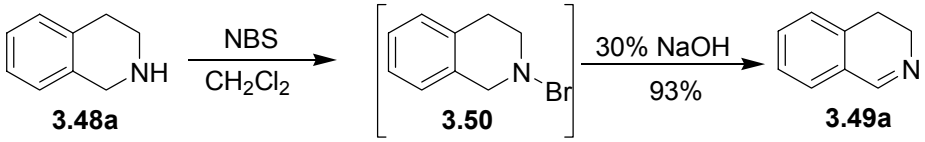
Three types of cyclic imines are of particular interest to us since their allylation products are potential precursors to numerous naturally occurring alkaloids (Figure 3.7).



3,4-dihydroisoquinoline **3,4-dihydro-β-carboline** **n = 0, 1-pyrroline**
n = 1, Δ^1-piperideine

Figure 3.7 Structures of typical cyclic imines.

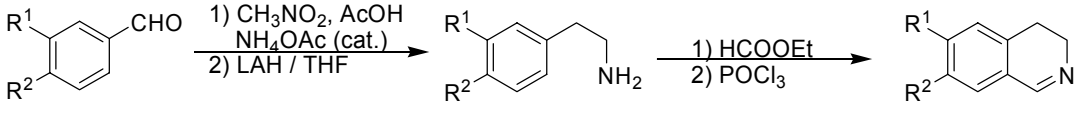
Unsubstituted 3,4-dihydroisoquinoline (**3.49a**) was synthesized from commercially available 1,2,3,4-tetrahydroisoquinoline (**3.48a**) following Pelletier's procedure (Scheme 3.20).[44]



3.48a **3.50** **3.49a**

Scheme 3.20

3,4-Dihydroisoquinolines bearing electron-donating groups (**3.49b** and **3.49c**) were synthesized *via* a Bischler-Napieralski reaction (Scheme 3.21).[45]



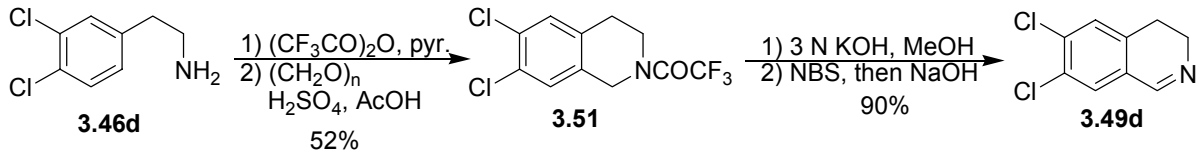
3.44b: $R^1 = R^2 = OMe$
3.44c: $R^1, R^2 = -OCH_2O-$
3.44d: $R^1 = R^2 = Cl$

3.46b: $R^1 = R^2 = OMe$
3.46c: $R^1, R^2 = -OCH_2O-$
3.46d: $R^1 = R^2 = Cl$

3.49b: $R^1 = R^2 = OMe$
3.49c: $R^1, R^2 = -OCH_2O-$

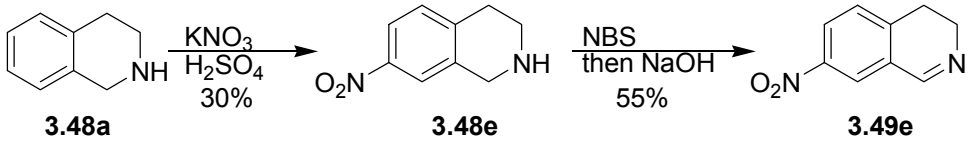
Scheme 3.21

For 3,4-dihydroisoquinolines bearing electron-withdrawing groups, Bischler-Napieralski reactions could not produce the desired cyclic imine products. Other synthetic strategies were applied. For instance, 3,4-dichlorophenethylamine **3.46d** was successfully converted to a cyclic trifluoroacetamide **3.51** using a modified Pictet-Spengler procedure[46] developed by Stokker. Removal of the trifluoroacetyl group followed by oxidation using NBS gave the desired cyclic imine **3.49d** in excellent yield (Scheme 3.22).



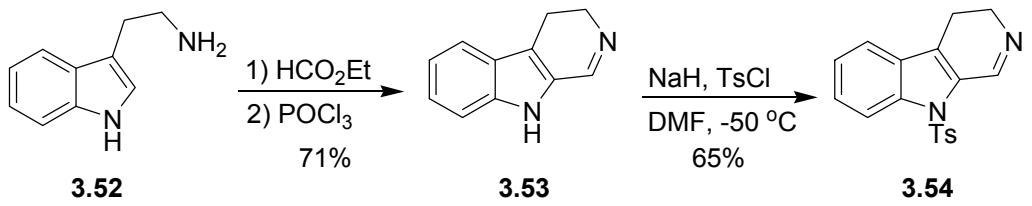
Scheme 3.22

Nitration of 1,2,3,4-tetrahydroisoquinoline (**3.48a)** using Grunewald's method gave 7-nitro-1,2,3,4-tetrahydroisoquinoline (**3.48e**) along with regioisomers.[47,48] Amine **3.48e** was then purified by the recrystallization of its HCl salt. Finally, the oxidation of **3.48e** using NBS afforded the nitrated cyclic imine **3.49e** (Scheme 3.23).



Scheme 3.23

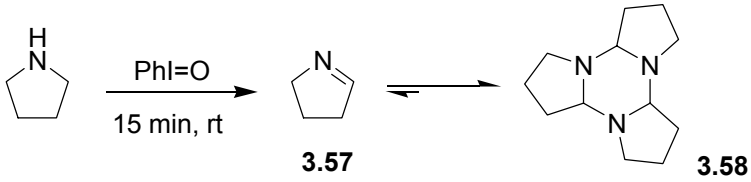
3,4-Dihydro-*β*-carboline (**3.53**) was prepared in a similar manner to the preparation of **3.49b** and **3.49c**.[49] The acidic indolic amine could be further protected using TsCl/NaH to give imine **3.54**.[50] The electron-withdrawing nature of the tosyl group also helps to stabilize the oxygen-sensitive indolic functionality (Scheme 3.24).



3.52 **3.53** **3.54**

Scheme 3.24

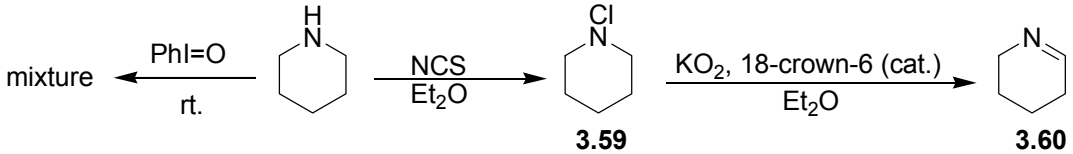
An unsubstituted cyclic imine, namely 1-pyrroline (**3.57**) was synthesized by the oxidation of pyrrolidine with iodosobenzene.[51] It has been reported that simple cyclic imines such as **3.57** undergo trimerization at room temperature. Indeed, we found imine **3.57** readily trimerized in CH_2Cl_2, which was indicated by the gradual disappearance of signals of imine **3.57** in ^{1}H NMR. Therefore, imine **3.57** has to be freshly prepared prior to use (Scheme 3.25).



3.57 **3.58**

Scheme 3.25

The same method was attempted to prepare the six-membered cyclic imine Δ^1-piperideine (**3.60**). However, complicated mixtures were obtained under various conditions. The desired product **3.60** was finally obtained using Scully's method. [52] It was observed that imine **3.60** also trimerized but at a slower rate than imine **3.57** (Scheme 3.26).

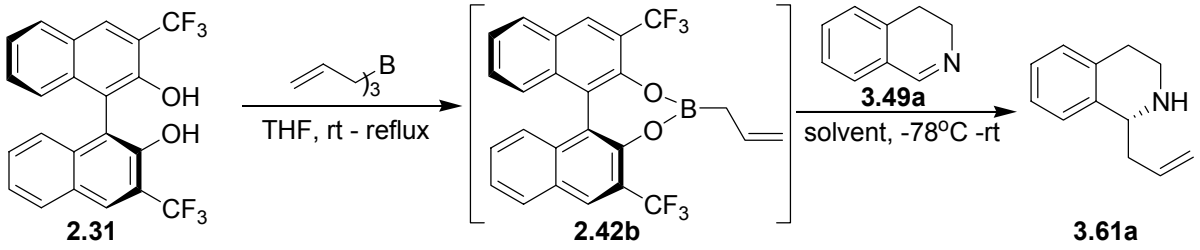


3.59 **3.60**

Scheme 3.26

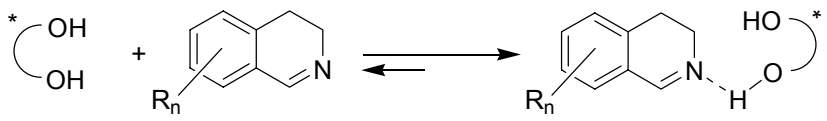
3.3.2 Allylboration of 3,4-Dihydroisoquinoline (3.49a): Condition Optimizations

With a variety of cyclic imine substrates in hand, we were able to take a look at the asymmetric allylboration itself. Thus chiral allylboronate (*S*)-**2.42b** was prepared by heating a mixture of one equivalent of (*S*)-BINOL **2.31** and one equivalent of triallylborane in THF. Volatiles were removed under high vacuum, and the crude boronate (*S*)-**2.42b** was dissolved in toluene (a small amount of THF was added to help dissolving the allylboronate) followed by the treatment of 0.66 equivalents of imine **3.49a** at low temperature (-78 ^{o}C - rt). The desired product **3.61a** with an *R* absolute configuration (based on the optical rotation[39]) was obtained in excellent yield and enantioselectivity (84% *ee*) (Scheme 3.27).



Scheme 3.27

It was also observed that an excess of ligand **2.31** caused (such as 1.2 equivalents, the amount typically used in the allylboration of aldehydes) incomplete reaction and diminished enantioselectivity as well. The problem became even worse when **3.49a** was replaced by an electron-rich imine **3.49b**. This is probably due to the coordination between the basic imine nitrogen and the proton on the free diol which prevents the allylboronate from coordinating with the imine and therefore leads to incomplete reaction (Scheme 3.28).



3.49a: R_n = H
or **3.49b**: R_n = 6,7-$(CH_3O)_2$

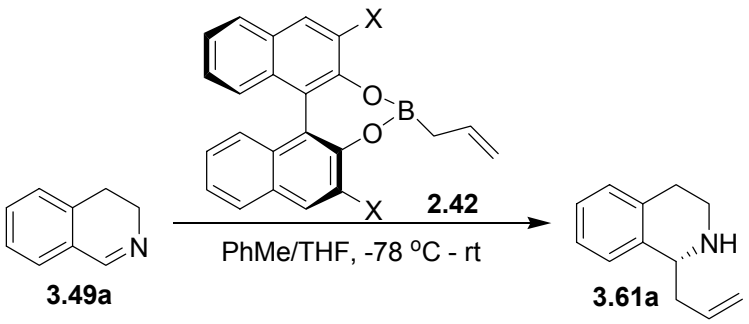
Scheme 3.28

Allylborations of 3,4-dihydroisoquinoline **3.49a** were also conducted using other 3,3′-disubstituted BINOL-modified allylboronates. The results were summarized in Table 3.2. The unsubstituted parent binaphthol (**2.42a**) exhibited essentially no stereoselectivity (Table 3.2, entry 1) while all of the 3,3′-disubstituted systems (Table 3.2, entries 2-10) examined gave reasonable to excellent enantioselectivities. For example, the best reagent for the allylboration of carbonyls, namely **2.42b**, gave 84% *ee*. 3,3′-Diphenyl reagent **2.42f** also gave comparable enantioselectivities (87% *ee*) in this reaction (Table 3.2, entry 6). An electron-rich 3,3′-diaryl reagent **2.42g** was tested giving essentially the same enantioselectivity as **2.42f** (Table 3.2, entry 7). Slightly increasing the bulkiness of the aryl groups on the 3 and 3′ positions did not effect on the enantioselectivity of the reaction (Table 3.2, entry 8) while a remarkable decrease in enantioselectivity was observed when a much bulkier reagent **2.42i** was introduced (Table 3.2, entry 10). It was finally found that reagent **2.42j** which bears 3,5-$(CF_3)_2$-C_6H_3 groups on the 3 and 3′ positions gave an outstanding enantioselectivity of 95% *ee* (Table 3.2, entry 9). The rationale for reagent **2.42j** giving better results than other 3,3′-diaryl reagents is not clear yet, but it is believed to be a combinational result of both steric and electronic effects.

It is worthwhile to point out that the chiral amine product could be isolated by a simple acid-base extraction and the chiral ligands were recycled from the organic phases without detectable

loss of enantiomeric purities. Thus, although stoichiometric amounts of reagents are employed, these reactions are quite practicable. Since **2.42j** gave the best enantioselectivity among all chiral allylboronates tested, it was chosen for further studies.

Table 3.2 Allylation of imine **3.49a** with allylboronates **2.42a-j**.



entry	X (compd no.)	yield (%)[a]	*ee* (%)[b]
1	H (**2.42a**)	<50	10
2	CH_3 (**2.42c**)	94	75
3	CH_2*t*-Bu (**2.42d**)	81	52
4	I (**2.42e**)	87	77
5	CF_3 (**2.42b**)	83	84
6	Ph (**2.42f**)	90	87
7	4-MeO-C_6H_4 (**2.42g**)	94	88
8	3,5-$(Me)_2$-C_6H_4 (**2.42h**)	88	87
9	3,5-$(CF_3)_2$-C_6H_4 (**2.42j**)	92	95
10	3,5-(*t*-Bu)$_2$-C_6H_4(**2.42i**)	86	66

[a] Isolated yields after acid-base extraction. [b] Determined by chiral HPLC analysis of the trifluoroacetamide on a Chiralcel OD column. Absolute configuration based on rotation.

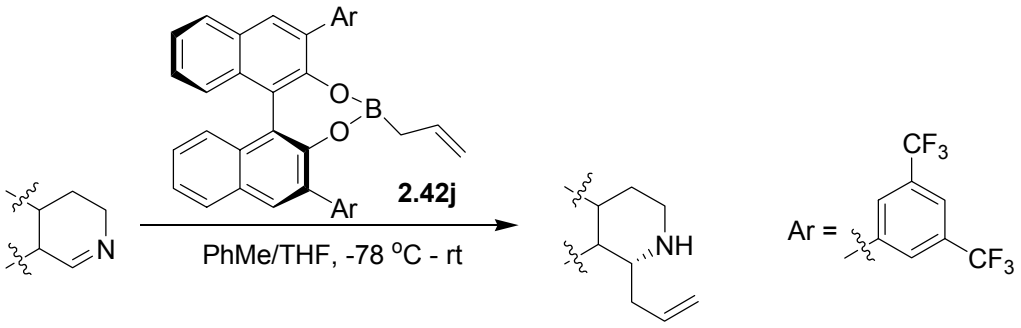
3.3.3 Allylboration of Cyclic Imines using Chiral Allylboronate 2.42j

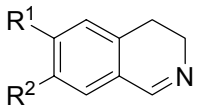
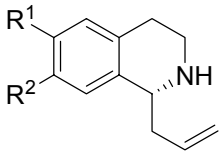
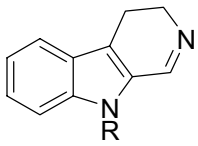
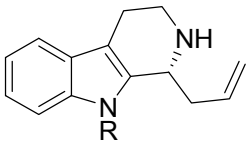
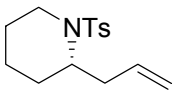
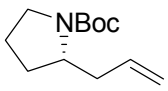
A variety of substituted dihydroisoquinolines (Table 3.3, entries 1-5) were subjected to the allylboration using **2.42j**. Reactions of electron rich substrates (Table 3.3, entries 2 and 3) were much

slower than those of electron poor substrates (Table 3.3, entries 4 and 5) and longer reaction times were required to obtain satisfactory yields. Nonetheless, good yields could be obtained in all cases and selectivities observed were uniformly excellent (95% to 99% *ee*). 3,4-Dihydro-*β*-carboline (**3.53)** could be allylated using **2.42j** without protecting the acidic indole functionality (Table 3.3, entry 6), and *N*-protected 3,4-dihydro-*β*-carboline **3.54** gave a similar result, indicating that the enantioselectivity of the reaction is not affected by the steric or electronic nature of the indole ring (Table 3.3, entry 7).

Aliphatic cyclic imines 1-pyrroline (**3.57)** and Δ^1-piperideine (**3.60)** were also subjected to the allylboration. Although imines **3.57** and **3.60** are enolizable, the allylation reactions were not affected and the desired chiral cyclic pyrrolidine and piperidine were obtained with high *ee*'s (92% and 91% *ee,* respectively, Table 3.3, entries 8 and 9). Slightly lower yields were obtained in both cases, likely due to the propensity of the starting imines to undergo rapid trimerization. In these cases, products were isolated as Boc or tosyl derivatives to avoid possible problems with volatility or water solubility.

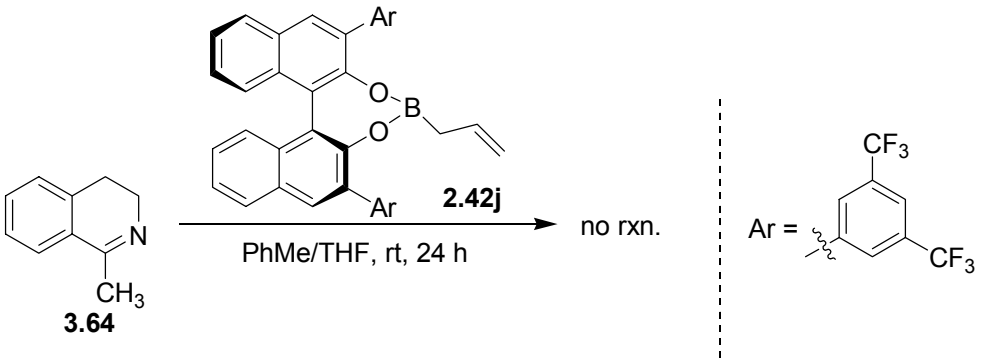
Table 3.3 Allylation of cyclic imines with chiral allylboronates **2.42j**.



entry	substrate	product	yield (%)[a]	*ee* (%)[c]
				
1	**3.49a** (R^1 =R^2 = H)	**3.61a**	92[b]	95
2	**3.49b** (R^1 = R^2 = OMe)	**3.61b**	78	98
3	**3.49c** (R^1, R^2 = OCH_2O)	**3.61c**	86	98
4	**3.49d** (R^1 = R^2 = Cl)	**3.61d**	88	95[d]
5	**3.49e** (R^1 = H, R^2 = NO_2)	**3.61e**	90	99
				
6	**3.53** (R = H)	**3.61f**	80	94
7	**3.54** (R = Ts)	**3.61g**	84	94
8	 **3.57**	 **3.62**	65	91[e]
9	 **3.60**	 **3.63**	71	92[e]

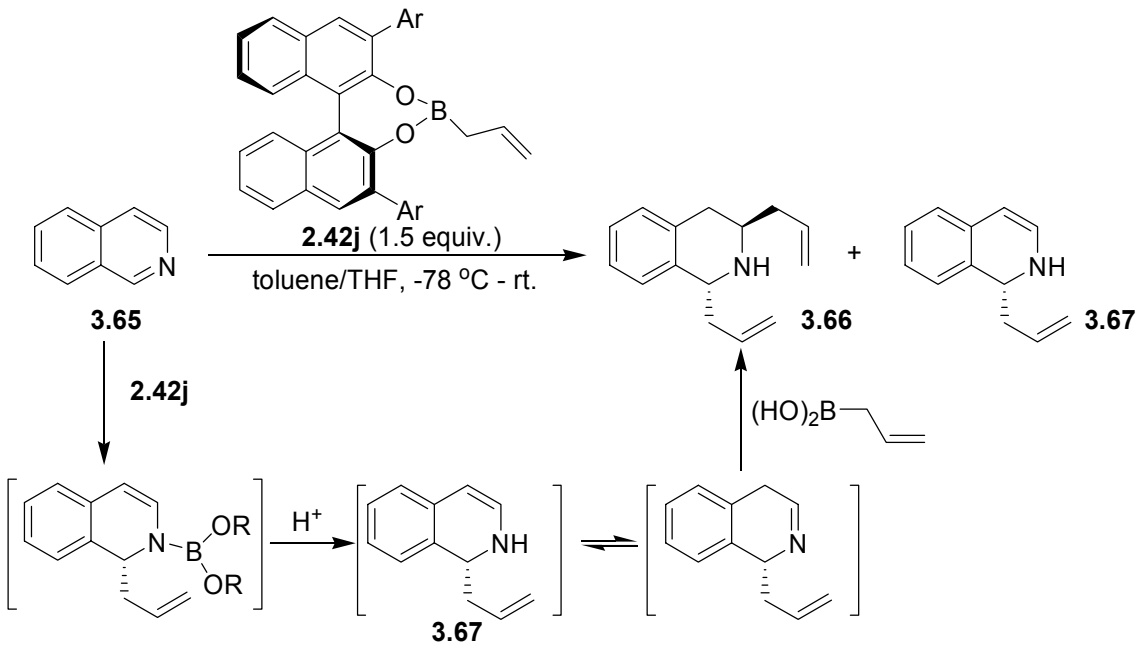
[a] Isolated yields after flash column chromatography on silica gel. [b] Isolated yields after acid-base extraction. [c] Determined by chiral HPLC analysis of trifluoroacetamides. [d] Determined by ^{19}F NMR of its *R*-MTPA amide. [e] The reaction was quenched using TsCl/pyridine/DMAP or $(Boc)_2O/Et_3N$/DMAP, and the *ee* of the product was determined by chiral HPLC analysis.

The allylboration of a cyclic ketimine **3.64** with allylboronate **2.42j** was tested. However, no reaction was observed even after 24 hours at room temperature (Scheme 3.29). Compared to aldimines, the low reactivity of ketimine **3.64** may be caused by the steric hindrance provided by the extra methyl group.



Scheme 3.29

In addition, isoquinoline (**3.65**) was treated with chiral allylboronate **2.42j**. A large amount of "double-allylation" product **3.66** was isolated along with the desired allylation product **3.67** (Scheme 3.33). A possible explanation is that the allylation product **3.67** was allylated again during the aqueous work-up by allylboronic acid which is the hydrolysis product of the extra chiral allylboronate **2.42j** (Scheme 3.30).[53]



Scheme 3.30

3.3.4 Transition State Model for Allylboration using Chiral Allylboronate 2.42

The sense of asymmetric induction observed may be explained using a six-membered chair transition-state model (Figure 3.8). The repulsion between one of the substituents on the BINOL and the methylene protons *α* to the imine nitrogen is the major destabilizing interaction in transition state **B** as was expected in the proposal section.

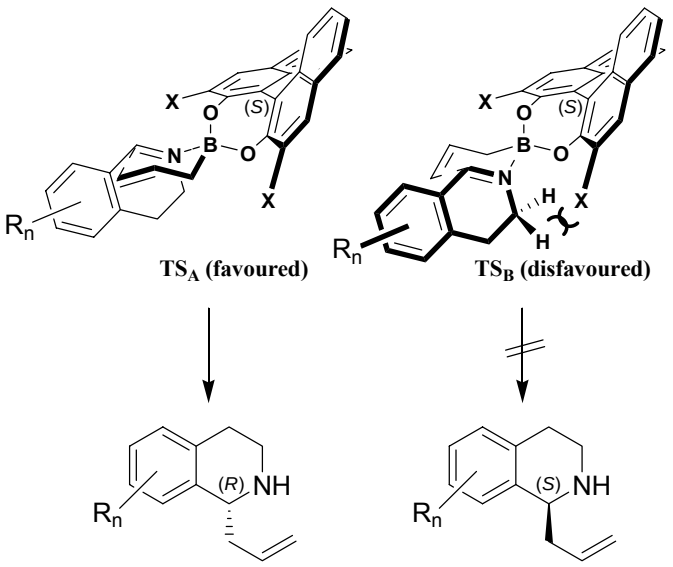
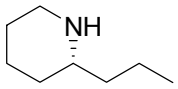


Figure 3.8 Transition state model for the allylboration of cyclic imines using allylboronates **2.42**.

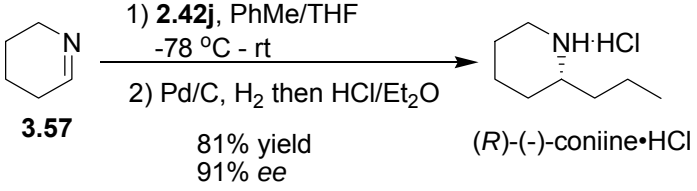
3.3.5 Application 1: Total Synthesis of (*R*)-(-)-Coniine



(*R*)-(-)-coniine

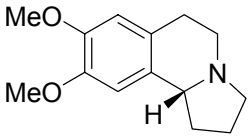
Figure 3.9 Structure of (*R*)-(-)-coniine.

As was previously mentioned, allylation products can serve as building blocks for the synthesis of natural products. For instance, (*R*)-(-)-coniine, an alkaloid which has been the target of innumerable demonstrations of synthetic methodologies,[54-59] could be obtained in one pot from cyclic imine **3.57** (Scheme 3.31).



Scheme 3.31

3.3.6 Application 2: Total Synthesis of (+)-Crispine A

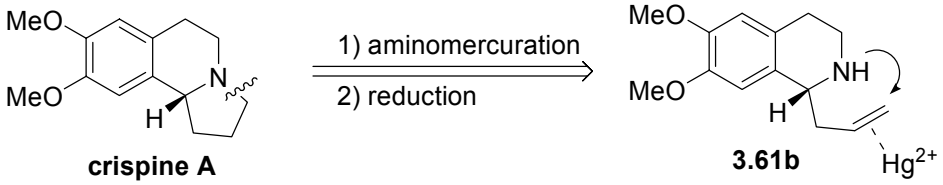


(+)-crispine A

Figure 3.10 Structure of (+)-crispine A.

(+)-Crispine A is a novel isoquinoline alkaloid that was isolated from *Carduus crispus* Linn. (welted thistle) by Zhao and coworkers. Important cytotoxic activity against SKOV3, KB and HeLa human cancer lines has been detected for crispine A according to their report.[60]

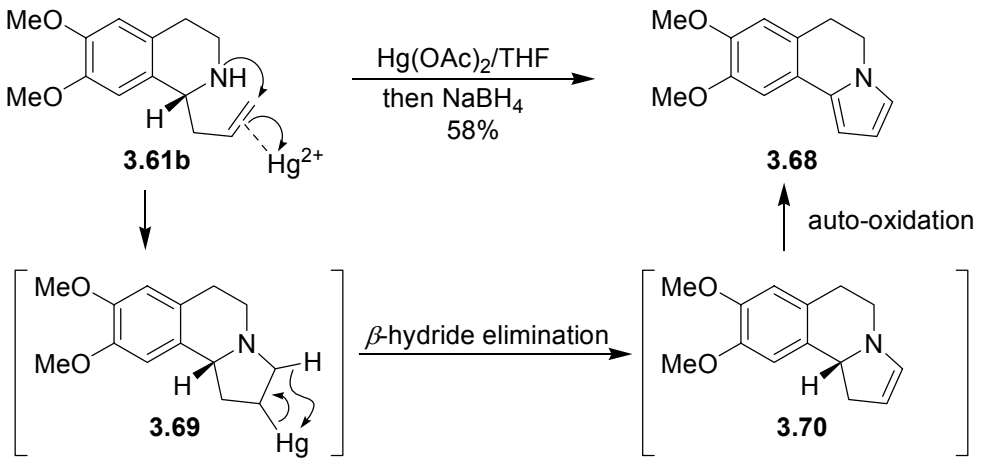
A retrosynthetic analysis indicated that the five-membered ring of crispine A may be constructed from one of the allylboration product **3.61b** *via* an intramolecular aminomercuration (Scheme 3.32).[61]



crispine A **3.61b**

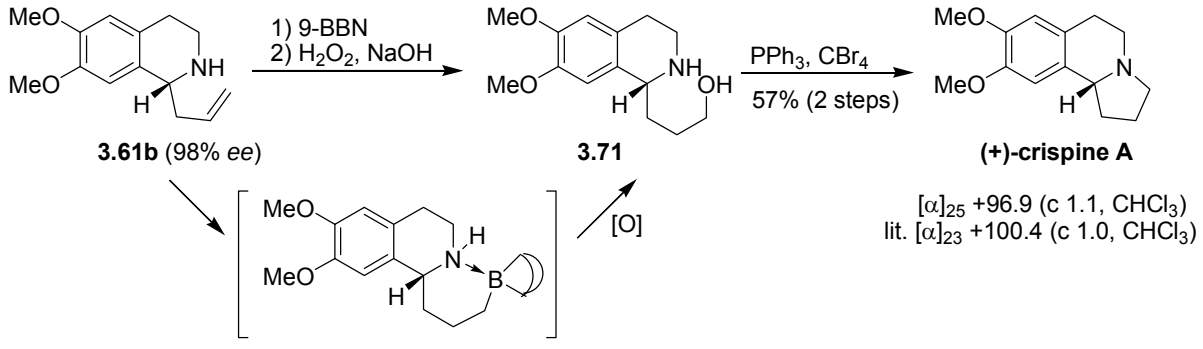
Scheme 3.32

However, treatment of **3.61b** with mercury(II) salts such as $Hg(OAc)_2$ led only to the formation of a pyrrolo[2,1-*a*]-isoquinoline **3.68** and no desired product was detected. This could be rationalized through the formation of intermediate organomecury species **3.69**, followed by a rapid *β*-hydride elimination to give an enamine **3.70** which could then be converted to the more stable aromatic compound **3.68** by an auto-oxidation process (Scheme 3.33).



Scheme 3.33

Since the one-pot aminomercuration-reduction strategy did not work as intended, a two-step hydroboration route was proposed. Thus the allylboration product **3.61b** was treated with 9-BBN in THF followed by an oxidation with H_2O_2/NaOH to produce the desired amino alcohol **3.71** in decent yield. Unlike common hydroboration/oxidation reactions, the oxidation step in this case only proceeds at elevated temperature due to the coordination between boron and the internal amino group. An intramolecular Mitsunobu reaction of **3.71** with PPh_3/DEAD furnished the desired product (+)-crispine A. Alternatively, PPh_3/CBr_4 could be used instead of PPh_3/DEAD to give cleaner and faster conversion (Scheme 3.34).



Scheme 3.34

3.3.7 Application 3: Studies Toward the Total Synthesis of Emetine

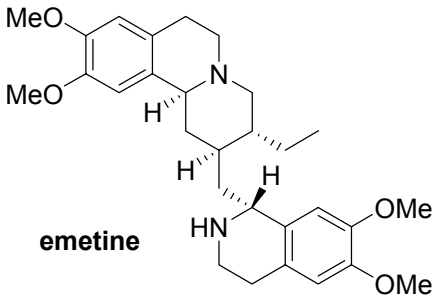
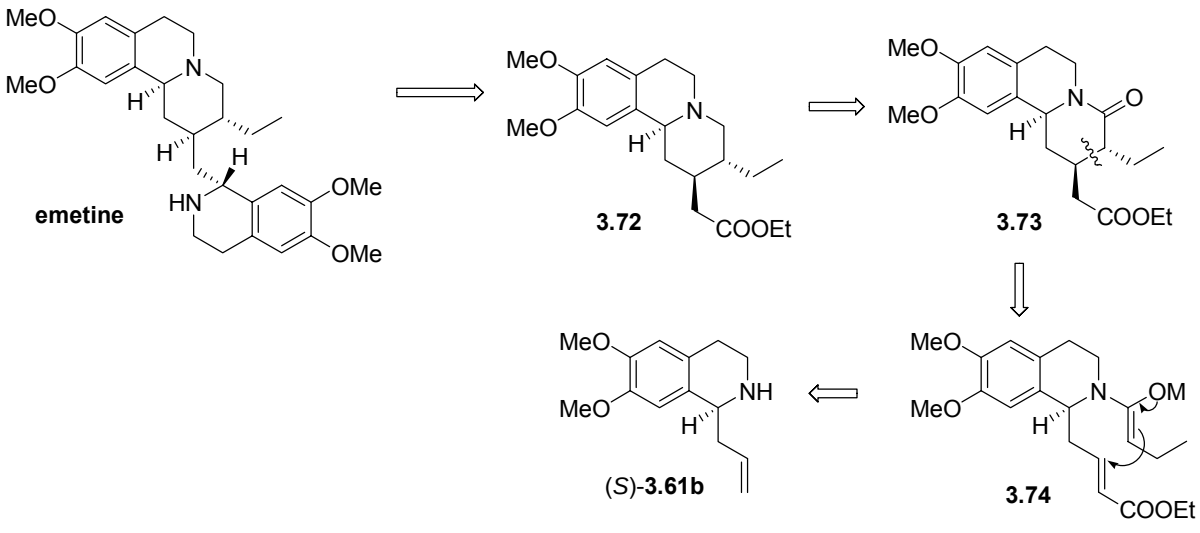


Figure 3.11 Structure of emetine.

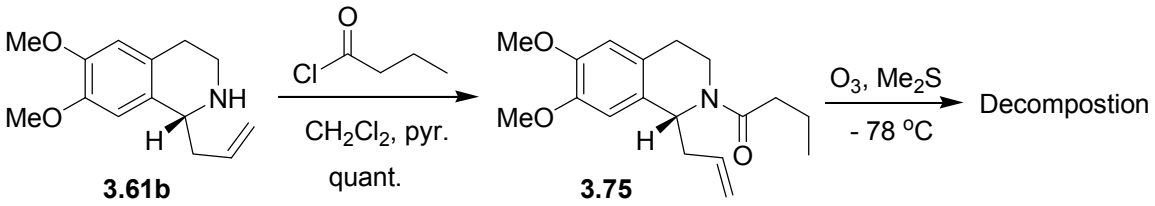
Emetine (Figure 3.9) is the principal alkaloid found in "ipecac root" which has been used for centuries for the treatment of amebiasis and as an emetic, and was subsequently found to be of greater importance for its antiamebic activity.[62]

The transformation of an advanced intermediate **3.72** to emetine has been described by others.[63] Amine **3.72** could be accessed from amide **3.73**, which is the product of an intramolecular Michael addition of enoate **3.74**. It was our contention that allylboration product **3.61b** could be converted to **3.74** through simple functional group manipulations (Scheme 3.35).



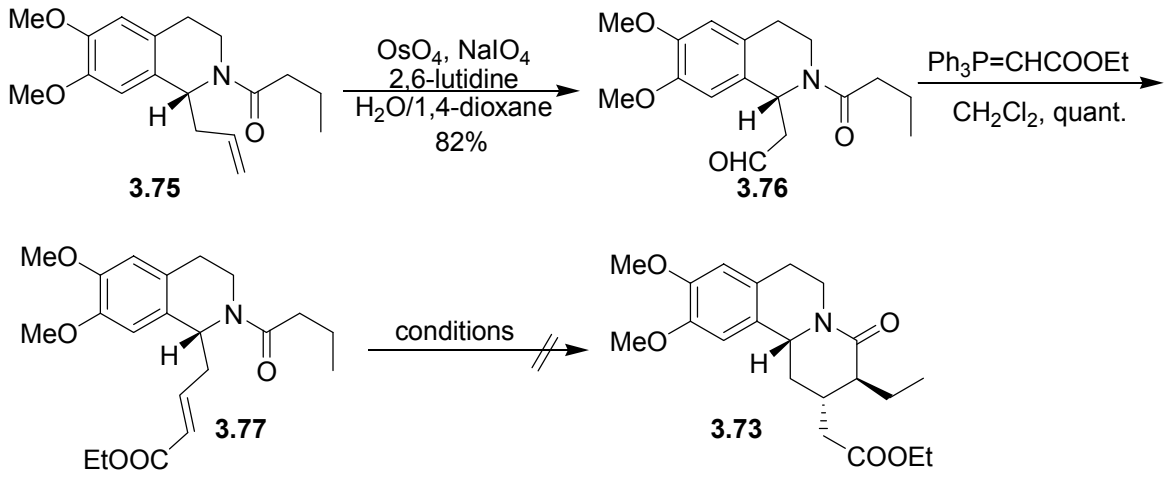
Scheme 3.35

Accordingly, homoallylic amine **3.61b** was treated with butyryl chloride to afford amide **3.75**. However, the ozonolysis of **3.75** under various conditions proved unfruitful. This problem was likely due to the electron-rich nature of the aromatic ring of **3.61b** which could be oxidized by ozone readily (Scheme 3.36).



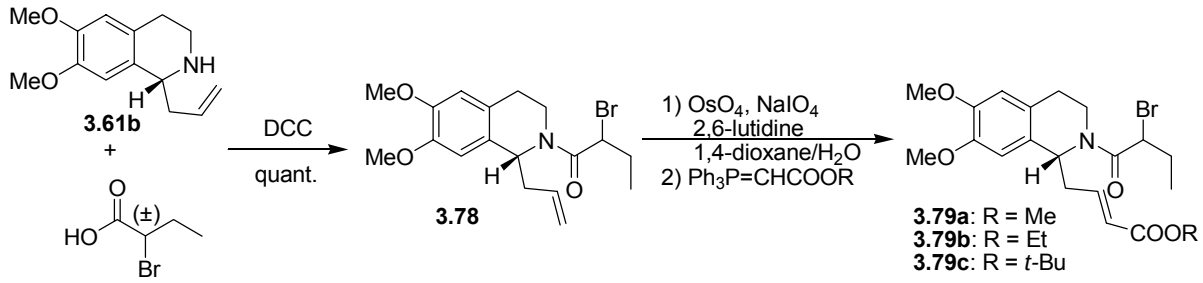
Scheme 3.36

Amide **3.75** was finally converted to the desired aldehyde **3.76** using a dihydroxylation-oxidation method developed by Jin and coworkers.[64] A Wittig reaction with aldehyde **3.76** then smoothly generated an α,β-unsaturated ester **3.77**. We were hoping that the **3.77** could be deprotonated at the α-postion of the amide functionality by bases and undergo an intramolecular Michael addition. However, several attempts using bases (such as LDA, LiHMDS, KH etc.) failed to give the cyclized product **3.73**. Either unreacted starting material or polymers were observed. **3.77** was also subjected to several Lewis acids [$Ti(O\textit{i}\text{-}Pr)_4$, $TiCl_4$, $BF_3{\cdot}OEt_2$] but gave no positive result (Scheme 3.37). These results indicated that deprotonation at the α-postion of the amide functionality is not as easy as what we had expected and a "handle" needed to be installed to facilitate this process.



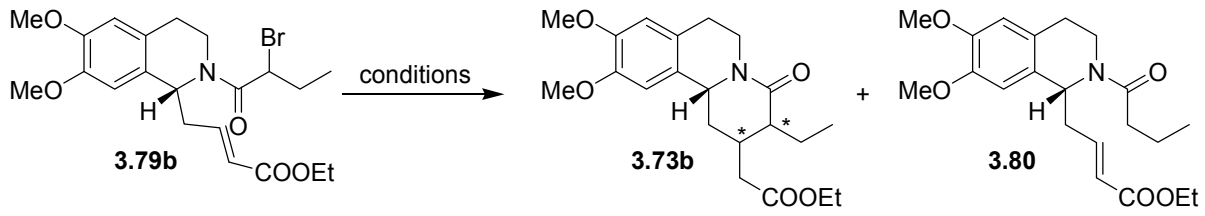
Scheme 3.37

It is known that α-halogenated carbonyl compounds could be converted to enolates under various mild conditions. Therefore, a bromine atom was placed at the α-position of the amide as illustrated in Scheme 3.38.



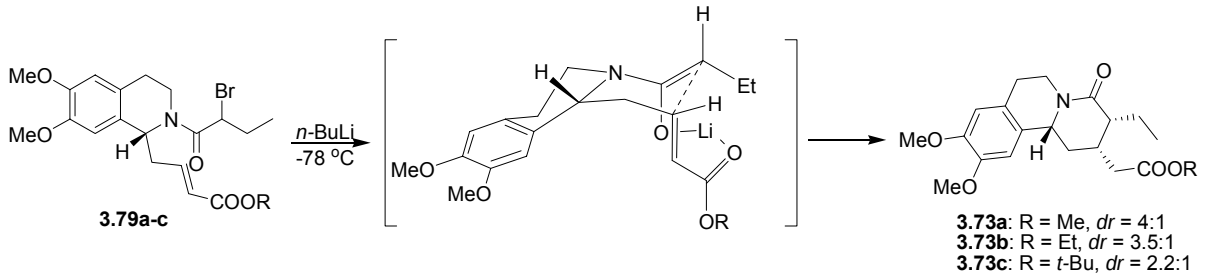
Scheme 3.38

The resulting bromoamide **3.79b** was treated with radical initiators such as Bu_3SnH/AIBN and $Bu_3SnH/BEt_3/O_2$. The desired cyclized product did form but with a large quantity of protonated side product **3.80**. Reformatsky conditions (CuCN/Zn, $ZnEt_2$) were also attempted but produced mostly **3.80** and polymers. Later, it was found that SmI_2 could induce the desired intramolecular Michael addition without producing side product **3.80**. However, ^{1}H NMR indicated the formation of 1:1 mixture of **3.73b** diastereomers (Scheme 3.39).



Scheme 3.39

Finally, it was realized that treatment of **3.79a-c** with 1.2 equivalents of *n*-BuLi at low temperature resulted in the formation of **3.73a-c** in high yield and moderate diastereoselectivities. The stereochemistry of the major diastereomer of lactam **3.73b** was determined by NOE experiments and H-H coupling patterns (Figure 3.12). Disappointingly, we found that it was not the desired diastereomer, but instead a *cis*-3,5,6-trisubstituted-*δ*-lactam (Scheme 3.40).



Scheme 3.40

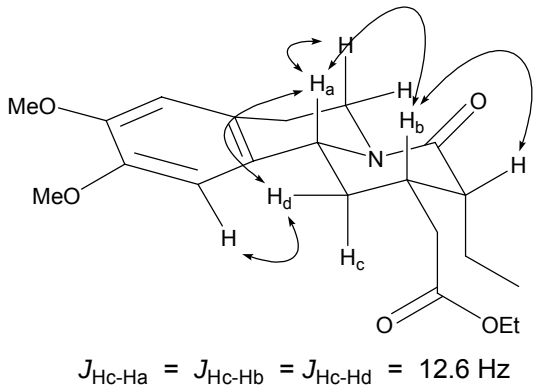
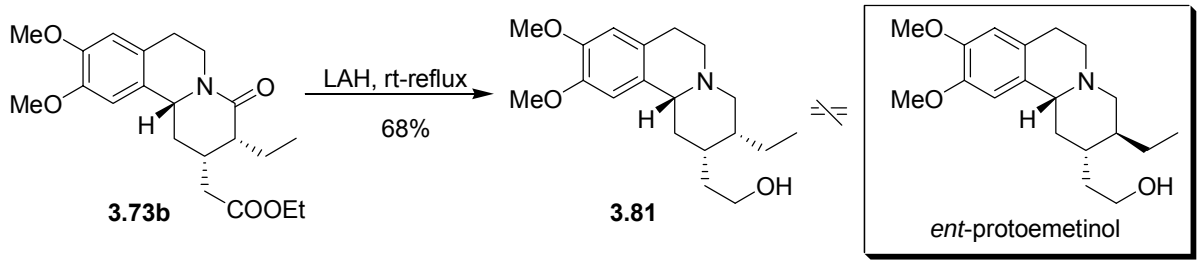


Figure 3.12 Selected NOE effects and H-H coupling constants for **3.73b**.

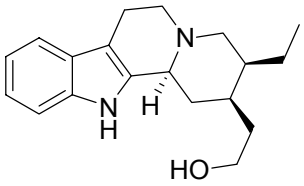
The proposed stereochemistry for **3.73b** was further supported by the ^{1}H NMR of the reduction product **3.81**, which does not match with literature values for protoemetinol (Scheme 3.41).[63]



Scheme 3.41

Although the attempt in synthesizing emetine was not fully successful, the novel all-*cis* trisubstituted *δ*-lactam formation induced by *n*-BuLi may become a useful tool for the synthesis of other natural products.

3.3.8 Application 4: Total Synthesis of *ent*-Corynantheidol

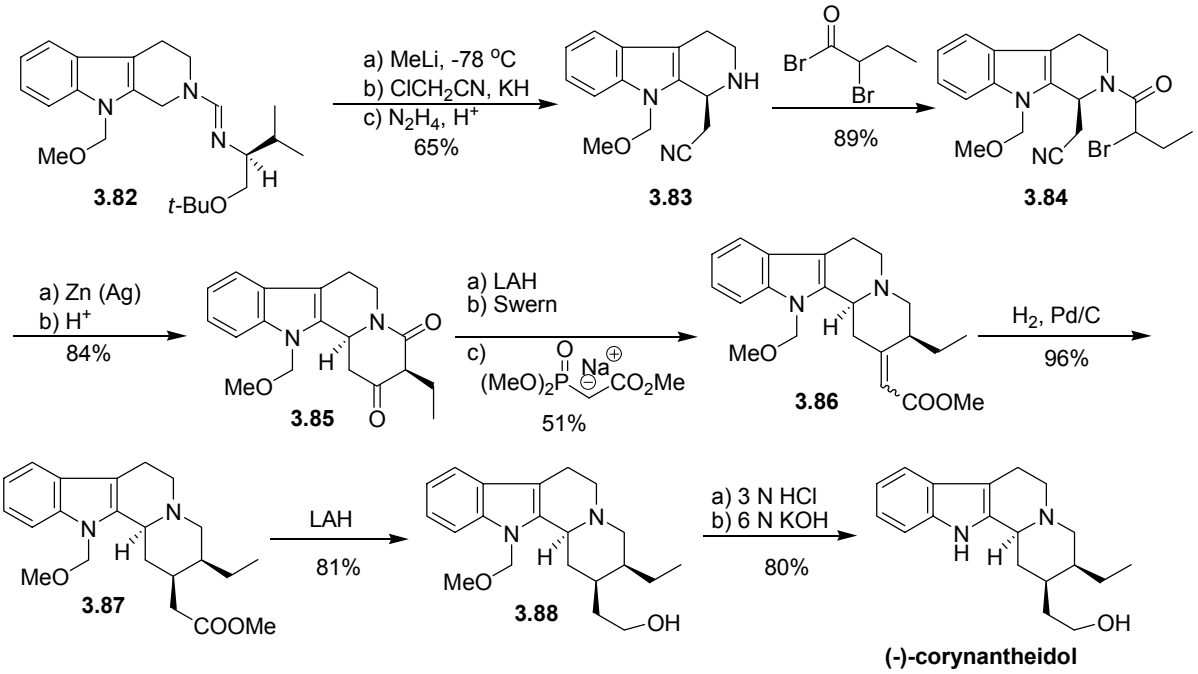


corynantheidol

Figure 3.13 Structure of corynantheidol.

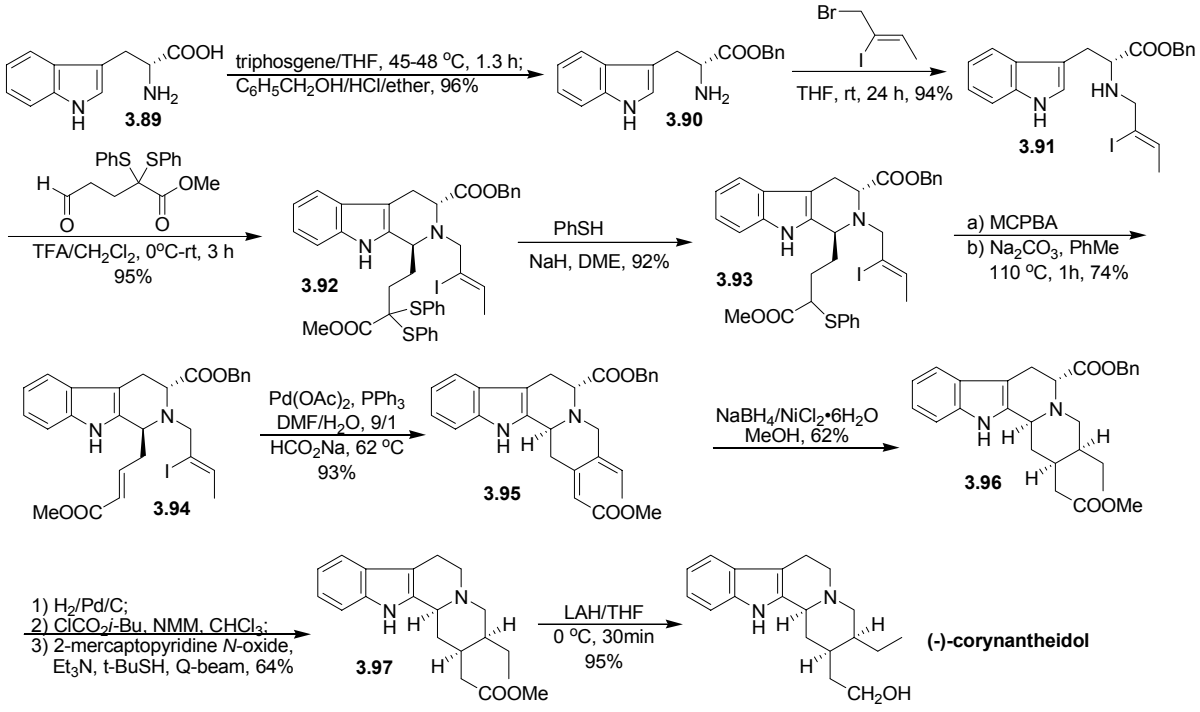
The alkaloid corynantheidol was isolated from leaves of *Mitragyna parvifolia* (Roxb.) Korth (Figure 3.11).[65] Several total syntheses of corynantheidol have been realized,[66,67] while only two approaches, by Meyers[68] and by Cook,[69] were enantioselective. Meyers and coworkers accomplished their synthesis from chiral *β*-carboline **3.82** in 10 steps with 15.4% overall yield (Scheme 3.42), while Cook's route took 12 steps from a natural amino acid D-tryptophan (**3.89**) in an overall yield of 20.5% (Scheme 3.43).

Meyers' Route:



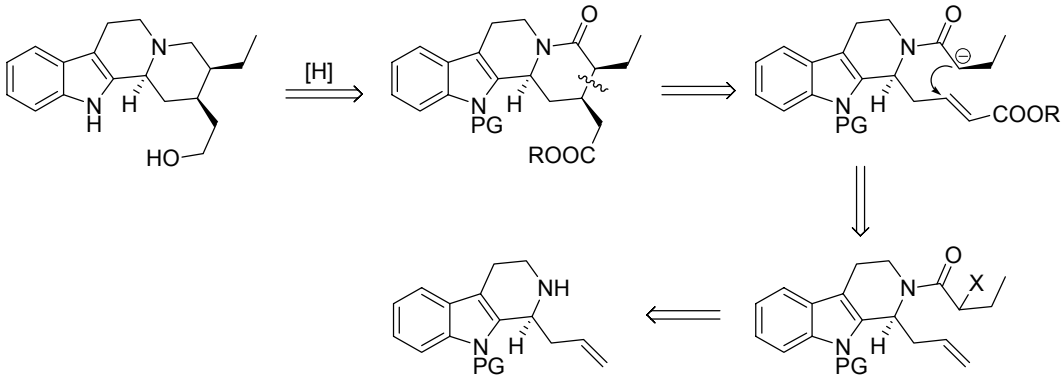
Scheme 3.42

Cook's Route:



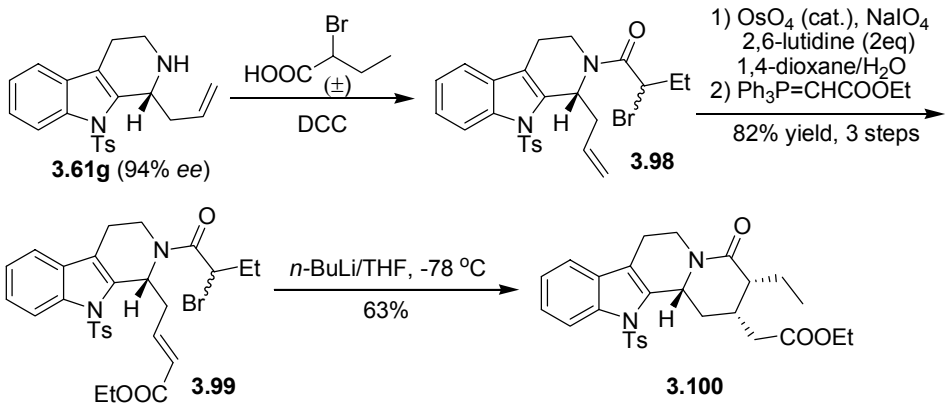
Scheme 3.43

As was previously mentioned, during a study toward the synthesis of emetine, we found that an all-*cis* trisubstituted *δ*-lactam could be formed from an *n*-BuLi induced intramolecular Michael addition. We figured that this methodology may be applied to the synthesis of corynantheidol according to a retrosynthetic analysis depicted in Scheme 3.44.



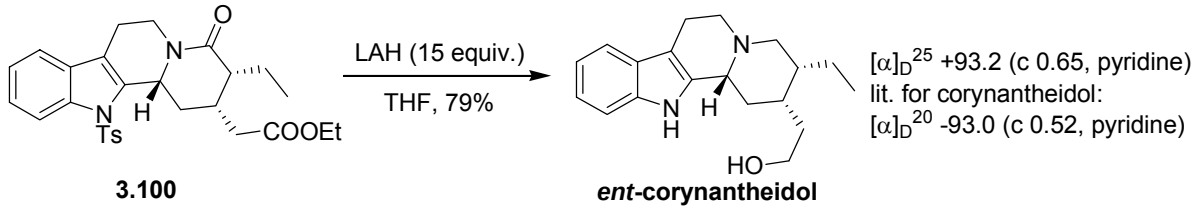
Scheme 3.44

Thus allylboration product **3.61g** was treated with racemic 2-bromobutyric acid and DCC to afford *α*-bromoamide **3.98** in quantitative yield. Amide **3.98** was then converted to *α,β*-unsaturated ester **3.99** uneventfully. Treatment of **3.99** with *n*-BuLi at low temperature gave the desired all-*cis* trisubstituted *δ*-lactam **3.100** in good yield (3.5:1 diastereomers, Scheme 3.45). The stereochemistry of **3.100** was proven by NOE experiments and H-H coupling patterns which were similar to that of compound **3.73**.



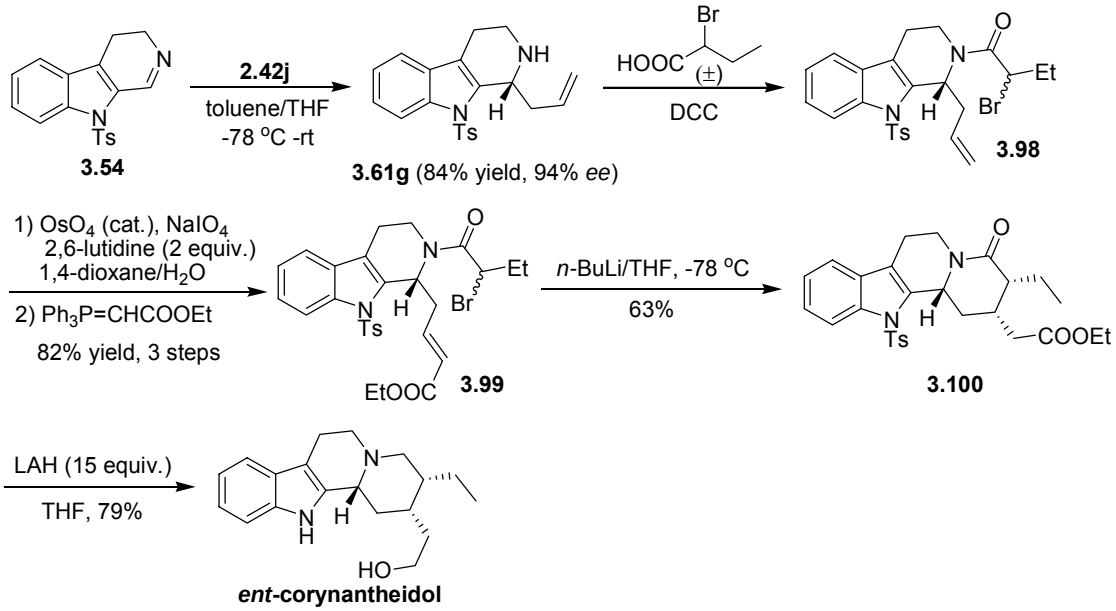
Scheme 3.45

Finally, the total synthesis of *ent*-corynantheidol was accomplished by a "global" reduction using LAH which reduced the amide, ester and *N*-tosylamide all in once (Scheme 3.46). The product *ent*-corynantheidol exhibits an optical rotation value of $[\alpha]_D^{25}$ +93.2 (c 0.65, pyridine) which is the opposite to the reported value for corynantheidol ($[\alpha]_D^{20}$ -93.0 (c 0.52, pyridine)) and its spectroscopic properties agree in all respects to those reported in the literature.[68,69]



Scheme 3.46

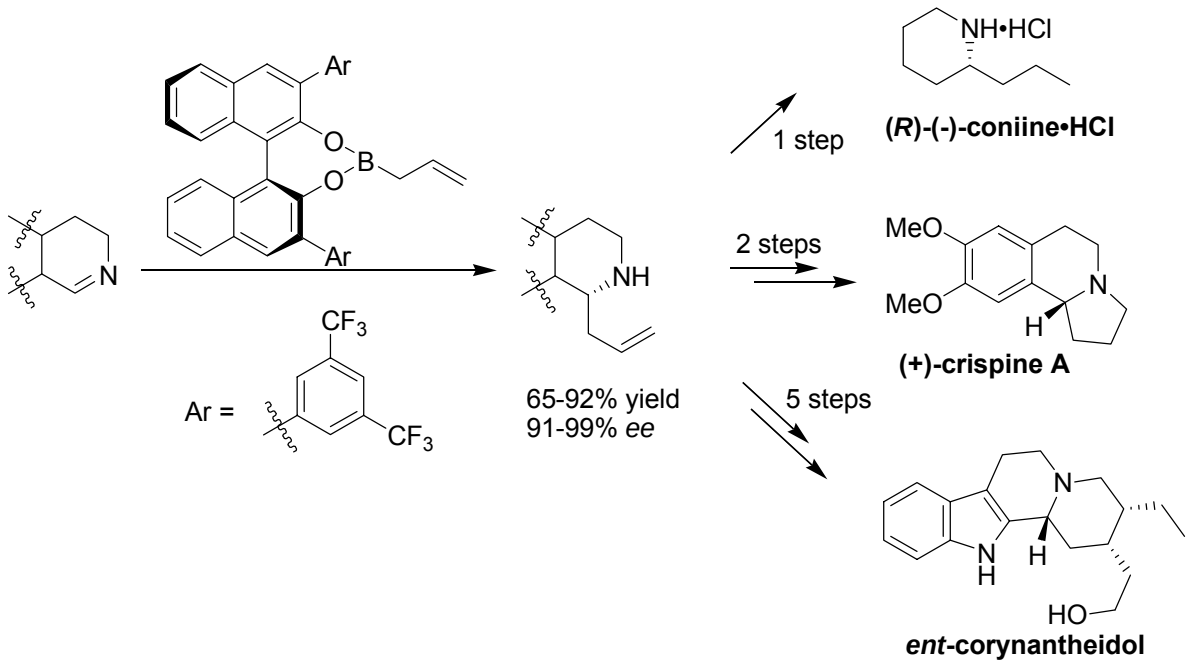
In summary, the total synthesis of *ent*-corynantheidol was furnished in 6 steps from a readily accessible material *N*-tosyl-3,4-dihydro-*β*-carboline (**3.54**) with an overall yield of 34% (Scheme 3.47). This enantioselective route compares very favourably with the two aforementioned syntheses in terms of both length and overall yield.


2.42j
toluene/THF
-78 °C -rt
3.54
3.61g (84% yield, 94% ee)
HOOC (±)
DCC
3.98
1) OsO4 (cat.), NaIO4
2,6-lutidine (2 equiv.)
1,4-dioxane/H2O
2) Ph3P=CHCOOEt
82% yield, 3 steps
3.99
n-BuLi/THF, -78 °C
63%
3.100
LAH (15 equiv.)
THF, 79%
ent-corynantheidol

Scheme 3.47

3.4 Summary

A general methodology for the enantioselective allylation of cyclic imines has been developed. Addition of 3,3'-disubstituted binaphthol-modified allylboronate **2.42j** to cyclic imines proceeded smoothly at low temperature to afford α-chiral cyclic homoallylic amines in excellent yields and enantioselectivities. The versatility of the allylation products has been demonstrated through efficient total syntheses of several alkaloids including (-)-coniine, (+)-crispine A and *ent*-corynantheidol (Scheme 3.48). Results from this chapter have been published in *Journal of the American Chemical Society* (Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 9646-9647).[70]



Scheme 3.48

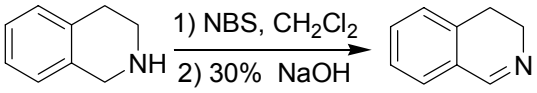
3.5 Experimental

3.5.1 General Experimental

All reactions were performed using flame-dried glassware under an argon atmosphere. Dichloromethane was freshly distilled from calcium hydride. Tetrahydrofuran, diethyl ether, and toluene were freshly distilled from sodium/benzophenone. Chiral 3,3′-disubstituted binaphthols were synthesized using procedures from Chapter 2. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$ at 300 MHz, 75 MHz and 282 MHz, respectively unless otherwise specified. Mass spectra were recorded on a Kratos MA890 mass spectrometer using electron impact (EI, 70 eV) ionization unless otherwise specified. Optical rotations were recorded in cells with 10 cm path length on a Perkin-Elmer 241 digital polarimeter.

3.5.2 Preparation of Cyclic Imines

3.5.2.1 Preparation of 3,4-Dihydroisoquinoline (**3.49a**)

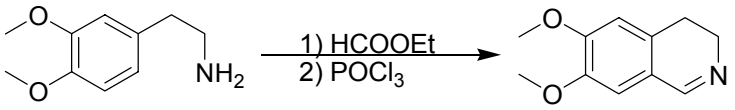


3.48a **3.49a**

Pelletier's procedure[44] was followed: to a solution of 1,2,3,4-tetrahydroisoquinoline (**3.48a**, 5.4 g, 40.6 mmol) in CH_2Cl_2 (100mL) was added NBS (7.95 g, 44.6 mmol) in portions. After the addition was complete, the mixture was stirred until TLC (CH_2Cl_2/MeOH = 9:1) indicated that the starting material was consumed (30 minutes). Sodium hydroxide (25 mL of a 30% aqueous solution) was added, and stirring was continued for 1 hour at 25 ^{o}C. The organic layer was separated and washed with water (50 mL), and the product was extracted with 10% HCl (2 x 50 mL). The combined acidic extracts were washed with CH_2Cl_2 (50 mL) and made basic with concentrated ammonia. The liberated

oil was extracted with CH_2Cl_2 (3 x 50 mL), dried over sodium sulfate, and evaporated *in vacuo*. The residue was subjected to bulb-to-bulb distillation [79-81 ^oC (2 mmHg)] to give 4.26 g (80%) of **3.49a** as a colorless oil. ^1H NMR ($CDC1_3$, 300 MHz): δ 2.64 ($ArC\underline{H_2}CH_2N$, t, J = 7.6 Hz, 2H), 3.68 ($ArCH_2C\underline{H_2}N$, dt, J = 1.8 Hz, 7.6 Hz, 2H), 7.04-7.29 (H_{Ar}, m, 4H), 8.24 (H_{imine}, d, J = 1.8 Hz, 1H).

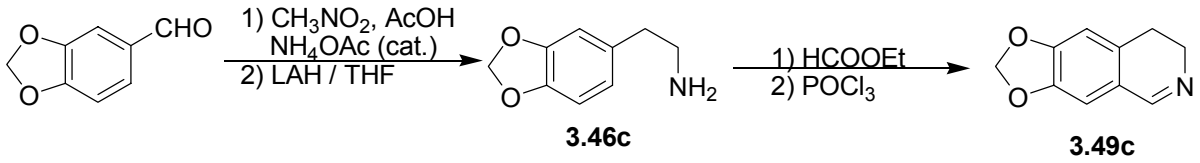
3.5.2.2 Preparation of 6,7-Dimethoxy-3,4-dihydroisoquinoline (**3.49b**)[45]



3.49b

3,4-dimethoxyphenethylamine (5.0 g, 27.6 mmol) was mixed with ethyl formate (25 mL) and was heated to reflux for 12 hours. Volatiles were removed *in vacuo* and the residue was treated carefully at 0 ^oC with freshly distilled $POCl_3$ (15 mL). When the vigorous initial reaction subsided, the mixture was warmed to room temperature over 10 minutes then heated to 40 ^oC for 10 minutes and finally kept at room temperature for 2 hours. The excess $POCl_3$ was evaporated *in vacuo*, and the residue was made basic with concentrated aqueous ammonia. The mixture was extracted with $CHCl_3$ (5 x 50 mL) and the organic extracts were combined and dried over sodium sulfate. Evaporation of volatiles leaves a brown oily residue which was purified using flash column chromatography on silica gel (10:1 CH_2Cl_2/MeOH) to afford **3.49b** (3.7 g) in 71 % yield. ^1H NMR ($CDC1_3$, 300 MHz): δ 2.73 ($ArC\underline{H_2}CH_2N$, t, J = 7.5 Hz, 2H), 3.82 ($ArCH_2C\underline{H_2}N$, t, J = 7.6 Hz, 2H), 3.93 (OMe, s, 3H), 3.95 (OMe, s, 3H), 6.71 (H_{Ar}, s, 1H), 6.85 (H_{Ar}, s, 1H), 8.31 (H_{imine}, s, 1H).

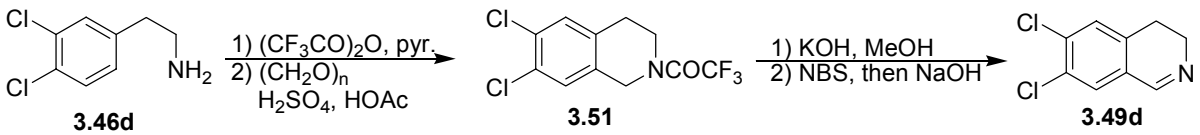
3.5.2.3 Preparation of 7,8-Dihydro-[1,3]dioxolo[4,5-*g*]isoquinoline (**3.49c**)[45]



3.46c **3.49c**

Piperonal (5.4 g, 36.0 mmol) was heated in a 1:1 mixture of CH_3NO_2 and AcOH (30 mL) at 100 ^oC in the presence of NH_4OAc (1.3 g, 16.9 mmol) for 12 hours. The resulting dark yellow solution was cooled to room temperature and was extracted with diethyl ether (5 x 30 mL). The combined ethereal solutions were washed several times with saturated $NaHCO_3$ and dried over Na_2SO_4. Solvents were removed under high vacuum. The residue was dissolved in 50 mL of THF and was added to a suspension of LAH (5.0 g, 131.8 mmol) in THF (200 mL) dropwise at 0 ^oC. The reaction was stirred at room temperature for 12 hours before quenching with saturated NH_4Cl (10 mL) carefully. Solids were filtered off and were washed with EtOAc (5 x 100 mL). The filtrate was concentrated to give crude amine **3.46c** (5.1 g) in 86% yield (2 steps). Amine **3.46c** was converted to imine **3.49c** using the same method for the preparation of **3.49b** in 62% yield. ^1H NMR ($CDC1_3$, 300 MHz): δ 2.60 ($ArC\underline{H_2}CH_2N$, t, J = 7.6 Hz, 2H), 3.64 ($ArCH_2C\underline{H_2}N$, dt, J = 1.8 Hz, 7.6 Hz, 2H), 5.92 (OCH_2O, s, 2H), 6.59 (H_{Ar}, s, 1H), 6.70 (H_{Ar}, s, 1H), 8.10 (H_{imine}, d, J = 1.8 Hz, 1H). ^{13}C NMR ($CDC1_3$, 75 MHz): δ 159.2 (C=N), 149.2 (C_{Ar}), 146.3 (C_{Ar}), 131.6 (C_{Ar}), 122.6 (C_{Ar}), 107.9 (C_{Ar}), 107.4 (C_{Ar}), 101.1 (OCH_2O), 47.1 ($ArCH_2\underline{C}H_2N$), 25.2 ($Ar\underline{C}H_2CH_2N$).

3.5.2.4 Preparation of 6,7-Dichloro-3,4-dihydroisoquinoline (**3.49d**)



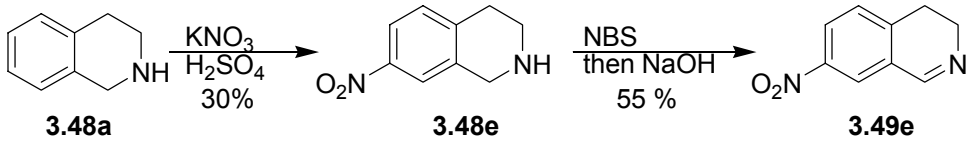
3.46d **3.51** **3.49d**

3,4-Dichlorophenethylamine (**3.46d**), which was prepared using the same method for the preparation of **3.46c,** was converted to trifluoroacetamide **3.51** using Stokker's procedure[46] with minor modifications: to a solution of amine **3.46d** (4.0 g, 21.0 mmol) in CH_2Cl_2 (5 mL) at 0 ^oC was added pyridine (10 mL) and trifluoroacetic anhydride (12 mL). The reaction was allowed to warm to room temperature for 6 hours before quenching with saturated NH_4Cl. The organic layer was separated and the aqueous was washed with CH_2Cl_2 (3 x 50 ml). The combined organic solution was washed with water (3 x 50 ml), dried over Na_2SO_4 then concentrated to give an oily residue. This crude trifluoroacetamide (3.9g, 13.6 mmol) was treated with paraformaldehyde (0.67 g, 21.4 mmol) in H_2SO_4/AcOH (38 mL, 3:2) at room temperature. After stirring for 16 hours, the reaction mixture was poured into cold water (300 mL) and EtOAc (200 mL). The organic layer was washed with saturated $NaHCO_3$ (300 mL), water (200 mL), dried over $MgSO_4$ and evaporated to dryness. ^{1}H NMR indicated that the crude material contained a 4:1 mixture of two regioisomers. The major isomer (**3.51**) could be isolated in 52% yield after flash column chromatography on silica gel (8:1 hexanes/EtOAc).

To a solution of **3.51** (1.3 g, 4.36 mmol) in MeOH (30 mL) was added 3 M KOH (20 mL) and the solution was brought to reflux for 4 hours. The reaction was cooled to room temperature and was extracted with ether (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated to dryness. The crude amine was converted to the desired imine **3.49d** following the procedure for the preparation of 3,4-dihydroisoquinoline (**3.49a**). IR (neat): 1629 (C=N) cm^{-1}; ^{1}H NMR ($CDC1_3$, 300 MHz): δ 2.68 ($ArC\underline{H_2}CH_2N$, t, J = 7.6 Hz, 2H), 3.76 ($ArCH_2C\underline{H_2}N$, dt, J = 1.9 Hz, 7.6 Hz, 2H), 7.24 (H_{Ar}, s, 1H), 7.33 (H_{Ar}, s, 1H), 8.25 (H_{imine}, d, J = 1.9 Hz, 1H). ^{13}C NMR ($CDC1_3$, 75 MHz): δ 158.0 (C=N), 135.8 (C_{Ar}), 134.7 (C_{Ar}), 130.9 (C_{Ar}), 129.4 (C_{Ar}), 128.7 (C_{Ar}),

127.6 (C_{Ar}), 46.9 ($ArCH_2\underline{C}H_2N$), 24.1 ($Ar\underline{C}H_2CH_2N$); MS *m/z* (relative intensity): 199 (M^+, 93), 198 (M^+-H, 100), 172 (M^+-HCN, 18), 164 (M+-Cl, 29).

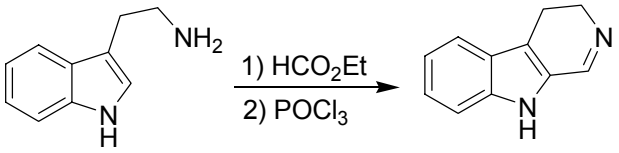
3.5.2.5 Preparation of 7-Nitro-3,4-dihydroisoquinoline (**3.49e**)



3.48a **3.48e** **3.49e**

1,2,3,4-Tetrahydroisoquinoline (11.6 g, 84.8 mmol) was added dropwise with care to stirred concentrated H_2SO_4 (42.0 mL) at 0 ^oC. Potassium nitrate (9.40 g, 93.0 mmol) was then added in small portions. After being stirred overnight at room temperature, the dark brown reaction mixture was added carefully to a stirred ice-cold concentrated NH_4OH solution. The basic mixture was extracted with $CHCl_3$ (3 x 100 mL), and the combined $CHCl_3$ extracts were washed with brine and dried over Na_2SO_4. Evaporation of the organic solvent gave a dark brown oil which was taken up in EtOH (65 mL) and cooled in an ice bath. Treatment of this reddish solution with concentrated HCl (11 mL) yielded a viscous yellow precipitate of the hydrochloride salt which was filtered and crystallized from methanol (250 mL) to yield **3.48e**·HCl as an off-white solid (5.36 g, 30%).[47,48] **3.48e** was oxidized using NBS/NaOH to afford imine **3.49e** in 55% yield. IR (neat): 1652 (C=N) cm^{-1}; ^1H NMR ($CDC1_3$, 300 MHz): δ 2.79 ($ArC\underline{H}_2CH_2N$, t, J = 8.0 Hz, 2H), 3.77 ($ArCH_2C\underline{H}_2N$, dt, J = 2.1 Hz, 8.0 Hz, 2H), 7.28 (H_{Ar}, d, J = 8.2 Hz, 1H), 8.04 (H_{Ar}, d, J = 2.1 Hz, 1H), 8.12 (H_{Ar}, dd, J = 2.1 Hz, 8.2 Hz, 1H), 8.34 (H_{imine}, d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDC1_3$, 75 MHz): δ 158.1 (C=N), 147.1 (C_{Ar}), 143.5 (C_{Ar}), 128.7 (C_{Ar}), 128.5 (C_{Ar}), 125.6 (C_{Ar}), 121.7 (C_{Ar}), 46.8 ($ArCH_2\underline{C}H_2N$), 25.0 ($Ar\underline{C}H_2CH_2N$); MS *m/z* (relative intensity): 176 (M^+, 100), 130 (M^+-NO_2, 44).

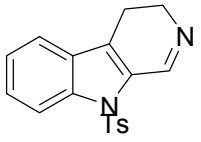
3.5.2.6 Preparation of 3,4-Dihydro-*β*-carboline (**3.53**)[49]



3.52 **3.53**

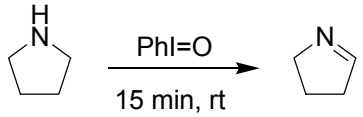
Tryptamine (**3.52**, 10.0 g, 62.4 mmol) was dissolved in ethyl formate (100 ml) and the solution was brought to reflux for 12 hours. Volatiles were removed *in vacuo* to give an oily residue formamide. To this crude formamide was added phosphorus oxychloride (60 mL) at 0 ^{o}C and the stirring was continued for another 12 hours at room temperature. The bright yellow suspension was slowly poured into diethyl ether (250 mL) with rapid stirring. The hydrochloride salt of the dihydro-*β*-carboline which precipitated was then collected by filtration and washed several times with ether. The solid was then dissolved in water (300 mL) and the solution was made basic by slow addition of aqueous sodium hydroxide (1 M), leading to precipitation of the *β*-carboline **3.53**. The mixture was extracted with ether (320 mL), the organic extracts were combined, washed with brine (200 mL), dried over sodium sulfate and the solvent removed under reduced pressure, leaving a pale yellow amorphous solid **3.53** (7.54 g) in 71% yield. ^{1}H NMR ($CDC1_3$, 300 MHz): δ 2.88 ($ArC\underline{H_2}CH_2N$, s, br, 2H), 3.92 ($ArCH_2C\underline{H_2}N$, s, br, 2H), 7.14 (H_{Ar}, t, J = 7.5 Hz, 1H), 7.26 (H_{Ar}, t, J = 7.5 Hz, 1H), 7.35 (H_{Ar}, d, J = 7.5 Hz, 1H), 7.57 (H_{Ar}, d, J = 7.5 Hz, 1H), 8.38 (H_{imine} or H_{indole}, s, br, 1H), 8.47 (H_{imine} or H_{indole}, s, br, 1H).

3.5.2.7 Preparation of 3,4-Dihydro-9-tosyl-*β*-carboline (**3.54**)



MacLean's procedure was followed with minor modifications.[50] To a suspension of NaH (1.16 g, 29.2 mmol) in DMF (40 mL) at -10 °C was added a solution of **3.53** (2.80g, 16.5 mmol) in DMF (10 mL). The mixture was stirred at that temperature for an hour before cooling down to - 45 °C. TsCl (6.3 g, 33.0 mmol) was added to the reaction quickly and the reaction was kept at -45 °C for another 1.5 hours. The reaction was poured in to 100 mL of 2 M HCl and 100 mL diethyl ether. The aqueous layer was separated and the organic layer was washed with 2 M HCl (2 x 50 mL). The combined aqueous layers were basified with concentrated ammonia and were extracted with EtOAc (3 x 100 mL). The Layers were separated and the aqueous phase was washed three times with EtOAc (50 mL). The combined organic solution was dried over sodium sulfate and was concentrated. Purification was done using flash column chromatography (1:1 EtOAc/hexanes) to produce the imine **3.54** (3.60 g) in 67% yield. ^{1}H NMR ($CDC1_3$, 300 MHz): δ 2.30 ($ArCH_3$, s, 3H), 2.76 ($ArC\underline{H_2}CH_2N$, t, J = 8.8 Hz, 2H), 3.92 ($ArCH_2C\underline{H_2}N$, dt, J = 2.1 Hz, 8.8 Hz, 2H), 7.04 (H_{Ar}, d, J = 8.6 Hz, 2H), 7.27 (H_{Ar}, t, J = 7.6 Hz, 1H), 7.37-7.47 (H_{Ar}, m, 2H), 7.64 (H_{Ar}, d, J = 8.6 Hz, 2H), 8.17 (H_{Ar}, d, J = 7.6 Hz, 1H), 8.99 (H_{imine}, d, J = 2.1 Hz, 1H).

3.5.2.8 Preparation of 1-Pyrroline (**3.57**)[51]

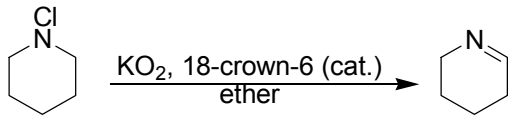


3.57

To a suspension of iodosobenzene (275 mg, 1.25 mmol) and MS 4Å (100 mg) in 5 mL of CH_2Cl_2 was added pyrrolidine (85.2 mg, 0.10 mL, 1.20 mmol). The completion of the reaction was indicated by the disappearance of most solid (20 minutes). ^{1}H NMR showed a 95:5 mixture of imine **3.57** and its trimer **3.58** (100% NMR yield). This imine solution was used immediately without

further purification. ^{1}H NMR (CH_2Cl_2 with D_2O in a sealed tube, 300 MHz, imine-H was not detected): δ 1.25-1.45 ($CH_2C\underline{H_2}CH_2$-N=C, m, 2H), 1.97-2.02 ($C\underline{H_2}CH_2CH_2$-N=C, m, 2H), 3.21-3.23 ($CH_2CH_2C\underline{H_2}$-N=C, m, 2H).

3.5.2.9 Preparation of Δ^1-Pypiperideine (**3.60**)[52]



3.59 **3.60**

To a solution of *N*-chloropiperidine (109 mg, 1.28 mmol) and 18-crown-6 (10 mg) in diethyl ether (3 mL) was added KO_2 (0.20 g, 2.82 mmol) quickly. The resulting pale yellow suspension was stirred at room temperature until TLC showed all starting material **3.59** was consumed (six hours). The solids were filtered off and the filtrate (**3.60** in ether) was used immediately without further purification. Spectra data are identical to those reported in the literature.

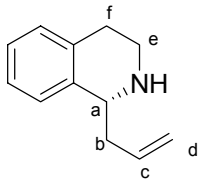
3.5.3 General Procedure for the Allylboration of Cyclic Imines

To a solution of the appropriate 3,3′-disubstitutedbinaphthol **2.42** (0.35 mmol) in THF (5 mL) was added triallylborane (46 mg, 0.34 mmol) dropwise. The reaction was stirred at room temperature for 2 hours then brought to reflux for 1 hour (2 hours for **2.42e-j**). The allylboronate solution was cooled to room temperature and concentrated under reduced pressure. The resulting white solid was dissolved in toluene (5 mL) and THF (1 mL) and the solution was cooled to -78 ^{o}C. A solution of the imine (0.21 mmol, 0.1 - 0.5 M) in THF was added dropwise over 2 minutes. The reaction was stirred at -78 ^{o}C for 24 hours and warmed to room temperature over an additional 24 hours. MeOH (5 mL) and aqueous NH_4Cl (5 mL) were used to quench the reaction. The organic phase was washed

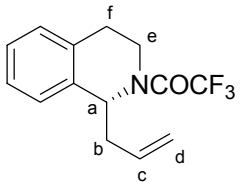
with brine and dried over Na_2SO_4. Purification using flash column chromatography on silica gel (EtOAc/MeOH/NH_4OH) gave the desired homoallylic amine and the chiral ligand in their pure forms.

Alternatively, the reaction mixture could be extracted with 2 M HCl (5 x 5 mL). The chiral ligand was recovered from the organic phase. The aqueous phase was then basified using 1 M NaOH and extracted with diethyl ether (5 x 5 mL). The combined ethereal extracts were dried over Na_2SO_4 and evaporation of the solvent gave the homoallylic amine. The enantiomeric purities of the products were determined by HPLC analysis (4.6 x 250 mm ChiralCel OD, hexanes/*i*-PrOH = 99.5/0.5-98/2) of their trifluoroacetamides unless otherwise specified.

3.5.3.1 (*R*)-1-Allyl-1,2,3,4-tetrahydroisoquinoline (**3.61a**)

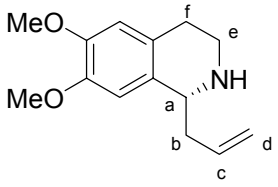


$[\alpha]^{25}_{589}$ +91 (95% *ee*, c 0.51, THF) [lit.[39] (*S* enantiomer): $[\alpha]^{25}_{589}$ -98.1 (94.8% *ee*, c 0.93, THF)]; IR (neat): 3304, 3073, 3018, 1639,1583, 913, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.92 (NH, s, br, 1H), 2.43-3.02 (H_b, H_e, H_f, m, 5H), 3.22 (H_e, dt, J = 11.1 Hz, 5.4 Hz, 1H), 4.03 (H_a, dd, J = 3.3 Hz, 9.0 Hz, 1H), 5.09-5.22 (H_d, m, 2H), 5.83 (H_c, m, 1H), 7.04-7.17 (H_{Ar}, m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6 (C_{Ar}), 135.5 (C_c), 135.3 (C_{Ar}), 129.2 (C_{Ar}), 125.9 (C_{Ar}), 125.9 (C_{Ar}), 125.7 (C_{Ar}), 117.8 (C_d), 55.0 (C_a), 41.0 (C_b or C_e), 40.5 (C_b or C_e), 29.9 (C_f); The enantiomeric excess of the product was determined by HPLC analysis of its trifluoroacetamide: (hexanes/*i*-PrOH = 99/1, flow rate = 1 mL/min), t_R = 13.1 min (*R*), t_R = 19.5 min (*S*).



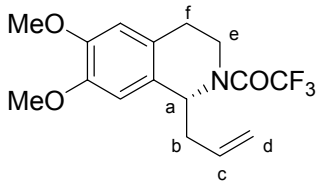
$[\alpha]^{25}_{589}$ -116.5 (95% *ee*, c 1.68, $CHCl_3$)[lit.[39] (*S* enantiomer): $[\alpha]^{27}_{589}$ +121.24 (94.8% *ee*, c 1.43, $CHCl_3$)]; IR (neat): 3079, 2913, 1689, 1642, 1462, 1270, 1197, 1179, 1141, 921, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 5.7 : 1 mixture of rotamers): δ 2.50-3.18 (H_b and H_f, m, 4H), 3.36 (H_e, dt, *J* = 4.8 Hz, 11.4 Hz, 0.15H), 3.60 (H_e, dt, *J* = 3.9 Hz, 12.8 Hz, 0.85H), 3.95-4.60 (H_e, m, 1H), 4.99-5.22 [H_a (0.15H) and H_d (2H), m, 2.15H] 5.48-6.02 [H_a (0.85H) and H_c (1H), m, 1.85H], 7.03-7.42 (H_{Ar}, m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 5.7 : 1 mixture of rotamers, signals for the minor isomer are in *italic* style): δ 156.2 (C=O, q, *J* = 35.3 Hz), *135.3 (C_{Ar})*, 135.2 (C_{Ar}), 133.7 (C_c), *133.0 (C_c)*, *132.8 (C_{Ar})*, 132.5 (C_{Ar}), *129.2* (C_{Ar}), 128.8 (C_{Ar}), *127.5* (C_{Ar}), 127.1 (C_{Ar}), 126.6 (C_{Ar}), *126.3* (C_{Ar}), *118.4* (C_d), 118.2 (C_d), 116.7 (CF_3, q, *J* = 288.5 Hz), *56.4 (C_a)*, 53.3 (C_a), *41.6 (C_b)*, 40.9 (C_b), 39.6 (C_e), *37.3 (C_e)*, 29.0 (C_f), *27.3 (C_f)*; MS *m/z* (relative intensity): 228 (M^+-allyl, 100).

3.5.3.2 (*R*)-1-Allyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**3.61b**)



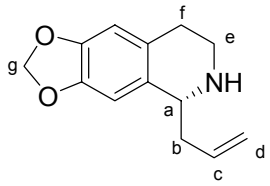
$[\alpha]^{25}_{589}$ +87.6 (98% *ee*, c 0.69, THF); IR (neat): 3333, 3072, 1639, 1610, 1515, 1261, 1224, 1118, 915, 857, 780 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.80 (NH, s, br, 1H), 2.30-3.15 (H_b, H_e and H_f, m, 6H), 3.72 (OMe, s, 6H), 3.85 (H_a, dd, *J* = 2.1 Hz, 8.4 Hz, 1H), 4.98-5.16 (H_d, m, 2H), 5.72 (H_c, m, 1H), 6.45 (H_{Ar}, s, 1H), 6.54 (H_{Ar}, s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.1 (C_{Ar}), 146.9 (C_{Ar}), 135.4 (C_c), 130.3 (C_{Ar}), 127.2 (C_{Ar}), 117.6 (C_d), 111.5 (C_{Ar}), 108.8 (C_{Ar}), 55.7 (O<u>C</u>H$_3$), 55.5 (O<u>C</u>H$_3$),

54.5 (C_a), 40.8 (C_b or C_e), 40.5 (C_b or C_e), 29.2 (C_f); MS *m/z* (relative intensity): 233 (M^+, 0.5), 232, (M^+-H, 2.5), 192 (M^+-allyl, 100); The enantiomeric excess of the product was determined by HPLC analysis of its trifluoroacetamide: (hexanes/*i*-PrOH = 98/2, flow rate = 1 mL/min), t_R = 17.6 min (*S*), t_R = 23.6 min (*R*).

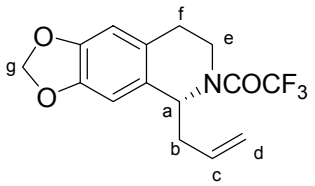


$[\alpha]^{25}_{589}$ -113.8 (98% *ee*, c 0.65, $CHCl_3$) [lit.[39] (*S* enantiomer): $[\alpha]^{25}_{589}$ +106.8 (95% *ee*, c 1.29, $CHCl_3$)]; IR (neat): 3075, 2937, 2837, 1688, 1642, 1520, 1464, 1256, 1232, 1178, 1195, 1178, 1140, 1118, 915, 857, 778, 754, 668, 654 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 6.1:1 mixture of rotamers): δ 2.48-2.78 (H_b and H_f, m, 3H), 2.86-3.02 (H_b or H_f, m, 1H), 3.29 (H_e, dt, *J* = 4.9 Hz, 12.6 Hz, 0.14H), 3.56 (H_e, ddd, *J* = 4.2 Hz, 12.2 Hz, 14.1 Hz, 0.86H), 3.82 (OMe, s, 3H), 3.83 (OMe, s, 3H), 3.95-4.05 (H_e, m, 0.86H), 4.53 (H_e, m, 0.14H), 4.88 (H_a, t, *J* = 7.1 Hz, 0.14H), 4.98-5.13 (H_d, m, 2H), 5.51 (H_a, dd, *J* = 5.2 Hz, 9.2 Hz, 0.86H), 5.69-5.88 (H_c, m, 1H), 6.54 (H_{Ar}, s, 0.14H), 6.56 (H_{Ar}, s, 0.86H), 6.59 (H_{Ar}, s, 0.14H), 6.60 (H_{Ar}, s, 0.86H); ^{13}C NMR (75 MHz, $CDCl_3$, 6.1:1 mixture of rotamers, signals for the minor isomer are in *italic* style): δ 155.9 (C=O, q, *J* = 35.6 Hz), *148.4 (C_{Ar})*, 148.1 (C_{Ar}), 147.8 (C_{Ar}), *147.5 (C_{Ar})*, 133.7 (C_c), *133.2 (C_c)*, *127.2 (C_{Ar})*, 127.1 (C_{Ar}), *124.9 (C_{Ar})*, 124.5 (C_{Ar}), *118.8 (C_d)*, 118.2 (C_d), 116.5 (CF_3, q, *J* = 287.9 Hz), *111.5 (C_{Ar})*, 111.1 (C_{Ar}), 109.7 (C_{Ar}), *109.5 (C_{Ar})*, 56.0 ($O\underline{C}H_3$), 55.9 ($O\underline{C}H_3$), 53.0 (C_a), *41.7 (C_b)*, 40.9 (C_b), 39.6 (C_e), *37.2 (C_e)*, 28.7 (C_f), *27.0 (C_f)*; MS *m/z* (relative intensity): 228 (M^+-allyl, 100).

3.5.3.3 (*R*)-5-Allyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinoline (**3.61c**)



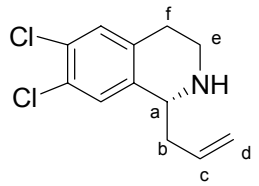
$[\alpha]^{25}_{589}$ +97.8 (98% *ee*, c 0.91, THF); IR (neat): 3305, 3073, 2910, 1638, 1503, 1484, 1248, 1229, 1040, 936, 861, 805 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.74 (NH, s, br, 1H), 2.31-3.22 (H_b, H_e and H_f, m, 6H), 3.89 (H_a, dd, J = 2.7 Hz, 8.4 Hz, 1H), 5.07-5.15 (H_d, m, 2H), 5.79 (H_c, m, 1H), 5.84 ($OC\underline{H_2}O$, s, 2H), 6.50 (H_{Ar}, s, 1H), 6.60 (H_{Ar}, s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.6 (C_{Ar}), 145.5 (C_{Ar}), 135.4 (C_c), 131.6 (C_{Ar}), 128.4 (C_{Ar}), 117.8 (C_d), 108.7 (C_{Ar}), 105.9 (C_{Ar}), 100.5 (C_g), 55.0 (C_a), 40.9 (C_b or C_e), 40.6 (C_b or C_e), 30.0 (C_f); MS *m/z* (relative intensity): 217 (M^+, 0.3), 216, (M^+-H, 1.6), 176 (M^+-allyl, 100); HRMS *m/z* Calcd for $C_{13}H_{14}NO_2$ (M^+-H): 216.1025. Found: 216.1027; The enantiomeric excess of the product was determined by HPLC analysis of its trifluoroacetamide: (hexanes/*i*-PrOH = 98/2, flow rate = 1 mL/min), t_R = 19.8 min (*S*), t_R = 22.1 min (*R*).



$[\alpha]^{25}_{589}$ -94.1 (98% *ee*, c 1.31, $CHCl_3$); IR (neat): 2910, 1690, 1642, 1506, 1487, 1240, 1199, 1140, 1040, 923, 864, 753, 668, 650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 6.3:1 mixture of rotamers): δ 2.48-3.04 (H_b and H_f, m, 4H), 3.32 (H_e, dt, J = 4.6 Hz, 11.6 Hz, 0.14H), 3.55 (H_e, dt, J = 3.5 Hz, 11.3 Hz, 0.86H), 3.91-4.52 (H_e, m, 1H), 4.82-5.54 (H_a and H_d, m, 3H), 5.70-5.86 (H_c, m, 1H), 5.89 (H_g, s, 2H), 6.53-6.58 (H_{Ar}, m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 6.3:1 mixture of rotamers, signals for the minor isomer are in *italic* style): δ 156.0 (C=O, q, J = 30.0 Hz), *149.0 (C_{Ar})*, 146.8 (C_{Ar}), 146.6 (C_{Ar}), *144.4 (C_{Ar})*, 133.6 (C_c), *133.1 (C_c)*, *128.4 (C_{Ar})*, 128.3 (C_{Ar}), *126.4 (C_{Ar})*, 125.9 (C_{Ar}), *119.0 (C_d)*,

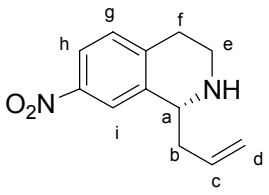
118.4 (C_d), 116.6 (CF_3, q, J = 285 Hz), *108.9 (C_{Ar})*, 108.4 (C_{Ar}), 106.9 (C_{Ar}), *106.7 (C_{Ar})*, 101.1 (C_g), *56.0 (C_a)*, 53.4 (C_a), *41.7 (C_b)*, 41.0 (C_b), 39.7 (C_e), *37.3 (C_e)*, 29.2 (C_f), *27.4 (C_f)*; MS *m/z* (relative intensity): 313 (M^+, 1.5), 272 (M^+-allyl, 100); HRMS *m/z* Calcd for $C_{15}H_{14}F_3NO_3$ (M^+-H): 313.0926. Found: 313.0934.

3.5.3.4 (*R*)-1-Allyl-6,7-dichloro-1,2,3,4-tetrahydroisoquinoline (**3.61d**)

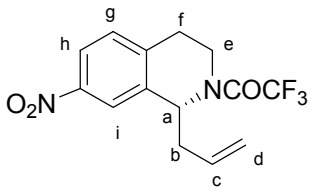


$[\alpha]^{25}_{589}$ +117.6 (95% *ee*, c 0.91, THF); IR (neat): 3339, 3076, 2926, 1640, 1472, 1136, 917, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.75 (NH, s, br, 1H), 2.31-3.33 (H_b, H_e and H_f, m, 6H), 3.90 (H_a, dd, J = 3.0 Hz, 8.7 Hz, 1H), 5.08-5.15 (H_c, m, 2H), 5.74 (H_d, m, 1H), 7.11 (H_{Ar}, s, 1H), 7.19 (H_{Ar}, s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9 (C_{Ar}), 135.8 (C_{Ar}), 134.8 (C_c), 130.9 (C_{Ar}), 129.7 (C_{Ar}), 129.5 (C_{Ar}), 127.9 (C_{Ar}), 118.6 (C_d), 54.6 (C_a), 40.7 (C_b or C_e), 40.4 (C_b or C_e), 29.3 (C_f); MS *m/z* (relative intensity): 241 (M^+, 0.3), 240, (M^+-H, 1.1), 200 (M^+-allyl, 100); HRMS *m/z* Calcd for $C_{12}H_{12}NCl_2$ (M^+-H): 240.0347. Found: 240.0345; The enantiomeric excess of the product was determined by ^{19}F NMR of its (*R*)-MTPA-amide [δ -69.55 (*RR*), -70.75 (*SR*)].

3.5.3.5 (*R*)-1-Allyl-7-nitro-1,2,3,4-tetrahydroisoquinoline (**3.61e**)



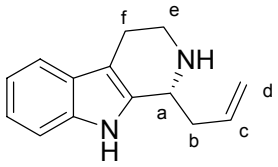
$[\alpha]^{25}_{589}$ +144 (99% *ee*, c 3.4, $CHCl_3$); IR (neat): 3344, 3074, 2927, 1640, 1587, 1518, 1345, 1279, 1134, 903, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.03 (NH, s, br, 1H), 2.44-3.32 (H_b, H_e and H_f, m, 6H), 4.08 (H_a, dd, J = 3.1 Hz, 8.6 Hz, 1H), 5.14-5.24 (H_c, m, 2H), 5.81 (H_d, m, 1H), 7.23 (H_g, d, J = 8.0 Hz, 1H), 7.97 (H_h, dd, J = 2.1Hz, 8.0 Hz, 1H); 8.05 (H_i, d, J = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.2 (C_{Ar}), 143.4 (C_{Ar}), 140.0 (C_{Ar}), 134.4 (C_c), 130.2 (C_{Ar}), 121.3 (C_{Ar}), 121.0 (C_{Ar}), 118.9 (C_d), 55.0 (C_a), 40.4 (C_b or C_e), 40.2 (C_b or C_e), 30.1 (C_f); MS *m/z* (relative intensity): 218 (M^+, 0.1), 217, (M^+-H, 0.6), 177 (M^+-allyl, 100), 131 (M^+-NO_2-allyl, 37); HRMS *m/z* Calcd for $C_9H_9N_2O_2$ (M^+-allyl): 177.0664. Found: 177.0662; The enantiomeric excess of the product was determined by HPLC analysis of its trifluoroacetamide: (hexanes/*i*-PrOH = 98/2, flow rate = 1 mL/min), t_R = 28.0 min (*S*), t_R = 29.8 min (*R*).



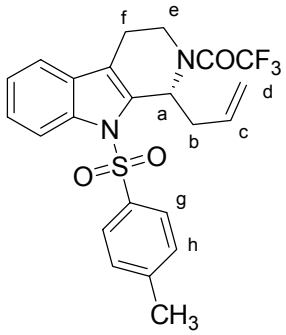
$[\alpha]^{25}_{589}$ -137 (99% *ee*, c 1.67, $CHCl_3$); IR (neat): 2959, 1692, 1640, 1525, 1467, 1346, 1282, 1260, 1195, 1158, 1141, 1045, 1000, 944, 928, 895, 834, 738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 5.6:1 mixture of rotamers): δ 2.52-3.16 (H_b and H_f, m, 4H), 3.35 (H_e, ddd, J = 5.4 Hz, 11.1 Hz, 13.5 Hz, 0.18H), 3.60 (H_e, ddd, J = 4.8 Hz, 11.1 Hz, 14.4 Hz, 0.82H), 4.02-4.65 (H_e, m, 1H), 4.99-5.85 (H_a, H_c and H_d, m, 4H), 7.25-7.36 (H_g, m, 1H), 7.95-8.07 (H_h and H_i, m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 5.6:1 mixture of rotamers, signals for the minor isomer are in *italic* style): δ 156.0 (C=O, q, J = 36.0 Hz), 146.6 (C_{Ar}), *146.3 (C_{Ar})*, *140.7 (C_{Ar})*, 140.3 (C_{Ar}), 136.8 (C_{Ar}), *136.7 (C_{Ar})*, 132.6 (C_c), *132.0 (c_r)*, *130.5 (C_{Ar})*, 130.0 (C_{Ar}), *122.4 (C_{Ar})*, 122.3 (C_{Ar}), 122.0 (C_{Ar}), *121.9 (C_{Ar})*, *119.9 (C_d)*,119.1 (C_d),

116.3 (CF_3, q, J = 288 Hz), *56.0 (C_a)*, 53.0 (C_a), *41.3 (C_b)*, 40.6 (C_b), 38.9 (C_e), *36.3 (C_e)*, 29.3 (C_f), *27.5 (C_f)*; MS *m/z* (relative intensity): 314 (M^+, 0.1), 273 (M^+-allyl, 100); HRMS *m/z* Calcd for $C_{11}H_8F_3N_2O_3$ (M^+-allyl): 273.0487. Found: 273.0496.

3.5.3.6 (*R*)-1-Allyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**3.61f**)[39]



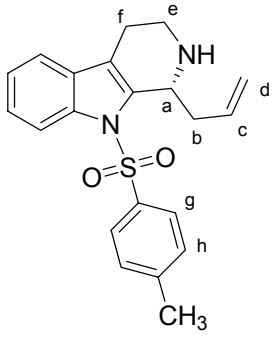
^{1}H NMR (300 MHz, $CDCl_3$): δ 2.25 (NH, s, br, 1H), 2.44-3.43 (H_b, H_e and H_f, m, 6H), 4.14 (H_a, t, J = 6.3 Hz, 1H), 5.16-5.30 (H_d, m, 2H), 5.87 (H_c, m, 1H), 7.08-7.22 (H_{Ar}, m, 2H), 7.27 (H_{Ar}, d, J = 7.2 Hz, 1H), 7.51 (H_{Ar}, d, J = 7.2 Hz, 1H), 8.40 (indole-H, s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.7 (C_{Ar}), 135.6 (C_{Ar}), 134.9 (C_c), 127.3 (C_{Ar}), 121.5 (C_{Ar}), 119.2 (C_{Ar}), 118.5 (C_d), 118.1 (C_{Ar}), 110.8 (C_{Ar}), 109.1 (C_{Ar}), 51.9 (C_a), 42.6 (C_b or C_e), 39.3 (C_b or C_e), 22.6 (C_f); **3.61f** was derivatized by sequential treatment with $(CF_3CO)_2O$/pyridine and TsCl/NaH. The enantiomeric excess of the product was then determined by chiral HPLC analysis of that derivative: (hexanes/*i*-PrOH = 98/2, flow rate = 1 mL/min), t_R = 8.7 min (*S*), t_R = 19.7 min (*R*).



$[\alpha]^{25}_{589}$ -173.2 (94% *ee*, c 0.50, $CHCl_3$); IR (neat): 3074, 2959, 2925, 1692, 1643, 1598, 1452, 1377, 1208, 1174, 1143, 1089, 1041, 1022, 800, 756, 666, 584, 572, 543 cm^{-1}; ^{1}H NMR (300 MHz,

$CDCl_3$, 5:1 mixture of rotamers): δ 2.27 (CH_3, s, 2.5H), 2.28 (CH_3, s, 0.5H), 2.42-4.80 (H_b, H_e and H_f, m, 6H), 5.04-5.16 (H_d, m, 2H), 5.68-5.98 [H_c (1H) and H_a (0.17H), 1.17H), 6.39 (H_g, dd, J = 2.8 Hz, 10.6 Hz, 0.83H), 7.14 (H_h, d, J = 8.3 Hz, 2H), 7.19-7.36 (H_{Ar}, m, 3H), 7.55 (H_h, d, J = 8.3 Hz, 0.34H), 7.67 (H_g, d, J = 8.3 Hz, 1.66H), 8.09 (H_{Ar}, d, J = 8.1 Hz, 0.17H), 8.17 (H_{Ar}, d, J = 8.3 Hz, 0.83H); ^{13}C NMR (75 MHz, $CDCl_3$, 5:1 mixture of rotamers, signals for the minor isomer are in *italic* style): δ 156.6 (C=O, q, J = 36.0 Hz), *145.3 (C_{Ar})*, 145.2 (C_{Ar}), *136.9 (C_{Ar})*, 136.7 (C_{Ar}), *134.7 (C_c)*, 134.3 (C_c), 134.0 (C_{Ar}), 133.5 (C_{Ar}), *133.0 (C_{Ar})*, 130.0 (C_{Ar}), 129.9 (C_{Ar}), *129.5 (C_{Ar})*, *129.4 (C_{Ar})*, 126.8 (C_{Ar}), *126.5 (C_{Ar})*, *125.5 (C_{Ar})*, 125.3 (C_{Ar}), 124.3 (C_{Ar}), *119.0 (C_{Ar})*, *118.8 (C_{Ar})*,118.6 (C_{Ar}), 118.2 (C_d), 117.2 (C_d), 115.6 (C_{Ar}), *115.4 (C_{Ar})*, 116.5 (CF_3, q, J = 269 Hz), *54.2 (C_a)*, 51.0 (C_a), *39.9 (C_b)*, 39.2 (C_b), 38.2 (C_e), *36.0* (C_e), *22.7 (CH_3)*, 22.2 (C_f), 21.6 (CH_3), *20.4 (C_f)*; MS *m/z* (relative intensity): 462 (M^+, 1.2), 421 (M^+-allyl, 100); HRMS *m/z* Calcd for $C_{20}H_{16}F_3N_2O_3S$ (M^+-allyl): 421.0834. Found: 421.0831.

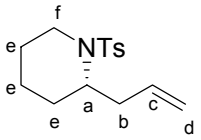
3.5.3.7 (*R*)-1-Allyl-9-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**3.61g**)



$[\alpha]^{25}_{589}$ -202.4 (94% *ee*, c 1.8, $CHCl_3$); IR (neat): 3337, 3070, 2925, 1639, 1597, 1450, 1366, 1172, 754, 667, 584, 573 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.06 (NH, s, br, 1H), 2.26 (CH_3, s, 3H), 2.41-3.15 (H_b, H_e and H_f, m, 6H), 4.53 (H_a, d, J = 9.3 Hz, 1H), 5.14-5.20 (H_d, m, 2H), 5.94 (H_c, m, 1H), 7.09 (H_h, d, J = 8.1 Hz, 2H), 7.19-7.34 (H_{Ar}, m, 3H), 7.51 (H_g, d, J = 8.1 Hz, 2H), 8.11 (H_{Ar}, J =

6.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.6 (C_{Ar}), 137.8 (C_{Ar}), 136.8 (C_{Ar}), 136.0 (C_{Ar}), 134.9 (C_c), 130.7 (C_{Ar}), 129.6 (C_{Ar}), 126.4 (C_{Ar}), 124.5 (C_{Ar}), 123.8 (C_{Ar}), 119.3 (C_{Ar}), 118.3 (C_{Ar}), 117.7 (C_d), 115.5 (C_{Ar}), 52.6 (C_a), 39.0 (C_b or C_e), 37.2 (C_b or C_e), 22.5 (CH_3), 21.5 (C_f); MS(CI) *m/e* (relative intensity): 367 ($[M+1]^+$, 100), 325(M^+-allyl, 14), 192 (M^+-allyl, 100); HRMS *m/z* Calcd for $C_{18}H_{17}N_2O_2S$ (M^+-allyl): 325.1011. Found: 325.1012; The enantiomeric excess of the product was determined by HPLC analysis of its trifluoroacetamide: (hexanes/*i*-PrOH = 98/2, flow rate = 1 mL/min), t_R = 8.7 min (*S*), t_R = 19.7 min (*R*).

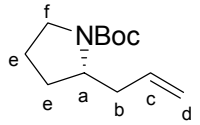
3.5.3.8 (*S*)-2-Allyl-1-tosylpiperidine (**3.62**)



The allylation of imine **3.57** (0.24 mmol) was accomplished according to the general procedure. To the crude reaction mixture was added TsCl (381 mg, 2 mmol) and DMAP (244 mg, 2 mmol). The reaction was stirred at room temperature overnight. Solvent was removed under reduced pressure. The residue was purified by column chromatography (1:1 hexanes/EtOAc) to give 43 mg of **3.62** (65%). $[\alpha]^{25}_{589}$ -42.2 (91% *ee*, c 2.22, CH_2Cl_2) [lit.[39] (*R* enantiomer): $[\alpha]^{27}_{589}$ +35.1 (89.4% *ee*, c 0.40, CH_2Cl_2)]; IR (neat): 3066, 2941, 2865, 1628, 1600, 1452, 1380, 1326, 1150, 926, 814, 658, 550 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16-1.60 (H_e, m, 6H), 2.26 (H_b, t, J = 7.7 Hz, 2H), 2.38 (CH_3, s, 3H), 2.94 (H_f, dt, J = 2.6 Hz, 13.7 Hz, 1H), 3.73 (H_f, dd, J = 3.7 Hz, 13.7 Hz, 1H), 4.07 (H_a, m, 1H), 4.97-5.02 (H_d, m, 2H), 5.65 (H_c, m, 1H), 7.24 (H_{Ar}, d, J = 8.0 Hz, 2H), 7.68 (H_{Ar}, d, J = 8.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.7 (C_{Ar}), 138.7 (C_{Ar}), 134.9 (C_c), 129.5 (C_{Ar}), 126.9 (C_{Ar}), 117.0 (C_d), 52.4 (C_a), 40.6 (C_f), 33.9 (C_b), 26.5 (C_e), 24.5 (C_e), 21.4 (CH_3), 18.1 (C_e); MS (CI) *m/z* (relative

intensity): 280 ([M+1]$^+$, 100), 238, (M$^+$-allyl, 37); The enantiomeric excess of the *N*-tosylamide **3.62** was determined by HPLC analysis: (hexanes/*i*-PrOH = 99.5/0.5, flow rate = 1 mL/min), t_R = 47.5 min (*R*), t_R = 51.2 min (*S*).

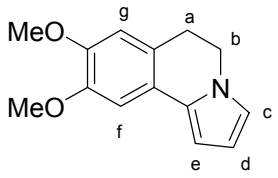
3.5.3.9 (*S*)-*tert*-Butyl 2-allylpyrrolidine-1-carboxylate (**3.63**)



The allylation of imine **3.60** (0.20 mmol) was accomplished according to the general procedure. To the crude reaction mixture was added $(Boc)_2O$ (436 mg, 2 mmol) and NEt_3 (0.2 mL). The reaction was stirred at room temperature overnight. Solvent was removed under reduced pressure. The residue was purified by column chromatography (3:1 hexanes/EtOAc) to give 30 mg of **3.63** (71%). $[\alpha]^{25}_{589}$ -45.4 (92% *ee*, c1.26, $CHCl_3$) [lit.[71] $[\alpha]^{25}_{589}$ -32.4 (c 1.56, $CHCl_3$)]; IR (neat): 3077, 2976, 1694, 1641, 1394, 1366, 1173, 1114 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43 (C$\underline{Me}_3$, s, 9H), 1.54-1.84 (H_e, m, 4H), 2.00-2.55 (H_b, m, 2H), 3.21-3.42 (H_f, m, 2H), 3.66-3.85 (H_a, m, 1H), 4.98-5.05 (H_d, m, 2H), 5.72 (H_c, m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.0 (C=O), 135.2 (C_c), 116.9 (C_d), 78.8 (O$\underline{C}$Me$_3$), 53.7 (C_a), 45.6 (C_f), 38.1 (C_b), 30.0 (C_e), 28.5 [OC($\underline{C}$H$_3$)$_3$], 23.1 (C_e); MS *m/z* (relative intensity): 211 (M$^+$, 0.1), 170 (M$^+$-allyl, 42), 114 (100); The enantiomeric excess of the product was determined by HPLC analysis: (hexanes/*i*-PrOH = 99.5/0.5, flow rate = 0.3 mL/min), t_R = 30.0 min (*R*), t_R = 32.3 min (*S*).

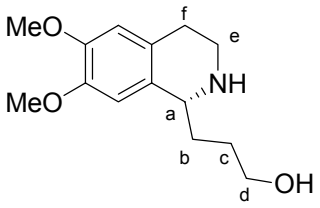
3.5.4 Total Synthesis of (+)-Crispine A

3.5.4.1 Preparation of 5,6-Dihydro-8,9-dimethoxy-pyrrolo[2,1-*a*]isoquinoline (**3.68**)[72]



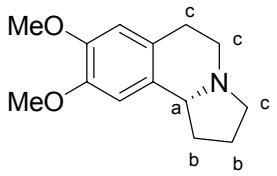
To a solution of amine (*R*)-**361b** (110 mg, 0.47 mmol) in THF (10 mL) was added $Hg(OAc)_2$. A white precipitate was formed in 30 minutes and TLC indicated that the starting material was all consumed. 10% NaOH (20 mL) was added followed by $NaBH_4$ (300 mg) in portions. The grey suspension was stirred at room temperature over night and was extracted with diethyl ether (3 x 15 mL). The combined organic extracts were washed with brine and water then concentrated. Purification was done by flash column chromatography (1:1 hexanes/EtOAc) to give the title compound (62 mg) in 58% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.98 (H_a, t, J = 6.6 Hz, 2H), 3.86 (OMe, s, 3H), 3.90 (OMe, s, 3H), 4.03 (H_b, t, J = 6.6 Hz), 6.18 (H_d, m, 1H), 6.37 (H_e, m, 1H), 6.62 (H_c, m, 1H), 6.68 (H_f, s, 1H), 7.00 (H_g, s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.0 (C_a), 44.2 (C_b), 55.9 (OMe), 56.0 (OMe), 102.2 (C_a), 105.9 (C_a), 108.3 (C_d), 111.3 (C_e), 120.4 (C_c), 122.5 (C_{Ar}), 122.7 (C_{Ar}), 129.9 (C_{Ar}), 147.2 (C_{Ar}), 148.2 (C_{Ar}).

3.5.4.2 Preparation of (*R*)-3-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-1-ol



To a solution of amine (*R*)-**3.61b** (110 mg, 0.47 mmol) in THF (2 mL) was added 9-BBN (3 mL, 0.5 M in THF) dropwise. The reaction was stirred at room temperature for 3 hours. A mixture of aqueous NaOH (3 M, 5 mL) and 30% H_2O_2 (5 mL) were added at room temperature. The exothermic reaction caused the temperature to quickly rise to 55 ^oC and this temperature was maintained for 25 minutes with external heat. The reaction mixture was then cooled to room temperature and extracted with Et_2O (3 x 5 mL). The combined ethereal extracts were washed with brine (10 mL) and dried over Na_2SO_4. Purification by flash column chromatography (10:1 CH_2Cl_2/MeOH, 0.5% NH_4OH) gave the intermediate alcohol (96 mg, 81 %). IR (neat): 3303, 2934, 1611, 1515, 1257, 1223, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.62-2.00 (H_b and H_c, m, 4H), 2.56-2.81 (H_f, m, 2H), 2.95-3.22 (H_e, m, 2H), 3.46-3.66 (H_d, m, 2H), 3.81 (OMe, s, 6H), 3.91 (H_a, dd, J = 4.5 Hz, 7.2 Hz, 1H), 4.72 (NH and OH, s, br, 2H), 6.52 (H_{Ar}, s, 1H), 6.55 (H_{Ar}, s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.5 (C_{Ar}), 147.4 (C_{Ar}), 130.2 (C_{Ar}), 126.6 (C_{Ar}), 111.6 (C_{Ar}), 109.3 (C_{Ar}), 62.8 (C_d), 56.0 (O<u>C</u>H_3), 55.8 (O<u>C</u>H_3), 55.4 (C_a), 39.7 (C_b, C_c or C_e), 35.5 (C_b, C_c or C_e), 30.5 (C_b, C_c or C_e), 28.6 (C_f); MS *m/z* (relative intensity): 251 (M^+, 0.5), 250 (M^+-H, 2.4), 232 (M^+-H-H_2O, 6.5), 192 (M^+-$CH_2CH_2CH_2OH$, 100). HRMS *m/z* Calcd for $C_{14}H_{20}NO_3$ (M^+-H): 250.1443. Found: 250.1444.

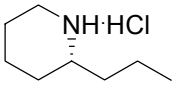
3.5.4.3 Preparation of (+)-Crispine A



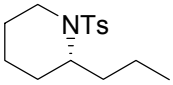
The alcohol (96 mg) obtained from the hydroboration of (*R*)-**361b** was stirred with PPh_3 (262 mg, 1.0 mmol), CBr_4 (331 mg, 1.0 mmol) and *i*-Pr_2NEt (0.3 mL) in THF (10 mL) at room temperature for 2 hours, followed by removal of the solvent under reduced pressure. Flash column

chromatography (3:1 EtOAc/MeOH, 1% NH_4OH) yielded the title compound (73 mg, 66% yield for 2 steps). $[\alpha]^{25}_{589}$ +96.9 (c 1.1, $CHCl_3$) [lit.[73] $[\alpha]^{23}_{589}$ +100.4 (>99% *ee*, c 1, $CHCl_3$)]; IR(neat): 3303, 2934, 1611, 1515, 1257, 1223, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.62-2.00 (H_b, m, 3H), 2.23-2.37 (H_b, m, 1H), 2.48-2.77 (H_c, m, 3H), 2.92-3.21 (H_c, m, 3H), 3.41 (H_a, t, J = 8.4 Hz, 1H), 3.82 (OMe, s, 6H), 6.54 (H_{Ar}, s, 1H), 6.58 (H_{Ar}, s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.2 (C_{Ar}), 147.1 (C_{Ar}), 130.9 (C_{Ar}), 126.2 (C_{Ar}), 111.2 (C_{Ar}), 108.8 (C_{Ar}), 62.9 (C_q), 55.9 (OCH_3), 55.8 (OCH_3), 53.0 (C_c), 48.2 (C_c), 30.4 (C_b or C_c), 27.9 (C_b or C_c), 22.2 (C_b); MS *m/z* (relative intensity): 233 (M^+, 43), 232 (M^+-H, 100), 205 (M^+-C_2H_4, 43), 190 (M^+-$CH_2CH_2CH_2OH$, 33).

3.5.5 Total Synthesis of *R*-(-)-Coniine·HCl

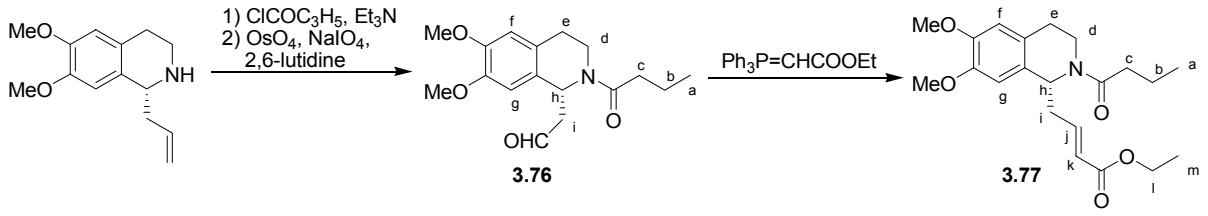


Allylation of imine **3.57** (0.32 mmol) was accomplished according to the general procedure. To the crude reaction mixture was added 10% Pd/C (5 mol%) and MeOH (3 mL). The suspension was stirred at room temperature under a H_2 atmosphere balloon for 12 hours before the addition of HCl/Et_2O (4 mL, 0.5 M). (*R*)-(-)-Coniine·HCl was obtained after column chromatography on silica gel (10:1-6:1 CH_2Cl_2/MeOH). $[\alpha]^{25}_{589}$ -6.8 (c 0.34, EtOH) [lit.[74] $[\alpha]^{22}_{589}$ -7.1 (c 1.0, EtOH)]; ^1H NMR (300 MHz, $CDCl_3$): δ 0.84 (t, J = 7.3 Hz, 3H), 1.20-1.95 (m, 10H), 2.65-2.94 (m, 2H), 3.23-3.42 (m, 1H), 9.10 (s, br, 1H), 9.34 (s, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 57.0, 44.6, 35.2, 28.0, 22.3, 22.0, 18.4, 13.6; The enantiomeric excess of the product was determined by HPLC analysis of its *p*-toluenesulfonamide: (hexanes/*i*-PrOH = 99/1, flow rate = 1 mL/min), t_R = 25.0 min (*S*), t_R = 27.1 min (*R*).



$[\alpha]^{25}_{589}$ -34.5 (c 1.0, benzene) [lit.[75] (for *S* enantiomer): $[\alpha]^{24}_{589}$ +39.6 (c 0.53, benzene)]; IR (neat): 3063, 3021, 2937, 2871, 1598, 1337, 1151, 1093, 932, 815, 712, 694, 653, 599, 552 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, J = 7.3 Hz, 3H), 1.10-1.65 (m, 10H), 2.39 (s, 3H), 2.96 (t, J = 13.5 Hz, 1H), 3.71 (dd, J = 3.7 Hz, 13.5 Hz, 1H), 3.95-4.06 (m, 1H), 7.25 (d, J = 7.8 Hz, 2H), 7.69 (d, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.2, 139.3, 129.5, 126.9, 52.7, 40.5, 31.6, 27.3, 24.4, 21.4, 19.6, 18.4, 13.9; MS (CI) *m/z* (relative intensity): 282 (M^+, 100), 238 (M^+-$CH_2CH_2CH_3$, 31).

3.5.6 Preparation of (*R*, *E*)-Ethyl 4-(2-Butyryl-6,7-dimethoxy-1,2,3,4-tetrahydro isoquinolin-1-yl)but-2-enoate (3.77)



To a solution of amine (*R*)-**3.61b** (300 mg, 1.29 mmol) in CH_2Cl_2 (5 mL) at 0 ^oC was added butyryl chloride (0.4 mL), triethylamine (0.80 mL) and DMAP (10 mg). The reaction mixture was stirred at room temperature overnight before quenching with $NaHCO_3$ (sat.). The organic layer was separated and the aqueous phase was washed with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with 1 M HCl (10 mL) and brine then dried over Na_2SO_4. Crude amide **3.75** was obtained in quantitative yield after evaporation of the solvent.

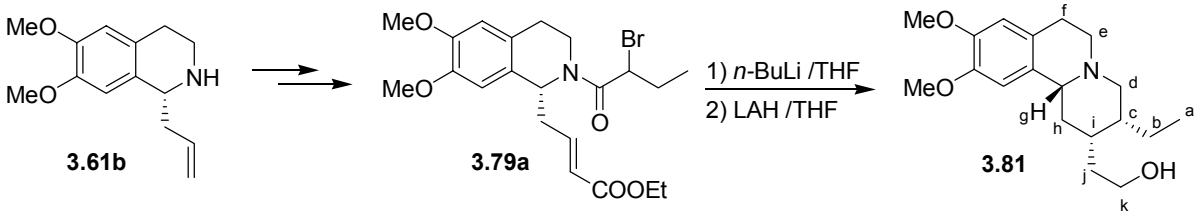
Amide **3.75** (170 mg, 0.56 mmol) was dissolved in 6 mL of dioxane/H_2O (3:1) and was treated with osmium tetroxide (0.55 mL, 0.012 mmol, 0.022 M in water, 2 mol%), $NaIO_4$ (480 mg, 2.24

mmol) and 2,6-lutidine (120 mg, 1.12 mmol). Ethyl acetate (15 mL) was added after the suspension was stirred at room temperature for 3 hours. The organic phase was separated and was washed with Na_2SO_3 (sat., 3 x 15 mL) then dried over Na_2SO_4. Evaporation of volatiles left a pale yellow oil which was purified by flash column chromatography (2:1 EtOAc/hexanes) to give pure aldehyde **3.76** (140 mg) in 82% yield. ^{1}H NMR (300 MHz, $CDCl_3$, 4.9:1 rotamers, signals for the minor isomer are in *italic* style): *δ 0.83 (H_a, t, J = 7.1 Hz, 0.51H)*, 0.85 (H_a, t, *J* = 7.4 Hz, 2.49H), 1.40-1.68 (H_b, m, 2H), 2.12-2.41 (H_c, m, 2H), 2.58-3.10 (H_e and H_i, m, 4H), 3.40 (H_d, ddd, J = 4.5 Hz, 10.3 Hz, 13.7 Hz, 0.83H), *3.47-3.58 (H_d, m, 0.17H)*, 3.66-3.83 (2 x OMe and H_d, m, 6.83H), *4.50-4.64 (H_d, m, 0.17H)*, *5.39 (H_h, t, J = 6.1 Hz, 0.17H)*, 5.94 (H_h, dd, *J* = 4.7 Hz, 9.2 Hz, 0.83H), *6.49 (H_{Ar}, s, 0.17H)*, *6.50 (H_{Ar}, s, 0.17H)*, 6.51 (H_{Ar}, s, 0.83H), 6.58 (H_{Ar}, s, 0.83H). ^{13}C NMR (75 MHz, $CDCl_3$, 4.9:1 rotamers, signals for the minor isomer are in *italic* style): *δ* 200.0 (C̲HO), *199.3 (C̲HO)*, 172.0 (N-C̲=O), *171.7 (N-C̲=O)*, *148.1 (C_{Ar})*, 147.9 (C_{Ar}), 147.8 (C_{Ar}), *147.5 (C_{Ar})*, *127.8 (C_{Ar})*, 127.6 (C_{Ar}), *126.3 (C_{Ar})*, 125.5 (C_{Ar}), *111.6 (C_{Ar})*, 111.2 (C_{Ar}), 109.6 (C_{Ar}), *108.9 (C_{Ar})*, 55.9 (OMe), 55.7 (OMe), *51.5 (C_h)*, 51.0 (C_h), *49.9 (C_i)*, 47.6 (C_i), 40.0 (C_d), *35.7* (C_d), 35.3 (C_c), *35.1* (C_c), 28.5 (C_e), *27.2 (C_e)*, *18.5 (C_b)*, 18.3 (C_b), *14.0 (C_a)*, 13.7 (C_a); MS (EI) *m/z* (relative intensity): 305 (M^+, 3), 287 (M^+-H_2O, 100).

To a solution of aldehyde **3.76** (100 mg, 0.33 mmol) in CH_2Cl_2 (5 mL) was added Ph_3P=CHCOOEt (150 mg, 0.431 mmol). The solution was stirred at room temperature for 2 hours. Evaporation of volatiles resulted in a pale yellow oil which was subjected to flash column chromatography (2:1 EtOAc/hexanes) to afford the title compound in quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$, 2.9:1 rotamers, signals for the minor isomer are in *italic* style): *δ* 0.83 *(H_a, t, J = 7.4 Hz, 0.78H)*, 0.87 (H_a, t, *J* = 7.4 Hz, 2.22H), 1.11-1.21 (H_m, m, 3H), 1.47-1.66 (H_b, m, 2H),

2.12-2.40 (H_c, m, 2H), 2.49-2.98 (H_e and H_i, m, 4H), 3.38 (H_d, ddd, J = 4.6 Hz, 10.3 Hz, 13.9 Hz, 0.74H), *3.46-3.55 (H_d, m, 0.26H)*, 3.63-3.84 (2 x OMe and H_d, m, 6.74H), 3.94-4.14 (H_l, m, 2H), *4.57-4.68 (H_d, m, 0.26H)*, *4.82 (H_h, dd, J = 6.1Hz, 7.9 Hz, 0.26H)*, 5.59 (H_h, t, J = 6.8 Hz, 0.74H), 5.63-5.83 (H_k, m, 1H), 6.46-6.54 (H_{Ar}, m, 2H), 6.73-6.93 (H_j, m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 2.9:1 rotamers, signals for the minor isomer are in *italic* style): δ 171.8 (N-C=O), *171.7 (N-C=O)*, 166.1 (O-C=O), *165.8 (O-C=O)*, *148.2 (C_{Ar})*, 147.9 (C_{Ar}), 147.6 (C_{Ar}), *147.4 (C_{Ar})*, 144.9 (C_j), *143.6 (C_j)*, 128.1 (C_{Ar}), *127.5 (C_{Ar})*, *126.7 (C_{Ar})*, 125.6 (C_{Ar}), *124.7 (C_k)*, 123.6 (C_k), *111.7 (C_{Ar})*, 111.2 (C_{Ar}), 110.0 (C_{Ar}), *109.5 (C_{Ar})*, 60.4 (C_l), 56.0 (OMe), 55.9 (OMe), *55.4 (C_h)*, 51.1 (C_h), 40.3 (C_d or C_i), *39.8 (C_d or C_i)*, 39.2 (C_d or C_i), 35.6 (C_c), 35.4 *(C_d or C_i or C_c)*, 35.2 *(C_d or C_i or C_c)*, 28.8 (C_e), *27.6 (C_e)*, *21.0 (C_b)*, 18.7 (C_b), 14.3 (C_m), 14.0 (C_a); MS (EI) *m/z* (relative intensity): 375 (M^+, 2), 262 (M^+-CH_2CH=CHCOOEt, 100).

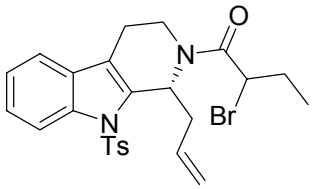
3.5.7 Preparation of 3-*epi*-Protoemetinol (3.81)[76,77]



Compound **3.79a** was synthesized using a similar procedure to the preparation of compound **3.77**. To a solution of **3.79a** (150 mg, 0.33 mol) in THF (40 mL) at -78 ^{o}C was added *n*-BuLi (0.27 mL, 0.40 mmol, 1.5 M in hexane, 1.2 equiv.) dropwise. The clear solution was stirred at that temperature for 2 minutes before 1 mL of MeOH was added. Solvents were removed *in vacuo* and the ^{1}H NMR of the residue (crude **3.73**) indicated the existence of two diastereomers (~ 4:1).

The crude δ-lactam **3.73** was then taken up in 5 mL of THF and LAH (120 mg, 3.16 mmol) was added in one portion at 0 ^{o}C. The suspension was brought to reflux for 2 hours before cooling down to 0 ^{o}C again. Saturated NH_4Cl solution (0.5 mL) was added very slowly to quench the reaction. Solids were filtered off and filtrate was concentrated to leave an oily residue. Purification of this oily residue by flash column chromatography (EtOAc) gave the title compound in 68% yield (from **3.79a**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (H_a, t, J = 7.3 Hz, 3H), 1.16-1.35 (H_b and H_f, m, 2H), 1.42 (H_c, m, 1H), 1.50-1.68 (H_b and H_j, m, 3H), 1.86 (H_i, m, 1H), 1.98 (H_h, m, 1H), 2.25 (H_d, dd, J = 1.6 Hz, 11.1 Hz, 1H), 2.40 (H_e, dt, J = 3.5 Hz, 11.7 Hz, 1H), 2.54 (H_f, dd, J = 3.5 Hz, 16.0 Hz, 1H), 2.81 (H_e, dd, J = 6.0 Hz, 11.7 Hz, 1H), 2.90-3.13 (H_c, H_e and H_g, m, 3H), 3.71 (H_k, t, J = 6.7 Hz, 2H), 3.81 (OMe, s, 3H), 3.82 (OMe, s, 3H), 6.54 (H_{Ar}, s, 1H), 6.66 (H_{Ar}, s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.3 (C_{Ar}), 147.0 (C_{Ar}), 130.6 (C_{Ar}), 127.0 (C_{Ar}), 111.5 (C_{Ar}), 108.1 (C_{Ar}), 63.3 (C_a), 60.7 (C_a), 59.0 (C_a), 56.1 (OMe), 55.8 (OMe), 53.0 (C_g), 39.0 (C_f), 36.6 (C_e), 36.3 (C_l), 33.8 (C_h), 29.3 (C_f), 17.5 (C_b), 12.5 (C_a).

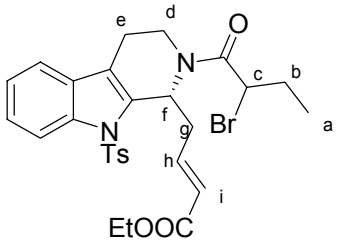
3.5.8 Preparation of 1-((*R*)-1-Allyl-9-tosyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)-2-bromobutan-1-one (3.98)



A solution of amine **3.61g** (220 mg, 0.60 mmol) in CH_2Cl_2 (20 mL) was treated with DCC (1.18 g, 5.72 mmol), 2-bromobutyric acid (957 mg, 5.73 mmol) and DMAP (20 mg) at -10 ^{o}C. The reaction was allowed to warm to room temperature for 2 hours. Solid material was filtered off and the

filtrate was washed with 10% $NaHCO_3$ (aq.). Removal of the volatiles gave the crude amide **3.98** in quantitative yield. This crude material was used without further purification.

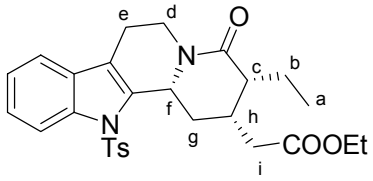
3.5.9 Preparation of (*E*)-Ethyl 4-((*R*)-2-(2-Bromobutanoyl)-9-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)but-2-enoate (3.99)



Amide **3.98** was dissolved in dioxane/H_2O (3:1, 15 mL). 2,6-Lutidine (0.15 mL), OsO_4 (0.6 mL, 0.022 M in water) and $NaIO_4$ (510 mg, 4.68 mmol) were added and the mixture was stirred at room temperature for 4 hours. The reaction mixture was then diluted with EtOAc (10 mL) and water (10 mL). The organic phase was separated and the aqueous phase was washed with EtOAc (3 x 10 mL). The combined organic phases were washed with saturated Na_2SO_3 and brine then dried over Na_2SO_4. Following removal of the solvent, the crude aldehyde was taken up in CH_2Cl_2 (10 mL) and treated with Ph_3P=CHCOOEt (0.28 g, 0.8 mmol) at room temperature for 2 hours. Solvent was then removed under reduced pressure. Flash column chromatography (2:1 EtOAc/hexanes) afforded the title compound (288 mg, 82% yield for three steps). ^{1}H NMR (300 MHz, DMSO, mixture of diastereomers and rotamers) δ 0.75-0.89 (H_a, m, 3H), 1.15 ($COOCH_2C\underline{H}_3$, t, J = 7.1 Hz, 3H), 1.79-2.26 (H_b and $ArCH_3$, m, 5H), 2.57-3.23 (H_e and H_g, m, 4H), 3.43-3.61 (H_d, m, 1H), 3.94-4.68 ($COOC\underline{H}_2CH_3$ and H_d, m, 3H), 4.76-5.64 (H_c, m, 1H), 5.81-7.08 (H_f, H_h and H_i, m, 3H), 7.15-7.48 (H_{Ar}, m, 5H), 7.55-7.69 (H_{Ar}, m, 1.74H), 7.74-7.81 (H_{Ar}, m, 0.26H), 7.94 (H_{Ar}, d, J = 8.4 Hz, 0.13H), 8.01 (H_{Ar}, d, J = 8.2 Hz, 0.87H); ^{13}C NMR (75 MHz, $CHCl_3$, signals for the major isomer): δ 167.8

(N-C=O), 165.9 (O-C=O), 144.9 (C_h), 144.0 (C_{Ar}), 136.7 (C_{Ar}), 134.8 (C_{Ar}), 133.9 (C_{Ar}), 129.7 (C_{Ar}), 129.6 (C_{Ar}), 129.3 (C_{Ar}), 126.7 (C_{Ar}), 125.0 (C_i or C_{Ar}), 124.1 (C_i or C_{Ar}), 118.5 (C_{Ar}), 118.0 (C_{Ar}), 115.4 (C_{Ar}), 60.1 ($COOCH_2CH_3$), 48.8 (C_c), 44.7 (C_f), 37.4 (C_d), 36.9 (C_e), 28.8 (C_g), 21.5 ($ArCH_3$), 20.4 (H_b), 14.2 ($COOCH_2CH_3$), 12.1 (C_a); MS (ESI) *m/z* (relative intensity): 558 (M^++H, 100), 238 (M^+-$CH_2CH_2CH_3$, 31); HRMS *m/z* Calcd for $C_{28}H_{32}BrN_2O_5S$ (M^++H): 587.1215. Found: 587.1207.

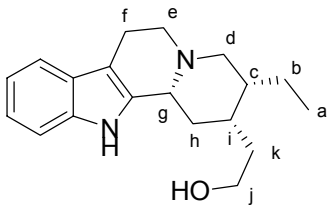
3.5.10 Preparation of Ethyl 2-((2*S*,3*R*,12*bR*)-3-Ethyl-4-oxo-12-tosyl-1,2,3,4,6,7,12,12*b*-octahydroindolo[2,3-*a*]quinolizin-2-yl)acetate (3.100)



To a solution of compound **3.99** (220 mg, 0.375 mmol) in THF (35 mL) at -78 °C was added *n*-BuLi (0.414 mmol, 0.28 mL, 1.48 M in hexane) dropwise. The resulting clear solution was stirred at that temperature for an additional 2 minutes. The reaction was quenched with a minimum amount of saturated NH_4Cl solution. Evaporation of the solvent gave an oily residue that was purified by flash column chromatography (2:1 EtOAc/hexanes) to afford the title compound (**3.100**) as a single diastereomer (119 mg, 63%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (H_a, t, J = 7.4 Hz, 3H), 1.18 ($COOCH_2CH_3$, t, J = 7.1 Hz, 3H), 1.45-1.81 [H_b and H_g (1H), m, 3H], 2.12 (H_i, dd, J = 9.4 Hz, 15.5 Hz, 1H), 2.23 ($ArCH_3$, s, 3H), 2.38 (H_i, dd, J = 5.7 Hz, 15.5 Hz, 1H), 2.45-2.81 [H_c, H_d (1H) and H_e, H_h, m, 5H], 3.05 (H_g, dt, J = 13.5 Hz, 5.2 Hz, 1H), 4.01-4.12 ($COOCH_2CH_3$, m, 2H), 4.96-5.11 [H_d (1H) and H_f, m, 2H], 7.04 (H_{Ts}, d, J = 8.2 Hz, 2H), 7.15-7.32 (H_{Ar}, m, 3H), 7.41 (H_{Ts}, d, J = 8.2 Hz, 2H), 8.06 (H_{Ar}, d, J = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5 (O-C=O), 172.0 (N-C=O), 144.9 (C_{Ts}), 138.1 (C_{Ar}), 135.7 (C_{Ar}), 133.2 (C_{Ts}), 130.2 (C_{Ar}), 129.2 (C_{Ts}), 126.4 (C_{Ts}), 125.2 (C_{Ar}),

124.5 (C_{Ar}), 123.1 (C_{Ar}), 118.6 (C_{Ar}), 116.3 (C_{Ar}), 60.5 (COO<u>C</u>$H_2$$CH_3$), 53.7 ($C_f$), 45.3 ($C_c$), 38.5 ($C_d$), 36.9 ($C_i$), 35.6 ($C_g$), 31.1 ($C_h$), 21.7 ($C_e$), 21.4 (Ar<u>C</u>$H_3$), 20.7 ($C_b$), 14.1 (COOCH$_2$<u>C</u>$H_3$), 12.8 ($C_a$).

3.5.11 Preparation of *ent*-Corynantheidol[66-69]



Ester **3.100** (110 mg, 0.216 mmol) was dissolved in THF (35 mL) and LAH (130 mg, 15 equiv.) was added in 4 portions over 2 hours. The suspension was stirred at ambient temperature over night. The reaction was then cooled to 0 ^oC and the unreacted LAH quenched carefully with saturated NH_4Cl. Removal of solid by filtration resulted in a clear solution that was concentrated to an oily residue. Purification by flash column chromatography (12:1 CH_2Cl_2/MeOH, 0.5% NH_4OH) gave the desired compound *ent*-corynantheidol as a white solid (57 mg, 88%), which has identical spectroscopic properties to those reported in the literature. $[\alpha]_D^{20}$ +93.2 (c 0.65, pyridine) [lit.[68] for corynantheidol: $[\alpha]_D^{20}$ -93.0 (c 0.52, pyridine)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (H_a, t, J = 7.3 Hz, 3H), 1.17-1.94 (H_b, H_c, H_h, H_i and H_k, m, 8H), 2.24 (OH, s, br, 1H), 2.32 (dd, J = 2.2 Hz, 11.5 Hz, 1H), 2.46-2.75 (H_d, m, 2H), 2.86-3.15 (H_e, H_f and H_g, m, 4H), 3.71 (H_j, dt, J = 2.5 Hz, 6.5 Hz, 2H), 7.04-7.15 (H_{Ar}, m, 2H), 7.28 (H_{Ar}, d, J = 7.4 Hz, 1H), 7.45 (H_{Ar}, d, J = 7.3 Hz, 1H), 8.05 (NH, s, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.0 (C_{Ar}), 135.4 (C_{Ar}), 127.4 (C_{Ar}), 121.0 (C_{Ar}), 119.2 (C_{Ar}), 118.0 (C_{Ar}), 110.8 (C_{Ar}), 107.9 (C_{Ar}), 60.7 (C_j). 60.4 (C_g), 57.9 (C_d or C_e), 53.5 (C_d or C_e), 39.6 (C_c), 36.5 (C_i), 36.0 (C_h), 31.9 (C_f), 21.7 (C_k), 17.7 (C_b), 12.6 (C_a);MS (EI) *m/z* (relative intensity): 298 (M^+, 85), 297 (M^+-H, 100); HRMS *m/z* Calcd for $C_{19}H_{25}NO_2$ (M^+-H): 297.1967. Found: 297.1974.

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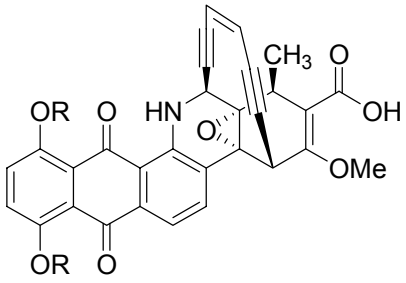
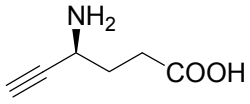
Chapter 4. Asymmetric Syntheses of Propargylamides *via* 3,3′-Disubstituted Binaphthol-modified Alkynylboronates

4.1 Introduction

Optically active propargyl amines may be encountered within bioactive natural products such as dynemicin A, a potent antibiotic and antitumour agent isolated from *Micromonospora chersina*.[1] They are also present in various synthetic medicinal agents such as (*S*)-γ-acetylenic GABA (γ-aminobutyric acid), which has been shown to be responsible for the inhibition of mammalian GABA transaminase. [2-5]



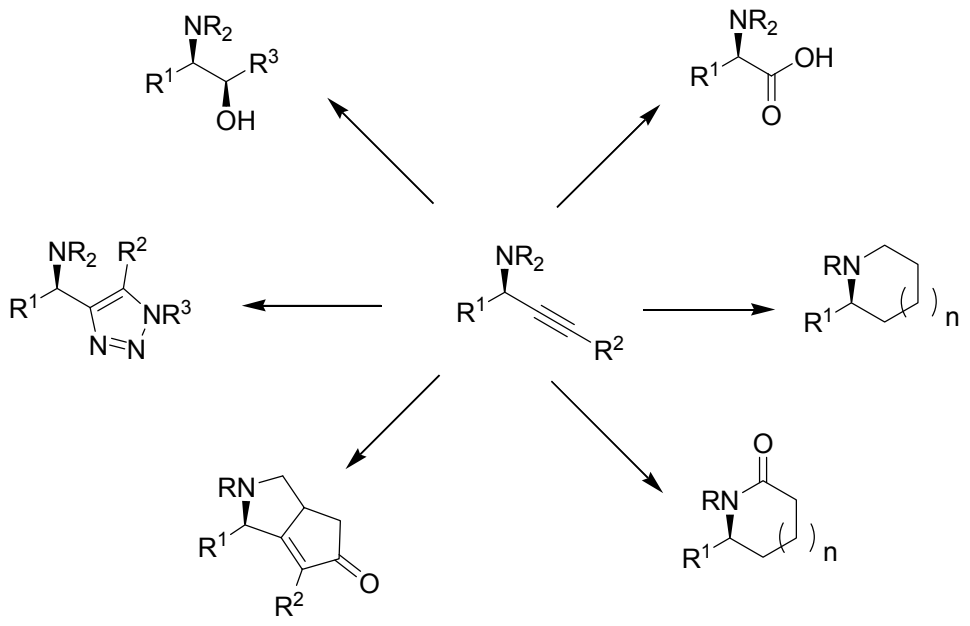
Dynemicin A



(*S*)-γ-acetylenic GABA

Figure 4.1 Examples of naturally occurring or bioactive chiral propargyl amines.

Although there are some interesting targets bearing propargyl amine subunits, the main significance of these compounds is from a broader synthetic perspective: Optically active propargyl amines serve as versatile synthetic intermediates in the total synthesis of natural products. They can be easily converted into various nitrogen-containing compounds such as amino alcohols, amino acids, cyclic amines, lactams, heterocycles and many other functionalities (Scheme 4.1). [6-11]

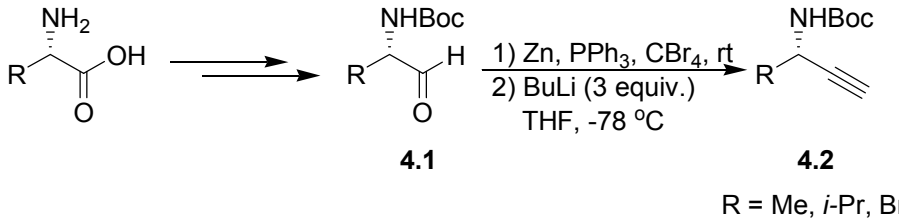


Scheme 4.1

Not surprisingly, the preparation of optically active propargyl amines has been an important topic of organic synthesis. Great efforts have been made in the past two decades to develop new methodologies for generating these optically active propargyl amines. These methodologies in general can be divided into three categories: (1) chiral pool and stereospecific reactions; (2) chiral auxiliary controlled reactions and (3) asymmetric catalytic reactions. Some typical examples are discussed below.

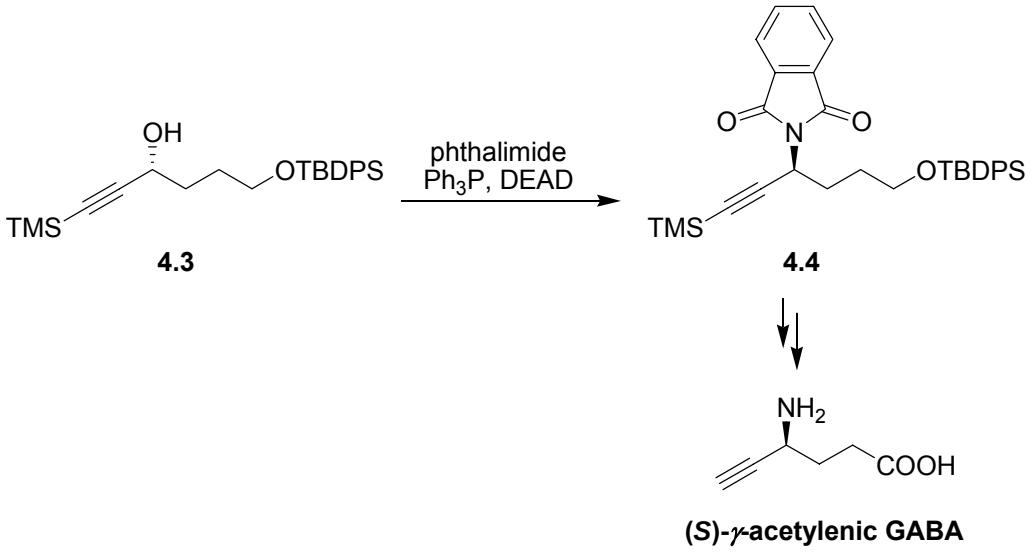
4.1.1 Chiral Pool and Stereospecific Reactions

A decade ago, when there were not many asymmetric reactions available, the synthesis of optically active propargyl amines relied to a great extent on chiral pool chemistry and stereospecific functional group transformations.[12-18] For instance, propargyl amines **4.2** could be obtained from naturally occurring amino acids without disturbing the chiral center adjacent to the amino group (Scheme 4.2).[12]



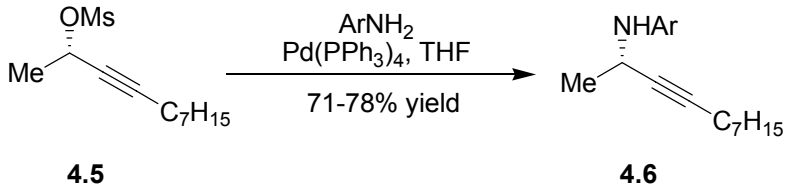
Scheme 4.2

Chiral propargyl alcohols, which could be obtained easily from the asymmetric reduction of alkynyl ketones or asymmetric alkynylation of aldehydes, are also good starting materials for the preparation of optically active propargyl amines. For example, Holmes and coworkers reported that chiral propargyl phthalimide **4.4** could be obtained from propargyl alcohol **4.3** using Mitsunobu chemistry.[5,16] Compound **4.4** was the key intermediate for the synthesis of (*S*)-*γ*-acetylenic GABA (Scheme **4.3**).[19]



Scheme 4.3

Similarly, propargyl alcohols could be converted to the corresponding propargyl amines **4.6** under palladium catalysis (Scheme **4.4**). The reaction is believed to go through an allenyl-Pd intermediate and products with retention of configuration were obtained.[13]

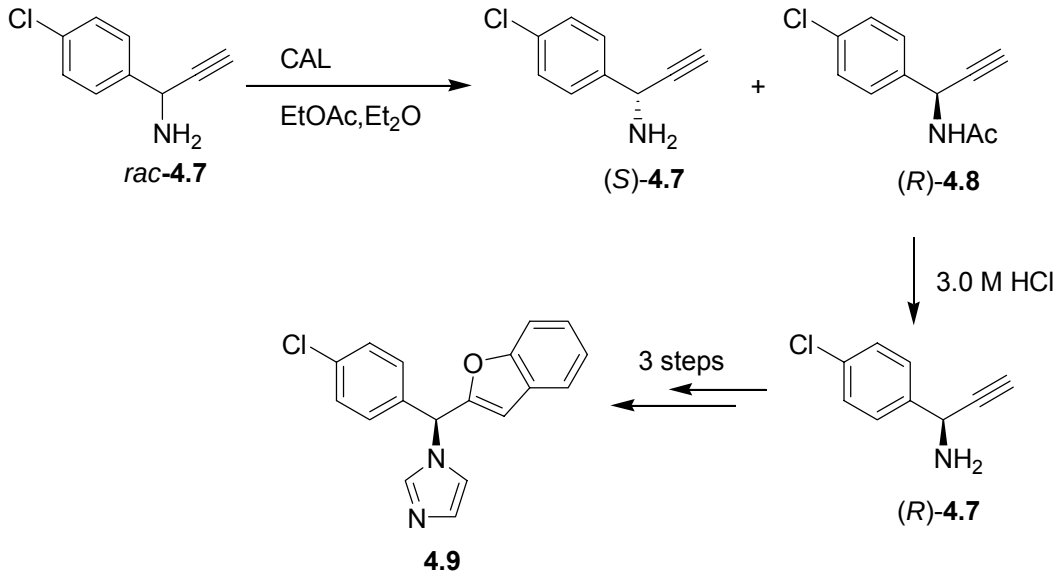


4.5 **4.6**

Scheme 4.4

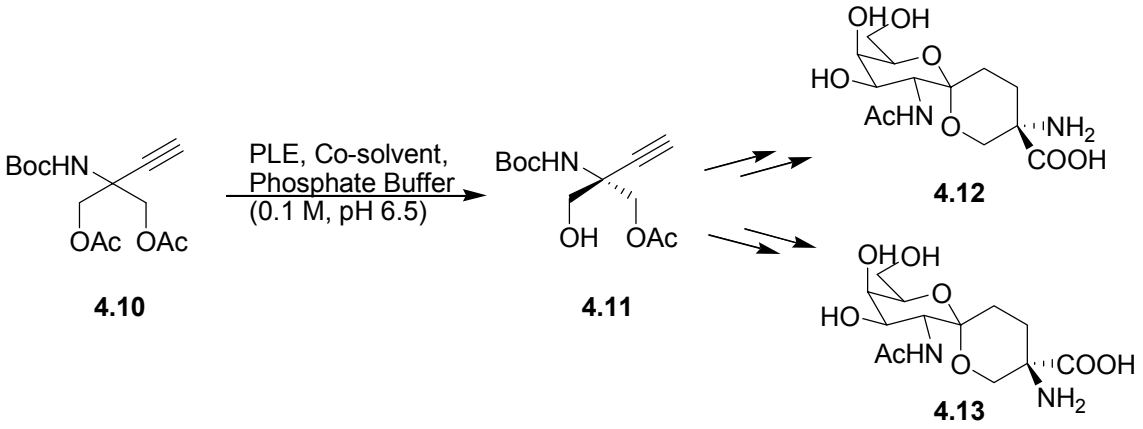
4.1.2 Enzyme Chemistry

The important role of enzymes in organic synthesis has been well-documented,[20] and the advantages include minimal byproducts and mild reaction conditions. In 1999, Botta reported an enzymatic resolution of racemic propargyl amine *rac*-**4.7**. Racemic propargyl amine **4.7** was mixed with lipase B from *Candida antarctica* in organic solvents such as ether and EtOAc to give both of the two enantiomers with >98% *ee*.[13,21] The produced optically active propargyl amine (*R*)-**4.7** was the key intermediate for the synthesis of **4.9**, which is a potent aromatase inhibitor (IC_{50} 5.3 nM *in vitro*) and has shown promise as chemotherapeutic agent for the treatment of estrogen-dependent tumors.[22-24]



Scheme 4.5

Another enzymatic desymmetrization of propargyl amine **4.10** was later developed by Halcomb in 2003. Amine **4.11** could be obtained from the diacetate **4.10** with moderate *ee*'s (76-80%) in the presence of pig liver esterase (PLE).[25] Syntheses of constrained glycopeptides **4.12** and **4.13** were accomplished using propargyl amine **4.11** as starting material. (Scheme 6)

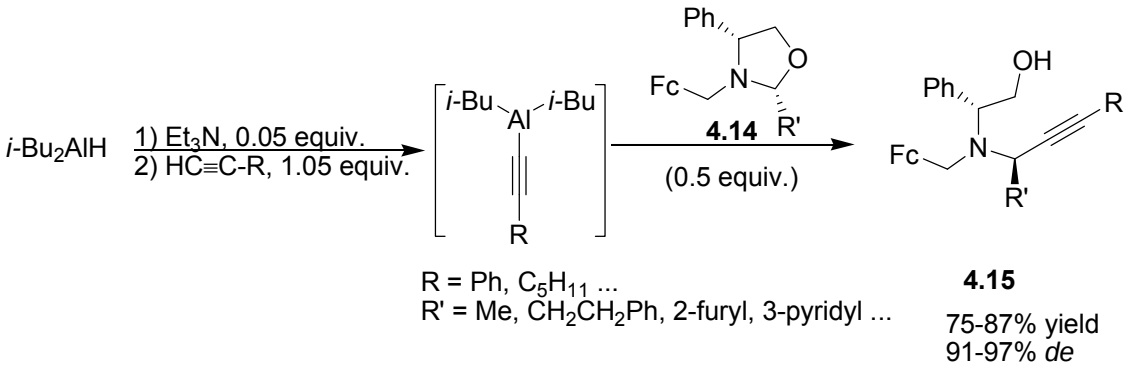


Scheme 4.6

4.1.3 Chiral Auxiliary Controlled Reactions

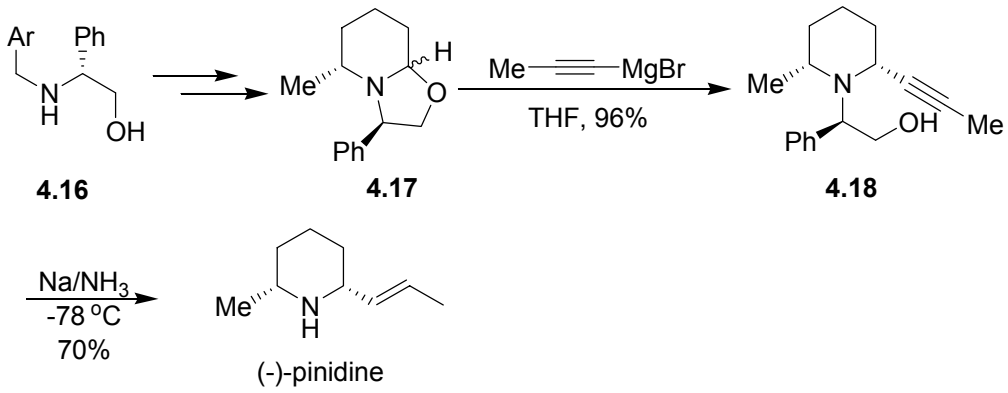
4.1.3.1 Alkynylation of Chiral 1,3-Oxazolidines

Chiral 1,3-oxazolidines **4.14**, which can be easily synthesized by the condensation of chiral 1,2-amino alcohols and aldehydes, are known to react with various organometallic reagents in a highly diastereoselective manner to give chiral amines in high chemical and optical yields.[26-32] Husson and coworkers found that **4.14** reacted with aluminum acetylides to give the desired propargylamines with excellent yields and diastereoselectivities (Scheme 4.7).[33-36]



Scheme 4.7

Alkynyl Grignard reagents could also be applied in this type of reaction. Thus chiral 1,3-oxazolidine **4.17** was treated with 1-propynyl magnesium bromide to give a cyclic propargylamine **4.18** in diastereomerically pure form. This resulting propargylamine was then treated with Na/NH_3 to give a natural product (-)-pinidine (Scheme 4.8).[37]



Scheme 4.8

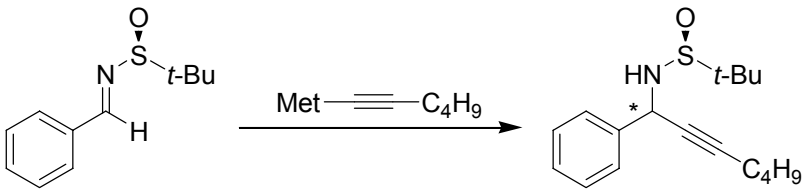
4.1.3.2 Alkynylation of Chiral Imino Compounds

The diastereoselective addition of organometallic reagents to the C=N bond of chiral imines or their derivatives has proven to be very efficient.[38] However, this strategy often gives unsatisfactory results for the preparation of propargylamines. Enders and coworkers described a general method for

the alkynylation of chiral imines in 1995. However, the reaction involved a 1,2-addition of organocerium reagents to aldimines bearing chiral auxiliaries which had to be performed at -100 ^{o}C and the cleavage of the chiral auxiliaries was sometimes problematic.[39,40] The nucleophilic addition of alkynyl Grignard reagents on chiral acyliminiums has recently been reported to proceed at more elevated temperature (35 °C) but with moderate diastereoselectivities *(ca* 65 % *de*) in most cases.[41,42]

Recently, Ellman's auxiliary has been found to be very efficient in inducing high diastereoselectivities in the metal acetylides addition to imines.[43-45] However, the stereoselectivity of this reaction is highly dependent on the metal that is connected with the acetylene (Table 4.1).[43]

Table 4.1 Alkynylation of *t*-butanesulfinimines.



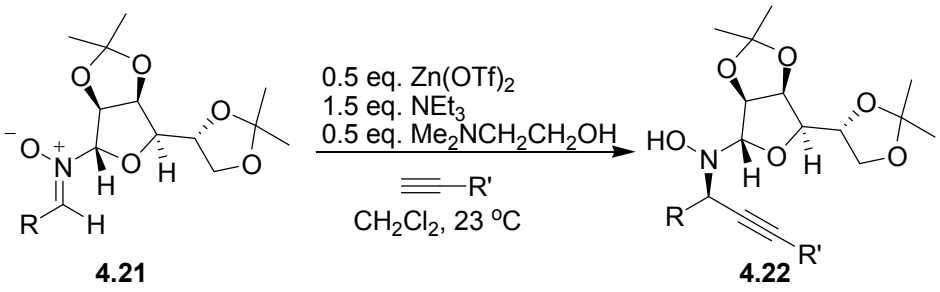
4.19 **4.20**

Met	dr (*R*:*S*)	Yield
MgEt	1:3	74%
Li	1:7	99%
K	2:1	30%
Si(OEt)$_3$[a]	**20:1**	**95%**

[a] Activated with 20 mol% of KOEt and 18-crown-6.

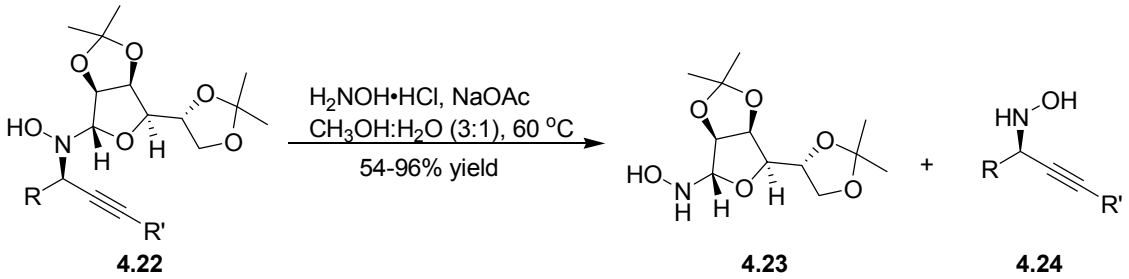
In 2002, Carreira reported a highly diastereoselective addition of terminal alkynes to chiral nitrones **4.21**. The method prescribes the use of nitrones which are conveniently prepared through condensation of the corresponding aldehydes and a mannose-derived glycosidic *N*-hydroxylamine.

The chiral nitrones were treated with a variety of terminal acetylenes in the presence of Zn (II) triflate, 2-dimethylaminoethanol and triethylamine to yield adducts in excellent yields and diastereoselectivites.[46]



Scheme 4.9

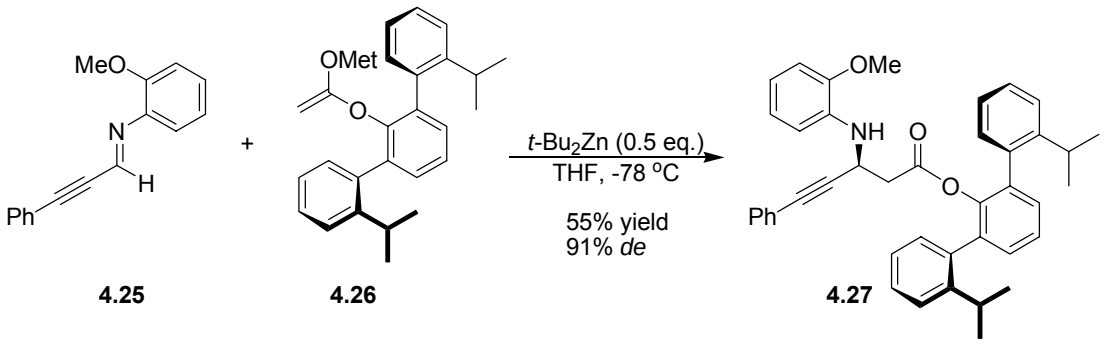
After the reaction was completed, the produced diastereomers **4.22** were treated with *N*-hydroxylamine hydrochloride to give enantiomerically enriched propargylhydroxylamines **4.24** and the chiral auxiliary **4.23** in good yields.



Scheme 4.10

4.1.3.3 Miscellaneous Reactions

Chiral propargylamines could also be prepared from a Mannich-type reaction between an achiral alkynylimine **4.25** and an enolate **4.26** bearing a chiral auxiliary. The resulting β-amino esters could be converted to other useful compounds such as β-amino ketones and 1,3-amino alcohols.[47]



4.25 **4.26** **4.27**

Scheme 4.11

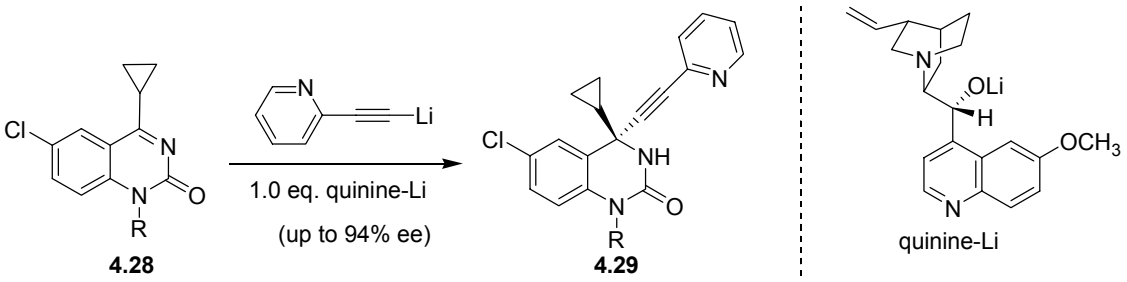
4.1.4 Asymmetric Catalysis

Although chiral auxiliary controlled approaches have proven useful, the requirement of the attachment and the removal of the chiral auxiliaries is a cumbersome feature. Also, another major drawback is that stoichiometric amounts of enantiomerically pure compounds (auxiliaries) are required in these processes. Throughout the last decades, numerous efforts have been made to avoid these problems. An important development in recent years has been the application of chiral catalysts to induce the formation of chiral propargyl amines from achiral starting materials.

4.1.4.1 Imine Alkynylation

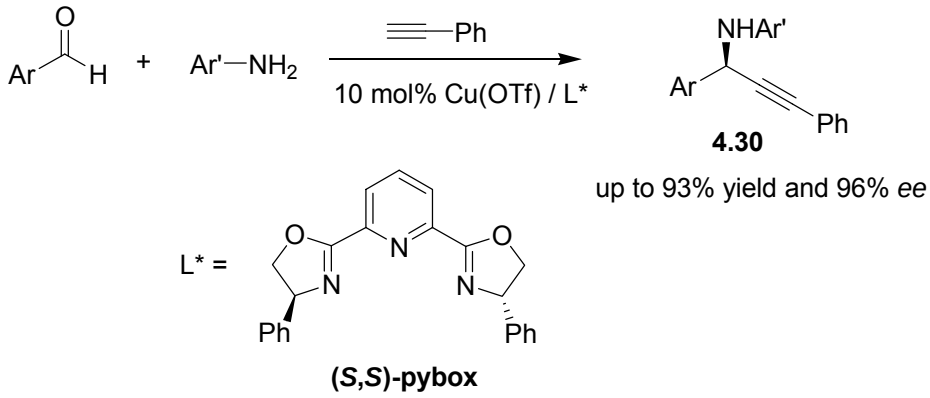
A pioneering work in the area of imine alkynylation was done by Huffman and coworkers in 1995. They found that lithium acetylides could add to imino compounds **4.28** in the presence of stoichiometric amounts of the lithium salt of quinine to afford enantiomerically enriched products

4.29 (Scheme 4.12).[2] However the enantioselectivity of this reaction is very sensitive to the structures of substrates and lithium acetylides. Although a stoichiometric amount of chiral inducer has to be used, tedious chiral auxiliary manipulation is not required in this case.



Scheme 4.12

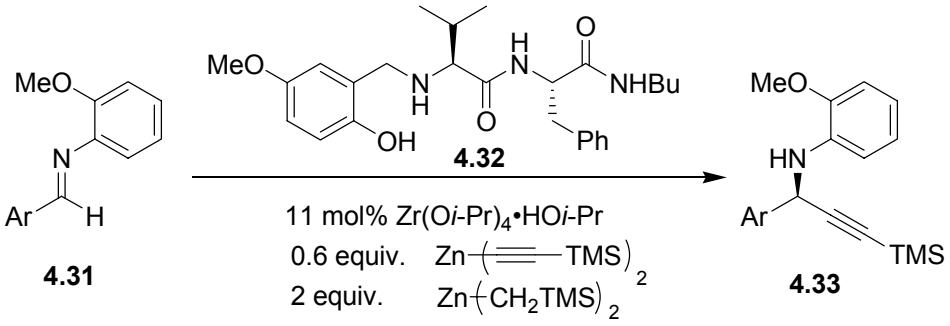
In 2002, Li and coworkers developed a highly enantioselective copper(I)-catalyzed direct alkyne-imine addition. The process is simple and provides a diverse range of propargylamines in high *ee*'s and good yields. The reaction could be carried out in various solvents (even in water!). However, aliphatic acetylenes gave lower enantioselectivities (60-85% *ee*) and the reaction seemed to be limited to aromatic amines.[48,49]



Scheme 4.13

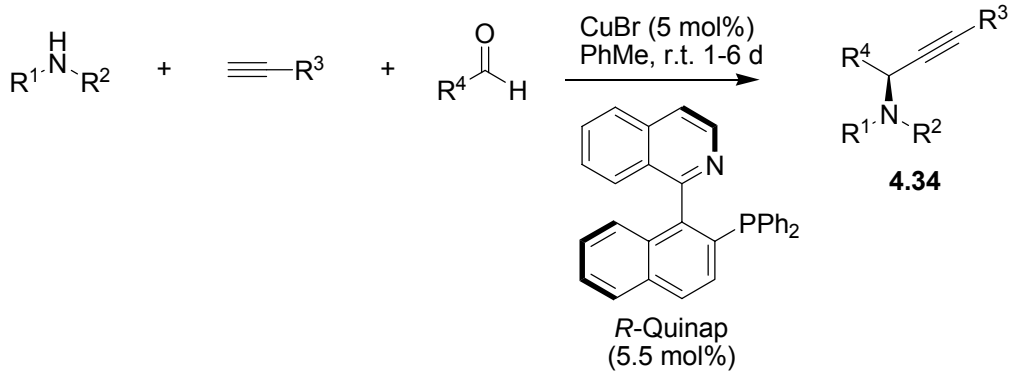
In 2003, Traverse, Hoveyda and Snapper reported a zirconium-catalyzed method for the

enantioselective addition of alkynylzinc reagents to arylimines to afford optically enriched propargylamines **4.33** in up to 90% *ee*. In addition, this study extends the utility of amino acid-based ligands such as **4.32**, which was prepared from inexpensive and commercially available amino acids and 5-methoxysalicylaldehyde.[50]



Scheme 4.14

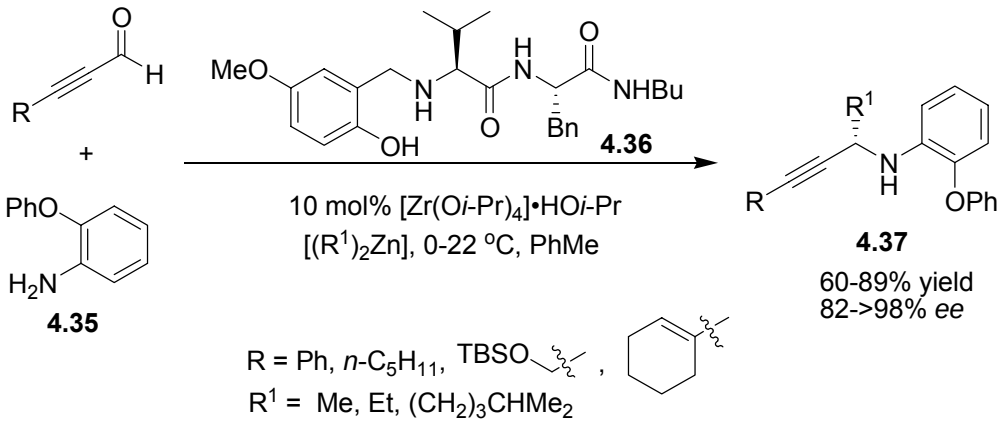
Almost at the same time, Knochel reported a copper-mediated three-component synthesis of chiral propargylamines. Aliphatic aldehydes, acetylenes and amines are compatible in this reaction while aromatic amines are not suitable. It makes this method a nice complement for Li's method (Scheme 4.15).[6,51,52]



Scheme 4.15

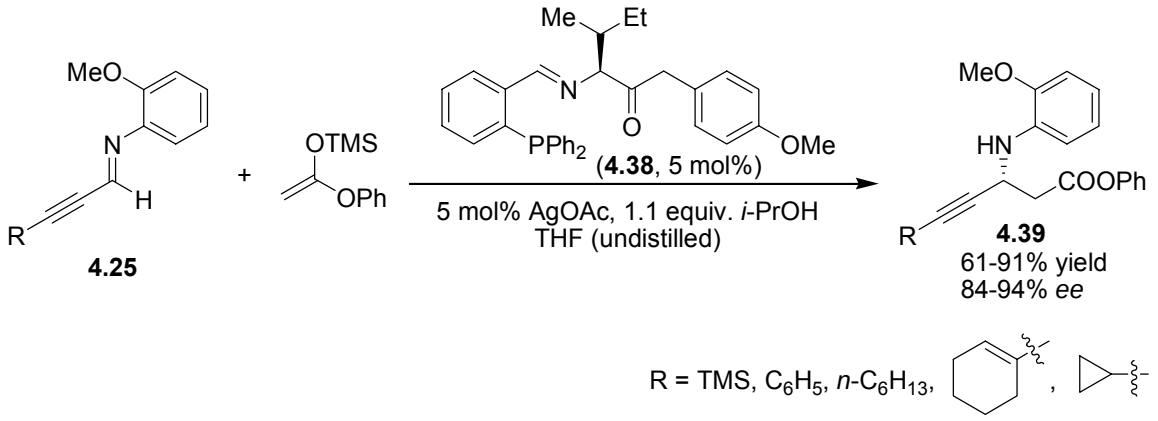
4.1.4.2 Alkynylimine Alkylation and Mannich-type Reaction

Chiral propargylamines can be prepared not only from asymmetric alkynylation of imines, but also from the asymmetric alkylation of alkynylimines. Recently, Hoveyda and Snapper disclosed an efficient zirconium-mediated process for alkylation of alkynylimines that lead to a wide range of enantiomerically enriched propargylamines.[53] Once again, the fact that chiral catalyst **4.36** can be prepared easily from commercially available and inexpensive amino acids in large quantities makes the methodology more promising.



Scheme 4.16

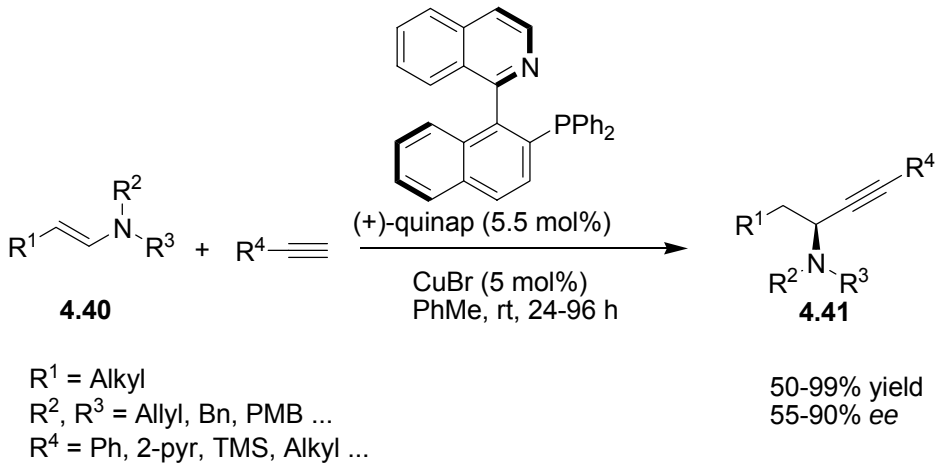
Later on, Hoveyda developed the first silver-catalyzed Mannich reaction for the enantioselective synthesis of *β*-alkynyl-*β*-aminoacids, a class of compounds that is very difficult to access by other catalytic protocols. The optically enriched (84-94% *ee*) products obtained can be further functionalized in a number of ways to afford a range of useful compounds.[54,55]



Scheme 4.17

4.1.4.3 Enamine Alkynylation

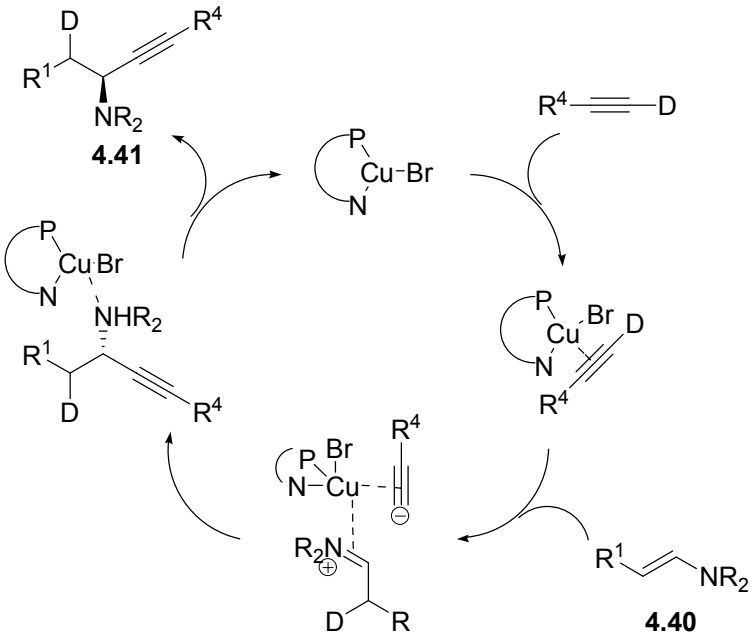
Another methodology developed by Knochel and coworkers is a type of reaction that is not very commonly seen in literature, namely the alkynylation of enamines. Enamines **4.40** reacted with terminal alkynes in the presence of a catalytic amount of CuBr and (+)-quinap to give chiral propargylamines in excellent yields and enantioselectivities. [8,56]



Scheme 4.18

A careful mechanistic study showed that the acetylenic deuterium atom of the [D]phenylacetylene is transferred to the *β*-position of enamine **4.40** leading to the formation of the

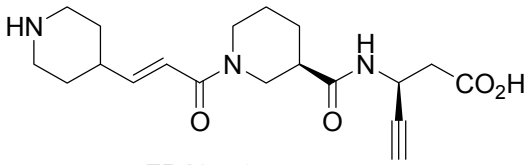
desired propargylamine **4.41** (Scheme 4.19).



Scheme 4.19

4.2 Proposal

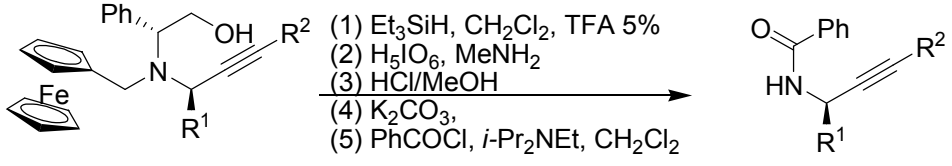
Very similar to chiral propargylamines, stereochemically defined propargylamides are also present in many bioactive compounds (such as FR184764)[57] and are important as synthetic intermediates for the preparation of natural products.[58-61]



FR184764

Figure 4.2 Structure of a bioactive compound FR184764.

Typical routes to prepare chiral propargylamides include metal complexes (Cu, Zn, and Zr) catalyzed terminal alkyne addition to achiral imines or the addition of alkynylmetallics to imino compounds or 1,3-oxazolidines bearing chiral auxiliaries. Protecting groups or auxiliaries are then removed, and the intermediate chiral propargylamines are acylated to provide the desired propargylamides. These procedures are sometimes tedious and possibly problematic. For example, in one of the chiral auxiliary-controlled alkynylation reactions mentioned above, diastereomerically pure propargylamines **4.15** could be obtained in good yields. However, to convert **4.15** to propargylamides such as **4.42** required 5 extra steps and the overall yields were only moderate (Scheme **4.20**).[35]



4.15 **4.42**

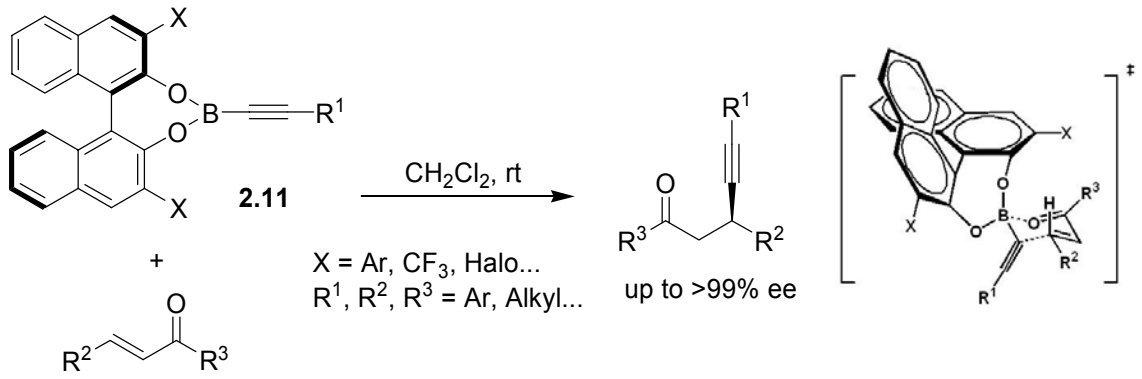
R^1 = Me, $(CH_2)_2$Ph, 2-fur
R^2 = C_5H_{11}, Ph
61-66% yield

Scheme 4.20

To our knowledge, a general method that provides reliable and direct access to enantiomerically

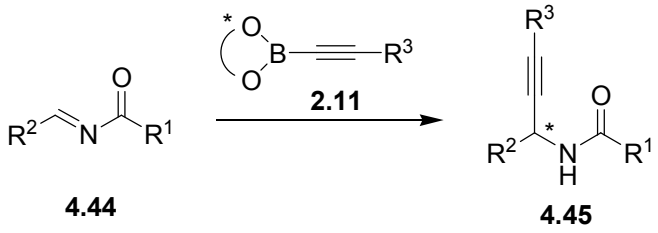
enriched propargylamides *via* asymmetric synthesis has not been reported. Therefore, it seemed worthwhile to look for an efficient method for the synthesis of these compounds.

Recently, our group found that 3,3′-disubstitutedbinaphthol-modified alkynylboronates **2.11** could deliver alkynyl groups onto enones in a conjugate fashion with excellent yields (up to 99%) and enantioselectivities (up to >99% *ee*, Scheme 4.21).[62]



Scheme 4.21

If the *α*-carbon of enone **4.43** is replaced by a nitrogen, the resulting structure will be an *N*-acylimine (**4.44**) which also bears a carbonyl group conjugated with a double bond (C=N instead of C=C). It is reasonable to believe that *N*-acylimines, being structurally similar to enones, may also react with alkynylboronates in a 1,4-addition manner to give chiral propargylamides. (Scheme 4.22)

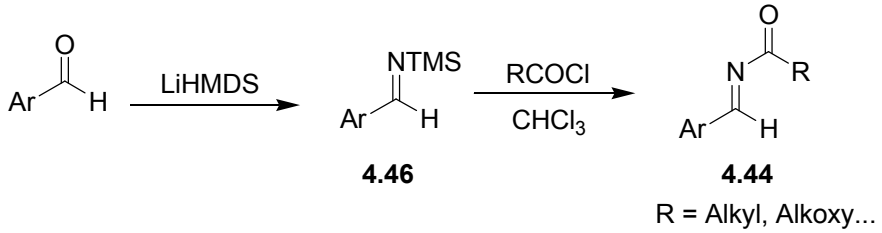


Scheme 4.22

4.3 Results and Discussions

4.3.1 Preparation of *N*-Acylimines

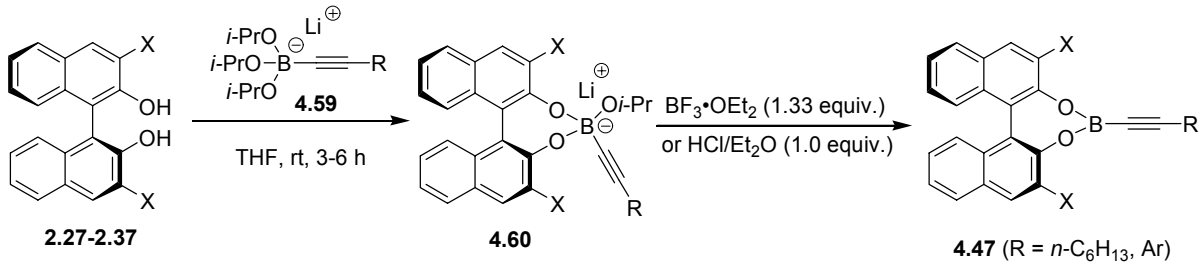
In order to examine our idea, *N*-acylimines needed to be synthesized. It was reported by Kupfer that *N*-acylimines **4.44** could be obtained from the reaction of *N*-TMS protected imines **4.46** and acyl chlorides in excellent yields and that *N*-TMS imines **4.46** were easily prepared from the corresponding aldehydes (Scheme 4.23).[63,64] Since *N*-acylimines are very sensitive to moisture, they were prepared freshly each time and were used immediately without further purification.



Scheme 4.23

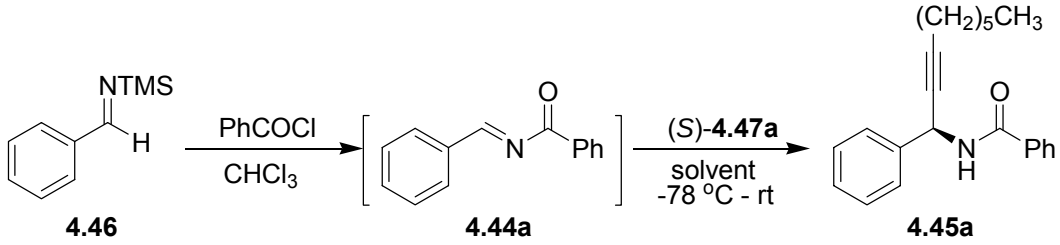
4.3.2 Optimization of Reaction Conditions

Binaphthol-modified alkynylboronates **4.47** were prepared according to a previous procedure (Scheme 4.24).[62] Upon treatment of boronate **4.47a** (X = H, R = *n*-C_6H_{13}) with *N*-benzoylbenzaldimine (**4.44a**) in various common organic solvents, the desired propargylamide **4.45a** was obtained in excellent chemical yields and moderate enantioselectivities. Dichloromethane, which gave the best results, became the solvent of choice for further studies (Table 4.2, entry 2).



Scheme 4.24

Table 4.2 Alkynylation of *N*-benzoylbenzaldimine with binaphthol-modified alkynylboronate.



entry	solvent	yield (%)	*ee* (%)[c]
1[a]	CH_2Cl_2	86	59
2[b]	**CH_2Cl_2**	**84**	**64**
3[a]	PhMe	92	48
4[a]	CH_3CN	80	35
5[a]	Et_2O	90	48

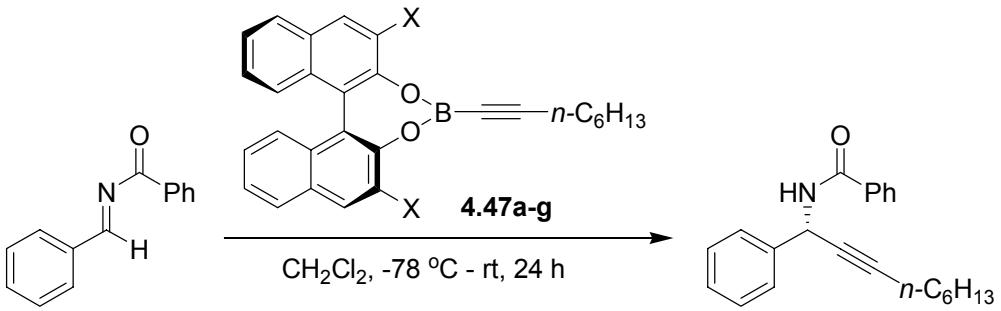
[a] the reaction was run at rt for 12 h. [b] reactants were mixed at 78 °C then warmed to rt for 12 h. [c] Determined by HPLC analysis with a Chiralcel OD column

4.3.3 Ligand Screening

When 3,3′-disubstitutedbinaphthols were used in place of the parent binaphthol, additions to *N*-benzoylbenzaldimine (**4.44a**) were considerably more selective (Table 4.3, entries 2-7). Among a variety of boronates (**4.47a-g**), 3,3′-diarylbinaphthol-modified boronates (**4.47f** and **4.47g**) gave the best results in terms of both yield and enantioselectivity (Table 4.3, entries 6 and 7). Boronates bearing electron-withdrawing groups on the binaphthol rings gave poor yields (Table 4.3, entries 3-5)

and possible reasons for this will be discussed later in this section.

Table 4.3 Alkynylation of *N*-benzoylbenzaldimine (**4.44a**) with 3,3′-disubstituted binaphthol-modified alkynyl boronates.



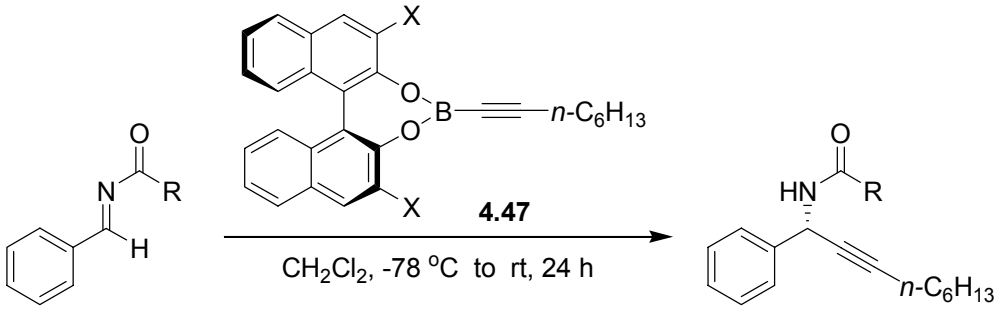
4.44a **4.45a**

entry	X	yield[a] (%)	*ee*[b] (%)
1	H (**4.47a**)	84	64
2	Me (**4.47b**)	85	67
3	I (**4.47c**)	30	80
4	CF_3 (**4.47d**)	<20	75
5	COO*i*-Pr (**4.47e**)	<20	N. D.[c]
6	Ph (**4.47f**)	82	80
7	4-$MeOC_6H_4$ (**4.47g**)	84	80

[a] Isolated yields of purified products based on chiral boronates (acylimines were generated in situ without isolation). [b] Determined by HPLC analysis with a Chiralcel OD column. [c] Not determined.

Reactions of imines bearing different *N*-acyl groups were also examined (Table 4.4). The best result (in terms of both enantioselectivity and yield) was obtained from the reaction of *N*-acetylimine **4.44c** and boronate **4.47f** (Table 4.4, entry 8).

Table 4.4 Alkynylation of *N*-acylbenzaldimines with 3,3′-disubstituted binaphthol-modified boronates.



R = Ph **(4.44a)**
OBn **(4.44b)**
CH_3 **(4.44c)**

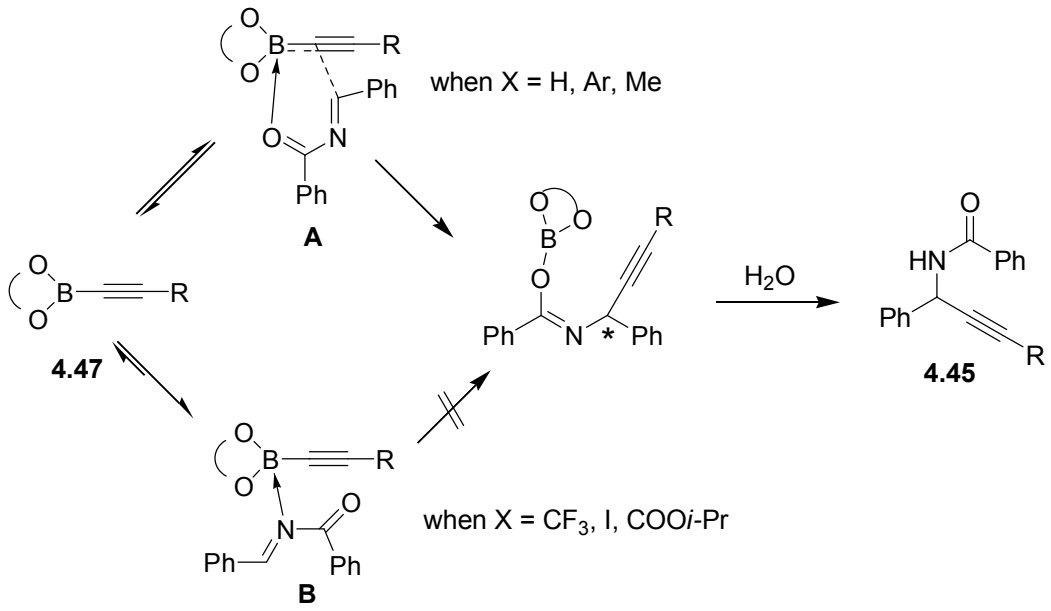
R = Ph **(4.45a)**
OBn **(4.45b)**
CH_3 **(4.45c)**

entry	R	X	yield (%)[a]	*ee* (%)[b]
1	Ph	I (**4.47c**)	30	80
2	Ph	Ph (**4.47f**)	82	80
3	OBn	I (**4.47c**)	40	80
4	OBn	Ph (**4.47f**)	90	40
5	OBn	3,5-$(Me)_2$-phenyl (**4.47h**)	86	15
6	OBn	3,5-$(CF_3)_2$-phenyl (**4.47i**)	83	14
7	CH_3	I (**4.47c**)	33	94
8	**CH_3**	**Ph** (**4.47f**)	**75**	**92**
9	CH_3	4-$MeOC_6H_4$ (**4.47g**)	74	90

[a] Isolated yields of purified products based on chiral boronates (acylimines were generated *in situ* without isolation). [b] Determined by HPLC analysis with a Chiralcel OD column.

As noted above, it was found that all boronates with relatively strong electron-withdrawing groups at the 3 and 3′ positions of the binaphthol rings gave poor yields (Table 4.4, entries 1, 3 and 7). This result may be rationalized by proposing that, to deliver the alkynyl group in a 1,4-fashion, alkynylboronates must coordinate with the oxygen atom of the *N*-acylimines (Scheme 4.25).

Electron-withdrawing groups (I, CF_3, COO*i*-Pr) increase the Lewis acidity of boronates and thus increase the possibility of boron coordinating with the nitrogen atom of the *N*-acylimine, leading to poor yields. We have no experimental evidence for this coordination, but it is offered as a speculation as to why electron-withdrawing groups have a major negative impact on reactions of alkynylboronates with acylimines but not on the analogous reactions with enones.



Scheme 4.25

4.3.4 Scope and Limitations

The alkynylation of other *N*-acetylimines using **4.47f** and **4.47j** were studied. All reactions proceeded smoothly to give products **4.45c-k** in high yields (Table 4.5). Excellent enantioselectivities (>90% *ee*) were observed for all of the aromatic imines examined (Table 4.5, entries 1-6, 8 and 9) with highest selectivities (99% *ee*) noted for aromatic groups that are ortho substituted (Table 4.5, entries 5 and 6). Similar to the results from our previous study on allylboration, high yield but lower selectivity were found with an alkenylimine (67% *ee*, Table 4.5, entry 7). However, with a larger

alkenyl group, excellent selectivity was obtained (92% *ee*, Table 4.5, entry 10). Aliphatic acylimines were not examined as the method of preparation used is applicable only to non-enolizable aldehydes. The adduct **4.45k** was prepared particularly to determine the absolute configuration of the addition products. (*S*)-Boronate **4.47j** produced propargylamide **4.45k** with *S* stereochemistry which has been proven by X-ray crystallographic analysis (Figure 4.3).

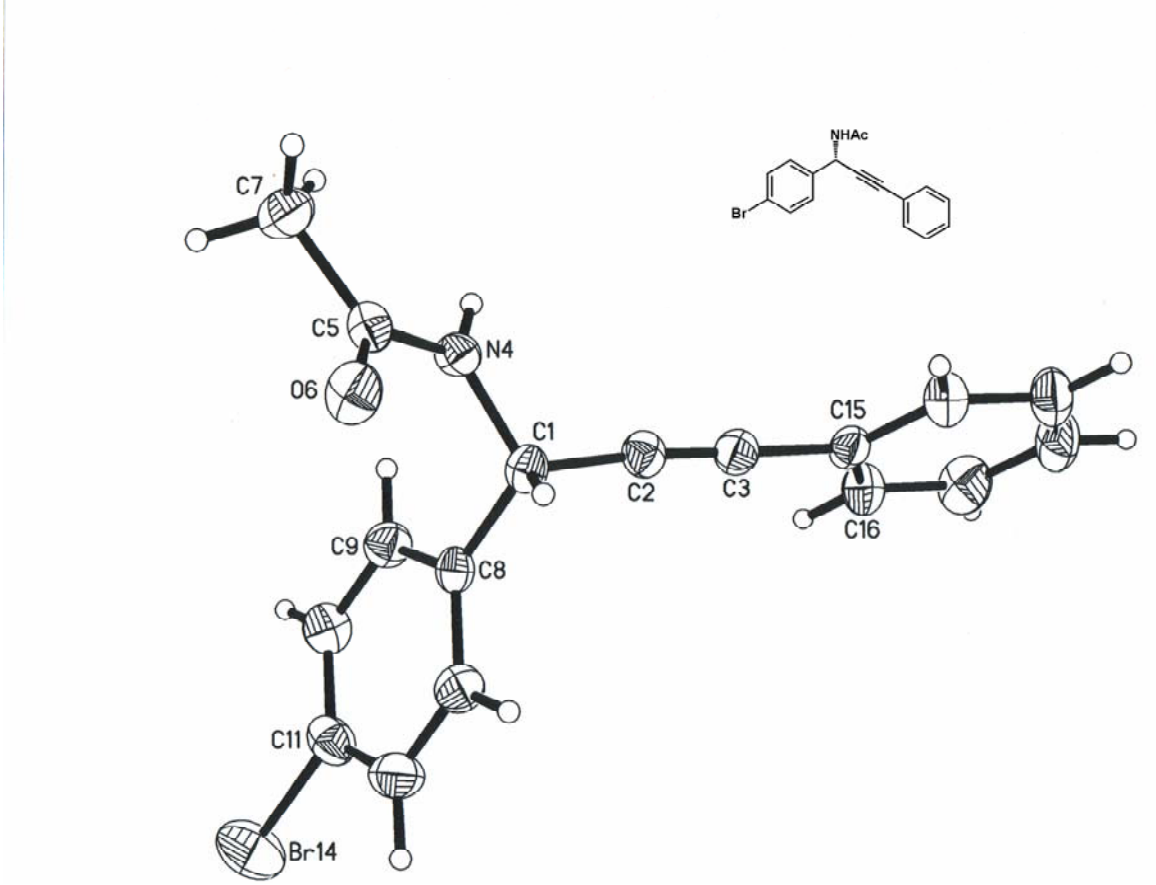
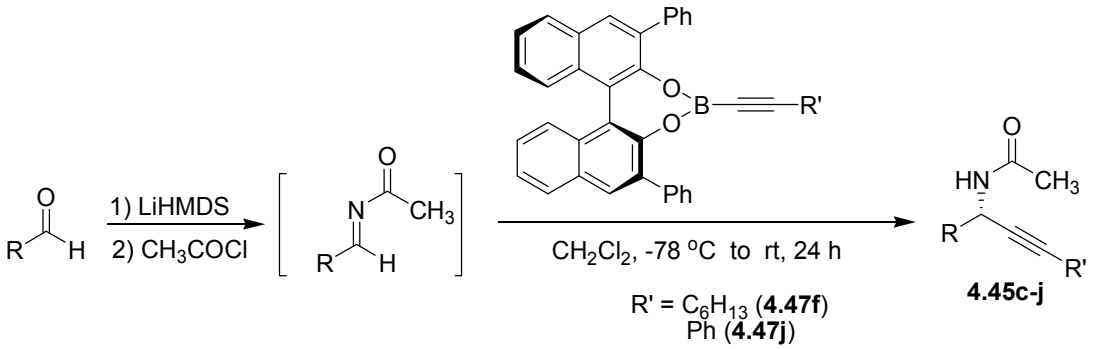


Figure 4.3 X-ray crystal structure of (*S*)-**4.45k**.

Table 4.5 Alkynylation of *N*-acetylimines with 3,3′-diaryl binaphthol-modified boronates.



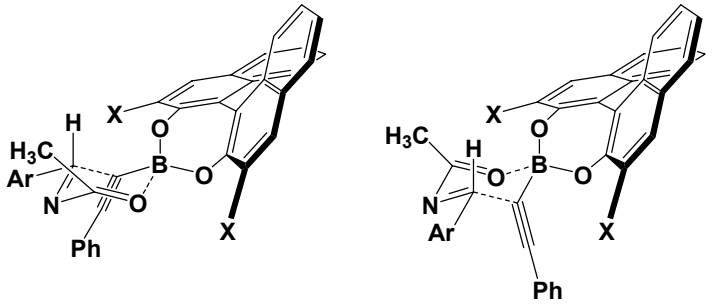
entry	R	R′	compd no.	yield (%)[a]	ee (%)[b]
1	Ph	*n*-C_6H_{13}	**4.45c**	75	92
2	4-ClC_6H_4	*n*-C_6H_{13}	**4.45d**	72	91
3	4-$MeOC_6H_4$	*n*-C_6H_{13}	**4.45e**	81	92
4	4-MeC_6H_4	*n*-C_6H_{13}	**4.45f**	76	92
5	2-MeC_6H_4	*n*-C_6H_{13}	**4.45g**	78	99
6	1-naphthyl	*n*-C_6H_{13}	**4.45h**	70	>99[c]
7	PhCH=CH	*n*-C_6H_{13}	**4.45i**	75	67
8	Ph	Ph	**4.45j**	85	92
9	4-BrC_6H_4	Ph	**4.45k**	75	91
10	PhCH=C(CH_3)	Ph	**4.45l**	80	93

[a] Isolated yields of purified products based on chiral boronates (acylimines were generated in situ without isolation). [b] Determined by HPLC analysis with a Chiralcel OD column. [c] The minor enantiomer was not detected by HPLC analysis.

4.3.5 Proposed Model

Given the fact that *S* boronates produce (*S*)-propargylamides, we were able to propose a working model for the transition state of the alkynylation. The stereochemical result could be explained using a cyclic six-membered chair transition state model similar to that proposed for additions of the same alkynylboronate reagents to enones (Figure 4.4).[62] In this model, the larger or aryl group occupies an

equatorial position in either of two possible transition states. The 3- and 3′-substituents on the binaphthol play an important role in destabilizing one of the possible transition states. The nonbonded interactions between the 3-substituent (phenyl) and the axial imine hydrogen presumably favour **B** over **A** in the six-membered ring transition state.



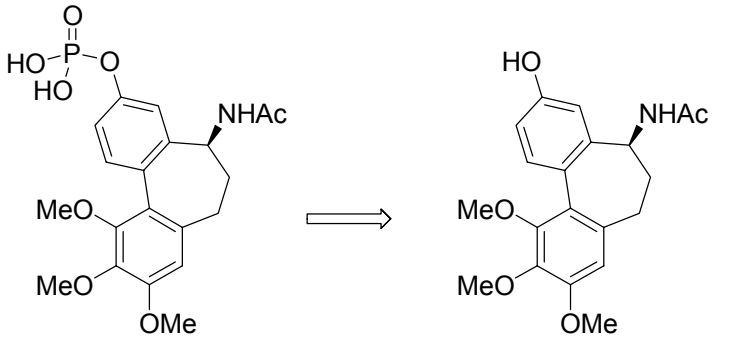
A (Disfavoured) **B (Favoured)**

Figure 4.4 Proposed transition state model of the asymmetric alkynylation of *N*-acylimines.

4.3.6 Synthesis of (-)-*N*-Acetylcolchinol (ZD6126 Phenol)

With this general methodology in hand, we were able to look into one of its potential applications in total synthesis: ZD6126 phenol.

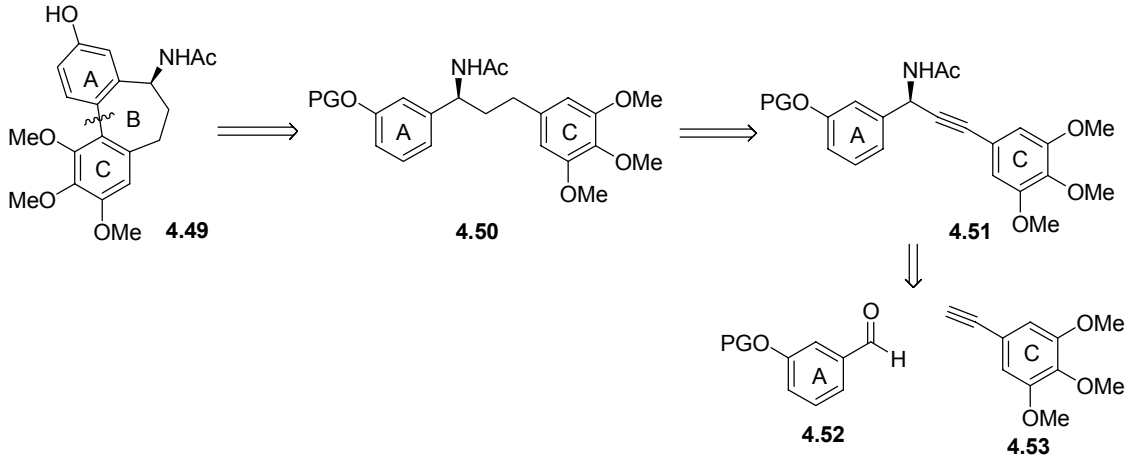
ZD6126 is a novel vascular targeting agent that was developed for its tubulin-binding properties and its ability to induce vascular damage in tumors. It is a phosphate prodrug of the tubulin binding agent *N*-acetylcolchinol (ZD6126 Phenol) that inhibits microtubule polymerization (Figure 4.5). Release of ZD6126 Phenol by phosphatases *in vivo* leads to the selective disruption of the cytoskeleton of tumor endothelial cells. This results in selective occlusion of tumor blood vessels, cessation of tumor blood flow, and death of tumor cells because of the starvation of oxygen and nutrition.[65-69]



4.48: ZD-6126 **4.49: (-)-*N*-acetylcolchinol**

Figure 4.5 Structures of ZD-6126 and (-)-*N*-acetylcolchinol.

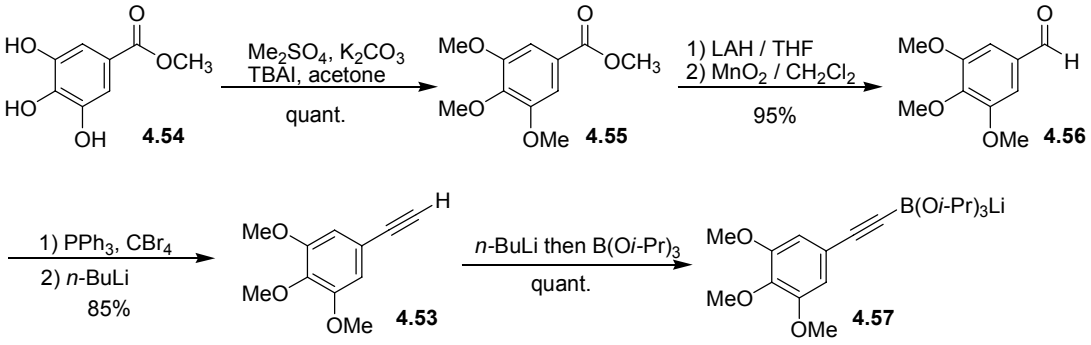
A retrosynthetic analysis indicated that the B ring of the final product could be formed by an intramolecular oxidative biaryl coupling of compound **4.50**. This acetamide could be obtained from a chiral propargyl acetamide **4.51** which might be achieved using the aforementioned alkynylation methodology.



Scheme 4.26

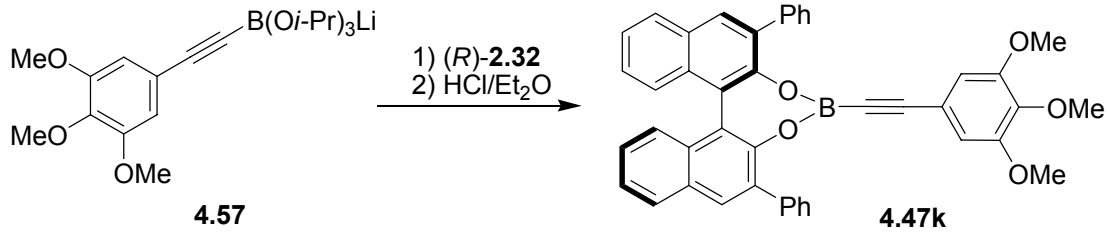
The total synthesis started with the commercially available methyl 3,4,5-trihydroxybenzoate (**4.54**). Protection of all three hydroxyl groups followed by the reduction of the ester gave aldehyde **4.56** which was easily converted to the corresponding aryl acetylene using Corey-Fuchs chemistry.[70]

Treatment of acetylene **4.53** with *n*-butyllithium and triisopropylborate sequentially gave an "ate" complex **4.57** in nearly quantitative yield.



Scheme 4.27

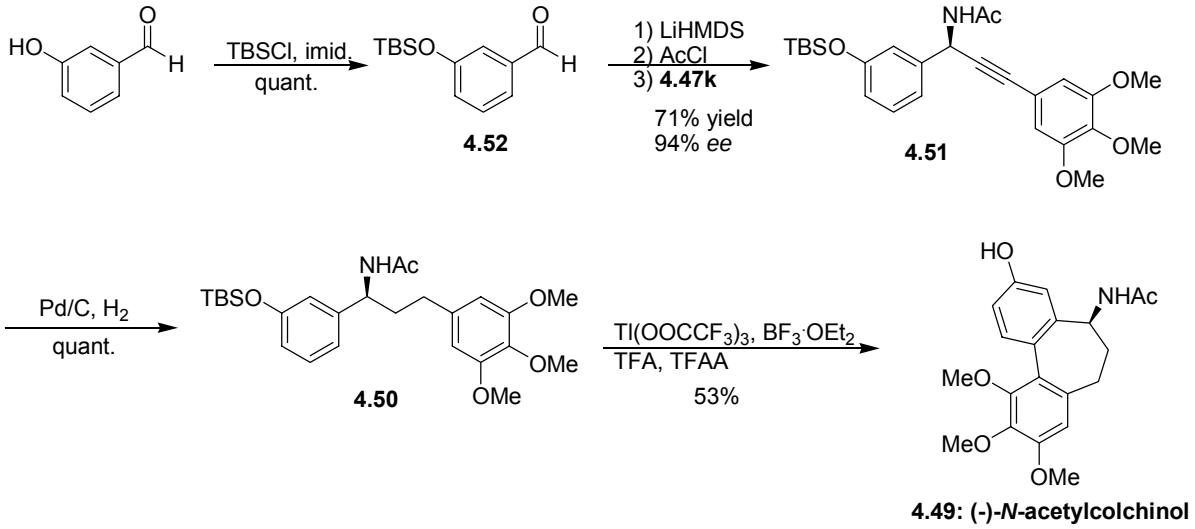
Mixing the "ate" complex with (*R*)-3,3′-diphenyl binaphthol (**2.32**), followed by the treatment with dry HCl in Et_2O, gave the chiral alkynylboronate **4.47k** (C ring precursor) which is moisture sensitive and requires immediate use.



Scheme 4.28

To prepare the requisite substrate, TBS protected 3-hydroxybenzaldehyde **4.52** was converted to the corresponding *N*-acetylimine which was then treated *in situ* with boronate **4.47k** to afford (*R*)-propargylacetamide **4.51** in 72% yield and 94% *ee*. (On the basis of the reaction model proposed, (*R*)-diphenylbinaphthol should give the natural enantiomer of the final product, whereas (*S*)-diphenylbinaphthol would give the other enantiomer). After hydrogenation over Pd/C, the

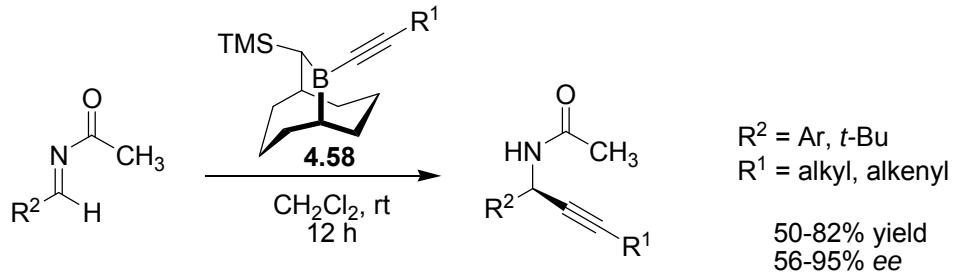
saturated compound (*S*)-**4.50** was obtained in quantitative yield. Finally, following Sawyer's procedure,[71] (*S*)-**4.50** was transformed into (-)-*N*-acetylcolchinol **4.50** by treatment with $(CF_3COO)_3Tl$ in the presence of freshly distilled $BF_3{\cdot}OEt_2$, trifluoroacetic acid and trifluoroacetic anhydride in an unoptimized yield of 53% (Scheme 4.29). This material exhibited an optical rotation of $[\alpha]^{25}_D$ -45.2 (*c* 0.6, $CHCl_3$), which is comparable to the literature value for (-)-*N*-acetylcolchinol obtained from degradation of (-)-colchicine ($[\alpha]_D^{20}$ -51.6 (*c* 1.23, $CHCl_3$)).[72] The biaryl coupling has also been attempted with other oxidizing reagents (such as $PhI(OAc)_2$, $PhI(O_2CCF_3)_2$, RuO_2, $RuCl_3/NaIO_4$), but either complex mixtures or the starting material **4.50** were isolated in each case.



Scheme 4.29

4.3.7 Recent Advances in the Asymmetric Alkynylation of *N*-Acylimines

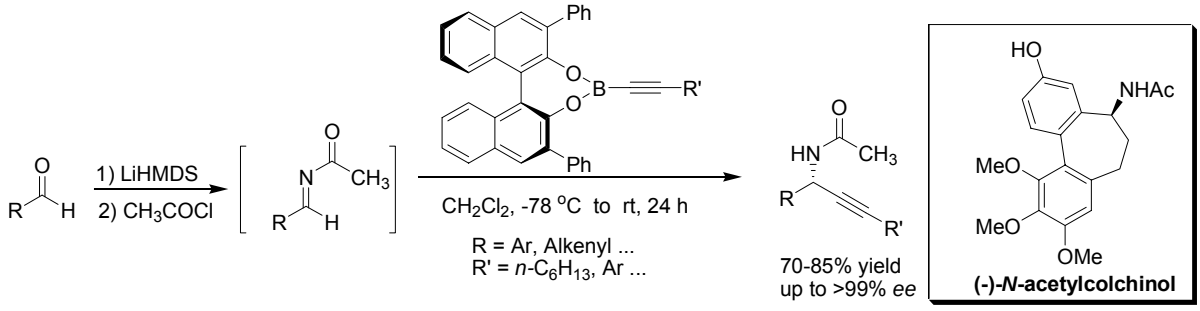
It needs to be mentioned that, during the preparation of this thesis, Soderquist also reported a very similar asymmetric alkynylation of *N*-acetylimines using chiral alkynylborane **4.58**.[73] A number of chiral propargylacetamides were prepared with moderate to good enantioselectivieties (Scheme 4.30).


TMS
R1
B
O
N
CH3
R2
H
4.58
CH2Cl2, rt
12 h
O
HN
CH3
R2
R1
R2 = Ar, t-Bu
R1 = alkyl, alkenyl
50-82% yield
56-95% ee

Scheme 4.30

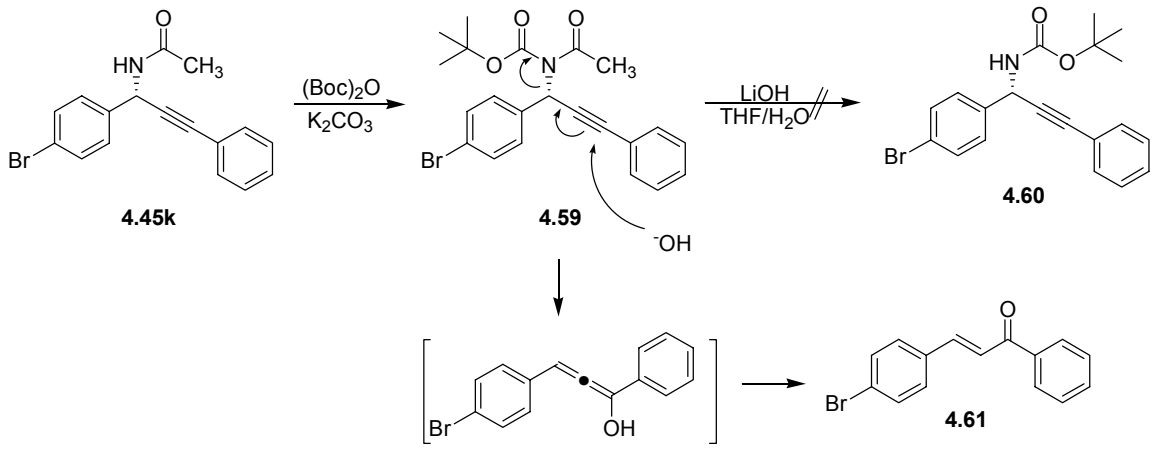
4.4 Summary and Future Work

In summary, we have shown that 3,3′-disubstituted binaphthol-modified alkynylboronates can be used to prepare chiral propargylamides in high yields (70-85%) and enantioselectivities (up to >99% *ee*). This represents the first direct enantioselective synthesis of chiral propargylamides and this methodology was also applied to the first enantioselective total synthesis of the antitubulin reagent (-)-*N*-acetylcolchinol (or ZD6126 phenol, Scheme 4.31). Part of this work has been published in *Organic Letters* (Wu, T. R.; Chong, J. M. *Org. Lett.* **2006**, *8*, 15-18).[74]



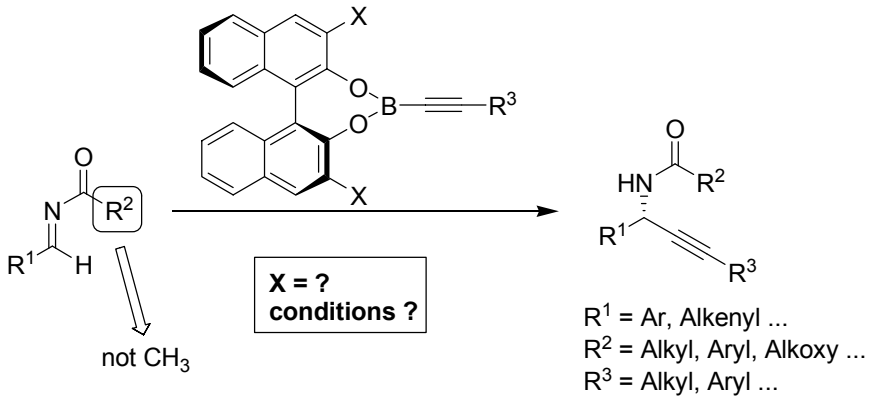
Scheme 4.31

In order to obtain high enantioselectivity in the alkynylation, an acetyl group needs to be present on the imine nitrogen. Acyl groups other than acetyl lead to low enantioselectivities (<80% *ee*). However, an acetyl group is not a very "handy" protecting group as taking it off can be problematic sometimes. For instance, in an effort to replace the acetyl group with a Boc group using a reported method, no desired Boc-protected product **4.60** was obtained (Scheme 4.32). A side product **4.61** was isolated instead.



Scheme 4.32

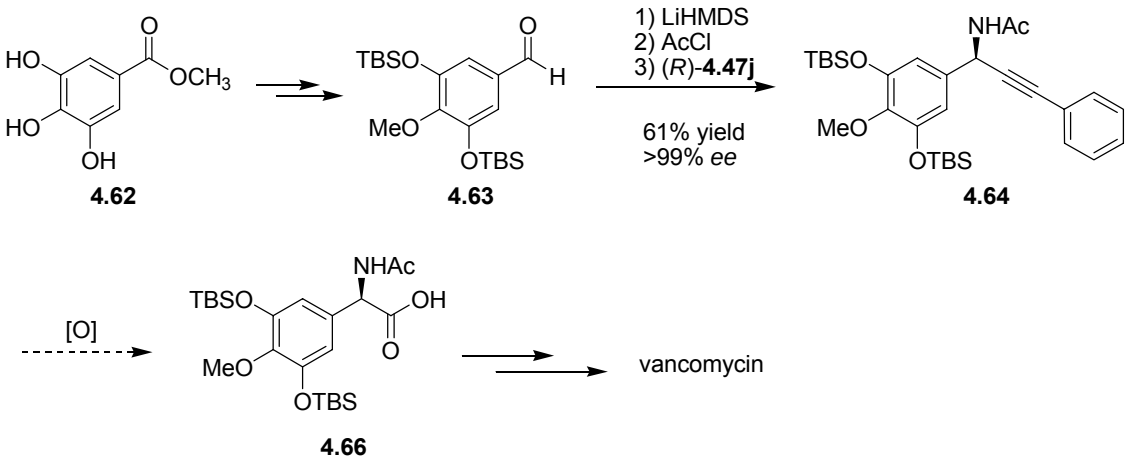
In the future, a mild method that removes the acetyl group on these chiral propargylamides should be investigated. On the other hand, in order to broaden the scope of this methodology, efforts could be directed toward the discovery of chiral alkynylboronates that can induce high enantioselectivity for other *N*-acylimines (Scheme 4.32).



Scheme 4.33

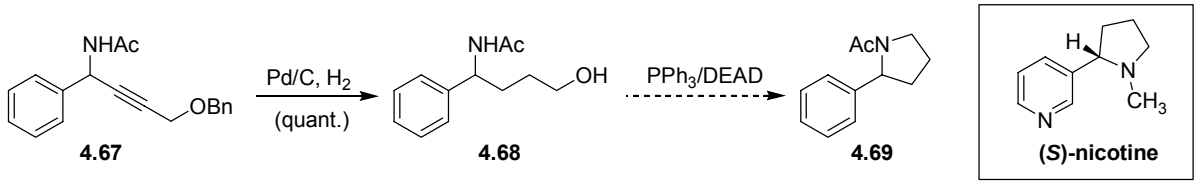
It is known that internal alkynes could be oxidized to afford carboxylic acids. The oxidation of chiral propargylamides might give arylglycines which are valuable precursors to many natural products. For example, an aldehyde **4.63** was prepared easily from commercially available methyl

3,4,5-trihydroxybenzoate (**4.62**). Aldehyde **4.63** was converted to the corresponding chiral propargylamide **4.64** in good yield (61%) and excellent enantioselectivity (>99% *ee*). Oxidation of **4.64** would give carboxylic acid **4.66** which may serve as the central-arylglycine synthon in the total synthesis of vancomycin. However, several attempts (such as $KMnO_4$ or O_3) to oxidize propargylamide **4.64** failed to give the desired product **4.66**. Instead, it seemed that the electron-rich aromatic ring of propargylamide **4.64** was oxidized in these cases. Therefore, reaction conditions that render the carboxylic acid **4.66** need to be found (Scheme 4.34).



Scheme 4.34

Another application of our methodology would be the synthesis of chiral piperidines and pyrrolidines which are encountered in many natural products. A model reaction suggested that a chiral pyrrolidine **4.69** may be obtained in two steps from propargylamide **4.67**. This method may be adopted in the synthesis of (*S*)-nicotine (Scheme 4.35).



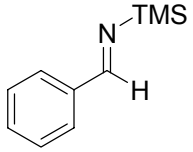
Scheme 4.35

4.5 Experimental

4.5.1 General Experimental

All reactions were performed using flame-dried glassware under an argon atmosphere. Dichloromethane was freshly distilled from CaH_2. THF and diethyl ether was freshly distilled from Na/benzophenone. $CHCl_3$ was freshly distilled from P_2O_5 then passed through a basic alumina column. Acetyl chloride was distilled prior to use. Chiral 3,3′-disubstituted binaphthols were synthesized using procedures from a previous report.[1] Lithium triisopropyl-*B*-1-alkynylborate was prepared according to a literature procedure.[2] ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 MHz and 75 MHz , respectively. Elemental analyses were conducted by M-H-W Laboratories, Phoenix, Arizona. Mass spectra were recorded on a Kratos MA890 mass spectrometer using electron impact (EI, 70 eV) ionization. Optical rotations were recorded in cells with 10 cm path length on a Perkin-Elmer 241 digital polarimeter.

4.5.2 Preparation of *N*-Trimethylsilyl Benzaldimine (4.46)[63]



To 4.59 mL (28.4 mmol) of 1,1,1,3,3,3-hexamethyldisilazane (HMDS) was added 16.1 mL (25.8 mmol) of a 1.6 M hexane solution of *n*-butyllithium over a 5-min period. Solvents were removed *in vacuo* until a white precipitate appeared. The resulting slurry was cooled in an ice bath, and 2.74 g (25.8 mmol) of benzaldehyde was added over a 10-min period. Direct fractional distillation of the resulting solution gave 3.7 g (89%) of imine **4.46** as a pale yellow liquid: bp 45-46

^{o}C (0.15 mmHg); ^{1}H NMR ($CDC1_3$): δ 0.26 ($SiMe_3$, s, 9H), 7.39-7.47 (H_{Ar}, m, 3 H), 7.77-7.83 (H_{Ar}, m, 2 H), 8.98 (CH=N, s, 1 H).

4.5.3 General Procedure for the Preparation of 3,3′-Disubstituted Binaphthol-modified Alkynylboronates (4.47a-i)[62]

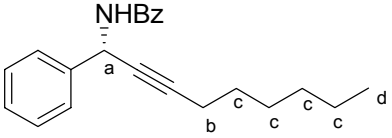
A literature procedure was followed with minor modifications: to a mixture of 3,3′-disubstitutedbinaphthol (0.51 mmol) and lithium triisopropyl-*B*-1-alkynylborate (0.50 mmol) was added 5 mL of THF at 0 ^{o}C. The resulting clear solution was stirred at room temperature for 6 h. Solvent was removed under reduced pressure. The residue was suspended in 5 mL of Et_2O before anhydrous HCl/Et_2O (1.0 mL, 0.50 M) was added dropwise at -78 ^{o}C. The solution was allowed to warm to room temperature for 0.5 h. Evaporation of volatiles gave the desired product as a white foam. Compounds **4.47a-i** are moisture sensitive and thus were used directly without isolation and further purification.

4.5.4 General Procedure for the Alkynylation of *N*-Acylimines

To a solution of lithium hexamethyldisilazide (1.1 mmol) in 1 mL of hexane was added aldehyde (1.0 mmol) at 0 ^{o}C. The resulting solution was stirred at room temperature for 30 minutes before TMSCl (1.1 mmol) in 1 mL of THF was added. The suspension was stirred at room temperature for another 0.5 h. Solvent was removed under high vacuum. To the oily residue was added 6 mL of $CHCl_3$ then acetyl chloride (1.5 mmol, 1.1 mmol for all other acyl chlorides) at 0 ^{o}C. The reaction was kept at 0 ^{o}C for 3 h (for other acetyl chlorides, the reaction was brought to reflux for 3 h). Volatiles were removed under high vacuum to give the acylimine as a pale yellow oil. To the crude material was added CH_2Cl_2 then the chiral alkynylboronate (0.5 mmol) in CH_2Cl_2 at -78 ^{o}C.

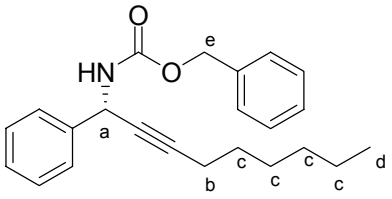
The reaction was allowed to warm to room temperature slowly for 24 h. Workup was done by quenching the reaction with saturated aqueous NH_4Cl. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 for three times. The organic layers were combined and dried over Na_2SO_4. Column chromatography (hexanes/EtOAc 2:1) gave the desired chiral propargyl amide and 3,3'-disubstitutedbinaphthol in pure form. The enantiomeric excesses of products were determined by the HPLC (4.6 x 250 mm Chiralcel OD) analysis.

4.5.4.1 (*S*)-*N*-(1-Phenyl-2-nonynyl)benzamide (**4.45a**)



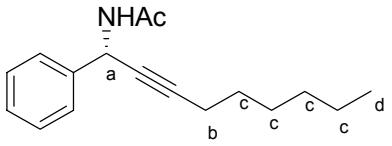
IR (KBr): 3295 (N-H), 1638 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (H_d, t, J = 6.9 Hz, 3H), 1.27-1.56 (H_c, m, 8H), 2.25 (H_b, dt, J = 1.8 Hz, 6.9 Hz, 2H), 6.21 (H_a, d, br, J = 8.4 Hz, 1H), 6.82 (NH, d, J = 8.4 Hz, 1H), 7.27-7.78 (H_{Ar}, m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.0 (C=O), 139.6 (C_{Ar}), 133.8 (C_{Ar}), 131.5 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 127.8 (C_{Ar}), 127.0 (C_{Ar}), 127.0 (C_{Ar}), 85.7 (C≡C), 77.8 (C≡C), 45.2 (C_a), 31.2 (C_c), 28.5 (C_c), 22.4 (C_c), 18.7 (C_b), 13.9 (C_d); MS *m/e* (relative intensity): 319 (M^+, 11), 290 (M^+-C_2H_5, 8), 248 (M^+-C_5H_{11}, 100); Anal. Calcd for $C_{22}H_{25}NO$: C, 82.72; H, 7.89; N, 4.38. Found: C, 82.53; H, 8.03; N, 4.53. The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 98/2, flow rate = 1 mL/min), t_R = 14.3 min (*S*), t_R = 19.6 min (*R*). $[\alpha]_D^{25}$ +8.9 (80% *ee*, c 0.9, $CHCl_3$).

4.5.4.2 (*S*)-Benzyl 1-Phenyl-2-nonynylcarbamate (**4.45b**)



IR (KBr): 3325 (N-H), 1702 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (H_d, t, J = 6.9 Hz, 3H), 1.28-1.60 (H_c, m, 8H), 2.20-2.25 (H_b, m, 2H), 5.06-5.23 (H_a and H_e, m, 3H), 5.68 (NH, d, br, J = 7.2 Hz, 1H), 7.28-7.50 (H_{Ar}, m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.5 (C=O), 139.8 (C_{Ar}), 136.4 (C_{Ar}), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 128.3 (C_{Ar}), 128.1 (C_{Ar}), 128.0 (C_{Ar}), 127.0 (C_{Ar}), 86.1 (C≡C), 78.0 (C≡C), 67.1 (C_e), 47.2 (C_a), 31.4 (C_c), 28.7 (C_c), 22.7 (C_c), 18.8 (C_b), 14.2 (C_d); MS *m/e* (relative intensity): 349 (M^+, 0.8), 258 (M^+-Bn, 100); Anal. Calcd for $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79; N, 4.01. Found: C, 79.25; H, 7.79; N, 4.02. The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 98/2, flow rate = 1.0 mL/min), t_R = 19.1 min (*R*), t_R = 26.3 min (*S*). $[\alpha]_D^{25}$ -6.2 (80% *ee*, c 1.29, $CHCl_3$).

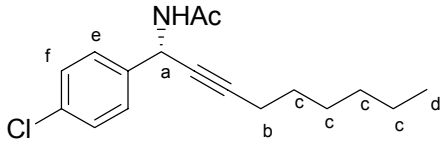
4.5.4.3 (*S*)-*N*-(1-Phenyl-2-nonynyl)acetamide (**4.45c**)



IR (KBr): 3269 (N-H), 1651 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.86 (H_d, t, J = 6.9 Hz, 3H), 1.27-1.52 (H_c, m, 8H), 1.92 (COC$\underline{H}_3$, s, 3H), 2.20 (C_b, t, J = 6.9 Hz, 2H), 5.94 (1H, d, J = 8.4 Hz, 1H), 6.45 (NH, d, br, J = 8.4 Hz, 1H), 7.23-7.47 (H_{Ar}, m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8 (C=O), 139.7 (C_{Ar}), 128.4 (C_{Ar}), 127.7 (C_{Ar}), 126.9 (C_{Ar}), 85.3 (C≡C), 77.9 (C≡C), 44.7 (C_a), 31.2 (C_a), 28.5 (C_c), 28.5 (C_c), 22.9 (CO$\underline{C}H_3$), 22.4 (C_c), 18.6 (C_b), 13.9 (C_d); MS *m/e* (relative intensity):

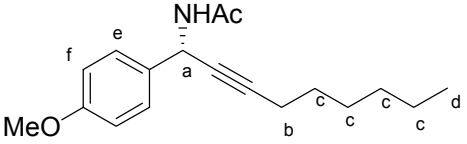
257 (M^+, 6), 186 (M^+-$C_5H_{11,}$ 100); Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.24; H, 8.97; N, 5.53. The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 95/5, flow rate = 1.0 mL/min), t_R = 11.1 min (*R*), t_R = 17.4 min (*S*). $[\alpha]_D^{25}$ +12 (92% *ee*, c 2.28, $CHCl_3$).

4.5.4.4 (*S*)-*N*-[1-(4-Chlorophenyl)-2-nonynyl]acetamide (**4.45d**)



IR (KBr): 3268 (N-H), 1651 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.84 (H_d, t, J = 6.9 Hz, 3H), 1.23-1.50 (H_c, m, 8H), 1.92 ($COC\underline{H}_3$, s, 3H), 2.18 (H_b, dt, J = 1.8 Hz, 6.9 Hz, 2H), 5.87 (H_a, d, br, J = 8.4 Hz, 1H), 6.55 (NH, d, br, J = 8.4 Hz, 1H), 7.23 (H_e, d, J = 8.4 Hz, 2H), 7.37 (H_f, d, J = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1 (C=O), 138.5 (C_{Ar}), 133.7 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 86.0 (C≡C), 77.6 (C≡C), 44.3 (C_a), 31.3 (C_c), 28.6 (C_c), 28.6 (C_c), 23.1 ($CO\underline{C}H_3$), 22.6 (C_c), 18.8 (C_b), 14.1 (C_a); MS *m/e* (relative intensity): 291 (M^+, 4), 220 (M^+-$C_5H_{11,}$ 100); Anal. Calcd for $C_{17}H_{22}ClNO$: C, 69.97; H, 7.60; N, 4.80. Found: C, 70.00; H, 7.42; N, 4.82. The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 95/5, flow rate = 1.0 mL/min), t_R = 9.2 min (*R*), t_R = 10.2 min (*S*). $[\alpha]_D^{25}$ +28.2 (91% *ee*, c 4.0, $CHCl_3$).

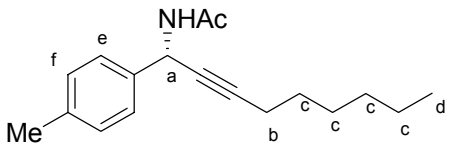
4.5.4.5 (*S*)-*N*-[1-(4-Methoxyphenyl)-2-nonynyl]acetamide (**4.45e**)



IR (KBr): 3272 (N-H), 1652 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.85 (H_d, t, J = 6.9 Hz, 3H), 1.25-1.53 (H_c, m, 8H), 1.92 ($COC\underline{H}_3$, s, 3H), 2.19 (H_b, dt, J = 1.8 Hz, 6.9 Hz, 2H), 3.74 (OMe, s,

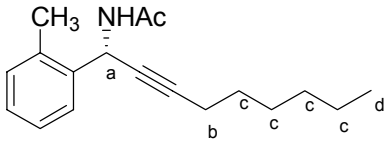
3H), 5.87 (H_a, d, br, J = 8.4 Hz, 1H), 6.27 (NH, d, br, J = 8.4 Hz, 1H), 6.81 (H_f, d, J = 8.5 Hz, 2H), 7.37 (H_e, d, J = 8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.7 (C=O), 159.1 (C_{Ar}), 131.9 (C_{Ar}), 128.2 (C_{Ar}), 113.7 (C_{Ar}), 85.1 (C≡C), 78.1 (C≡C), 55.2 (O<u>C</u>H$_3$), 44.2 (C_a), 31.2 (C_c), 28.5 (C_c), 28.4 (C_c), 23.0 (CO<u>C</u>H$_3$), 22.4 (C_c), 18.6 (C_b), 13.9 (C_d); MS *m/e* (relative intensity): 287 (M^+, 8), 216 (M^+-$C_5H_{11,}$ 100); Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.30; H, 8.64; N, 4.86. The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 94.8/5.2, flow rate = 1.0 mL/min), t_R = 14.0 min (*R*), t_R = 14.9 min (*S*). $[\alpha]_D^{25}$ +22.8 (92% *ee*, c 1.80, $CHCl_3$).

4.5.4.6 (*S*)-*N*-(1-*p*-Tolyl-2-nonynyl)acetamide (**4.45f**)



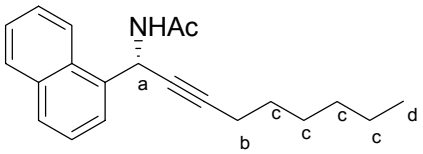
IR (KBr): 3271 (N-H), 1651 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (H_d, t, J = 6.9 Hz, 3H), 1.25-1.53 (H_c, m, 8H), 1.94 (COC<u>H</u>$_3$, s, 3H), 2.20 (H_b, dt, J = 2.0 Hz, 6.9 Hz, 2H), 2.31 (ArC<u>H</u>$_3$, s, 3H), 5.90 (H_a, d, br, J = 8.5 Hz, 1H), 6.16 (NH, d, br, J = 8.5 Hz, 1H), 7.11 (H_f, d, J = 7.9 Hz, 2H), 7.36 (H_e, d, J = 7.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6 (C=O), 137.5 (C_{Ar}), 136.8 (C_{Ar}), 129.1 (C_{Ar}), 126.9 (C_{Ar}), 85.2 (C≡C), 78.0 (C≡C), 44.5 (C_a), 31.2 (C_c), 28.5 (C_c), 28.5 (C_c), 23.1 (CO<u>C</u>H$_3$), 22.4 (C_c), 21.0 (ArCH$_3$), 18.7 (C_b), 13.9 (C_d); MS *m/e* (relative intensity): 271 (M^+, 6), 200 (M^+-$C_5H_{11,}$ 100); Anal. Calcd for $C_{18}H_{25}NO$: C, 79.66; H, 9.28; N, 5.16. Found: C, 79.53; H, 9.22; N, 5.18. The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 98/2, flow rate = 1.0 mL/min), t_R = 20.3min (*R*), t_R = 22.6 min (*S*). $[\alpha]_D^{25}$ +29.9 (92% *ee*, c 0.94, $CHCl_3$).

4.5.4.7 (*R*)-*N*-(1-*o*-Tolyl-2-nonynyl)acetamide (**4.45g**)



IR (KBr): 3265 (N-H), 1651 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.86 (H_d, t, J = 6.8 Hz, 3H), 1.24-1.53 (Hc, m, 8H), 1.95 ($COC\underline{H}_3$, s, 3H), 2.20 (H_b, dt, J = 2.0 Hz, 6.9 Hz, 2H), 2.35 ($ArC\underline{H}_3$, s, 3H), 5.80 (NH, d, br, J = 8.1 Hz, 1H), 5.99 (H_a, d, br, J = 8.1 Hz, 1H), 7.12-7.60 (H_{Ar}, m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1 (C=O), 137.2 (C_{Ar}), 135.8 (C_{Ar}), 130.6 (C_{Ar}), 127.8 (C_{Ar}), 126.7 (C_{Ar}), 126.0 (C_{Ar}), 84.8 (C≡C), 78.0 (C≡C), 42.5 (C_a), 31.1 (C_c), 28.3 (C_c), 22.9 ($CO\underline{C}H_3$) , 22.3 (C_c), 18.8 ($Ar\underline{C}H_3$), 18.6 (C_b), 13.8 (C_d); MS *m/e* (relative intensity): 271 (M^+, 6), 200 (M^+-$C_5H_{11,}$ 100); Anal. Calcd for $C_{18}H_{25}NO$: C, 79.66; H, 9.28; N, 5.16. Found: C, 79.50; H, 9.25; N, 5.06. The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 95/5, flow rate = 1.0 mL/min), t_R = 10.2 min (*R*), t_R = 11.9 min (*S*). $[\alpha]_D^{25}$ -7.10 (99% *ee*, c 0.67, $CHCl_3$).

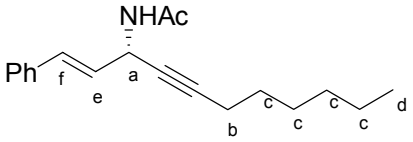
4.5.4.8 (*R*)-*N*-[1-(Naphthalen-1-yl)-2-nonynyl]acetamide (**4.45h**)



IR (KBr): 3269 (N-H), 3050 (C_{Ar}-H), 1649 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.87 (H_d, t, J = 6.9 Hz, 3H), 1.24-1.56 (H_c, m, 8H), 1.95 ($COC\underline{H}_3$, s, 3H), 2.25 (H_b, dt, J = 1.7 Hz, 6.9 Hz, 2H), 6.05 (NH, d, br, J = 8.5 Hz, 1H), 6.62 (H_a, d, br, J = 8.5 Hz, 1H), 7.41-8.11 (H_{Ar}, m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5 (C=O), 134.5 (C_{Ar}), 133.8 (C_{Ar}), 130.4 (C_{Ar}), 129.0 (C_{Ar}), 128.6 (C_{Ar}), 127.1 (C_{Ar}), 126.6 (C_{Ar}), 125.3 (C_{Ar}), 125.1 (C_{Ar}), 123.4 (C_{Ar}), 85.8 (C≡C), 78.0 (C≡C), 42.5 (C_a), 31.2 (C_c), 28.5 (C_c), 23.0 ($CO\underline{C}H_3$), 22.4 (C_c), 18.6 (C_b), 13.9 (C_d); MS *m/e* (relative intensity):

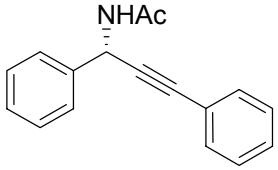
307 (M^+, 18), 236 (M^+-$C_5H_{11,}$ 100); Anal. Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 82.10; H, 8.21; N, 4.63. The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 95/5, flow rate = 1.0 mL/min), t_R = 13.4 min (*R*), t_R = 39.0 min (*S*). $[\alpha]_D^{25}$ +31.3 (>99% *ee*, c 0.78, $CHCl_3$).

4.5.4.9 (*S*,*E*)-*N*-(1-Phenylundec-1-en-4-yn-3-yl)acetamide (**4.45i**)



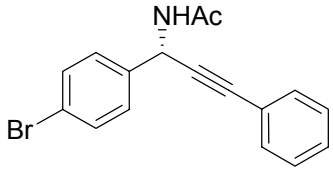
IR (KBr): 3270 (N-H), 1652 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.87 (H_d, t, J = 6.8 Hz, 3H), 1.28-1.55 (H_c, m, 8H), 1.99 ($COC\underline{H}_3$, s, 3H), 2.23 (H_b, dt, J = 1.5 Hz, 7.0 Hz, 2H), 5.51-5.52 (H_a, m, 1H), 5.87 (NH, d, J = 8.2 Hz, 1H), 6.14 (H_e, dd, J = 5.2 Hz, 15.7 Hz, 1H), 6.77 (H_f, d, J = 15.7 Hz, 1H), 7.19-7.36 (H_{Ar}, m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.7 (C=O), 136.2 (C_{Ar}), 131.5 (C_{Ar}), 128.5 (C_f), 127.8 (C_{Ar}), 126.7 (C_{Ar}), 126.6 (C_e), 85.9 (C≡C), 76.8 (C≡C), 42.9 (C_a), 31.3 (C_c), 28.6 (C_c), 28.5 (C_c), 23.2 ($CO\underline{C}H_3$), 22.5 (C_c), 18.7 (C_b), 14.0 (C_d); MS *m/e* (relative intensity): 283 (M^+, 15), 212 (M^+-$C_5H_{11,}$ 100); Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.30; H, 9.03; N, 5.13. The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 95/5, flow rate = 1.0 mL/min), t_R = 16.7 min (*R*), t_R = 20.6 min (*S*). $[\alpha]_D^{25}$ +55.4 (67% *ee*, c 1.0, $CHCl_3$).

4.5.4.10 (*S*)-*N*-(1,3-Diphenyl-2-propynyl)acetamide (**4.45j**)



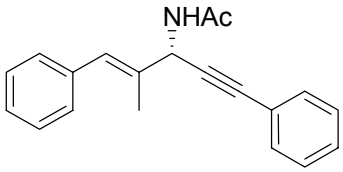
IR (KBr): 3264 (N-H), 1648 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.01 (CH_3, s, 3H), 6.22-6.24 (ArC<u>H</u> and N<u>H</u>, m, 2H), 7.30-7.85 (H_{Ar}, m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.9 (C=O), 139.1 (C_{Ar}), 131.9 (C_{Ar}), 128.8 (C_{Ar}), 128.7 (C_{Ar}), 128.4 (C_{Ar}), 128.2 (C_{Ar}), 127.2 (C_{Ar}), 122.5 (C_{Ar}), 87.1 (C≡C), 84.8 (C≡C), 45.2 (Ar<u>C</u>H), 23.3 (CH_3); MS *m/e* (relative intensity): 249 (M^+, 15), 207 (M^+-C_2H_2O, 100); The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 94.8/5.2, flow rate = 1.0 mL/min), t_R = 19.5 min (*R*), t_R = 22.4 min (*S*). $[\alpha]_D^{25}$ -29.1 (92% *ee*, c 0.67, $CHCl_3$).

4.5.4.11 (*S*)-*N*-[1-(4-Bromophenyl)-3-phenyl-2-propynyl]acetamide (**4.45k**)



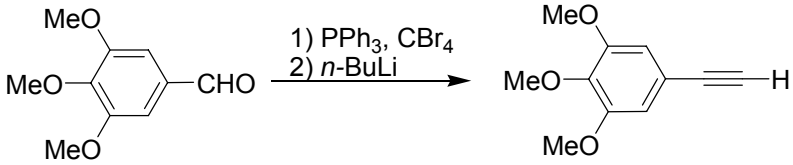
IR (KBr): 3270 (N-H), 1634 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.03 (CH_3, s, 3H), 6.08 (NH, d, br, *J* = 8.4 Hz, 1H), 6.19 (ArC<u>H</u>, d, *J* = 8.4 Hz, 1H), 7.27-7.49 (H_{Ar}, m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.9 (C=O), 138.3 (C_{Ar}), 131.9 (C_{Ar}), 128.9 (C_{Ar}), 128.9 (C_{Ar}), 128.5 (C_{Ar}), 122.2 (C_{Ar}), 86.4 (C≡C), 85.3 (C≡C), 44.8 (Ar<u>C</u>H), 23.3 (CH_3); MS *m/e* (relative intensity): 327 (M^+, 9), 206 (M^+-C_2H_2O-Br, 100); Anal. Calcd for $C_{17}H_{14}BrNO$: C, 62.21; H, 4.30; N, 4.27. Found: C, 62.14; H, 4.27; N, 4.17. The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 95/5, flow rate = 1.0 mL/min), t_R = 24.5 min (*R*), t_R = 28.6 min (*S*). $[\alpha]_D^{25}$ -6.7 (91% *ee*, c 0.67, $CHCl_3$).

4.5.4.12 (*S*,*E*)-*N*-(2-Methyl-1,5-diphenylpent-1-en-4-yn-3-yl)acetamide (**4.45l**)



IR (KBr): 3264 (N-H), 1651 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.96 ($COCH_3$, s, 3H), 2.06 (C=C-C<u>H</u>$_3$, s, 3H), 5.68 (C≡C-C<u>H</u>, d, J = 8.8 Hz, 1H), 6.08 (NH, d, J = 8.8 Hz, 1H), 6.83 (<u>H</u>C=C, s, 1H), 7.21-7.45 (H_{Ar}, m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0 (C=O), 137.1, 134.5, 131.7, 128.9, 128.4, 128.2, 128.0, 127.4, 126.7, 122.4, 86.6 (C≡C), 84.8 (C≡C), 48.4(C≡C-<u>C</u>H), 23.2 (CO<u>C</u>H$_3$), 15.2 (C=C-<u>C</u>H$_3$); MS *m/e* (relative intensity): 289 (M^+, 21), 247 (M^+-C_2H_2O, 100); Anal. Calcd for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 83.14; H, 6.57; N, 4.86. The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 95/5, flow rate = 1.0 mL/min), t_R = 24.9 min (*R*), t_R = 29.2 min (*S*). $[\alpha]_D^{25}$ -2.0 (93% *ee*, c 0.75, $CHCl_3$).

4.5.5 Preparation of 5-Ethynyl-1,2,3-trimethoxybenzene (4.53)

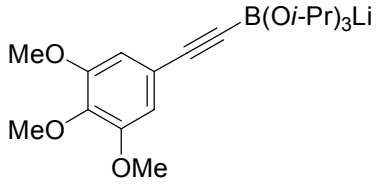


A literature procedure[70] was followed: Triphenylphosphine (23.0 g, 88 mmol) was added to CBr_4 (14.5 g, 44 mmol) in CH_2Cl_2 (270 mL) at 0 °C and the mixture was stirred at that temperature for 5 minutes. 3,4,5-Trimethoxybenzaldehyde (5.70 g, 29 mmol) was added and the resulting mixture was stirred at 0 °C for 10 minutes before the addition of H_2O (75 mL). The organic phase was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The yellow slurry obtained was triturated with hexanes and then Et_2O to remove Ph_3P=O. The organic washings were dried ($MgSO_4$) and

concentrated *in vacuo* to give the dibromoalkene (9.3 g, 91%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83 (OCH_3, s, 6H), 3.84 (OCH_3, s, 3H), 6.77 (H_{Ar}, s, 2H), 7.64 (Br_2C=CH, s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.1 (C_{Ar}), 138.4 (C_{Ar}), 136.7 ($\underline{C}H=CBr_2$), 130.6 (C_{Ar}), 105.8 (C_{Ar}), 88.8 ($CH=\underline{C}Br_2$), 60.9 (OCH_3), 56.2 (OCH_3).

To a solution of the dibromoalkene (9.3 g, 26.4 mmol) in 180 mL of THF at -78 ^{o}C was added *n*-BuLi (34.3 mL, 55 mmol, 1.6 M in hexane) slowly over 30 minutes. The resulting solution was stirred at -78 ^{o}C for 1 h then warmed to room temperature for 2 hours. Saturated NH_4Cl (100 mL) was added and the mixture was extracted with ether (3 x 100 mL). The combined ethereal extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow solid. Flash column chromatography on silica gel (2:1 hexanes/EtOAc) gave the alkyne **4.53** (4.8 g, 93%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.89 ($C\equiv C\underline{H}$, s, 1H), 3.75 (OCH_3, s, 6H), 3.76 (OCH_3, s, 3H), 6.64 (H_{Ar}, s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.1 (C_{Ar}), 139.2 (C_{Ar}), 117.1 (C_{Ar}), 109.3 (C_{Ar}), 83.7 ($\underline{C}\equiv CH$), 76.4 ($C\equiv\underline{C}H$), 60.9 (OCH_3), 56.1 (OCH_3).

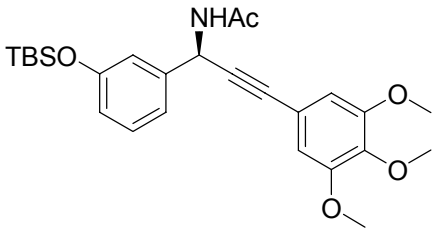
4.5.6 Preparation of Lithium Triisopropyl-*B*-1-(3,4,5-trimethoxyphenyl)ethynylborate (4.57)



To a solution of alkyne **4.53** (384 mg, 2.0 mmol) in THF (10 mL) at -78 ^{o}C was added *n*-BuLi (1.6 M in hexane). After stirring at that temperature for 30 minutes, the resulting solution was added slowly to a solution of triisopropyl borate (395 mg, 2.1 mmol) in THF (10 mL) at -78 ^{o}C. The reaction mixture was allowed to warm to room temperature for 6 hours. Volatiles were removed *in vacuo* and

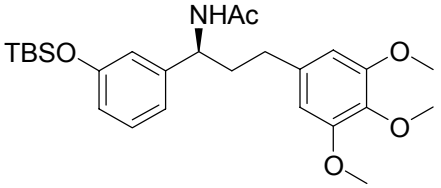
the crude product **4.57** was obtained as an off-white powder in quantitative yield. This product was used without further purification and identification.

4.5.7 Preparation of (*R*)-*N*-(1-(3-(*tert*-Butyldimethylsilyloxy)phenyl)-3-(3,4,5-trimethoxy phenyl)prop-2-ynyl)acetamide (4.51)



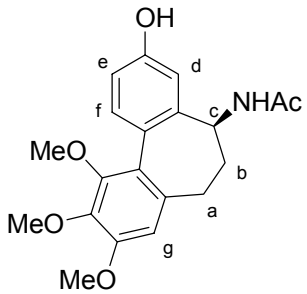
The title compound was prepared in 72% yield and 94% *ee* from TBS protected 3-hydroxybenzaldehyde[75] and borate **4.57** using the general procedure for the alkynylation of acylimines. IR (KBr): 3272 (N-H), 1655 (C=O), 1130 (C-O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.17 [Si($C\underline{H}_3$)$_2$, s, 6H], 0.94 [Si-C($C\underline{H}_3$)$_3$, s, 9H], 1.99 ($COCH_3$, s, 3H), 3.79 (2 x MeO, s, 6H), 3.80 (MeO, s, 3H), 6.15 (Ar-C$\underline{H}$, d, J = 8.6 Hz, 1H), 6.28 (NH, d, br, J = 8.6 Hz, 1H), 6.65 (H_{Ar}, s, 2H), 6.75-7.22 (H_{Ar}, m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8 (C=O), 155.8 (C_{Ar}), 152.9 (C_{Ar}), 140.3 (C_{Ar}), 138.8 (C_{Ar}), 129.6 (C_{Ar}), 119.9 (C_{Ar}), 119.7 (C_{Ar}), 118.7 (C_{Ar}), 117.4 (C_{Ar}), 108.9 (C_{Ar}), 86.0 (C≡C), 84.4 (C≡C), 60.8 (O$\underline{C}H_3$), 56.0 (O$\underline{C}H_3$), 44.8 (Ar$\underline{C}$H), 25.6 [C($\underline{C}H_3$)$_3$], 23.1 (CO$\underline{C}H_3$), 18.1 [$\underline{C}$(CH_3)$_3$], -4.5 [Si($\underline{C}H_3$)$_2$]; HRMS *m/z* Calcd for $C_{26}H_{35}NO_5Si$ (M^+): 469.2285. Found: 469.2293. *ee* was determined by HPLC (hexanes/*i*-PrOH = 95.6/4.4, flow rate = 1.0 mL/min), t_R = 35 min (*R*), t_R = 39 min (*S*). $[\alpha]_D^{25}$ +18.7 (94% *ee*, c 1.4, $CHCl_3$).

4.5.8 Preparation of (*S*)-*N*-(1-(3-(*tert*-Butyldimethylsilyloxy)phenyl)-3-(3,4,5-trimethoxy phenyl)propyl) acetamide (4.50).



Compound **4.51** (1 mmol) was taken up in 5 mL of MeOH and 10% Pd/C (20 mg) was added. The reaction was stirred at room temperature under 1 atm of H_2 for 24 h. Compound **4.50** was obtained as a colorless oil in quantitative yield after column chromatography (EtOAc/hexanes: 2/1). IR (KBr): 3285 (N-H), 1649 (C=O), 1129 (C-O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.05 [Si(C$\underline{H}_3$)$_2$, s, 6H], 0.95 [Si-C(C$\underline{H}_3$)$_3$, s, 9H], 1.93-2.17 (ArCH$_2$C$\underline{H}_2$ and CO$\underline{CH}_3$, m, 5H), 2.45-2.54 (ArC$\underline{H}_2$CH$_2$, m, 2H), 3.78 (2 x MeO, s, 6H), 3.79 (MeO, m, 3H), 4.93 (ArC$\underline{H}$NH, q, J = 8.3 Hz, 1H), 5.88 (NH, d, J = 8.3 Hz, 1H), 6.33 (H_{Ar}, s, 2H), 6.71-7.19 (H_{Ar}, m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1 (C=O), 155.9 (C_{Ar}), 153.0 (C_{Ar}), 143.3 (C_{Ar}), 137.1 (C_{Ar}), 136.0 (C_{Ar}), 129.6 (C_{Ar}), 119.5 (C_{Ar}), 119.0 (C_{Ar}), 118.4 (C_{Ar}), 105.2 (C_{Ar}), 60.7 (MeO), 56.0 (MeO), 53.0 (ArC$\underline{H}$NH), 37.4 (Ar$\underline{C}$H$_2$CH$_2$), 32.8 (ArCH$_2\underline{C}$H$_2$), 25.6 [Si-C(C$\underline{H}_3$)$_3$], 23.3 (CO$\underline{C}$H$_3$), 18.1 [$\underline{C}$(CH$_3$)$_3$], -4.5 [Si(C$\underline{H}_3$)$_2$]; HRMS *m/z* Calcd for $C_{26}H_{39}NO_5Si$ (M^+): 473.2598. Found: 473.2591. $[\alpha]_D^{25}$ -35 (c 1.1, $CHCl_3$).

4.5.9 Preparation of (-)-*N*-Acetylcolchinol (4.49)



Sawyer's procedure[71] was followed with minor modifications: $Tl(O_2CCF_3)_3$ (65 mg, 0.121 mmol) and 1.0 mL of freshly distilled $BF_3{\cdot}OEt_2$ were dissolved in 23 mL of trifluoroacetic acid (contains 5% trifluoroacetic anhydride) in the presence of 4Å molecular sieves (0.5 g). A solution of compound **4.50** (55 mg, 0.115 mmol) in 5 mL of trifluoroacetic acid was then added at 0 ^oC and the resulting brown solution was stirred at ambient temperature for 4 h. 30 mL of $CHCl_3$ was added before the reaction was quenched with 20 mL of water. The organic layer was separated and the aqueous layer was extracted with 3 x 15 mL $CHCl_3$. The organic layers were combined and dried over Na_2SO_4. After evaporating the volatiles, the residual brown oil was purified by column chromatography (EtOAc) to give 22 mg (53%) of **4.49** as an off-white powder. ^1H NMR spectrum of compound **4.49** in $CDCl_3$ showed 2.5:1 mixture of conformational isomers (doubled resonances for all protons). In d_6-DMSO, only one set of peaks was observed due to either fast equilibration between the two diastereomers or the presence of a single diastereomer. ^1H NMR (300 MHz, d_6-DMSO): δ 1.78-1.90 ($COC\underline{H_3}$ and H_b, m), 2.00-2.15 (H_a and H_b, m, 2H), 2.38-2.52 (H_a, m, 1H), 3.45 (OMe, s, 3H), 3.75 (OMe, s, 3H), 3.80 (OMe, s, 3H), 4.40-4.47 (H_c, m, 1H), 6.67 (H_e, dd, J = 2.4 Hz, 8.3 Hz, 1H), 6.73 (H_g, s, 1H), 6.74 (H_d, d, J = 2.4 Hz, 1H), 7.09(H_f, d, J = 8.3 Hz, 1H), 8.31(NH, d, J = 8.4 Hz, 1H), 9.36(OH, s, 1H); ^{13}C NMR (75 MHz, d_6-DMSO): δ 168.2 (C=O), 156.4 (C_{Ar}), 151.8 (C_{Ar}), 150.3 (C_{Ar}), 141.7 (C_{Ar}), 140.5 (C_{Ar}), 134.7 (C_{Ar}), 130.4 (C_{Ar}), 124.7 (C_{Ar}), 124.4 (C_{Ar}), 112.9 (C_{Ar}), 110.2 (C_{Ar}), 107.9 (C_{Ar}), 60.5 (OMe), 60.4 (OMe), 55.8 (OMe), 48.1 (C_c), 38.4 (H_b), 30.1 (H_a), 22.6 ($COCH_3$); HRMS *m/z* Calcd for $C_{20}H_{23}NO_5$ (M^+): 357.1576. Found: 357.1579. $[\alpha]_D^{25}$ -45.2 (c 0.6, $CHCl_3$, Lit.[72] $[\alpha]_D^{20}$ -51.6, c 1.123, $CHCl_3$).

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Chapter 5

Catalytic Asymmetric Conjugate Alkynylation of Enones

5.1 Introduction: Boron in Asymmetric Catalysis

Asymmetric catalysis has received explosive interest in the past few decades since the use of only catalytic amounts of chiral catalysts has obvious economic and practical advantages. Some famous catalytic reactions such as the Sharpless asymmetric epoxidation[1] and Noyori's hydrogenation[2] have been widely applied in the pharmaceutical and agricultural industries. Boron reagents also play an important role in asymmetric catalysis as various chirally modified boron reagents have been applied in catalytic processes such as the reduction of carbonyls and C=N bonds, Diels-Alder reactions, aldol and alkylation reactions, etc.[3,4] This section discusses some typical examples of catalytic reactions involving chiral boron reagents.

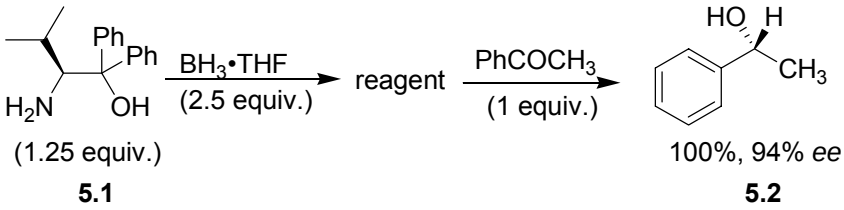
5.1.1 Catalytic Reductions

5.1.1.1 Ketone Reductions

The stereoselective reduction of ketones has been one of the most studied transformations because the resulting chiral alcohols are present in numerous natural products and are key intermediates for many complex molecule syntheses.[5] In the past 50 years, the asymmetric reduction of carbonyl compounds with stoichiometric quantities of chiral-modified boron or aluminum reagents

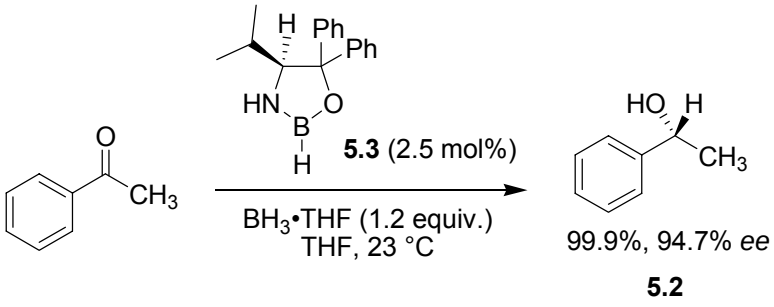
has been studied.[6] However, the asymmetric reduction of carbonyls induced by a catalytic amount of chiral boron reagents remained unexploited until the early 1980's.

In 1981, Itsuno reported that mixtures of chiral amino alcohols such as alcohol **5.1** and BH_3·THF in a ratio of 1:2 in THF could reduce achiral ketones enantioselectively to chiral secondary alcohols in nearly quantitative yield and up to 94% *ee* (Scheme 5.1).[7-10] It was noted that at least two equivalents of BH_3·THF are required in order to obtain high enantioselectivity.



Scheme 5.1

Later, a mechanistic study on this stoichiometric reaction was conducted by Corey and co-workers.[11,12] It was found that when tertiary alcohol **5.1** was treated with one equivalent of BH_3·THF, an oxazaborolidine **5.3** was generated. Surprisingly, this oxazaborolidine **5.3** did not reduce ketones even after several hours at room temperature. However, a mixture of compound **5.3** and BH_3·THF (0.6 equiv.) effected the rapid reduction of acetophenone at 23 ^{o}C to afford secondary alcohol **5.2** in 94.7% *ee* which is comparable to the results obtained by Itsuno. More interestingly, they soon realized that only a catalytic amount of compound **5.3** was required in this reaction to achieve high enantioselectivities (Scheme 5.2).



Scheme 5.2

Since the initial report, many variations and improvements of the original catalyst **5.3** have been published (Figure 5.1). These oxazaborolidines**,** which were later named CBS catalysts (after the developers ***C***orey, ***B***akshi and ***S***hibata), exhibited high enantioselectivities toward a wide range of substrates and were applied in the total synthesis of numerous bioactive compounds and natural products.[5]

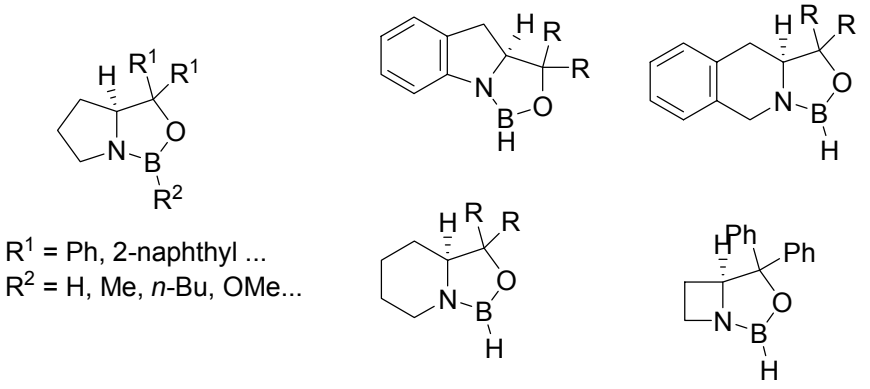
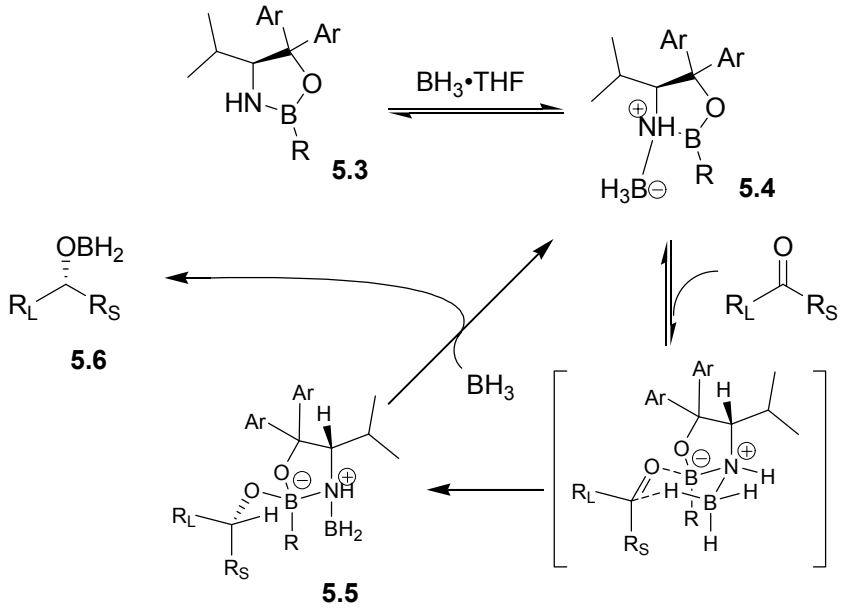


Figure 5.1 Variations of the original oxazaborolidine catalyst **5.3**.

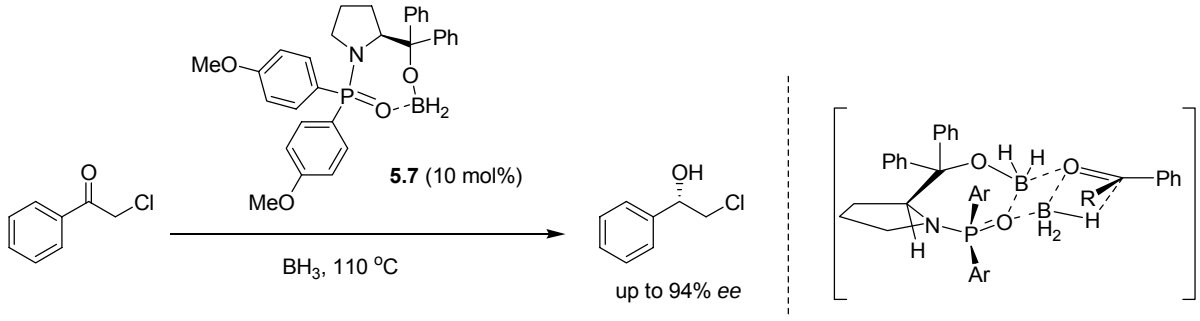
A general mechanistic model was proposed to rationalize the selectivity of the CBS reduction (Scheme 5.3). The initial step in the pathway is the rapid coordination of BH_3 to the Lewis-basic nitrogen atom on oxazaborolidine **5.3** to form oxazaborolidine-BH_3 complex **5.4**. The strongly Lewis-acidic complex **5.4** then readily binds to the ketone substrate at the more sterically accessible

electron lone pair. Facially-selective hydride transfer *via* a six-membered transition state forms the reduction product **5.5**. The final ligand exchange gives the alkoxyborane **5.6** and completes the catalytic cycle.[12]



Scheme 5.3

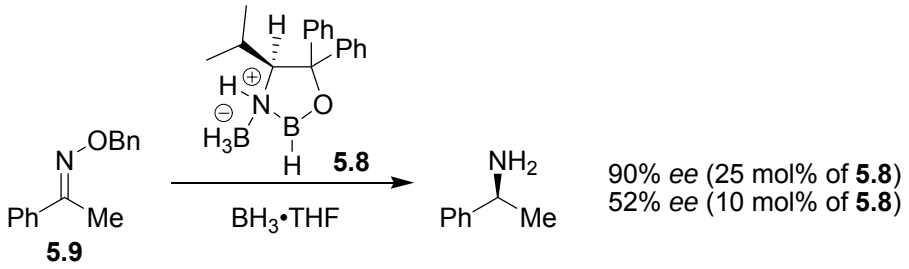
Similar to oxazaborolidines, chiral oxazaphospholidine-borane complexes are also capable of catalyzing the reduction of ketones enantioselectively. Buono has reported that catalyst **5.7** could reduce a range of aryl alkyl ketones in up to 94% *ee*.[13,14] Interestingly, in contrast to CBS catalysts, catalyst **5.7** showed increased selectivity at elevated temperature (Scheme 5.4).



Scheme 5.4

5.1.1.2 C=N Double Bond Reductions

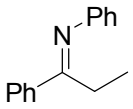
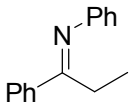
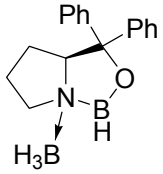
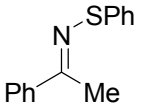
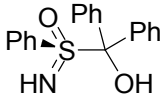
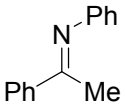
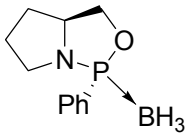
Although effective catalytic asymmetric reduction of carbonyl compounds has been extensively studied, the catalytic reduction of imine derivatives to chiral amines has been relatively neglected. Consequently, less success has been achieved. The first catalytic asymmetric reduction of imino compounds was realized by Itsuno in the late 1980's.[15] It was found that oxazaborolidine·BH_3 complex **5.8** could reduce oxime ether **5.9** to give chiral secondary amines in good chemical and optical yields. Compared to the catalytic reduction of ketones, the reduction of oxime ether **5.9** requires much higher catalyst loading (25 mol%). Lower catalyst loadings (10 mol%) resulted in lower enantioselectivities (Scheme 5.5).



Scheme 5.5

Results of several other catalytic asymmetric reductions of imino compounds are summarized in Table 5.1.

Table 5.1 Catalytic asymmetric reduction of imino compounds.

entry	substrate	catalyst	borane	yield (%)	*ee* (%)
1[16,17]		**5.8**	BH_3·THF	95	66
2[17]			BH_3·THF	92	70
3[18]			BH_3·SMe_2	64	70
4[19]			BH_3·SMe_2	59	63

5.1.2 Boron Reagents as Chiral Lewis Acids

Chiral Lewis acids are very versatile mediators of a variety of stereoselective organic transformations. Boron reagents are potentially excellent Lewis acids due to the electron deficient nature of boron atom (Figure 5.2). To date, numerous asymmetric reactions induced by chiral boron Lewis acids have been developed. Some of the important processes will be discussed.

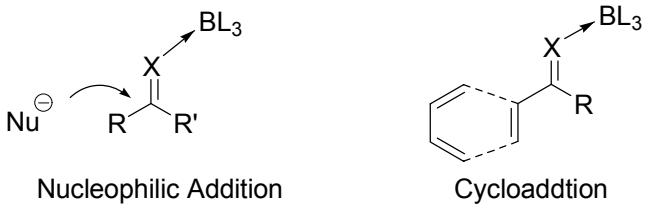
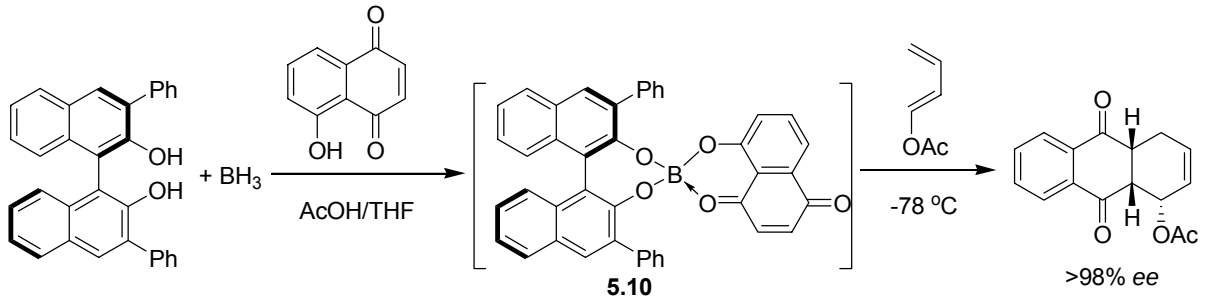


Figure 5.2 Examples of boron-based Lewis acid catalyzed reactions.

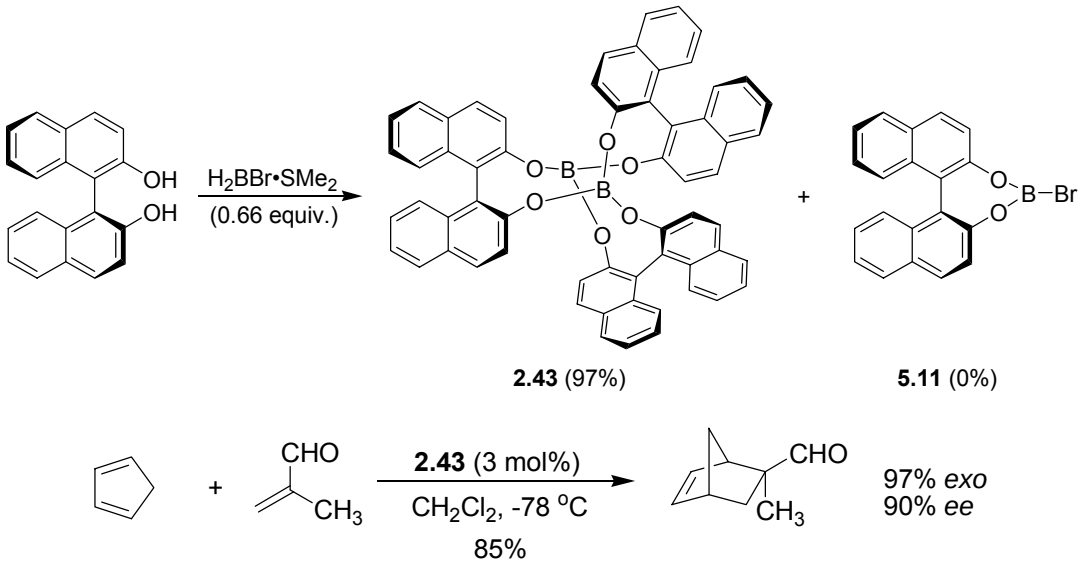
5.1.2.1 Diels-Alder Reactions

The first highly enantioselective Diels-Alder reaction induced by a chiral boron complex was reported by Kelly in 1986.[20] Complex **5.10** was prepared from juglone (a *peri*-hydroxyquinone which is the dienophile for the Diels-Alder reaction) and a 3,3'-diphenyl-l,1'-binaphthol. It reacted with various dienes to give the desired Diels-Alder adducts in excellent optical yields (Scheme 5.6). However, since this reaction proceeds via the binding of the boron to the dienophile, the use of a stoichiometric amount of chiral boron reagent is required.



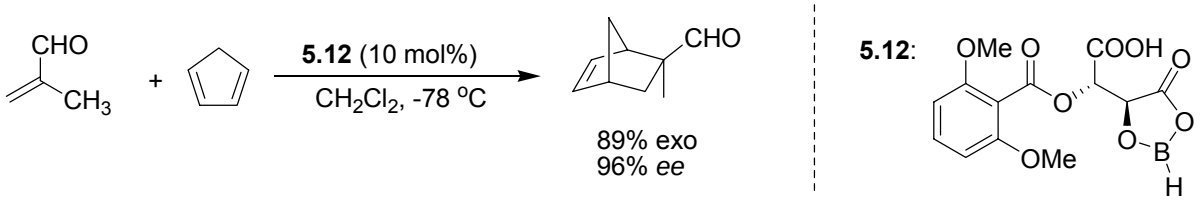
Scheme 5.6

A "propeller-shaped" complex **2.43** was obtained by Kaufmann and co-workers when they were trying to synthesize compound **5.11**. This complex dramatically accelerated the Diels-Alder reaction between cyclopentadiene and methacrolein. [21] The *exo*-selectivity (97%) of the reaction is outstanding, as is the observed enantioselectivity (90% *ee*). In contrast to Kelly's reaction, only 3 mol% of chiral Lewis acid **2.43** was needed in this case (Scheme 5.7).



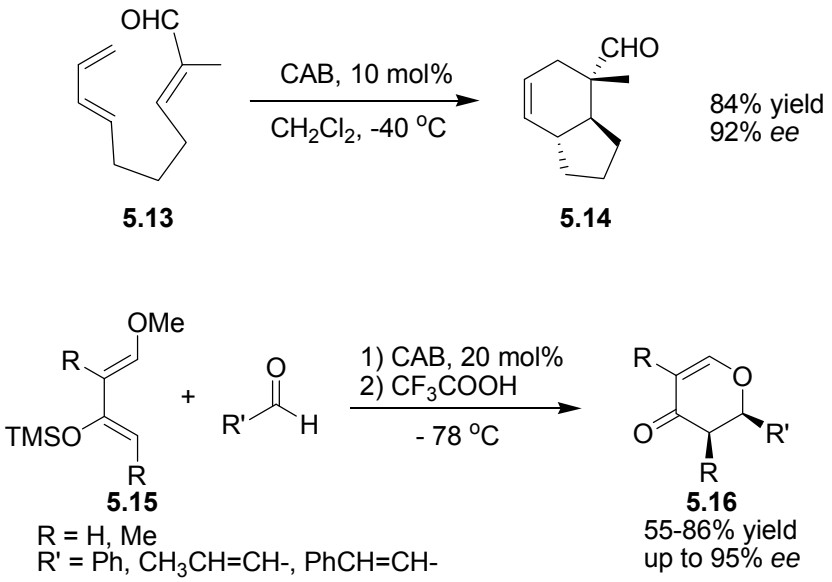
Scheme 5.7

Another example is Yamamoto's CAB catalysts (***C***hiral ***A***cy1oxy***B***orane).[22] They are very effective Lewis acids for the Diels-Alder reactions between a wide range of dienes and dienophiles (Scheme 5.8).



Scheme 5.8

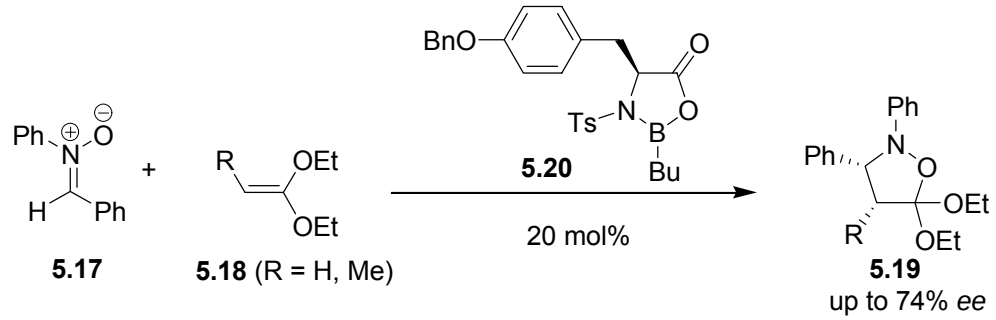
Moreover, this CAB catalyst could also induce high enantioselectivities in intramolecular-[23] and hetero-Diels-Alder reactions (Scheme 5.9).[24]



Scheme 5.9

5.1.2.2 1,3-Dipolar Cycloaddtions

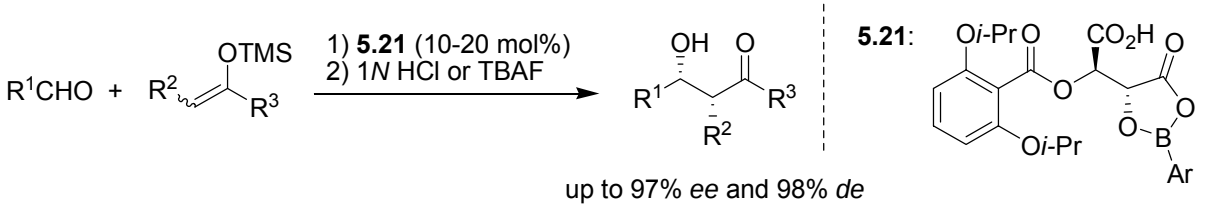
Boron-based chiral Lewis acids are also able to catalyze other type of cyclization reactions such as the 1,3-dipolar cycloaddition reaction between nitrones and electron-rich alkenes.[25] Although only moderate enantioselectivities could be obtained (Scheme 5.10).



Scheme 5.10

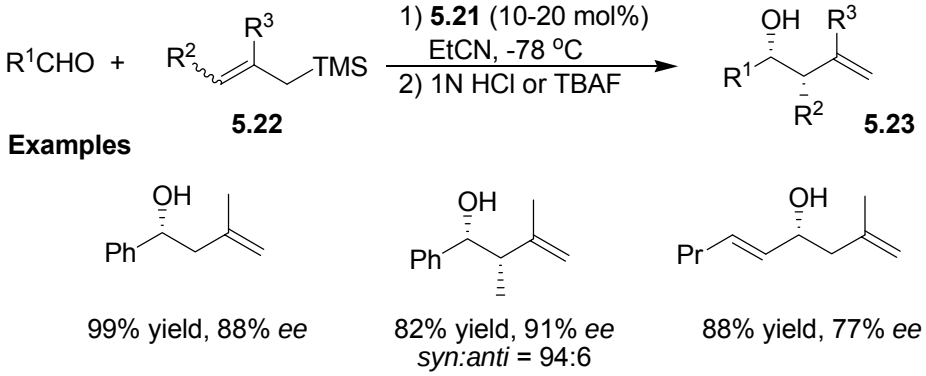
5.1.2.3 Aldol and Allylation Reactions

Enantioselective Mukaiyama aldol and Sakurai-Hosomi allylation reactions catalyzed by chiral Lewis acids are of great interest since the products of these reactions are valuable building blocks for total syntheses of complex molecules. Yamamoto and coworkers have reported CAB catalyst **5.21** to be an excellent catalyst for the enantioselective Mukaiyama condensation of enol silyl ethers with various aldehydes (Scheme 5.11).[26]



Scheme 5.11

They also found that CAB catalysts **5.21** are powerful catalyst in the Sakurai-Hosomi allylation reactions of aldehydes.[27] Crotylation catalyzed by **5.21** exhibits the same level of high enantioselectivity as that of the allylation. Regardless of the geometry of the starting allylsilane, the *syn*-isomer is always the major product (Scheme 5.12).



Scheme 5.12

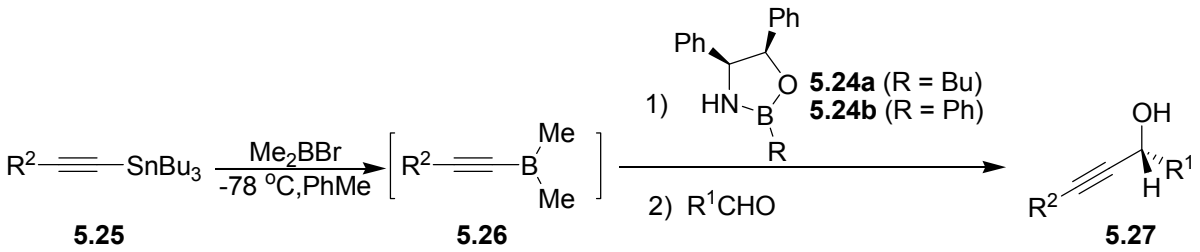
5.1.2.4 Other Catalytic Processes

In addition to the catalytic reactions mentioned above, boron-based chiral Lewis acids are also involved in many other asymmetric catalytic reactions such as the asymmetric cyanation of aldehydes,[28] the catalytic addition of dialkylzinc to aldehydes[29] and asymmetric cyclopropanation reactions.[30] Details of those reactions have appeared in several review papers.[3-5,13,28]

5.1.3 Miscellaneous Reactions

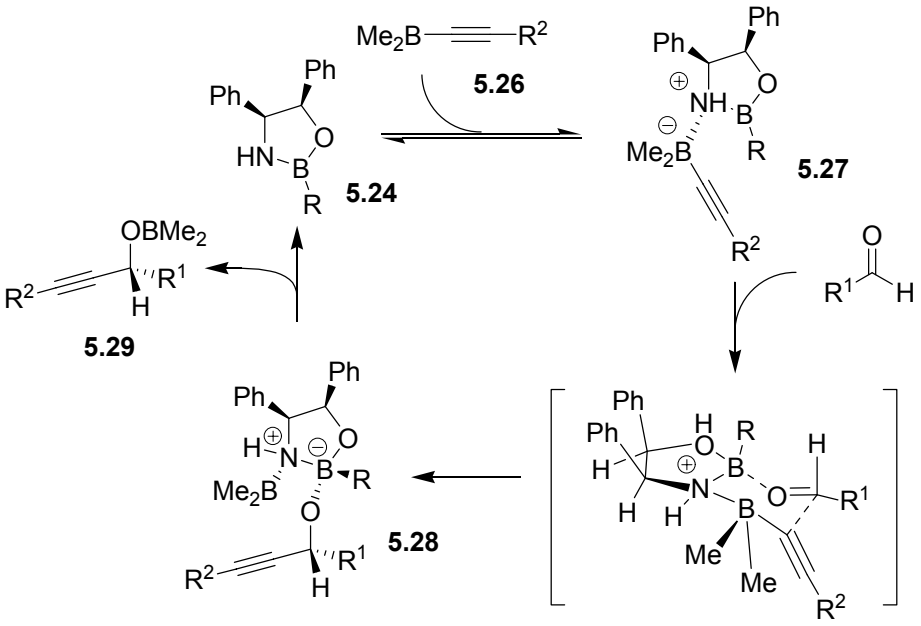
In 1994, Corey reported an asymmetric alkynylation of aldehydes catalyzed by chiral oxazaborolidines **5.24**.[31] Alkynylborane **5.26** was prepared *in situ* from the corresponding alkynylstananne **5.25**. In the presence of a stoichiometric amount of catalyst **5.24a**, alkynylborane **5.26** added to aldehydes to afford the desired propargyl alcohols in excellent yields (up to 96%) and enantioselectivities (85-97% *ee,* Table 5.2, entries 1-5), while oxazaborolidine **5.24b** (R = Ph) efficiently promotes the same alkynylation reactions in substoichiometric quantities (25 mol%, Table 5.2, entries 6 and 7).

Table 5.2 Asymmetric alkynylation of aldehydes catalyzed by oxazaborolidines **5.24**.



entry	R^1	R^2	catalyst (equiv.)	yield (%)	*ee* (%)
1	*c*-C_6H_{11}	Ph	**5.24a** (1.0)	96	90
2	*c*-C_6H_{11}	*n*-C_5H_{11}	**5.24a** (1.0)	82	95
3	Ph	Ph	**5.24a** (1.0)	78	96
4	*n*-C_5H_{11}	Ph	**5.24a** (1.0)	90	96
5	*t*-Bu	Ph	**5.24a** (1.0)	71	93
6	Ph	Ph	**5.24b** (0.25)	72	97
7	*n*-C_5H_{11}	Ph	**5.24b** (0.25)	71	93

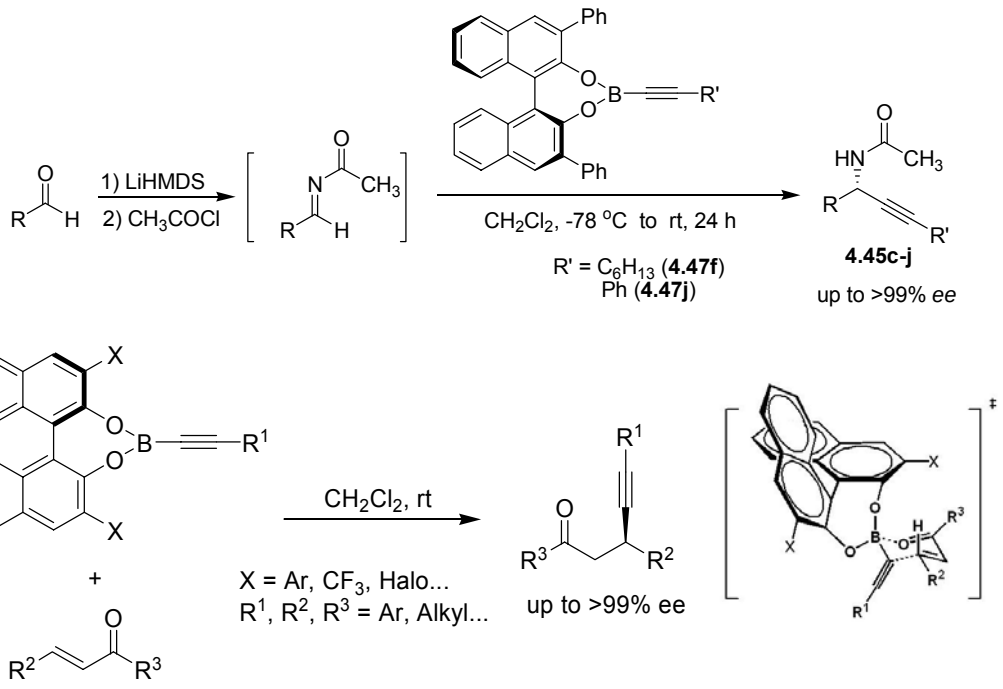
The rationale for this enantioselective alkynylation process is outlined in Scheme 5.13. The first step of the reaction is the coordination of alkynylborane **5.26** with the basic nitrogen on oxazaborolidine **5.24** to form a complex **5.27**. The coordination of the alkynylborane **5.26** to the nitrogen atom of **5.24** serves to activate **5.26** as an alkynyl group donor and also to increase the Lewis acidity of the endocyclic boron atom. The strongly Lewis acidic complex **5.27** then binds with aldehydic oxygen and transfers the alkynyl group to the aldehyde through a six-membered transition state to provide the adduct **5.28**. The catalytic cycle was finally completed by the breakdown of **5.28**.


Me2B—≡—R2
5.26
Ph
Ph
HN
B
O
R
5.24
Ph
Ph
NH
B
O
Me2B
R
5.27
R2
O
R1
H
OBMe2
R2
R1
H
5.29
Ph
Ph
H
N
B
O
Me2B
R
O
R2
R1
H
5.28
Ph
Ph
H
H
O
B
R
N
H
B
O
R1
H
Me
Me
R2

Scheme 5.13

5.2 Proposal

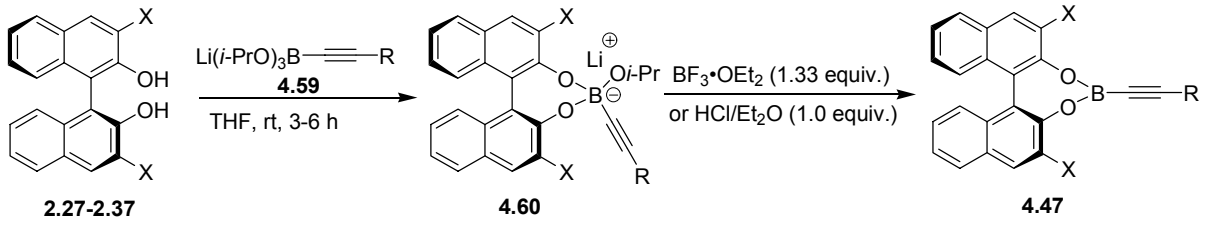
As was discussed previously in Chapter 4, 3,3′-disubstituted binaphthol-modified alkynylboronates **4.47** are able to deliver alkynyl groups to acylimines or enones in a highly enantioselective manner (Scheme 5.14).[32]



Scheme 5.14

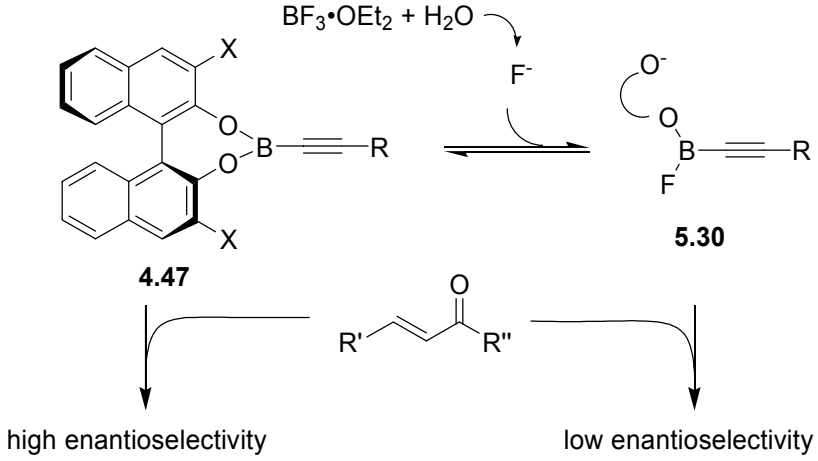
Regardless of the fact that these alkynylation reactions are very effective, the enantioselectivities of these reactions are sensitive to impurities that are introduced during the preparation of chiral alkynylboronates **4.47**. As illustrated in Scheme 5.15, alkynylboronates **4.47** were prepared from "ate" complexes **4.60** which were obtained from the ligand exchange reaction between the corresponding binaphthols and achiral alkynylborates **4.59**.[33,34] It was found that if "aged" $BF_3{\cdot}OEt_2$

was used, the alkynylations suffered lower enantioselectivities. In addition, an excess amount of $BF_3{\cdot}OEt_2$ or HCl/Et_2O was also found to induce low enantioselectivities.[33]



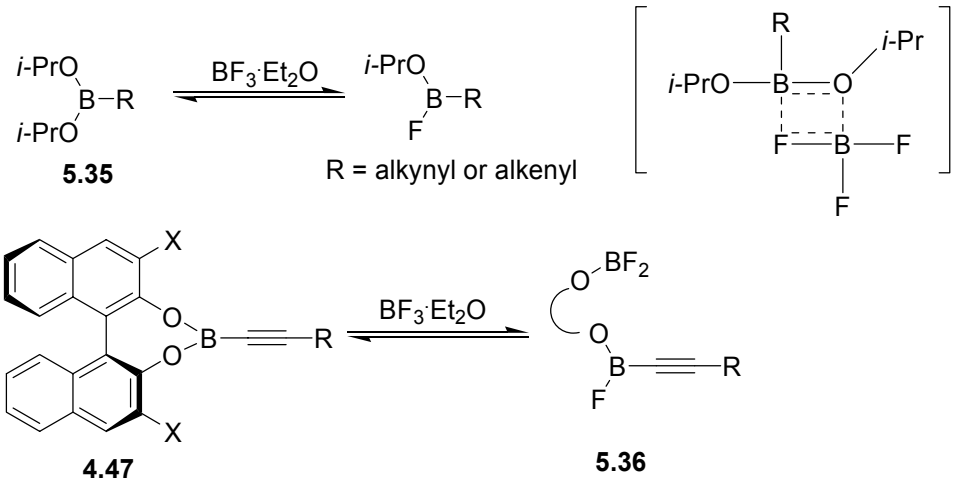
Scheme 5.15

To explain the observation that "aged" $BF_3{\cdot}OEt_2$ induces low enantioselectivity, we proposed that the free fluoride anion (F^-), which is present in unpurified or aged $BF_3{\cdot}OEt_2$, can readily replace the chiral ligands on alkynylboronates **4.47** in a reversible fashion and the resulting boronates **5.30** are still active enough to react with electrophiles (acylimines or enones) to give alkynylation products but with a different sense of enantioselectivity (Scheme 5.16). In addition, if an excess amount of HCl is used, a similar reaction would also occur.



Scheme 5.16

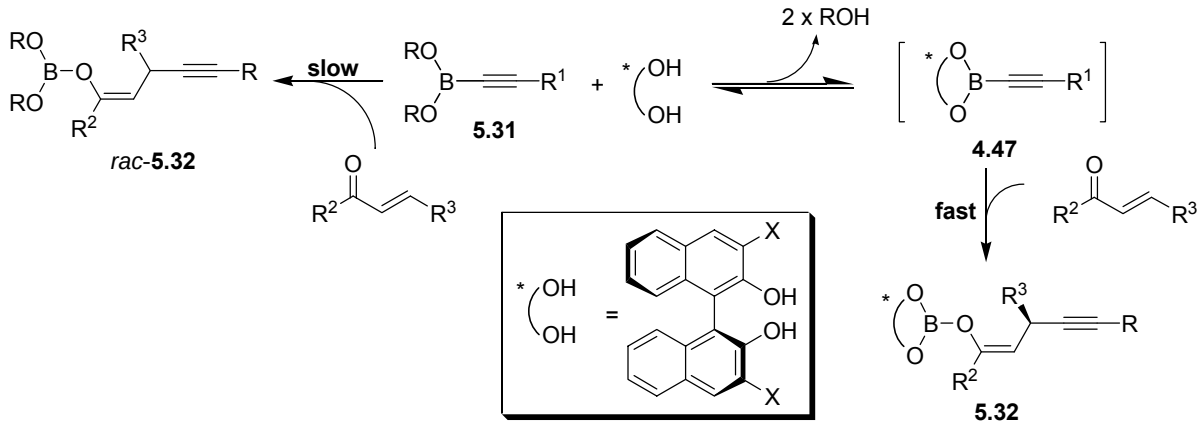
Besides, previously, Suzuki and co-workers found that alkenyl or alkynyl boronates **5.35** could readily undergo a reversible ligand exchange with $BF_3{\cdot}OEt_2$ (*via* a four-membered transition state, Scheme 5.17).[35,36] This implies that an excess amount of $BF_3{\cdot}OEt_2$ might also react with chiral boronates **4.47** to form new boronates **5.36** which in turn produce low enantioselectivities.



Scheme 5.17

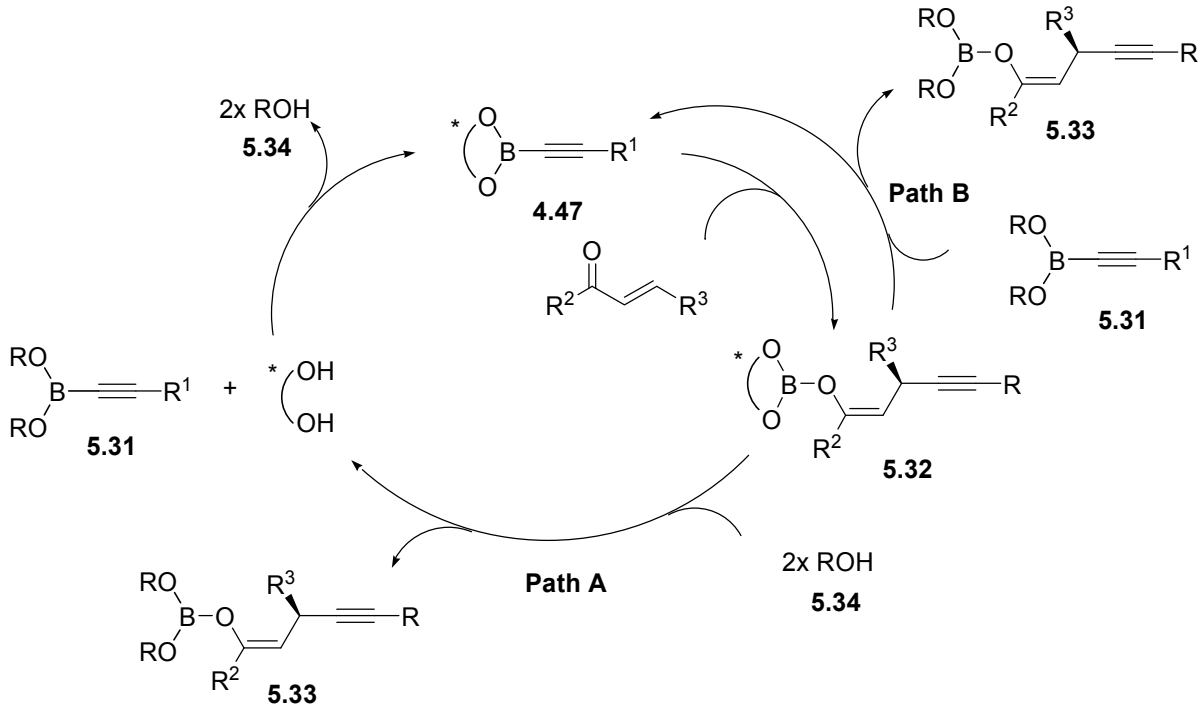
These problems, however, prompted us to think about the alkynylation chemistry from a different angle. Given the fact that the "stereoselective" chiral alkynylboronates **4.47** and the "non-stereoselective" alkynylboronates such as **5.30** and **5.36** are interconvertible, we envisaged a scenario wherein an achiral (non-stereoselective) alkynylboronate **5.31** is mixed with chiral binaphthols and electrophiles (enones or *N*-acylimines). Achiral alkynylboronate **5.31** may undergo ligand exchange with chiral binaphthols to form chiral boronates **4.47** *in situ* which then immediately induce the asymmetric alkynylation reaction with electrophiles. The alkynylation reaction will be highly enantioselective as long as chiral boronates **4.47** are far more reactive than the starting achiral

alkynylboronate **5.31**. This would allow us to carry out the asymmetric alkynylation without pre-forming chiral alkynylboronates **4.47** (Scheme 5.18).



Scheme 5.18

Moreover, if the chiral ligand could be freed from the intermediate borate **5.32**, it could react with more of **5.31** to generate more chiral boronate **4.47** and hence render a catalytic reaction. As is depicted in Scheme 5.19, borate **5.32** might undergo a ligand exchange with achiral alkynylboronate **5.31** to yield alkynylation product **5.33** and regenerate the active chiral alkynylboronate **4.47** (Path B). Alternatively, **5.32** might also react with alcohol **5.34** which is released in the initial step to complete a catalytic cycle (Path A).



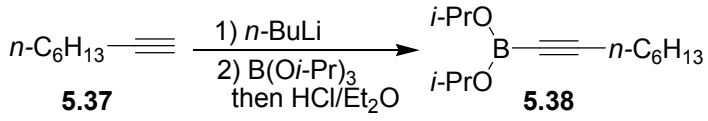
Scheme 5.19

The use of catalytic amounts of chiral catalysts has obvious economic and practical advantages. While various boron complexes, especially CBS and CAB reagents, have been used as catalysts in asymmetric reactions, a catalytic asymmetric reaction that is promoted by a catalytic amount of an "exchangeable" chiral ligand on the boron has not been reported. It seemed worthwhile to develop an asymmetric reaction based on the catalytic cycle demonstrated above.

5.3 Results and Discussions

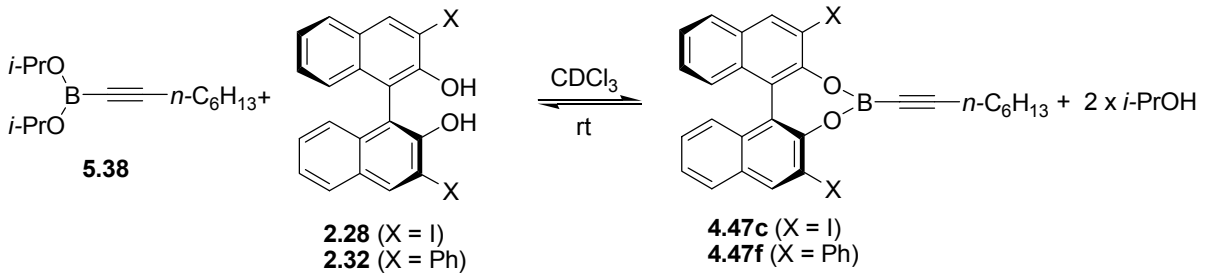
5.3.1 Initial Studies on the Catalytic Alkynylation of Enones

In order to examine the proposed catalytic cycle, achiral alkynylboronates that do not react with electrophiles (enones or *N*-acylimines) are required. It was reported by Suzuki that diisopropyl alkynylboronate **5.38** is inert toward enones in the absence of $BF_3{\cdot}OEt_2$.[36] Therefore, **5.38** was synthesized following Brown's method (Scheme 5.20).[37]



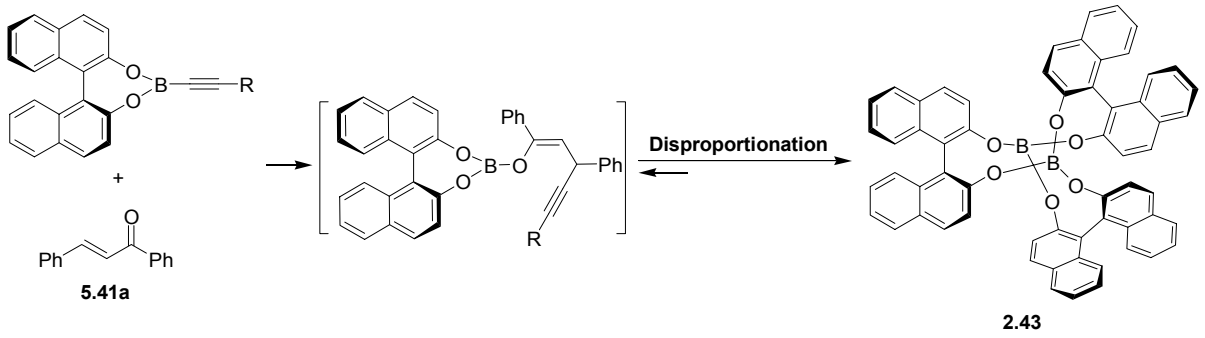
Scheme 5.20

1H NMR studies have shown that when alkynylboronate **5.38** was mixed with substituted binaphthols, an equilibrium between boronates **5.38** and **4.47** was established rapidly at room temperature and it seemed that the equilibrium predominantly favours **5.38** over **4.47**. It could be explained by proposing that since binaphthol-modified boronate **4.47** is a much stronger Lewis acid than the starting dialkyl boronate **5.38**, the stronger Lewis acid **4.47** is more likely to react with isopropanol to form the weaker Lewis acid **5.38** according to the acid-base theory. Nonetheless, it proved that the initial transesterification between binaphthol and dialkyl boronate **5.38** did occur.



Scheme 5.21

To examine whether binaphthols can induce the alkynylation of enone, various substituted binaphthols were tested. The results are summarized in Table 5.3. When chiral ligands were not present in the reaction (Table 5.3, entry 1), alkynylboronate **5.38** indeed did not react with chalcone (**5.41a**, an *α,β*-unsaturated ketone). However, 20 mol% of the parent binaphthol could induce the alkynylation giving more than 20% but less than 50% conversion. This indicated that a catalytic cycle was running but not very smoothly. The sluggish catalytic cycle might be the result of the formation of the thermodynamically stable compound **2.43** (Scheme 5.22) which prevents the chiral ligand from going back to the catalytic cycle.

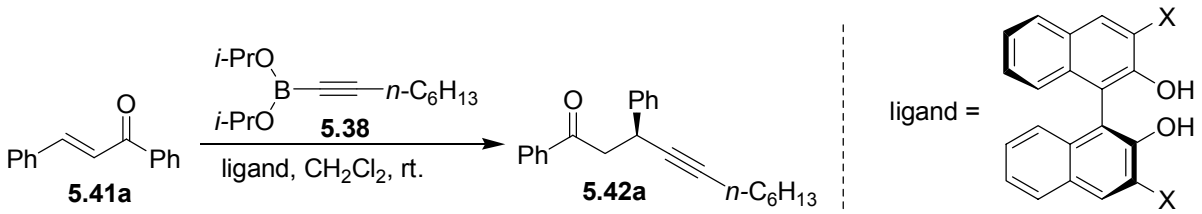


Scheme 5.22

When substituted binaphthol **2.32** (X = Ph) was used, an increased yield of 60% was obtained after the reaction was run for 5 days at room temperature (Table 5.3, entry 2). The enantioselectivity obtained in this catalytic reaction is very close to the result obtained using a stoichiometric amount of

diphenyl binaphthol-modified alkynylboronates **4.47f** (Table 5.3, entry 3). Electron deficient ligands gave excellent conversions and identical enantioselectivities as those of the corresponding stoichiometric reactions (Table 5.3, entry 4-6). Since diiodo binaphthol (**2.28**) gave the best chemical and optical yields in this reaction, it was chosen for further investigation.

Table 5.3 Binaphthol-catalyzed alkynylations of chalcone.



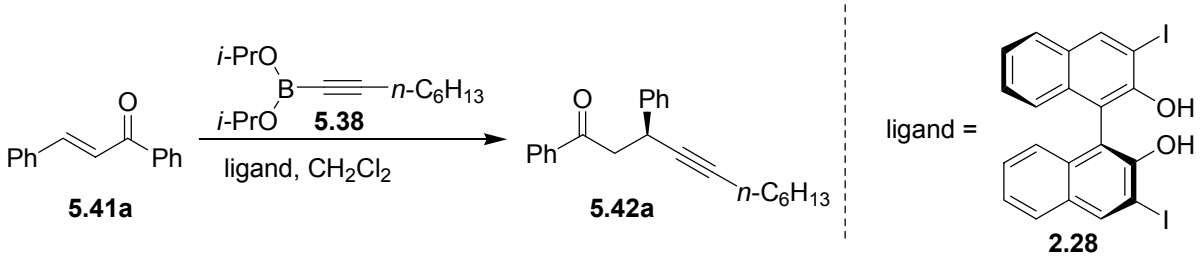
entry	X (ligand no., mol%)	time (h)	yield (%)[b]	*ee* (%)[c]
1	- (0)	96	0	--
2	H(**2.12**, 20)	96	<50[d]	n.d.[e]
3	Ph(**2.32**, 20)	120	60[d]	83 (85)
4	3,5-$(CF_3)_2$-C_6H_3(**2.36**, 20)	96	80	83 (82)
5	CF_3(**2.31**, 20)	96	90	83 (83)
6	I(**2.28**, 20)	96	95	87 (86)

[a] Reactions were carried out in CH_2Cl_2 at 25 °C unless otherwise noted. [b] % isolated yields of chromatographed products. [c] Determined by HPLC analysis on a Chiralcel OD column; values in parentheses are for reactions using stoichiometric amounts of binaphthol-modified alkynylboronates. [d] Estimated conversion based on ^{1}H NMR analysis. [e] Not determined.

Although diiodo binaphthol **2.28** could induce the alkynylation of chalcone in excellent yield and enantioselectivity, the fact that the reaction takes 4 days to complete at room temperature is not very practical (Table 5.4, entry 2). Further probing of this reaction revealed that warming to 40 ^oC (reflux CH_2Cl_2) decreased the reaction time substantially, with essentially negligible change in yield

and enantioselectivity (Table 5.4, entry 2). Decreasing the amount of ligand **2.28** to 10 mol% or 5 mol% affected the reaction rate but not the yield or enantioselectivity (Table 5.4, entry 3 and 4). A further decrease to 2 mol% resulted in incomplete reaction after 72 h but the enantioselectivity still remained high (Table 5.4, entry 5).

Table 5.4 Diiodo binaphthol-catalyzed alkynylations of chalcone.



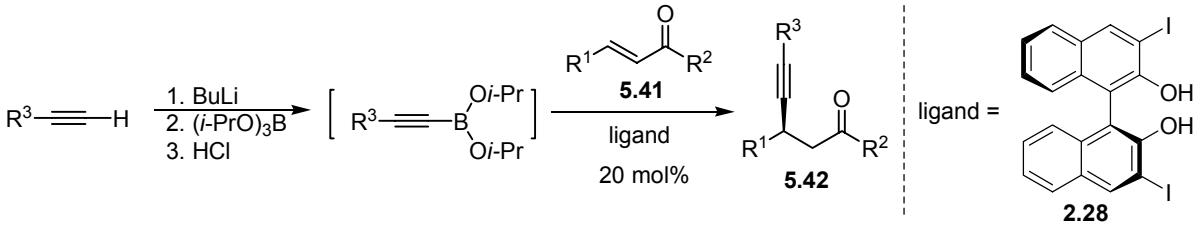
entry	catalyst loading (mol%)	time (h)	yield (%)	*ee* (%)
1	20	96[a]	95	87
2	20	24[b]	94	86
3	10	48[b]	91	85
4	5	72[b]	90	85
5	2	72[b]	70[c]	85

[a] The reaction was carried out at room temperature. [b] Reaction warmed to reflux. [c] Estimated conversion based on ^{1}H NMR analysis.

5.3.2 Scope of the Catalytic Reaction

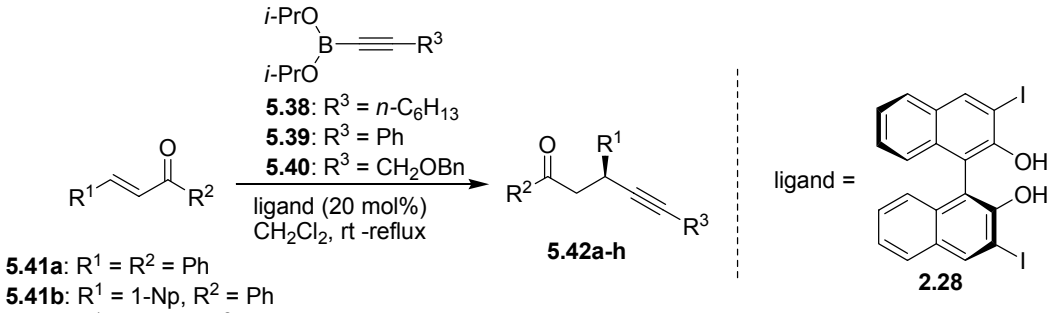
Use of 3,3′-diiodo binaphthol **2.28** in catalytic alkynylations of other enones gave consistently excellent results (Table 5.5). High yields of products were obtained in all cases, and the enantioselectivities were essentially the same as those obtained in stoichiometric reactions. Other than the obvious advantage of using less ligand, this new catalytic alkynylation has other benefits. For example, it is no longer necessary to pre-make chiral alkynyl boronate **4.47**, as it can be generated *in situ*. In addition, a one-pot procedure (Scheme 5.23) starting with 1-alkynes can be used to effect

asymmetric conjugate alkynylation in an operationally simple manner (Table 5.5, entries 5-8).



Scheme 5.23

Table 5.5 Diiodo binaphthol-catalyzed alkynylations of enones.



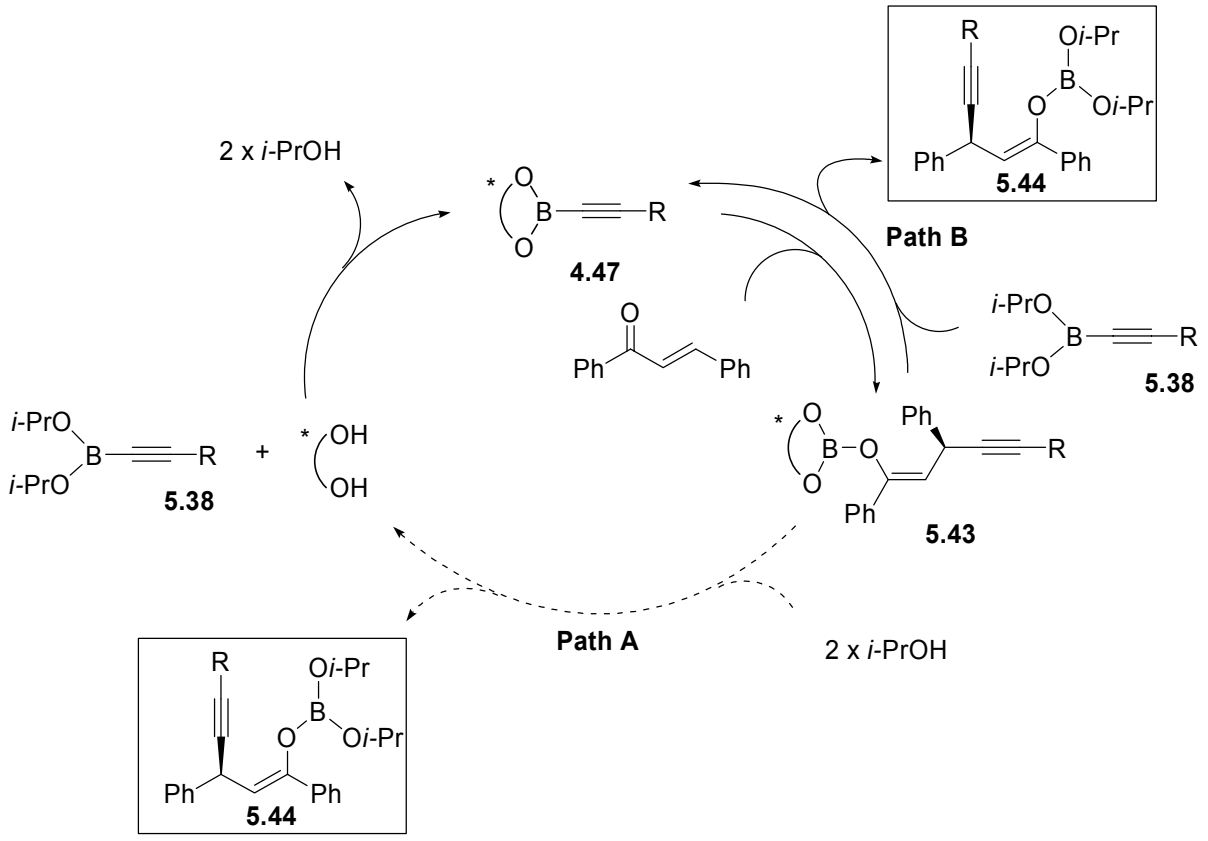
5.41a: $R^1 = R^2 = Ph$
5.41b: R^1 = 1-Np, R^2 = Ph
5.41c: R^1 = 2-furyl, R^2 = Ph
5.41d: R^1 = Ph, R^2 = Me

Entry	R^1	R^2	R^3	Product no.	time (h)	yield (%)[b]	ee (%)[c]
1	Ph	Ph	*n*-C_6H_{13}	**5.42a**	24	94	86 (86)
2	1-Np	Ph	*n*-C_6H_{13}	**5.42b**	12	93	96 (96)
3	2-furyl	Ph	*n*-C_6H_{13}	**5.42c**	36	78	88 (88)
4	Ph	Me	*n*-C_6H_{13}	**5.42d**	48	89	94 (96)
5	Ph	Ph	Ph	**5.42e**	24	95[d]	82 (84)
6	1-Np	Ph	Ph	**5.42f**	24	97[d]	90 (92)
7	Ph	Ph	CH_2OBn	**5.42g**	24	91[d]	86 (87)
8	1-Np	Ph	CH_2OBn	**5.42h**	24	94[d]	95 (96)

[a] 3 equiv. of *B*-1-alkynyldiisopropylboronate was used. [b] isolated yields of chromatographed products. [c] Determined by HPLC analysis on Chiralcel OD column; values in parentheses are for reactions using stoichiometric amounts of binaphthol-modified alkynyl boronates. [d] A one-pot procedure starting from a 1-alkyne was used. See text for details.

5.3.3 Catalytic Cycle

The results obtained from the catalytic asymmetric alkynylation reaction suggest that this reaction represents an example of ligand-accelerated asymmetric processes. Given the fact that the enantioselectivities obtained in all catalytic reactions are identical to those obtained from the corresponding stoichiometric reactions, it is reasonable to believe that binaphthol-modified alkynylboronates **4.47** are the key intermediates in this catalytic asymmetric induction. Hence, a catalytic cycle is proposed (Scheme 5.23). The reaction is initiated by the transesterification of achiral boronate **5.38** and binaphthol **2.28** to give an active species **4.47** which undergoes conjugate addition to the enone producing a boron enolate **5.43**. At this stage, there are two possible pathways (Path A and B) for the regeneration of chiral boronate **4.47** as was purposed earlier (Scheme 5.18). It was noticed by Brown that isopropanol could react with alkynylboronate **5.38** slowly at room temperature to form the corresponding terminal alkyne and triisopropyl borate.[37] Therefore, under the catalytic reaction conditions, there should not be any isopropanol left to react with **5.38** to regenerate the chiral binaphthol (Path A). Accordingly, this pathway (Path A) is ruled out and the catalytic cycle therefore has to be driven by the ligand exchange pathway (Path B, Scheme 5.24).



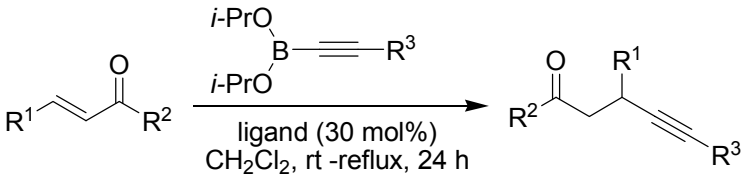
Scheme 5.24

In order to figure out which step is the rate-determining step, the conjugate addition or the ligand exchange, results from Table 5.5 are reviewed. It was observed that the overall reaction rate is dependent on the *β*-substituent of the enone (Table 5.5, entry 1-3). The same trend was also observed in the alkynylation of those substrates using stoichiometric amounts of chiral alkynylboronates **4.47**.[33] Since the rate of ligand exchange should not be affected by this remote substituent, it is very likely that the rate-determining step is the nucleophilic addition step.

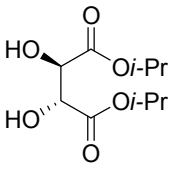
5.3.4 Examination of Other Bidentate Ligands

Diols other than binaphthols were also examined. Simple aliphatic diols such as ethylene glycol and pinacol gave no product, while diisopropyl tartrate, an electron deficient diol used very

effectively in allylborations,[38] catalyzed the reaction (88% yield of **7a**) but gave racemic product. Other bidentate ligands, such as amino alcohols **5.46** and **5.47**, amino acid **5.48** or an activated chiral diamine **5.50**, did not induce the catalytic alkynylation. However chiral *N*-tosyl-amino acids were found to catalyze the reaction but afforded only low enantioselectivities (<45% *ee*) thus far (Scheme 5.25).

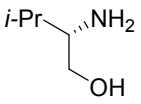


ligand:



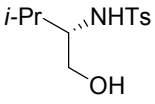
5.45

100% conversion
0% ee



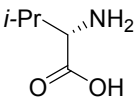
5.46

N.R.



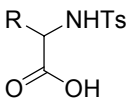
5.47

N.R.



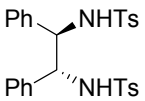
5.48

N.R.



5.49

100% conversion
(*S*)-**5.49a**: R = *i*-Pr, 26% *ee*
(*R*)-**5.49b**: R = Ph, 15% *ee*
(*S*)-**5.49c**: R = Bn, 45% *ee*



5.50

N.R.

Scheme 5.25

5.3.5 Alkynylation of Other 1,4-Addition Acceptors

Other types of substrates such as ester **5.51** and amide **5.52** were subjected to the catalytic alkynylation. Unfortunately, the desired products were not observed in these cases (Scheme 5.25). We reasoned that the electron donating nature of alkoxy and amino group makes those substrates less reactive toward nucleophilic attack. Introduction of electron withdrawing groups on the amide nitrogen (substrate **5.53**) did not bring any positive result either.

It was reported that α,β-unsaturated carboxylic acid imidazolides (such as **5.54**) behaved similarly to enones in reactions such as a lanthanum catalyzed asymmetric α,β-epoxidation.[39,40] However, **5.54** could not be alkynylated under the catalytic conditions (Figure 5.3).

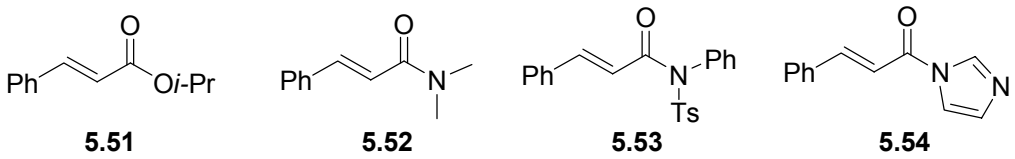
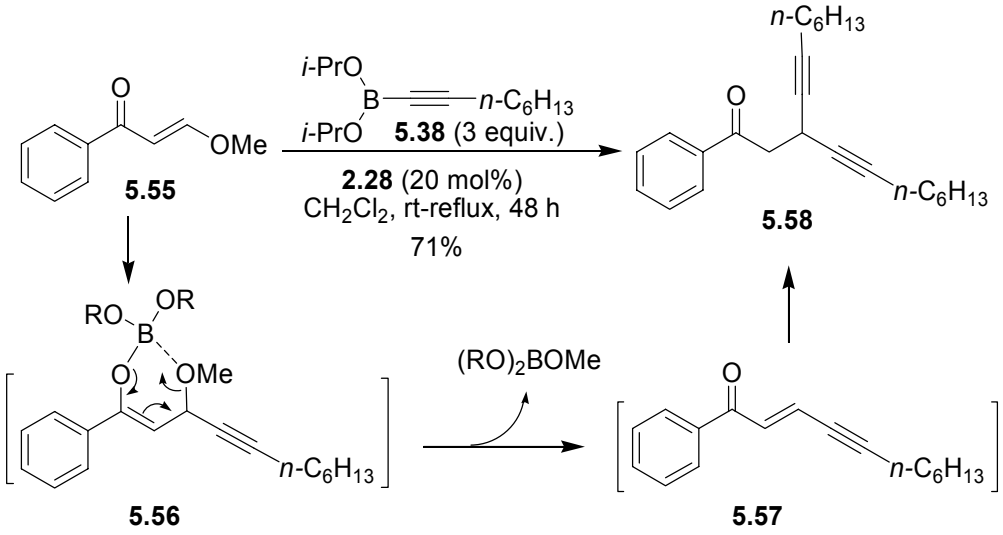


Figure 5.3 Selected 1,4-addition acceptors for the catalytic alkynylation.

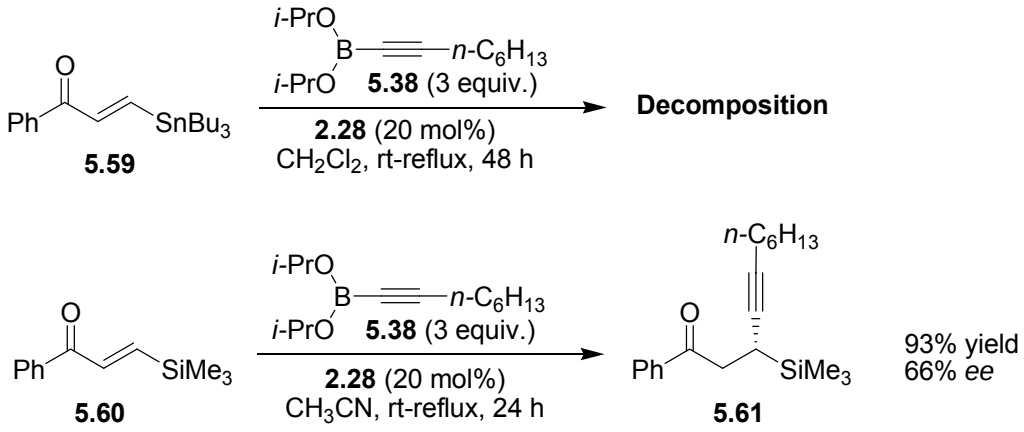
An enone bearing β-alkoxy substituent **5.55** was examined.[41] Instead of the desired product β-alkynyl-β-methoxy ketone, a β,β-dialkynyl ketone **5.58** was isolated. It can be explained by proposing that the alkynylation of substrate **5.55** gives a *cis*-enolate **5.56** which undergoes a retro-Michael addition (subsequent loss of $(RO)_2BOMe$) to form a new enone **5.57**. This enone **5.57** is then immediately alkynylated to afford the "double alkynylated" product **5.58** (Scheme 5.26).



Scheme 5.26

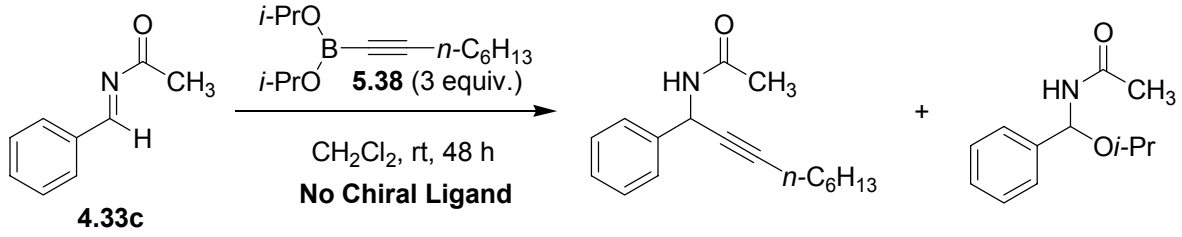
Chiral propargyl stannanes and silanes are potentially useful precursors for the synthesis of chiral propargyl and allenyl alcohols.[42,43] Therefore, a β-tributylstannyl enone **5.59** was subjected to the

catalytic alkynylboration. However, only the decomposition of starting materials was observed. A *β*-trimethylsilyl enone **5.60** could be alkynylated under elevated temperature (81 °C), but the enantiomeric excess of the product was only moderate (66% *ee*) (Scheme 5.27).



Scheme 5.27

In Chapter 4, we reported that substituted binaphthol-modified alkynylboronates **4.47** are excellent reagents for the asymmetric alkynylation of *N*-acylimines. Hence *N*-acetylbenzaldimine **4.43c** was tested in the catalytic reactions. However, the "background" reaction is too rapid and some side reactions also occur readily (Scheme 5.28).



Scheme 5.28

5.3.6 Comparison with Other Catalytic Reactions Involving Boron Reagents

Compared to other boron-reagent catalyzed reactions, the catalytic asymmetric alkynylation reaction seems to be unique. For instance, in CBS reductions or CAB catalyzed Diels-Alder reactions,

bonds between chiral ligands and the central boron atom are not broken during the entire catalytic reactions (Figure 5.4). Breaking of these bonds would diminish the impact of chiral ligands on the transition states and lead to non-stereoselective inductions. On the contrary, in the catalytic alkynylation reactions, the breaking of the bonds between chiral ligand and the central boron atom is the driving force of the catalytic cycle.

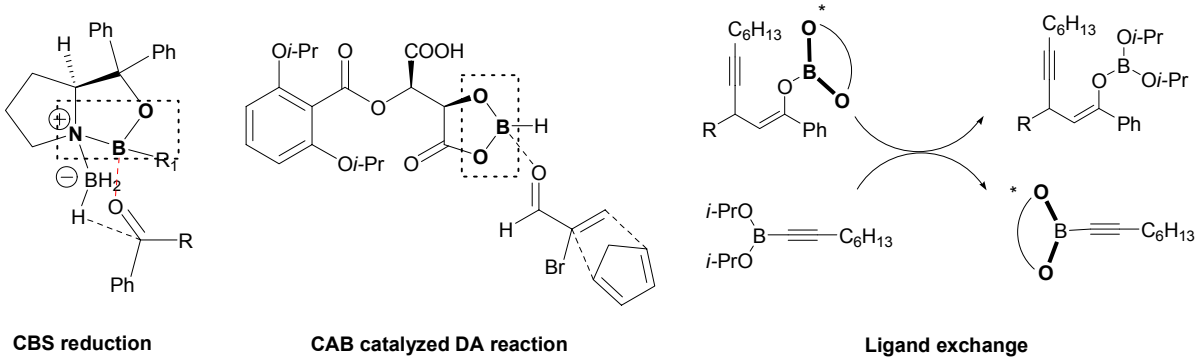
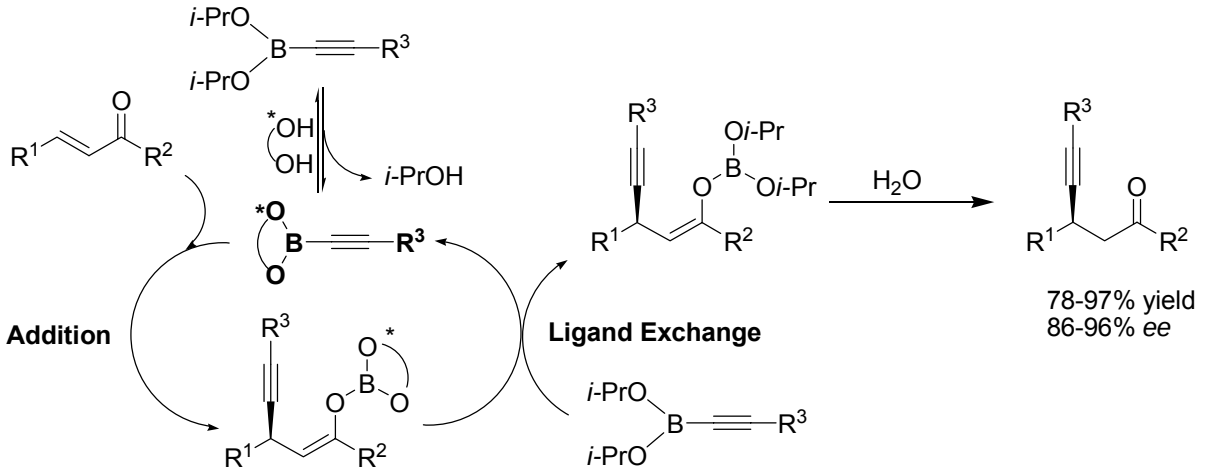


Figure 5.4 Working models for different boron-induced catalytic asymmetric reactions.

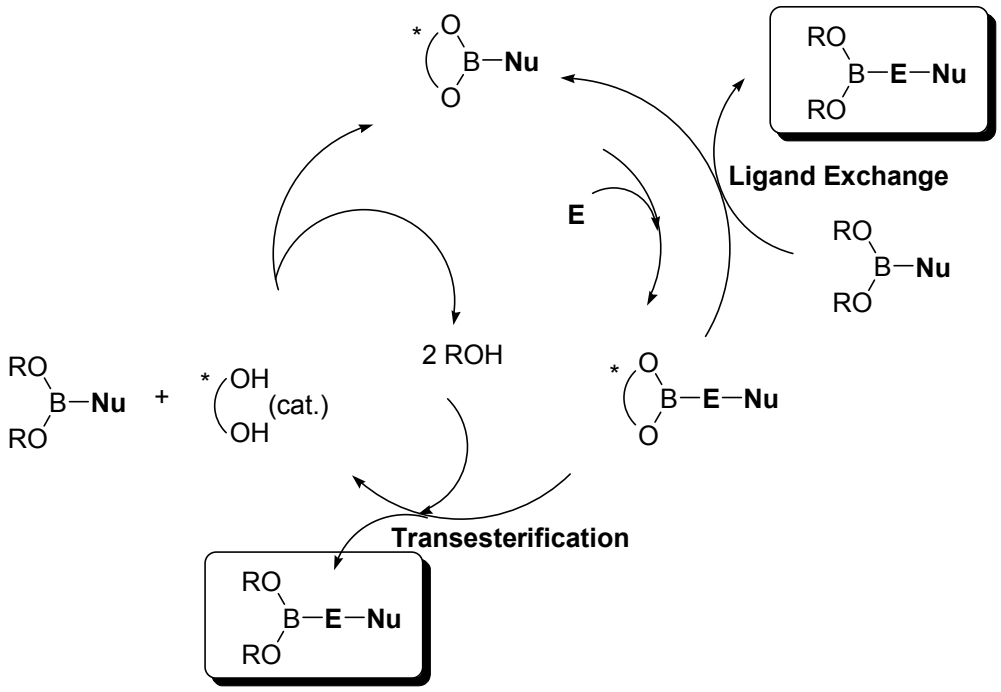
5.4 Summary and Future Work

In summary, we have shown that the asymmetric alkynylation of enones can be carried out very efficiently using catalytic amounts of binaphthol ligands (Scheme 5.29). This constitutes a major advance over the previous stoichiometric reaction in terms of preparative simplicity and economy.



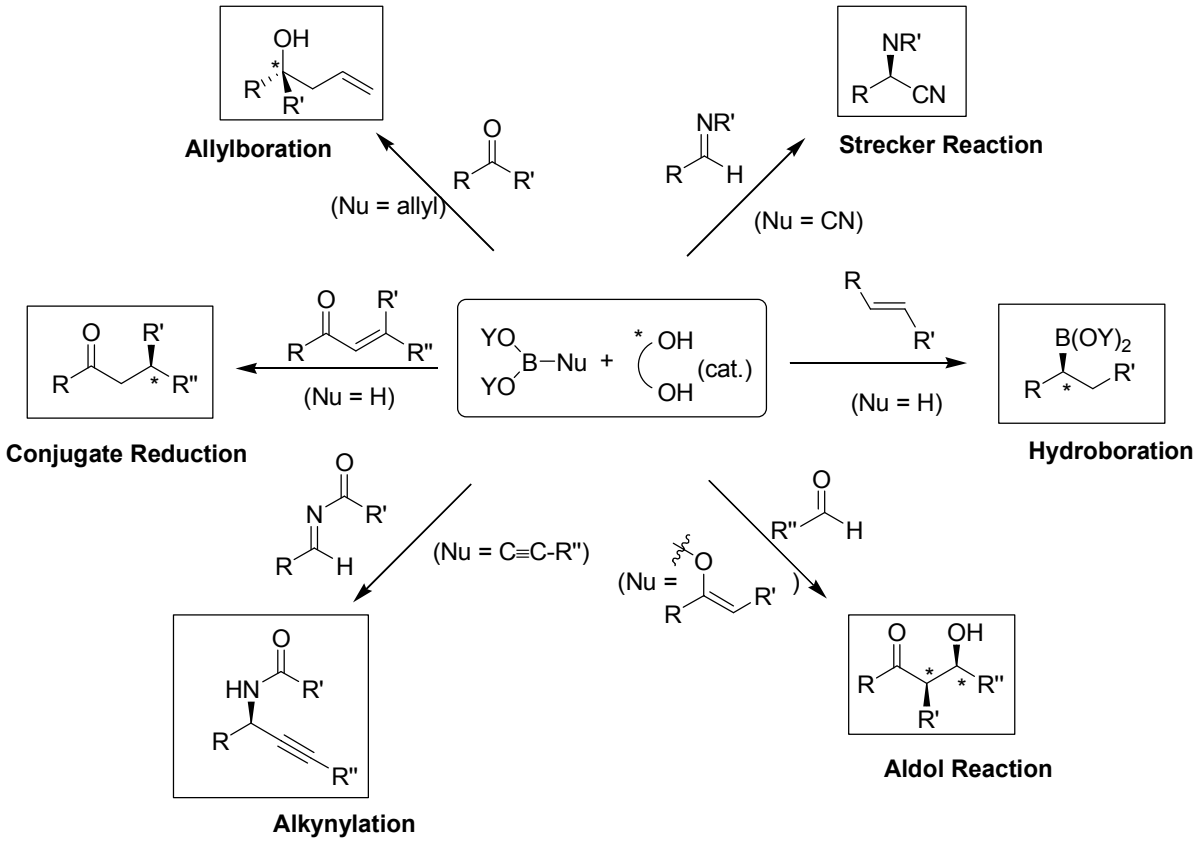
Scheme 5.29

More importantly, we have demonstrated a proof of principle that ligand exchange with boronates can be sufficiently fast that catalytic amounts of chiral ligands can be used to effect high levels of stereoselectivity. This catalytic protocol can potentially be applied to other asymmetric reactions providing the follow three requirements are met: (1) the starting achiral boronate does not react with the electrophile (no background reaction); (2) the chiral boronate reacts with the electrophile and (3) ligand exchange or transesterification occurs under the reaction conditions (Scheme 5.30). Some results from this chapter have been published in *Journal of the American Chemical Society* (Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 3244-3245).[44]



Scheme 5.30

Some prospective ligand-accelerated asymmetric reactions are illustrated in Scheme 5.31. These include asymmetric allylboration, hydroboration, and aldol reaction, just to name a few. Efforts are underway to develop these catalytic asymmetric processes.



Scheme 5.31

Another potential variation of this catalytic process is to bind chiral ligands onto solid support which makes the recovery of chiral ligands much easier.

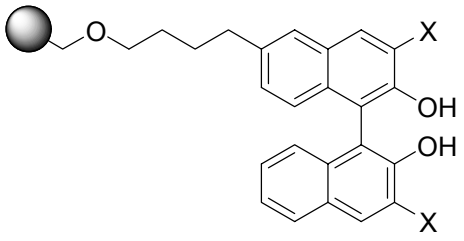


Figure 5.5 Solid-support chiral binaphthols.

5.5 Experimental

5.5.1 General Experimental

All reactions were performed using flame-dried glassware under an argon atmosphere. Dichloromethane was freshly distilled from CaH_2. Diethyl ether was freshly distilled from Na/benzophenone. Diisopropyl octynylboronate **5.38** was prepared according to Brown's procedure.[37] Chiral 3,3′-disubstituted binaphthols were synthesized using procedures described previously.[45] ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 MHz and 75 MHz, respectively.

5.5.2 General Procedure for the Stoichiometric Alkynylation of Enones

Alkynylations of enones using stoichiometric amounts of binaphthol-modified alkynylboronates were carried out according to a previous procedure:[34] (*S*)-3,3′-diiodo-2,2′-dihydroxy-1,1′-binaphthyl (**2.28**) (127 mg, 0.236 mmol) and lithium triisopropyl *B*-1-alkynylborate **4.59** (0.232 mmol) were placed in a 25 mL round-bottomed flask under argon. THF (5 mL) was added slowly to the mixture at 0 ^{o}C. The solution was stirred at 0 ^{o}C for 1 h then warmed up to room temperature for 5 h. Solvent was evaporated under high vacuum. The enone (0.154 mmol) and CH_2Cl_2 (15 mL) were added followed by $BF_3{\cdot}OEt_2$ (58 μL, 0.461 mmol). The reaction was stirred at room temperature for 3 h. After the reaction was complete, saturated NH_4Cl (aq.) was added to quench the reaction. The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (2 x 5 mL). The combined organic phase was washed with water and dried over Na_2SO_4. Most of the binaphthol was collected by crystallization from CH_2Cl_2/hexanes and the mother liquid was purified by column chromatography (acetone/hexanes 1:10) to give the 1,4-addition product. Enantiomeric excesses of all products were determined by HPLC with a Chiralcel OD column. Absolute

configurations for phenylacetylene and 1-octyne adducts to 1,3-bis(4-bromophenyl)-2-propen-1-one were determined by X-ray crystallography.[33,34] The absolute configurations of other adducts have been assigned based on these known absolute configurations and the assumption that the enones are sufficiently similar in structure (all with *β*-aryl substituents) that the sense of asymmetric induction should be invariant.

5.5.3 General Procedure for the Catalytic Alkynylation of Enones (Procedure A)

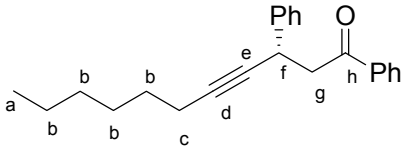
A mixture of diisopropyl *B*-1-octynylboronate **5.38** (215 mg, 0.9 mmol), enone (0.3 mmol) and (*S*)-3,3′-diiodo-2,2′-dihydroxy-1,1′-binaphthyl (**2.28**) (32 mg, 0.06 mmol) were stirred in CH_2Cl_2 (4 mL) under argon at room temperature for 6 h, then brought to reflux for 24 h. The reaction was quenched with saturated aqueous NH_4Cl. The organic phase was washed with brine and dried over Na_2SO_4. Purification was done by column chromatography (acetone/hexanes 1:10) on silica gel. The chiral ligand was recovered in quantitative yield.

5.5.4 One-pot Procedure for Catalytic Alkynylation of Enones from 1-Alkyne (Procedure B)

To a solution of 1-alkyne (1.0 mmol) in Et_2O (5 mL) was added 0.63 mL of *n*-BuLi (1.0 mmol, 1.6 M) dropwise at -78 ^oC. The resulting solution was stirred at that temperature for 20 min then added dropwise to a mixture of $(i\text{-PrO})_3B$ in 5 mL Et_2O at -78^oC. The suspension was stirred at -78 ^oC for 2 h and warmed up to room temperature for 1 h. The reaction was again cooled to -78 ^oC, and 0.5 mL anhydrous HCl in Et_2O (2 M, 1 mmol) was added slowly. The reaction was allowed to warm to room temperature and volatiles were removed *in vacuo*. To the yellowish oily residue was added CH_2Cl_2 (4 mL), enone (0.3 mmol) and catalyst (0.06 mmol) at room temperature. The mixture was

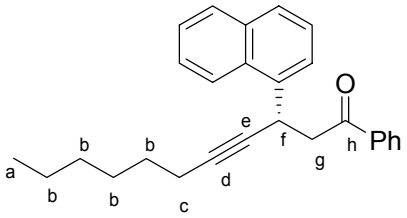
stirred at ambient temperature for 6 h then brought to reflux for 24 h. Workup was the same as in procedure A.

5.5.5 (*S*)-1,3-Diphenyl-4-undecyn-1-one (5.42a)



$[\alpha]_D^{25}$ +31.4 (c 2.04, $CHCl_3$, 85% *ee*); IR (neat): C=O 1684 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.86 (H_a, 3H, t, J = 6.7 Hz), 1.15-1.48 (H_b, 8H, m), 2.14 (H_c, 2H, dt, J = 2.2 Hz, 6.8 Hz), 3.26 (H_g, 1H, dd, J = 16.4 Hz, 6.0 Hz), 3.52 (H_g, 1H, dd, J = 16.4 Hz, 8.3 Hz), 4.38 (H_f, 1H, ddd, J = 8.3 Hz, 6.0 Hz, 2.2 Hz), 7.18-7.94 (H_{Ar}, 10H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.3 (C=O), 141.9 (C_{Ar}), 136.9 (C_{Ar}), 132.9 (C_{Ar}), 128.4 (C_{Ar}), 128.0 (C_{Ar}), 127.4 (C_{Ar}), 126.6 (C_{Ar}), 83.5 (C_d or C_e), 80.9 (C_d or C_e), 47.6 (C_j), 33.3 (C_b), 31.2 (C_f), 28.7 (C_b), 28.4 (C_b), 22.4 (C_b), 18.7 (C_c), 13.9 (C_a); MS (EI), m/e (relative intensity) 318 (1, M^+), 247 (13), 233 (33), 128 (20), 105 (100), 91 (27), 77 (53). Anal. Calcd for $C_{23}H_{26}O$: C, 86.75; H, 8.23. Found C, 86.55; H, 8.20. The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 99.9/0.1, flow rate = 0.5 mL/min), t_R = 55 min (*S*), t_R = 61 min (*R*).

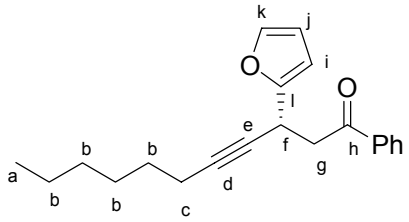
5.5.6 (*R*)-3-Naphthalen-1-yl-1-phenyl-4-undecyn-1-one (5.42b)



$[\alpha]_D^{25}$ -13.1 (c 1.39, $CHCl_3$, 96% *ee*); IR (neat): C=O 1684 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.87 (H_a, 3H, t, J = 6.9 Hz), 1.12-1.47 (H_b, 8H, m), 2.17 (H_c, 2H, dt, J = 2.2 Hz, 6.8 Hz), 3.32 (H_g, 1H,

dd, J = 16.8 Hz, 3.9 Hz), 3.65 (H_g, 1H, dd, J = 16.8 Hz, 9.6 Hz), 5.20 (H_f, 1H, ddd, J = 9.6 Hz, 3.9 Hz, 2.2 Hz), 7.43-8.18 (H_{Ar}, 12H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.6 (C=O), 137.4 (C_{Ar}), 137.0 (C_{Ar}), 134.0 (C_{Ar}), 133.0 (C_{Ar}), 130.3 (C_{Ar}), 129.0 (C_{Ar}), 128.5 (C_{Ar}), 128.2 (C_{Ar}), 127.6 (C_{Ar}), 126.2 (C_{Ar}), 125.5 (C_{Ar}), 125.4 (C_{Ar}), 125.2 (C_{Ar}), 123.0 (C_{Ar}), 84.1 (C_d or C_e), 80.8 (C_d or C_e), 46.5 (C_g), 31.2 (C_b), 30.0 (C_f), 28.7 (C_b), 28.4 (C_b), 22.4 (C_b), 18.8 (C_c), 14.0 (C_a); MS (EI), m/e (relative intensity) 368 (3, M^+), 284 (23), 283 (83), 179 (48), 178 (32), 165 (30), 105 (100). Anal. Calcd for $C_{27}H_{28}O$: C, 88.00; H, 7.66. Found C, 88.10; H, 7.58. The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 99.5/0.5, flow rate = 1 mL/min), t_R = 17 min (*S*), t_R = 24 min (*R*). Note that the difference in absolute configuration between **5.42a** and **5.42b** is due to differences in CIP priorities: 1-naphthyl > 1-octynyl > phenyl.

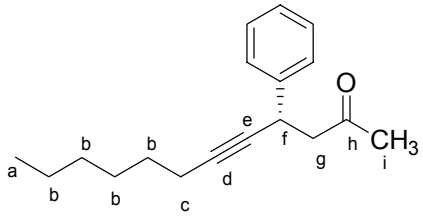
5.5.7 (*R*)-3-(2-Furyl)-1-phenyl-4-undecyn-1-one (5.42c)



$[\alpha]_D^{25}$ -10.4 (c 2.0, $CHCl_3$, 88% *ee*); IR (neat): C=O 1689 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84 (H_a, 3H, t, J = 6.9 Hz), 1.10-1.50 (H_b, 8H, m), 2.09-2.15 (H_c, 2H, dt, J = 2.4 Hz, 6.9 Hz), 3.43-3.46 (H_g, 2H, m), 4.43-4.49 (H_f, 1H, m), 6.22 (H_i, 1H, dd, J = 3.3 Hz, 0.9 Hz), 6.27 (H_j, 1H, dd, J = 3.3 Hz, 1.9 Hz), 7.30 (H_k, 1H, dd, J = 0.9 Hz, 1.9 Hz), 7.39-7.60 (H_{Ar}, 3H, m), 7.90-8.02 (H_{Ar}, 2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.9 (C=O), 154.1 (C_l), 141.6 (C_k), 136.9 (C_{Ar}), 133.1 (C_{Ar}), 128.5 (C_{Ar}), 128.2 (C_{Ar}), 110.3 (C_i or C_j), 105.9 (C_i or C_j), 82.9 (C_d or C_e), 78.3 (C_d or C_e), 43.8 (C_g), 31.3 (C_b), 28.7 (C_b), 28.4 (C_b), 27.2 (C_f), 22.5 (C_b), 18.7 (C_c), 14.0 (C_a); MS (EI), m/e (relative

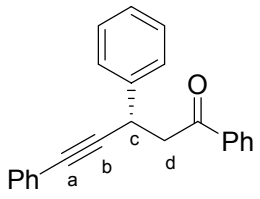
intensity) 308 (1, M^+), 105 (100), 77 (43). Anal. Calcd for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found C, 81.90; H, 7.76. The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 99.8/0.2, flow rate = 0.5 mL/min), t_R = 34 min (*R*), t_R = 36 min (*S*).

5.5.8 (*S*)-4-Phenyl-5-dodecyn-2-one (5.42d)



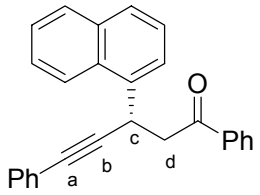
$[\alpha]_D^{25}$ +2.4 (c 1.4, $CHCl_3$, 94% *ee*); IR (neat): C=O 1706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.87 (H_a, 3H, t, J = 6.9 Hz), 1.26-1.49 (H_b, 8H, m), 2.11 (H_i, 3H, s), 2.15-2.19 (H_c, 2H, dt, J = 2.1Hz, 6.9Hz), 2.69 (H_g, 1H, dd, J = 16.1 Hz, 6.1 Hz), 2.86 (H_g, 1H, dd, J = 16.1 Hz, 8.5 Hz), 4.13 (H_f, 1H, ddd, J = 8.5 Hz, 6.1 Hz, 2.1 Hz), 7.17-7.40 (H_{Ar}, 5H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.1 (C=O), 141.6 (C_{Ar}), 128.5 (C_{Ar}), 127.3 (C_{Ar}), 126.8 (C_{Ar}), 83.6 (C_d or C_e), 80.6 (C_d or C_e), 52.3 (C_g), 33.2 (C_i), 31.3 (C_b), 30.6 (C_f), 28.9 (C_b), 28.5 (C_b), 22.5 (C_b), 18.8 (C_c), 14.0 (C_a); MS (EI), m/e (relative intensity) 256 (1, M^+), 185 (52), 171 (49), 129 (39), 128 (41), 43 (100). Anal. Calcd for $C_{18}H_{24}O$: C, 84.32; H, 9.44. Found C, 84.26; H, 9.32. The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 99.9/0.1, flow rate = 0.5 mL/min), t_R = 54 min (*R*), t_R = 60 min (*S*).

5.5.9 (*S*)-1,3,5-Triphenyl-4-pentyn-1-one (5.42e)



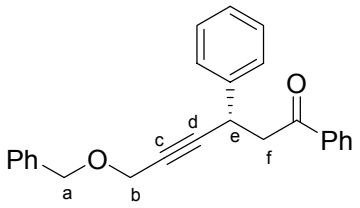
$[\alpha]_D^{25}$ +30.1 (c 1.44, $CHCl_3$, 82% *ee*); IR (KBr): C=O 1680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.39 (H_d, 1H, dd, J = 16.5 Hz, 6.2 Hz), 3.65 (H_d, 1H, dd, J = 16.5 Hz, 7.8 Hz), 4.63 (H_c, 1H, dd, J = 6.2 Hz, 7.8 Hz), 7.31-8.05 (H_{Ar}, 15 H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.0 (C=O), 141.2 (C_{Ar}), 136.8 (C_{Ar}), 133.1 (C_{Ar}), 131.6 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.1 (C_{Ar}), 127.8 (C_{Ar}), 127.5 (C_{Ar}), 127.0 (C_{Ar}), 123.3 (C_{Ar}), 90.7 (C_b), 83.3 (C_a), 47.2 (C_d), 33.7 (C_c); MS (EI), m/e (relative intensity) 310 (10, M^+), 205 (100), 191 (44), 105 (71), 77 (57). Anal. Calcd for $C_{23}H_{18}O$: C, 89.00; H, 5.84. Found C, 89.13; H, 5.83. The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 99.8/0.2, flow rate = 0.5 mL/min), t_R = 100 min (*R*), t_R = 115 min (*S*).

5.5.10 (*R*)-3-(1-Naphthalenyl)-1,5-diphenyl-4-oentyn-1-one (5.42f)



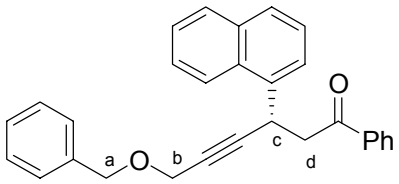
$[\alpha]_D^{25}$ +37.3 (c 1.01, $CHCl_3$, 90% *ee*); IR (KBr): C=O 1686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.45 (H_d, 1H, dd, J = 16.8 Hz, 4.2 Hz), 3.81 (H_d, 1H, dd, J = 16.8 Hz, 9.6 Hz), 5.42 (H_c, 1H, dd, J = 9.6 Hz, 4.2 Hz), 7.33-8.30 (H_{Ar}, 17H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.2 (C=O), 136.8 (C_{Ar}), 136.7 (C_{Ar}), 134.1 (C_{Ar}), 133.2 (C_{Ar}), 131.6 (C_{Ar}), 130.3 (C_{Ar}), 129.0 (C_{Ar}), 128.6 (C_{Ar}), 128.2 (C_{Ar}), 128.1 (C_{Ar}), 127.9 (C_{Ar}), 127.8 (C_{Ar}), 126.4 (C_{Ar}), 125.7 (C_{Ar}), 125.5 (C_{Ar}), 125.4 (C_{Ar}), 123.4 ($C_{Ar,}$), 122.9 (C_{Ar}), 90.6 (C_b), 83.8 (C_a), 46.2 (C_d), 30.4 (C_c); MS (EI), m/e (relative intensity) 360 (11, M^+), 255 (35), 207 (100). Anal. Calcd for $C_{27}H_{20}O$: C, 89.97; H, 5.59. Found C, 90.05; H, 5.58. The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 99/1, flow rate = 1 mL/min), t_R = 17 min (*S*), t_R = 22 min (*R*). Note that the difference in absolute configuration between **5.42e** and **5.42f** is due to differences in CIP priorities: 1-naphthyl > phenylethynyl > phenyl.

5.5.11 (*S*)-6-Benzyloxy-1,3-diphenyl-4-Hexyn-1-one (5.42g)



$[\alpha]_D^{25}$ -1.5 (c 1.6, $CHCl_3$, 86% *ee*); IR (neat): 3062, 3030, 2232, 1684, 1598, 1495, 1450, 1352, 1255, 1205, 1072, 1035 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.33 (H_f, 1H, dd, J = 16.8 Hz, 6 Hz), 3.58 (H_f, 1H, dd, J = 16.8 Hz, 7.8 Hz), 4.17 (H_b, 2H, d, J = 2.0 Hz), 4.48 (H_e, 1H, ddt, J = 7.8 Hz, 6.0 Hz, 2.0 Hz), 4.53 (H_a, 2H, s), 7.26-7.99 (H_{Ar}, 15H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.8 (C=O), 140.9 (C_{Ar}), 137.5 (C_{Ar}), 136.7 (C_{Ar}), 133.2 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.3 (C_{Ar}), 128.1 (C_{Ar}), 128.0 (C_{Ar}), 127.7 (C_{Ar}), 127.5 (C_{Ar}), 127.0 (C_{Ar}), 87.9 (C_d), 78.7 (C_c), 71.2 (C_a), 57.5 (C_b), 47.0 (C_f), 33.0 (C_e); MS (EI), m/e (relative intensity) 354 (1, M^+), 105 (100), 77 (31). Anal. Calcd for $C_{25}H_{22}O_2$: C, 84.72; H, 6.26. Found C, 84.98; H, 6.17. The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 97/3, flow rate = 1 mL/min), t_R = 16 min (*R*), t_R = 26 min (*S*).

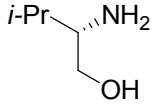
5.5.12 (*S*)-6-Benzyloxy-3-naphthyl-1-phenyl-4-hexyn-1-one (5.42h)



$[\alpha]_D^{25}$ +10.5 (c 0.84, $CHCl_3$, 95% *ee*); IR (neat): C=O 1683 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.41(H_d, 1H, dd, J = 17.1 Hz, 4.2 Hz), 3.75 (H_d, 1H, dd, J = 17.1 Hz, 6.6 Hz), 4.18 (H_b, 2H, d, J = 2.0 Hz), 4.52 (H_a, 2H, s), 5.27-5.32 (H_c, 1H, ddd, J = 2.0 Hz, 4.2 Hz, 6.6 Hz), 7.26-8.24 (17H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.1 (C=O), 137.5 (C_{Ar}), 136.7 (C_{Ar}), 136.4 (C_{Ar}), 134.1 (C_{Ar}), 133.3

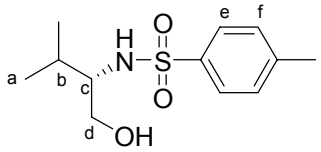
(C_{Ar}), 130.3 (C_{Ar}), 129.1 (C_{Ar}), 128.6 (C_{Ar}), 128.3 (C_{Ar}), 128.2 (C_{Ar}), 128.1 (C_{Ar}), 128.0 (C_{Ar}), 127.7 (C_{Ar}), 126.4 (C_{Ar}), 125.7 (C_{Ar}), 125.5 (C_{Ar}), 125.3 (C_{Ar}), 122.9 (C_{Ar}), 87.9 (C≡C), 79.4 (C≡C), 71.2 (C_a), 57.5 (C_b), 46.0 (C_d), 29.8 (C_c); MS (EI), m/e (relative intensity) 404 (1, M^+), 296 (17), 105 (100), 91 (33), 77 (33). Anal. Calcd for $C_{29}H_{24}O_2$: C, 86.11; H, 5.98. Found C, 85.99; H, 5.91. The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 99/1, flow rate = 1 mL/min), t_R = 58 min (*R*), t_R = 63 min (*S*).

5.5.13 Preparation of (*S*)-2-Amino-3-methylbutan-1-ol (5.46)



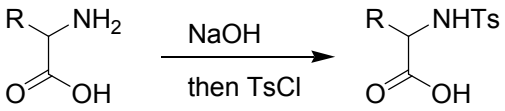
Meyers' procedure was followed:[46] to a mixture of 3.88 g (103 mmol) sodium borohydride and 100 mL of THF was added L-valine (5 g, 42.7 mmol) in one portion and the reaction flask was cooled to 0 "C in an ice bath. A solution of 10.84 g (42.7 mmol) of iodine dissolved in 50 mL of THF was added slowly over 30 min. After addition of the iodine was complete and gas evolution had ceased, the reaction was heated to reflux for 18 h and then cooled to room temperature, and methanol was added cautiously until the mixture became clear. After stirring 30 min, the solvent was removed by rotary evaporation leaving a white paste which was dissolved by addition of 150 mL of 20% aqueous KOH. The solution was stirred for 4 h and extracted with 3 x 150 mL of methylene chloride. The organic extracts were dried over sodium sulfate and concentrated *in vacuo*, affording a white semisolid (100%) which was subjected to a bulb-to-bulb distillation to afford **5.46** (3.9 g) in 89% yield. bp 75-77 ^oC/7 mm. The ^1H NMR data of the product was identical to reported values.[47]

5.5.14 Preparation of (*S*)-*N*-(1-Hydroxy-3-methylbutan-2-yl)-*p*-toluenesulfonamide (5.47)[48]



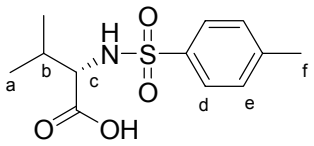
To a solution of amino alcohol **5.46** (0.912 g, 8.84 mmol) in 8 mL of CH_2Cl_2 at 0 ^oC were added triethylamine (0.895 g, 8.84 mmol), tosyl chloride (1.69 g, 8.84 mmol) and DMAP (98 mmol, 0.8 mmol). The reaction was stirred at 0 ^oC for 2 h then warmed to room temperature over night. Volatiles were removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (EtOAc) to give the desired product (2.2 g) in 97 % yield. ^1H NMR (300 MHz, $CDCl_3$): δ 7.76 (H_a, d, J = 6.8 Hz, 3H), 7.77 (H_a, d, J = 6.9 Hz, 3H), 1.74 (H_b, m, 1H), 1.98 (OH, s, br, 1H), 2.40 ($ArCH_3$, s, 3H), 3.02 (H_c, m, 1H), 3.49-3.58 (H_d, m, 2H), 4.92 (NH, d, br, J = 8.4 Hz, 1H), 7.27 (H_f, d, J = 8.1 Hz, 2H), 7.65 (H_e, d, J = 8.1 Hz, 2H).

5.5.15 Preparation of *N*-Tosyl-α-amino Acids (5.49a-c)



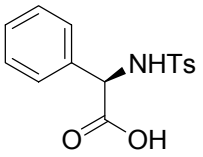
McChesney's method was followed.[49] An amino acid (10 mmol) was dissolved in 20 mL of 1 N sodium hydroxide. An ethereal solution of *p*-toluenesulfonyl chloride (2.0 g, 10 mmol) was added, and the mixture is stirred at room temperature overnight. The ethereal solution is then separated and the aqueous solution is acidified with hydrochloric acid. The derivative begins to crystallize at once. The crystals are collected through filtration and are recrystallized from 60% Ethanol.

5.5.15.1 (*S*)-*N*-Tosyl-valine (**5.49a**)[50]



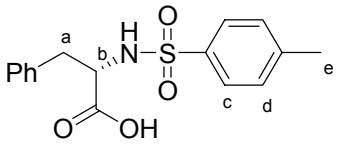
^{1}H NMR (300 MHz, d_4-MeOH): δ 0.86 (H_a, d, J = 6.9 Hz, 3H), 0.91 (H_a, d, J = 6.9 Hz, 3H), 2.04 (H_b, m, 1H), 2.44 (H_f, s, 3H), 3.62 (H_c, d, J = 7.5 Hz, 1H), 7.33 (H_e, d, J = 8.1 Hz, 2H), 7.73 (H_d, d, J = 8.1 Hz, 2H).

5.5.15.2 (*R*)-*N*-Tosyl-phenylglycine (**5.49b**)[51]



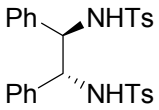
^{1}H NMR (300 MHz, d_6-DMSO): δ 2.34 ($ArCH_3$, s, 3H), 5.06 (ArCHN, d, J = 7.5 Hz, 1H), 5.62 (NH, d, br, J = 7.5 Hz, 1H), 7.08-7.60 (H_{Ar}, m, 9H).

5.5.15.3 (*S*)-*N*-Tosyl-phenylalanine (**5.49c**)[52]



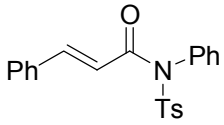
^{1}H NMR (300 MHz, D_6-DMSO): δ 2.36 (H_e, s, 3H), 2.97 (H_a, dd, J = 13.8 Hz, 6.3 Hz, 1H), 3.06 (H_a, dd, J = 13.8 Hz, 5.5 Hz, 1H), 4.14 (H_b, ddd, J = 8.5 Hz, 6.3 Hz, 5.5 Hz, 1H), 5.25 (NH, d, br, J = 8.5 Hz, 1H), 7.04-7.23 (H_{Ar}, m, 7H), 7.58 (H_c, d, J = 8.2 Hz, 2H).

5.5.16 Preparation of *N*,*N*′-[(1*R*,2*R*)-1,2-Diphenyl-1,2-ethanediyl]bis(*p*-toluene sulfonamide) (5.50)[53]



To a solution of (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine[53] (531 mg, 2.5 mmol) in 12 mL of CH_2Cl_2 at 0 ^oC were added triethylamine (759 mg, 7.5 mmol), *p*-toluenesulfonyl chloride (1.14g, 6 mmol) and DMAP (6.1 mg). The reaction mixture was allowed to warm to room temperature for 12 h. Volatiles were removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:1) to give the desired product in quantitative yield. ^1H NMR (300 MHz, $CDCl_3$): δ 2.30 ($ArCH_3$, s, 6H), 4.44 (ArC<u>H</u>N, m, 2H), 5.48 (NH, m, 2H), 6.64 (H_{Ar}, d, J = 7.5 Hz, 4H), 6.93 (H_{Ar}, t, J = 7.4 Hz, 4H), 6.98-7.07 (H_{Ar}, m, 6H), 7.46 (H_{Ar}, d, J = 7.5 Hz, 4H).

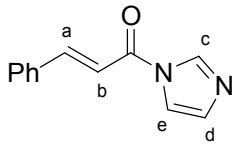
5.5.17 Preparation of *N*-Phenyl-*N*-tosylcinnamamide (5.53)



N-tosyl aniline (531 mg, 2.15 mmol) and cinnamoyl chloride (0.43 g, 2.58 mmol) were mixed in 15 mL of THF. Finely ground potassium carbonate (1.48 g, 10.8 mmol) was added to the solution and the resulting suspension was stirred at room temperature over night. The solid was filtered off and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 4:1) to give the desired product (800 mg) in 98% yield. ^1H NMR (300 MHz, $CDCl_3$): δ 2.43 ($ArCH_3$, s, 3H), 6.03 (ArCH=C<u>H</u>, d, J = 15.6 Hz, 1H), 7.17-7.36 (H_{Ar}, m, 9H), 7.48-7.52 (H_{Ar}, m, 3H), 7.65 (ArC<u>H</u>=CH, d, J = 15.6 Hz, 1H), 7.95 (H_{Ar}, d, J = 8.3 Hz, 2H);^{13}C NMR (75 MHz, $CDCl_3$): δ 165.4 (C=O), 145.7 (Ar<u>C</u>H=CH), 144.9 (C_{Ar}), 136.2 (C_{Ar}), 136.0 (C_{Ar}), 134.0 (C_{Ar}), 130.6 (C_{Ar}), 130.4 (C_{Ar}), 130.0 (C_{Ar}), 129.8 (C_{Ar}), 129.4 (C_{Ar}), 129.3 (C_{Ar}), 128.8 (C_{Ar}), 128.2 (C_{Ar}), 117.7 (ArCH=<u>C</u>H), 21.7 (CH_3); MS (EI), m/e (relative intensity): 377 (0.1, M^+), 313 (5,

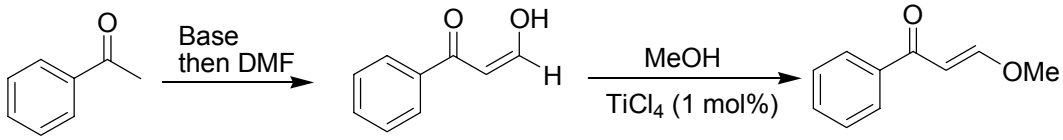
M^+-SO_2), 131 (100, M^+-PhNTs); HRMS *m/z* Calcd for $C_{22}H_{19}NO$ (M^+-SO_2): 313.1467. Found: 313.1463.

5.5.18 Preparation of (*E*)-1-(1*H*-Imidazol-1-yl)-3-phenylprop-2-en-1-one (5.54)[39,40]



Cinnamoyl chloride (0.366 g, 2.2 mmol) and imidazole (0.350 g, 5.1 mmol) were mixed in 5 mL of CH_2Cl_2. The mixture was stirred at room temperature for 1 h. The white precipitate was filtered off and the filtrate was purified by passing through a short silica column (EtOAc). Solvents were removed *in vacuo* to give the title compound (0.435 g) in quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.05 (H_b, d, J = 15.4 Hz, 1H), 7.14 (H_d, s, 1H), 7.39-7.50 (H_{Ar}, m, 3H), 7.59-7.65 (H_{Ar} and H_e, m, 3H), 8.05 (H_a, d, J = 15.4 Hz, 1H), 8.30 (H_c, s, 1H).

5.5.19 Preparation of (*E*)-3-Methoxy-1-phenylprop-2-en-1-one (5.55)[41]

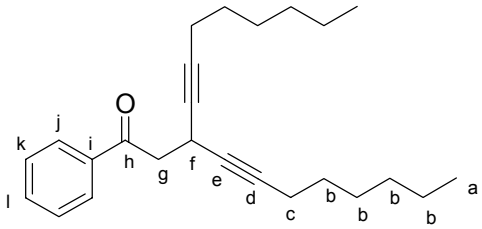


The unstable 3-oxo-3-phenylpropanal was prepared from acetophenone and DMF using standard Claisen condensation techniques (with NaOMe in THF). This compound stays predominantly in its enol form (<10% aldehyde). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.14 (OH, s, 1H), 6.02 (COC<u>H</u>=CH, d, J = 4.2 Hz, 1H), 7.24 (H_{Ar}, dd, J = 7.0 Hz, 8.2 Hz, 2H), 7.33 (H_{Ar}, t, J = 7.0 Hz, 1H), 7.79 (H_{Ar}, d, J = 8.2 Hz, 2H), 8.05 (COCH=C<u>H</u>, d, J = 4.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$):

δ 188.0 (C=O), 178.8 (COCH=CH), 135.0 (C_{Ar}), 133.0 (C_{Ar}), 128.8 (C_{Ar}), 127.5 (C_{Ar}), 98.4 (COCH=CH,).

3-Oxo-3-phenylpropanal (1.48 g, 10 mmol) was dissolved in 20 mL of MeOH. To the stirred solution, at room temperature, was added 0.1 mL (0.1 mmol, 1 mol%) of a 1.0 M $TiCl_4$ solution in CH_2Cl_2. After 10 min, the reaction was quenched with 5 mL of H_2O and was then extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with water and dried over sodium sulfate. Evaporation of the solvent afforded the crude product in 90% yield. This crude material is pure enough to use without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.80 (OMe, s, 3H), 6.29 (CH=CHOMe, d, J = 12.2 Hz, 1H), 7.40-7.53 (H_{Ar}, m, 3H), 7.76 (CH=CHOMe, d, J = 12.2 Hz, 1H), 7.87 (H_{Ar}, d, J = 7.1 Hz, 2H).

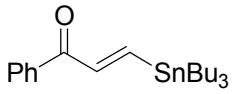
5.5.20 Preparation of 3-(Oct-1-ynyl)-1-phenylundec-4-yn-1-one (5.58)



A mixture of diisopropyl *B*-1-octynylboronate (**5.38)** (300 mg, 1.26 mmol), enone **5.55** (0.3 mmol) and (*S*)-3,3′-diiodo-2,2′-dihydroxy-1,1-binaphthyl (**2.28**) (32 mg, 0.06 mmol) were stirred in CH_2Cl_2 (4 mL) under argon at room temperature for 6 h, then brought to reflux for 24 h. The reaction was quenched with saturated aqueous NH_4Cl. The organic phase was washed with brine and dried over Na_2SO_4. Purification was done by column chromatography (acetone/hexanes 1:10) on silica gel to afford the title compound in 71% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83 (H_a, t, J = 7.0 Hz, 6H),

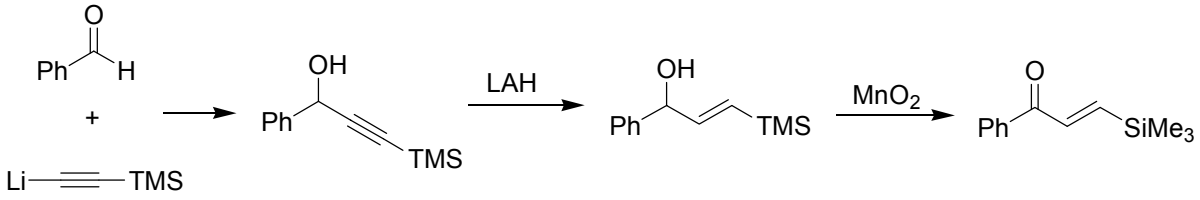
1.16-1.48 [H_b, m, 16H], 2.09 (H_c, dt, J = 2.2 Hz, 6.9 Hz, 4H), 3.32 (H_g, d, J = 7.2 Hz, 2H), 4.02 (H_f, m, 1H), 7.43 (H_k, t, J = 7.7 Hz, 2H), 7.54 (H_l, tt, J = 7.7 Hz, 1.2 Hz, 1H), 7.95 (H_j, dd, J = 7.7 Hz, 1.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.6 (C=O), 136.8 (C_i), 133.2 (C_l), 128.5 (C_k or C_j), 128.2 (C_k or C_j), 81.3 (C_e), 78.2 (C_d), 45.3 (C_g), 31.3 (C_b), 28.6 (C_b), 28.4 (C_b), 22.5 (C_b), 19.3 (C_f), 18.7 (C_c), 14.0 (C_a). MS (EI), m/e (relative intensity): 350(14, M^+), 349 (15, M^+-H), 279 (62 M^+-C_5H_{11}), 265 (46, M^+-C_6H_{13}), 105 [100, $(O{\equiv}C\text{-}Ph)^+$]; HRMS *m/z* Calcd for $C_{25}H_{34}O$ (M^+): 350.2610. Found: 350.2602.

5.5.21 Preparation of (*E*)-1-Phenyl-3-(tributylstannyl)prop-2-en-1-one (5.59)[54,55]



Anhydrous aluminum chloride (0.1330 g, 1 mmol) was added to a solution of *trans*-1,2-bis(tributylstannyl)ethylene (0.61 g, 1.0 mmol) and benzoyl chloride (0.155 g, 1.1 mmol) in dichloromethane (5 mL) at -78 "C under an argon atmosphere. The reaction mixture was stirred for 1 h at that temperature and was allowed to warm to 0 ^{o}C slowly. The reaction mixture was poured into 20 mL of water containing KF (1 g) and stirred vigorously for 5 min. The mixture was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated. Flash chromatography using 30:l hexanes/EtOAc gave the title compound (0.262 g) in 62% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84-1.59 (Sn$\underline{Bu}_3$, m, 27H), 7.29 (COC$\underline{H}$=CH, d, J = 19.3 Hz, 1H), 7.39-7.54 (H_{Ar}, m, 3H), 7.78 (COCH=C$\underline{H}$, d, J = 19.3 Hz, 1H), 7.90 (H_{Ar}, d, J = 7.6 Hz, 2H).

5.5.22 Preparation of (*E*)-1-Phenyl-3-(trimethylsilyl)prop-2-en-1-one (5.60)

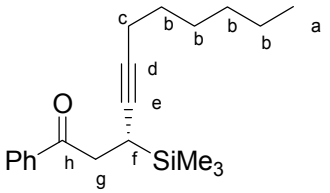


A literature procedure[56] was followed with some modifications. *n*-BuLi (6.7 mL, 10 mmol, 1.50 M solution in hexane) was added to a solution of (trimethylsilyl)acetylene (1.0 g, 10.2 mmol) in THF (30 mL) at -50 ^{o}C and the mixture was stirred for 20 min. Benzaldehyde (977 mg, 9.18 mmol) was then added and the resulting solution was stirred for 1 h at room temperature. The reaction was quenched with water, poured into NaCl (aqueous, saturated), and extracted with Et_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude propargyl alcohol (quantitative yield) was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.188 (Si$\underline{Me}_3$, s, 9H), 2.43 (OH, d, J = 6.0 Hz, 1H), 5.43 (ArC$\underline{H}$, d, J = 6.0 Hz, 1H), 7.30-7.55 (H_{Ar}, m, 5H).

A solution of this propargyl alcohol (1.80 g, 8.8 mmol) in THF (5 mL) was added to a suspension of $LiAlH_4$ (237 mg, 6.25 mmol) in 30 mL of THF at 0 °C, and the mixture was stirred for 2 days at 30 °C. After quenching with NH_4Cl, the precipitate was removed by filtration and the resulting solution was dried over $MgSO_4$, filtered, and concentrated under vacuum to afford a mixture of *E*- and *Z*-1-phenyl-3-trimethylsilyl-2-propen-1-ol[57] as a colorless oil in a ratio of 2.85:1 (by ^{1}H NMR). ^{1}H NMR (for the *E*-alcohol, 300 MHz, $CDCl_3$): δ 0.15 (Si$\underline{Me}_3$, s, 9H), 3.32 (OH, s, br, 1H), 5.13 (ArC$\underline{H}$, d, J = 4.9 Hz, 1H), 6.02 (TMSC$\underline{H}$=CH, d, J = 18.6 Hz, 1H), 6.24 (TMSCH=C$\underline{H}$, dd, J = 18.6 Hz, 4.9 Hz, 1H), 7.26-7.55 (H_{Ar}, m, 5H).

The *Z/E*-alcohol mixture (0.208g, 0.99 mmol) was dissolved in dichloromethane (7 mL) and activated MnO_2 (0.606 g, 6.97 mmol) was added at 0 ^oC. After stirring for 12 h at room temperature, the mixture was filtered through celite. The resulting solution was dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/hexanes = 1/30 to afford (*E*)-enone **5.60** as a pale yellow oil (184 mg, 60% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 0.22 (Si$\underline{Me}_3$, s, 9H), 7.22 (TMSC$\underline{H}$=CH, d, J = 18.7 Hz, 1H), 7.30 (TMSCH=C$\underline{H}$, d, J = 18.7 Hz, 1H), 7.42-7.93 (H_{Ar}, m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.4 (C=O), 149.5 (TMSCH=$\underline{C}$H), 138.0 (TMSCH=$\underline{C}$H), 137.5 (C_{Ar}), 132.7 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), -1.8 (Si$\underline{Me}_3$).

5.5.23 Preparation of (*R*)-1-Phenyl-3-(trimethylsilyl)undec-4-yn-1-one (5.61)



A mixture of diisopropyl *B*-1-octynylboronate **5.38** (215 mg, 0.9 mmol), enone **5.60** (64 mg, 0.3 mmol) and (*S*)-3,3′-diiodo-2,2′-dihydroxy-1,1-binaphthyl (**2.28**) (32 mg, 0.06 mmol) were stirred in CH_3CN (5 mL) under argon at room temperature for 6 h, then brought to reflux for 24 h. The reaction was quenched with saturated aqueous NH_4Cl. The organic phase was washed with brine and dried over Na_2SO_4. Purification was done by column chromatography (acetone/hexanes 1:10) on silica gel to afford the title compound in 93% yield. ^1H NMR (300 MHz, $CDCl_3$): δ 0.10 (Si$\underline{Me}_3$, s, 9H), 0.84 (H_a, t, J = 7.0 Hz, 3H), 1.20-1.44 (H_b, m, 8H), 2.05 (H_c, dt, J = 2.5 Hz, 6.8 Hz, 2H), 2.30 (H_f, m, 1H), 2.87 (H_g, dd, J = 4.4 Hz, 16.2 Hz, 1H), 3.11 (H_g, dd, J = 6.3 Hz, 16.2 Hz, 1H), 7.40-7.96 (H_{Ar}, m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.2 (C=O), 137.1 (C_{Ar}), 132.8 (C_{Ar}), 128.4 (C_{Ar}), 128.2

(C_{Ar}), 81.0 (C_e), 80.6 (C_d), 38.9 (C_g), 31.3 (C_b), 29.2 (C_b), 28.4 (C_b), 22.5 (C_b), 18.9 (C_c), 15.3 (C_f), 14.0 (C_a), -3.2 (Si$\underline{Me_3}$). The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH = 99.9/0.1, flow rate = 1 mL/min), t_R = 13.9 min (*S*), t_R = 19.1 min (*R*).

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Appendix. X-ray Crystallographic Data of 4.45k

Table 1. Crystal data and structure refinement

Identification code	mc1258m
Empirical formula	$C_{17}H_{14}BrNO$
Formula weight	328.20
Temperature	180(1) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 4.9357(6) Å alpha = 90° b = 10.2602(12) Å beta = 98.542(2)° c = 14.7445(17) Å gamma = 90°
Volume, Z	738.40(15) $Å^3$, 2
Density (calculated)	1.476 Mg/m^3
Absorption coefficient	2.778 mm^{-1}
F(000)	332
Crystal size	0.27 x 0.17 x 0.15 mm
θ range for data collection	2.43 to 30.01°
Limiting indices	$-6 \le h \le 6$, $-14 \le k \le 14$, $-20 \le l \le 20$
Reflections collected	7515
Independent reflections	4105 (R_{int} = 0.0272)
Completeness to θ = 30.01°	99.8 %
Absorption correction	Integration
Max. and min. transmission	0.708 and 0.573
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4105 / 0 / 182
Goodness-of-fit on F^2	1.338
Final R indices [I>2σ(I)]	R1 = 0.0293, wR2 = 0.0527
R indices (all data)	R1 = 0.0339, wR2 = 0.0532
Absolute structure parameter	-0.013(6)
Extinction coefficient	0.0289(14)
Largest diff. peak and hole	0.440 and -0.408 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3]. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
Br(14)	3702(1)	10000	4520(1)	58(1)
C(1)	5359(4)	6844(2)	8136(1)	24(1)
C(2)	7141(4)	5697(2)	8067(1)	27(1)
C(3)	8382(4)	4736(2)	7958(1)	28(1)
N(4)	6416(3)	7657(1)	8916(1)	24(1)
C(5)	4706(4)	8377(2)	9336(1)	25(1)
O(6)	2204(3)	8266(1)	9161(1)	35(1)
C(7)	6025(4)	9357(2)	10030(1)	35(1)
C(8)	4958(4)	7612(2)	7237(1)	24(1)
C(9)	6823(4)	8562(2)	7076(1)	31(1)
C(10)	6443(4)	9279(2)	6273(1)	33(1)
C(11)	4213(4)	9014(2)	5623(1)	34(1)
C(12)	2345(4)	8057(2)	5758(1)	36(1)
C(13)	2721(4)	7370(2)	6570(1)	31(1)
C(15)	9761(4)	3514(2)	7869(1)	27(1)
C(16)	11476(4)	3349(2)	7209(1)	35(1)
C(17)	12750(5)	2155(2)	7129(2)	45(1)
C(18)	12294(4)	1134(2)	7705(2)	44(1)
C(19)	10631(4)	1302(2)	8357(2)	40(1)
C(20)	9363(4)	2477(2)	8442(1)	34(1)

Table 3. Bond lengths [Å] and angles [°]

Br(14)-C(11)	1.8992(19)	C(1)-N(4)	1.454(2)
C(1)-C(2)	1.482(2)	C(1)-C(8)	1.528(2)
C(2)-C(3)	1.184(2)	C(3)-C(15)	1.442(2)
N(4)-C(5)	1.341(2)	C(5)-O(6)	1.229(2)
C(5)-C(7)	1.512(3)	C(8)-C(9)	1.385(2)
C(8)-C(13)	1.388(3)	C(9)-C(10)	1.383(3)
C(10)-C(11)	1.375(3)	C(11)-C(12)	1.382(3)
C(12)-C(13)	1.378(3)	C(15)-C(20)	1.390(3)
C(15)-C(16)	1.392(3)	C(16)-C(17)	1.391(3)
C(17)-C(18)	1.388(3)	C(18)-C(19)	1.365(3)
C(19)-C(20)	1.373(3)		

N(4)-C(1)-C(2)	111.29(15)	N(4)-C(1)-C(8)	112.05(13)
C(2)-C(1)-C(8)	110.60(15)	C(3)-C(2)-C(1)	174.2(2)
C(2)-C(3)-C(15)	175.52(18)	C(5)-N(4)-C(1)	120.33(15)
O(6)-C(5)-N(4)	122.29(17)	O(6)-C(5)-C(7)	121.47(16)
N(4)-C(5)-C(7)	116.23(15)	C(9)-C(8)-C(13)	118.88(17)
C(9)-C(8)-C(1)	120.49(17)	C(13)-C(8)-C(1)	120.64(16)
C(10)-C(9)-C(8)	120.82(19)	C(11)-C(10)-C(9)	119.00(18)
C(10)-C(11)-C(12)	121.45(18)	C(10)-C(11)-Br(14)	118.86(15)
C(12)-C(11)-Br(14)	119.69(16)	C(13)-C(12)-C(11)	118.8(2)
C(12)-C(13)-C(8)	121.01(18)	C(20)-C(15)-C(16)	119.20(17)
C(20)-C(15)-C(3)	119.94(16)	C(16)-C(15)-C(3)	120.86(17)
C(17)-C(16)-C(15)	119.72(19)	C(18)-C(17)-C(16)	119.8(2)
C(19)-C(18)-C(17)	120.36(18)	C(18)-C(19)-C(20)	120.3(2)
C(19)-C(20)-C(15)	120.58(19)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2$ x 10^3]

The anisotropic displacement factor exponent takes the form:

$-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^* b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
Br(14)	62(1)	69(1)	41(1)	23(1)	6(1)	2(1)
C(1)	22(1)	23(1)	30(1)	-2(1)	7(1)	0(1)
C(2)	30(1)	25(1)	27(1)	2(1)	7(1)	-2(1)
C(3)	30(1)	27(1)	28(1)	-1(1)	5(1)	-1(1)
N(4)	17(1)	28(1)	27(1)	-2(1)	1(1)	3(1)
C(5)	26(1)	25(1)	26(1)	3(1)	9(1)	4(1)
O(6)	21(1)	37(1)	49(1)	-7(1)	8(1)	3(1)
C(7)	34(1)	39(1)	32(1)	-8(1)	3(1)	1(1)
C(8)	24(1)	21(1)	27(1)	-3(1)	7(1)	5(1)
C(9)	25(1)	32(1)	34(1)	-2(1)	2(1)	-2(1)
C(10)	32(1)	33(1)	36(1)	4(1)	9(1)	-2(1)
C(11)	36(1)	37(1)	29(1)	5(1)	8(1)	9(1)
C(12)	33(1)	42(1)	31(1)	-2(1)	-2(1)	2(1)
C(13)	29(1)	30(1)	34(1)	-1(1)	2(1)	-3(1)
C(15)	24(1)	24(1)	33(1)	-5(1)	-1(1)	2(1)
C(16)	37(1)	29(1)	40(1)	0(1)	9(1)	3(1)
C(17)	39(1)	46(1)	54(1)	-10(1)	15(1)	10(1)
C(18)	37(1)	28(1)	67(2)	-4(1)	6(1)	9(1)
C(19)	42(1)	26(1)	52(1)	3(1)	6(1)	3(1)
C(20)	35(1)	27(1)	41(1)	1(1)	9(1)	1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3)

	x	y	z	U(eq)
H(1)	3522	6514	8238	29
H(4)	8188	7676	9114	29
H(7X)	5418	10237	9837	53
H(7Y)	8022	9302	10073	53
H(7Z)	5489	9168	10630	53
H(9)	8381	8723	7523	37
H(10)	7704	9944	6172	40
H(12)	828	7875	5299	44
H(13)	1429	6721	6674	37
H(16)	11775	4050	6814	42
H(17)	13929	2038	6681	54
H(18)	13144	314	7645	53
H(19)	10350	602	8754	48
H(20)	8202	2583	8896	41