Asymmetric Conjugate Addition of Boronates to *N*-Acylimines and β-Silyl-α,β-unsaturated Ketones Catalyzed by 3,3′-Disubstituted Binaphthols

by

Alice Sin Hang Chan

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I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

In order to extend the scope of asymmetric conjugate alkenylation catalyzed by 3,3′-disubstituted binaphthols, two classes of compounds were examined.

Asymmetric 1,4-addition of alkenylboronates onto *N*-acylimines was investigated. Chiral allylic amides were obtained in good yields and high enantioselectivities. This represents one of the very few methods for synthesizing chiral allylic amides without the use of transition metal catalysts.

Chiral binaphthol-catalyzed conjugate addition of alkenylboronates to β-silyl-α,β-unsaturated ketones afforded highly enantioenriched chiral β-silylcarbonyls. Asymmetric addition onto β-silyl-enones is still a largely unexplored area, with only a handful of transition metal-catalyzed reactions reported. The first asymmetric reaction using these silicon-containing enones without using transition metal were described.

Acknowledgements

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List of abbreviations and tradenames

9-BBN	9-borabicyclo[3.3.1]nonyl
Ac	acetyl
ACA	asymmetric conjugate addition
acac	acetylacetonato
aq	aqueous
Ar	aryl
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2,2'-naphthol
BMS	borane-dimethyl sulfide complex
Boc	*tert*-butoxycarbonyl
br	broad
Bu	butyl
Bz	benzoyl
c	concentration (g per 100 mL)
cat.	catalytic
Cbz	benzyloxycarbonyl
cm	centimeter
cod	1,5-cyclooctadiene

coe	cyclooctene
COP	cyclobutadienyl-cobalt palladacycle
d	doublet
de	diastereomeric excess
DME	dimethoxyethane
dppe	1,2-*bis*(diphenylphosphino)ethane
E^+	electrophile
ee	enantiomeric excess
equiv	equivalent(s)
er	enantiomeric ratio
Et	ethyl
ether	diethyl ether
EtOAc	ethyl acetate
EDG	electron donating group
EWG	electron withdrawing group
GC	gas chromatography
GC-MS	gas chromatography and mass spectrometry
h	hour
HMDS	1,1,1,3,3,3-hexamethyldisilazane

HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
Ipc_2BH	*bis*isopinocampheylborane
i-Pr	isopropyl
J	coupling constant (in NMR spectrometry)
L	ligand
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
m	multiplet
M	molar
m/z	mass/charge
M^+	parent molecular ion
Me	methyl
MeLi	methyllithium
MEPY	methyl 2-pyrrolidone carboxylate
MeOH	methanol
min.	minute
mL	millilitre
mmol	millimole

MOM	methoxymethyl
MSA	methanesulfonic acid
n-BuLi	*n*-butyllithium
NMR	nuclear magnetic resonance
Nu	nucleophile
o-	*ortho*-
p-	*para*-
Ph	phenyl
pin	pinacol
PMHS	polymethylhydrosiloxane
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
q	quartet
quant	quantitative
rac	racemic
rt	room temperature
s	singlet
S_N2	bimolecular nucleophilic substitution
t	triplet

TADDOL	2,2-dimethyl-*α,α,α′,α′*-tetraaryldioxolane-4,5-dimethanol
TBS	*t*-butyldimethylsilyl
t-Bu	*tert*-butyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
t_R	retention time
triflate	trifluoromethanesulfonate
Ts	*p*-toluenesulfonyl
XS	excess

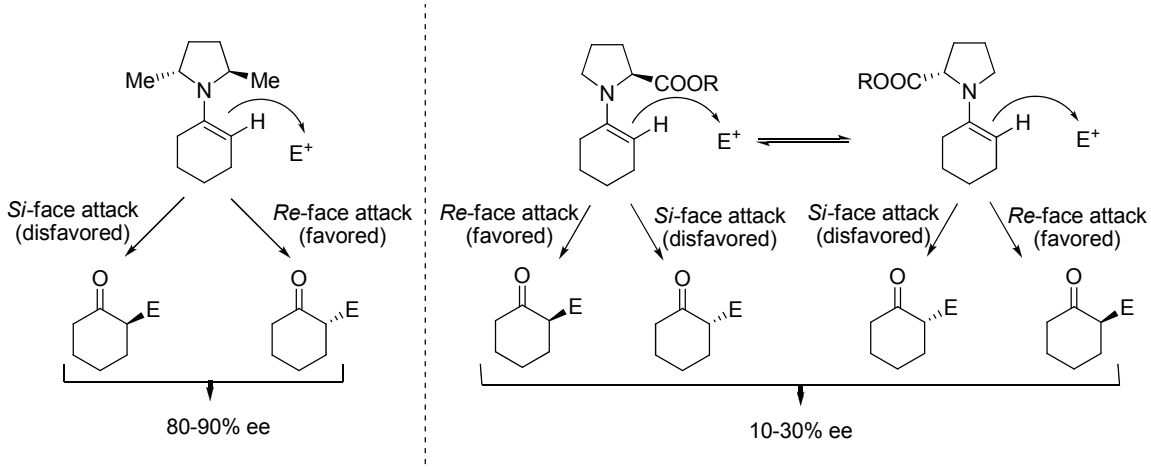
Chapter 1 Introduction

1.1 Binaphthols in asymmetric syntheses

1.1.1 C_2 symmetry, binaphthyl groups and binaphthols

Recent advances in enantioselective synthesis enable efficient synthesis of chiral organic compounds from achiral substrates in the presence of chiral reagents. Stereodifferentiation can be achieved because of the difference in energy barriers leading to two or more diastereomeric transition states, in which the one with lowest activation energy could lead to the preferential formation of one of the enantiomers.[1,2]

Using molecules possessing only simple rotation and belonging to C_n or D_n symmetry, especially reagents with C_2 symmetry, reduces the complexity in predicting enantioselectivity because the number of competing diastereomeric transition states is greatly reduced.



Scheme 1.1

For instance, in enantioselective alkylation of cyclohexanone enamines, low enantioselectivities (10-30% *ee*) were reported using chiral auxillaries with non-C_2 symmetric proline esters (Scheme 1.1, right);[3-5] whereas much higher *ee's* were achieved when utilizing a C_2-symmetrical *trans*-2,5-dimethylpyrrolidine (80-90% *ee;* Scheme 1.1,

left).[6,7] The difference in stereoselectivities can be explained by the number of favored diastereomeric pathways.

An enamine generated from cyclohexanone and (*S*)-methyl proline has two possible conformations, resulting in four possible diastereomeric transition states in which only one of them is disfavored. The remaining three are favored which leads to the formation of products in *R* and *S* configurations. Subsequently low *ee'*s were observed. However, the enamine produced by *trans*-2,5-methylpyrrolidine has only one possible conformation and thus two possible diastereomeric transition states, in which one of them is disfavored. Therefore, the C_2 symmetric chiral auxiliary gives alkylated product in high stereoselectivity.

C_2-symmetric reagents have been extensively utilized in asymmetric synthesis over the past decades, either as ligands in metal complexes or as organocatalysts. High degrees of stereodifferentiation are often observed in a wide range of reactions. Selected examples are shown in Figure 1.1. [8-14]

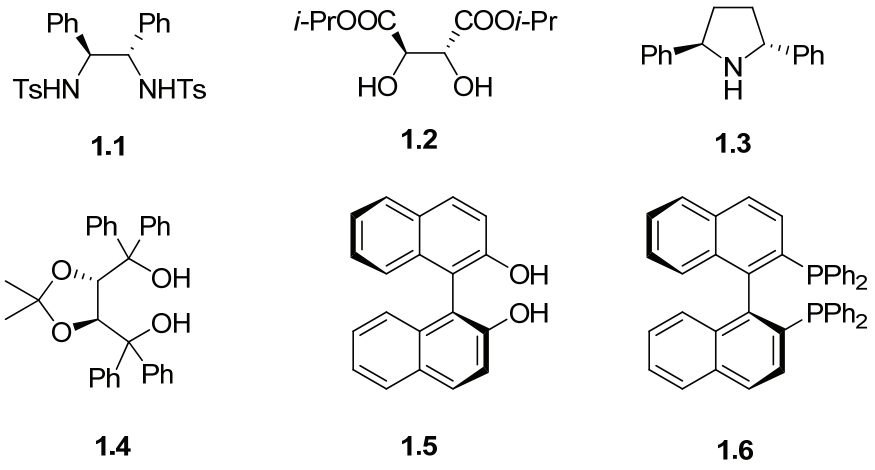
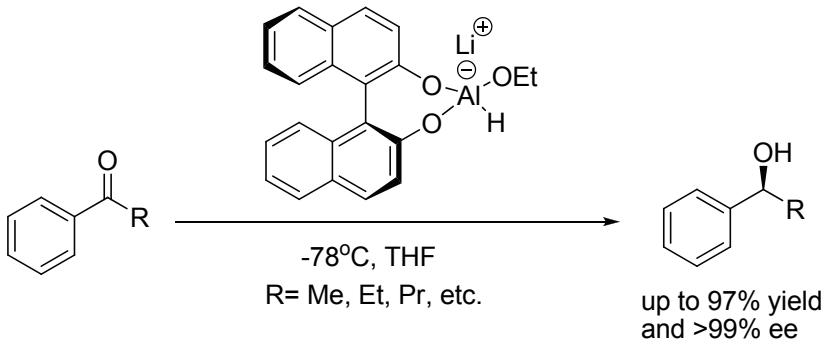


Figure 1.1 Selected examples of C_2-symmetric reagents in asymmetric synthesis

1.1.2 Binaphthols in asymmetric syntheses

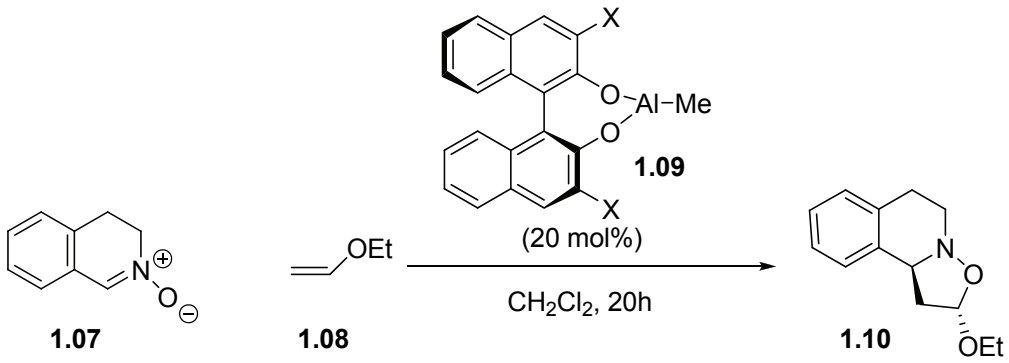
Stereoselective transformations promoted by organic molecules have proved to be powerful in obtaining chiral building blocks for organic synthesis. 2,2′-Dihydroxy-1,1′-binaphthyl (BINOL, **1.5**) is one of the most commonly used C_2-symmetric reagents in the past twenty years. Interestingly, even though it was first synthesized by Pummerer in 1926, its application in asymmetric synthesis was only realized 63 years later: Noyori's reduction of aromatic ketones and aldehydes.[13] (Scheme 1.2)



Scheme 1.2

Since then, BINOL has been used in various types of asymmetric reactions including Diels-Alder reactions, hydrogenations, Michael additions, and 1,2-additions such as allylations, Mannich-type reactions and Reformatsky reactions.[2,15-18] An update on recent advances in using BINOL in asymmetric synthesis was published in 2007.[2] Although it has been described as a 'versatile' reagent, BINOL does not always perform as well as one expects. To improve the reactivity and stereoselectivity, BINOLs are modified such that substitutions would change the steric and electronic environments of the ligand, thereby making BINOLs more efficient in asymmetric inductions.

One of the simplest ways to modify BINOL is to substitute its 3 and 3′ positions in **1.11** (Figure 1.2). The Jørgensen group demonstrated in the case of enantioselective 1,3-dipolar cycloaddition of nitrones **1.07** and ethyl vinyl ether **1.08** catalyzed by **1.09**, bulkier and more electron-donating substituents on the 3 and 3′ positions in the binaphthyl-based catalysts dramatically increase yields, enantioselectivities and *exo*/*endo*-selectivities (Table 1.1).



entry	X	conversion (%)	*exo* : *endo*	*ee* (% of *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

Table 1.1 Effects of 3,3′-substituents in 1,3-dipolar cycloaddition

Other types of modified BINOLs include H_8-BINOLs **1.12**, F_8-BINOLs **1.13** and 6,6′-, 7,7′- and 4,4′-substituted BINOLs **1.15**. In recent years, efforts were also directed towards linked BINOLs **1.14**, polymer-supported BINOLs, BINOL-derived phosphoramidites and phosphoric acid, as well as multimetallic BINOLs in enhancing the performance of the catalysts in various reactions (Figure 1.2).[16, 19-23]

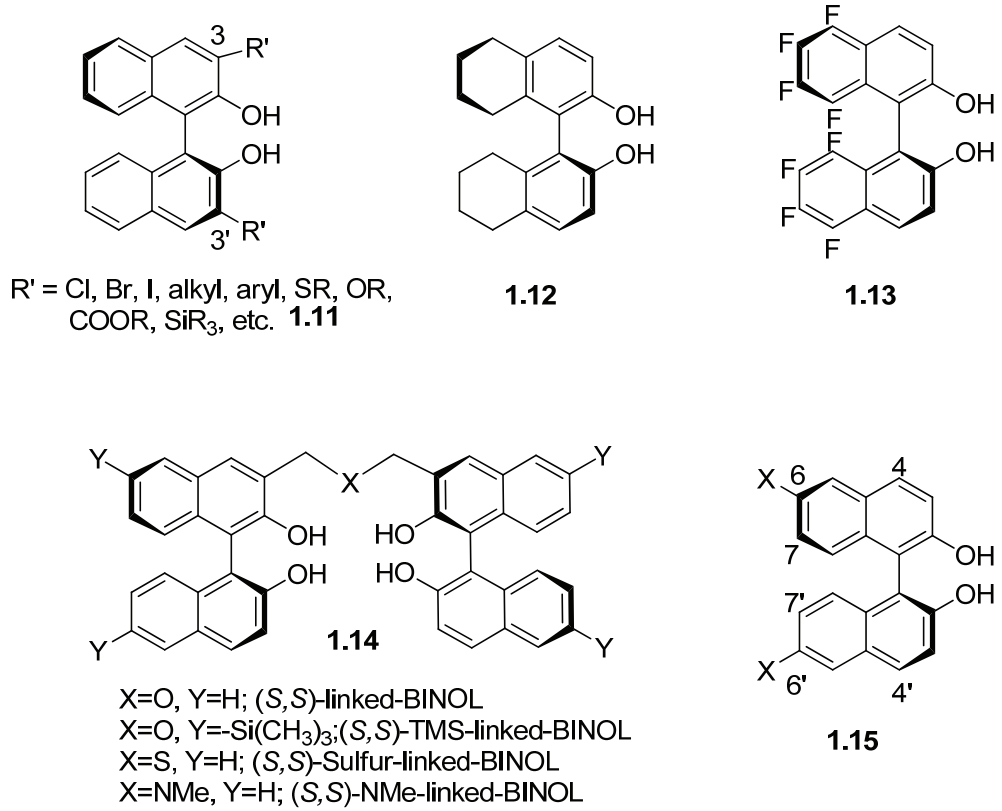


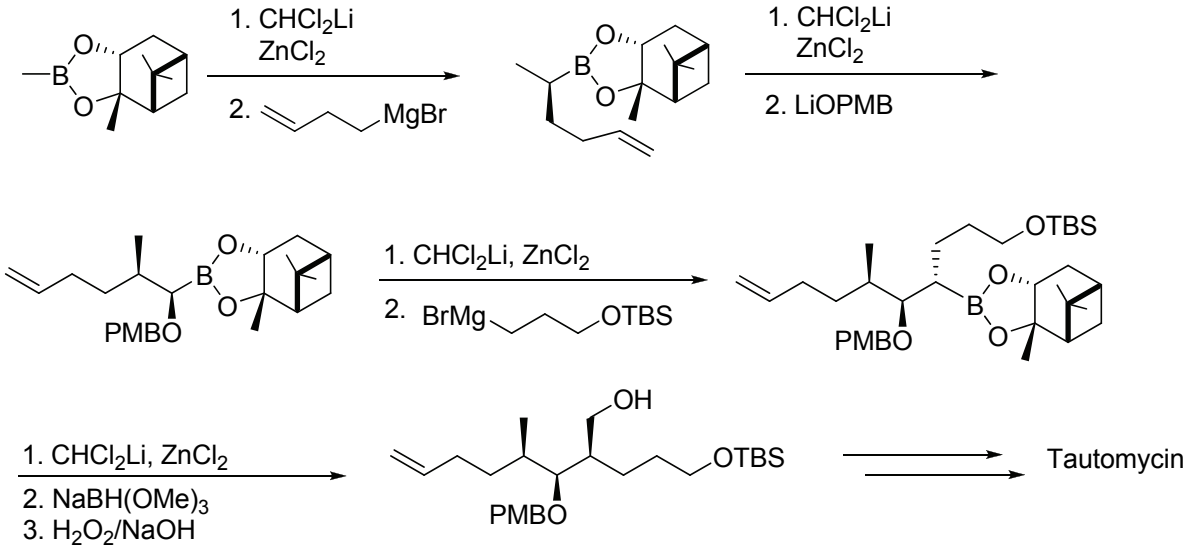
Figure 1.2 Examples of modified BINOLs used in organic synthesis

1.2 Boron in asymmetric syntheses

Boron reagents occupy a unique position in asymmetric synthesis. Distinct physical properties of the boron atom offer advantages in asymmetric induction, yielding products with high enantiomeric purity.[24] Pioneered by Brown and Zweifel, the first non-enzymatic asymmetric synthesis with high stereoselectivity ever performed was the hydroboration of *cis*-2-butene with diisopinocampheylborane $(Ipc)_2BH$.[25] Methodologies involving chiral organoboron compounds have been well developed in numerous reactions, e.g. allylation of carbonyls, Diels-Alder reactions and reduction of ketones.[26-28]

Perhaps less well-known compared to the ones mentioned above, Matteson homologation of organoboranes is a powerful approach to vicinal stereocenters.[29] In the

total synthesis of tautomycin, three vicinal stereocenters were constructed using a sequence involving four homologations (Scheme 1.3).[30]



Scheme 1.3 Synthesis of a fragment of tautomycin using Matteson homologation

The other merit of using organoboron reagents is the low cost and toxicity which allows scaling up.[31] Protocols for asymmetric reductions of various functional groups have been established in process chemistry for decades.[32]

1.2.1 Catalytic enantioselective C-C bond formation using organoboron reagents

Recent studies on enantioselective C-C bond formation using organoboranes can be categorized in the following areas:

a) transition metal-catalyzed reactions

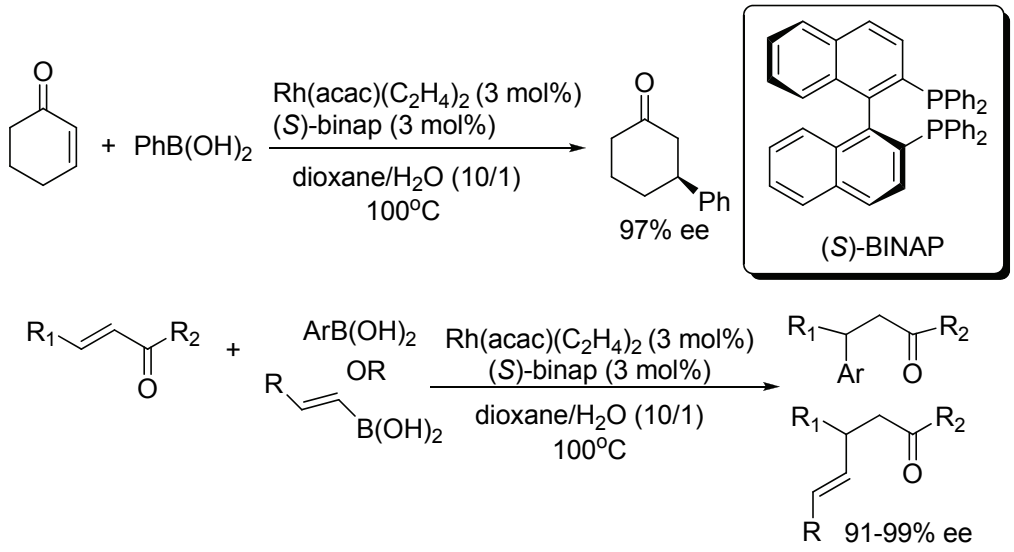
b) boronate activation by interference of electron donation to the boron atom

c) boronate activation by ligand exchange

1.2.1.1 Transition metal-catalyzed reactions

A) 1,4-additions

Boronic acids and derivatives are widely used in metal-catalyzed 1,4-additions. Rhodium-catalyzed reactions developed by the Hayashi group are commonly used over the past decade, partly because of the broad scope of substrates that can be used (Scheme 1.4).[33] α,β-Unsaturated aldehydes, ketones, esters **1.16**, amides **1.17**, lactones **1.18** and lactams **1.19** give good yields and enantioselectivities.[34-38] Acetamidoacrylic esters **1.20**, alkenylphosphonates **1.21** as well as nitroolefins **1.22** have also been exploited (Figure 1.3).[33,39-41] Other organoboron compounds such as potassium organotrifluoroborates **1.23**, **1.24** and boroxines **1.25** provide good selectivity as well.[33,42]



Scheme 1.4 Rhodium-catalyzed conjugate addition of aryl/alkenylboronic acid

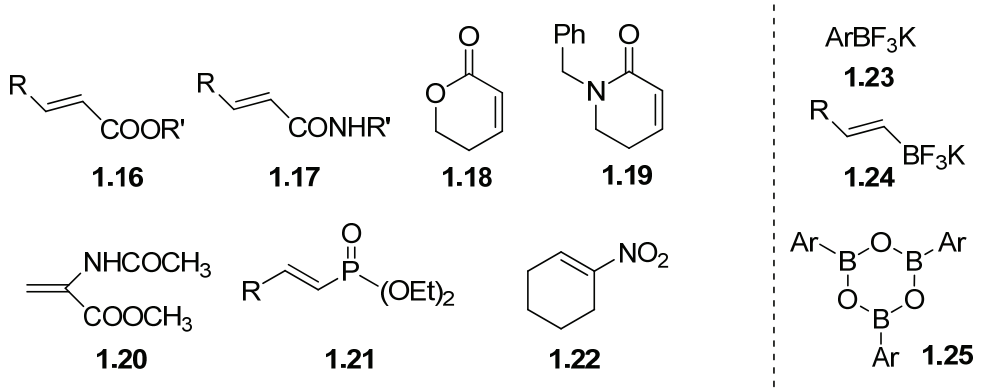
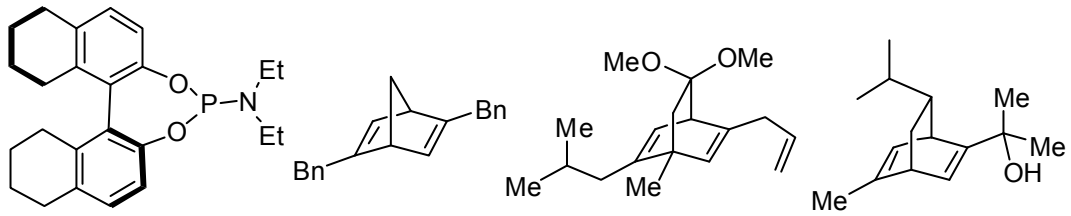


Figure 1.3 Scope of rhodium-catalyzed conjugate addition

Extensive studies have been done on the Rh-catalyzed reactions. Figure 1.4 shows the types of ligands that have been developed for the reaction.[43] Feringa's monodentate phosphoramidite **1.26** offers excellent enantioselectivities and high reaction rates. High ee's were still observed even under high temperature and in polar solvents because of the stable metal complexes formed. The Miyaura group applied the phosphoramidite ligand to accelerate the transformation by addition of a base such as Et_3N or KOH.[44] It is noteworthy that the diene ligands **1.27** and **1.28**, independently developed by Hayashi and

Carreira, offer excellent results in the Rh(I)-catalyzed 1,4-addition to enones at low catalyst loadings.[45-47] However, both diene ligands require at least seven steps to be synthesized. Very recently, Hayashi and Rawal reported diene ligand **1.29** which only takes two steps to be synthesized from an inexpensive terpene. The novel ligand is as effective as the other diene ligands in the Rh-catalyzed reactions.[43]



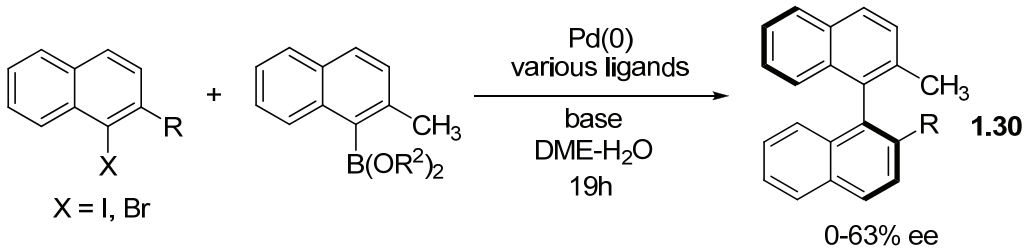
1.26 **1.27** **1.28** **1.29**

Figure 1.4 Various ligands which were exploited in Rh-catalyzed 1,4-addition

Palladium and nickel complexes are also effective catalysts in 1,4-additions.[48] The most recent discovery is the ruthenium-catalyzed variant which suppresses Heck-type and reduced products.[49] Unfortunately, 1,4-addition using Pd, Ni and Ru complexes appear to be inferior to the Rh complexes in the catalysis.[49]

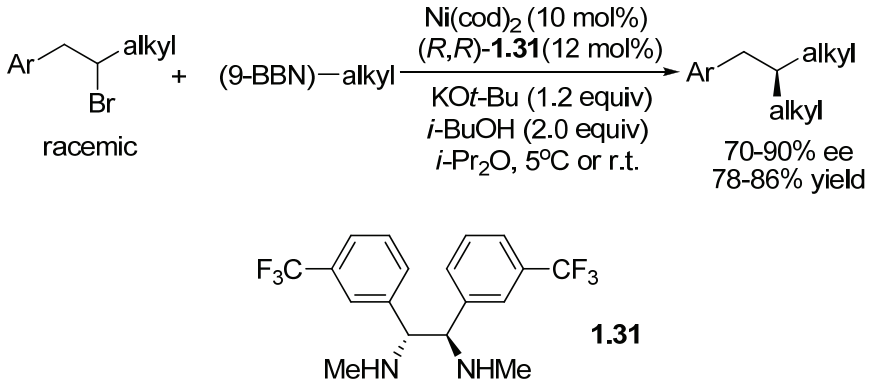
B) Asymmetric Suzuki cross-coupling reaction

The first enantioselective variant of the Suzuki reaction was achieved by Cammridge in coupling naphthalene units into binaphthalenes **1.30**. This palladium-catalyzed reaction offered modest ee's and yields (Scheme 1.5).[50] The palladium nanoparticle variant of this reaction gave similar experimental results.[51]



Scheme 1.5

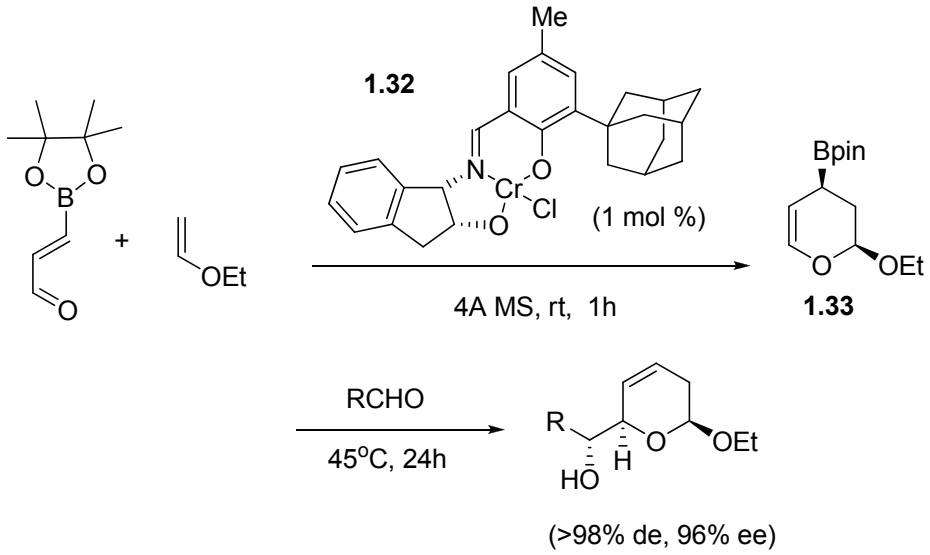
A breakthrough came when the Fu group at MIT exploited nickel-catalyzed conditions in unactivated alkyl-alkyl cross-coupling reactions. Excellent enantioselectivities were accomplished with acyclic homobenzylic bromides. However, cyclic substrates or substrates with long side chains offered products with low enantiopurities (Scheme 1.6).[52,53]



Scheme 1.6

C) Hetero [4+2] cycloaddition/allylboration

Using Jacobsen's Cr(III) catalyst **1.32**, the Hall group reported a one-pot hetero Diels-Alder reaction/allylboration reaction, yielding α-hydroxyalkyl dihydropyrans such as **1.33** with excellent de and ee.[54,55] This protocol was later used to build substituted pyran units in the first total synthesis of a thiomarinol antibiotic.[56]

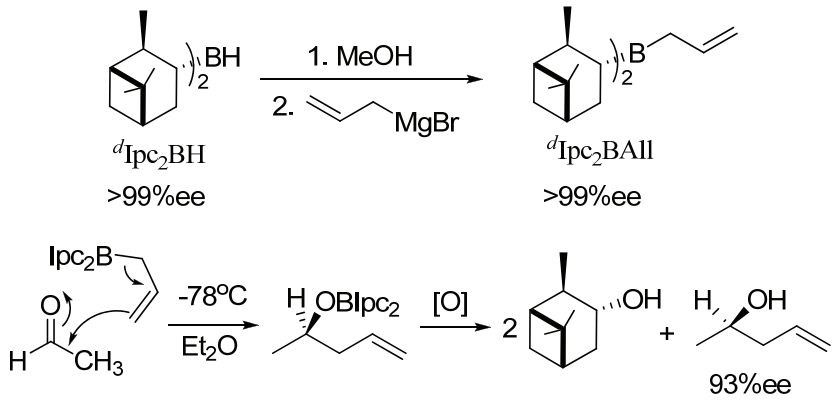


Scheme 1.7

1.2.1.2 Boronate activation by interference of electron donation to the boron atom

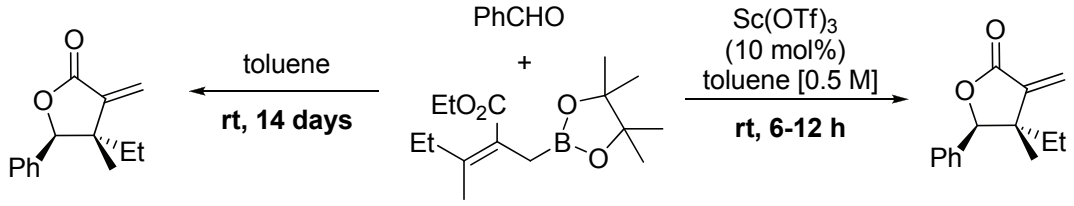
A) Allylboration catalyzed by Lewis/Brønsted acids

Even twenty years after its discovery, Brown's allylation using a pinene-based system is still the method of choice for asymmetric allylboration (Scheme 1.8).[24] However, this methodology requires the use of a stoichiometric amount of the chiral director. Besides, the allylboranes are very moisture sensitive and hence inconvenient to handle. More moisture-stable surrogates, allylboronates, were thus harnessed. Unfortunately, these reactions often take more than 10 days to complete (Scheme 1.9)![57]



Scheme 1.8

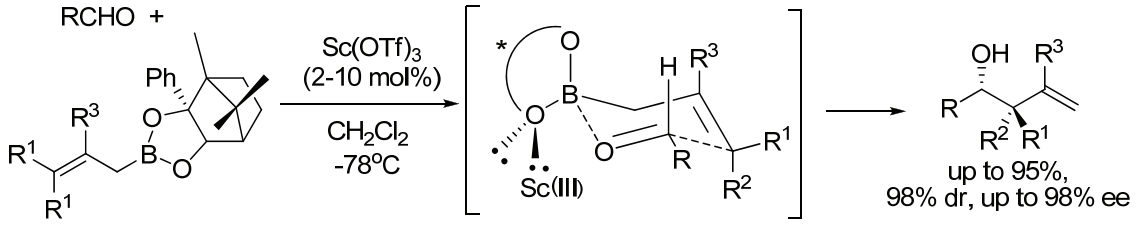
Type 1 allylation such as allylboration generally proceeds via a closed, six-membered transition state. Contrary to the intuition that Lewis acids are not suitable to catalyze closed transition states, Hall and co-workers demonstrated the use of $Sc(OTf)_3$ and other Lewis acids dramatically accelerated allylation reactions using boronates (Scheme 1.9). [58]



Scheme 1.9

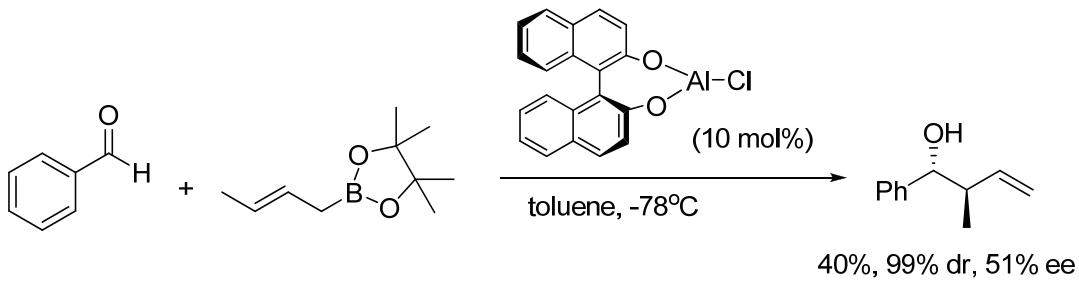
The rationale for the rate acceleration was suggested to be the coordination of the Lewis acid catalyst onto one of the boronate oxygen atoms in a closed transition state (Scheme 1.10). The Lewis acid interrupts the donation of an oxygen lone-pair to the empty *p*-orbital of the boron atom. The interaction between the boron and the carbonyl oxygen is thus increased, resulting in a decrease of the activation energy in the allylation reaction. This rationale is consistent with the mechanistic study conducted by Brown, which

suggested that the reactivity of boron-based allylation correlates to the availability of lone pair electrons on the oxygen atoms to the boron.[59] Omoto and Fujimoto also found that the strength of coordination between the boron and the aldehyde in the transition states governs the rate of allylboration reactions.[60]



Scheme 1.10

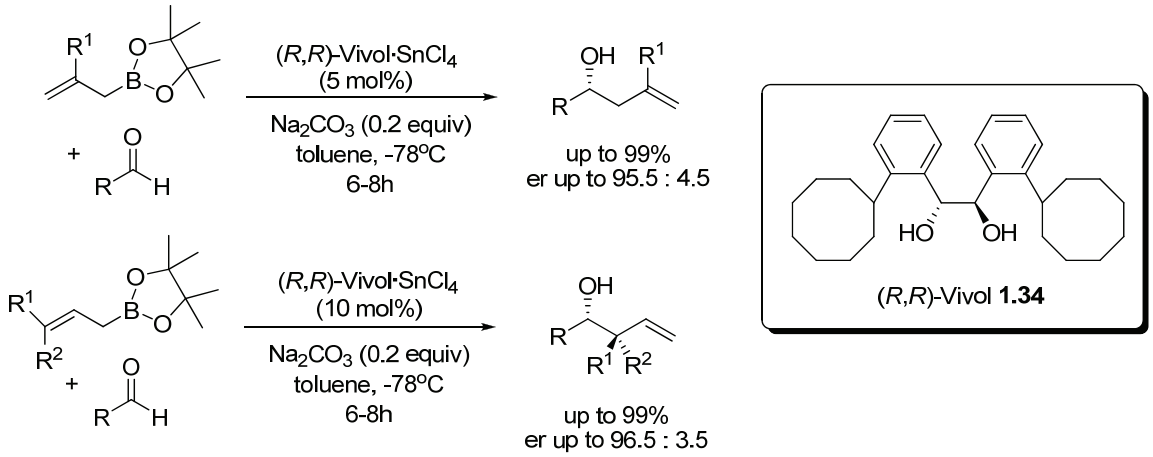
At around the same time, Miyaura et al. realized chiral BINOL-aluminum system-catalyzed allylboration. The crotylation of benzaldehyde using Et_2AlCl and (*S*)-BINOL yielded products with high dr, but low er (Scheme 1.11).[61]



Scheme 1.11

The Hall group further expanded their scope of reaction towards electron-rich and sterically hindered aldehydes by catalysis using triflic acid (Brønsted acid). Utilizing Yamamoto's concept of Lewis acid-assisted Bronsted acidity, Hall explored the use of $SnCl_4$ and diols **1.34** to catalyze allylboration.[57,62] This protocol allows allylboration of aliphatic and aromatic aldehydes in high enantioselectivity (Scheme 1.12). Similar to the

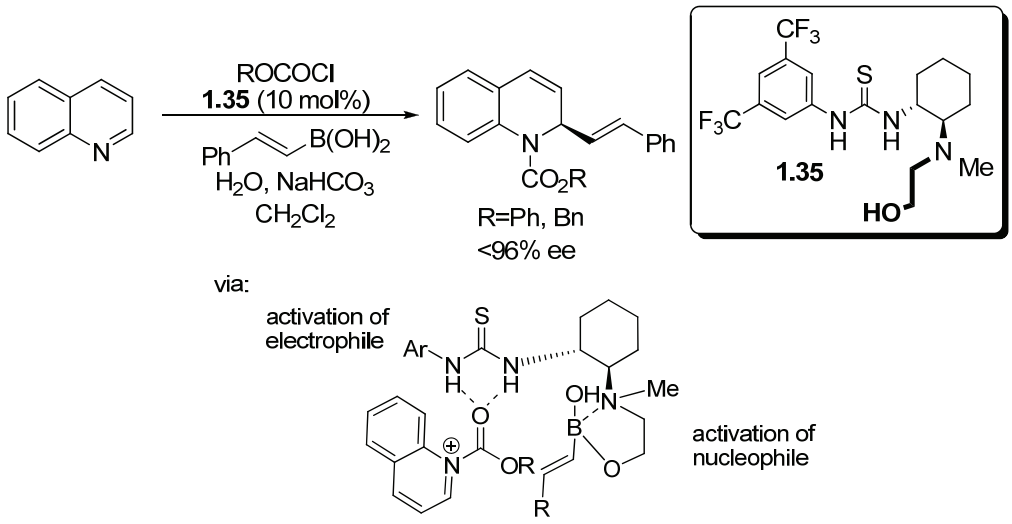
explanation in $Sc(OTf)_3$ catalyzed reactions, the hydroxyl protons in the tin-BINOL complex coordinate to the boronate oxygen atoms. Na_2CO_3 acts to sequester HCl (residual HCl in commercial $SnCl_4$) which may activate the non-stereoselective pathway. An X-ray structure of the complex of $SnCl_4$ and **1.34** as well as ^{119}Sn NMR studies provided support to the proposed mechanism of the reaction.[62]



Scheme 1.12

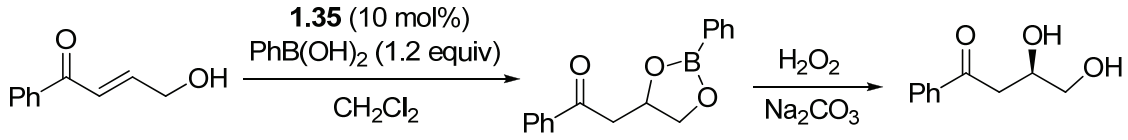
B) Addition of boronic acids/esters by thiourea catalysts

Thiourea catalysts were used in the Petasis-type reaction of quinolines using alkenylboronic acids. Takemoto et al. proposed that the thiourea catalyst not only brings boronates and *N*-acylated quinolinium salts in close proximity, but also activates the quinolinium salts through hydrogen bonding. In the presence of water and Na_2CO_3, high stereoselectivities were furnished at around -60°C (Scheme 1.13).[63]



Scheme 1.13

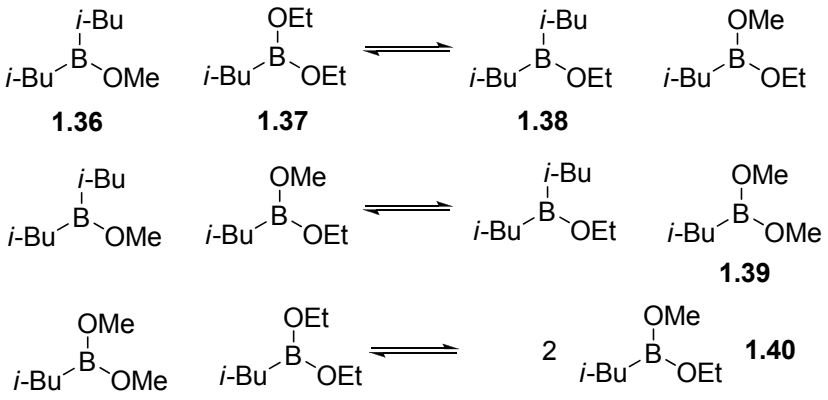
This idea was also used in an oxy-Michael addition of γ-hydroxy-α,β-enones by the Falck group. A "push-pull" mechanism was suggested; a hydroxyl group is transferred to the β-position of enone by the formation of an amine-borate complex. If the amino-alcohol group was changed to a *i*Pr (bonds in bold of **1.35**), the reaction proceeded very slowly.[64]



Scheme 1.14

1.2.1.3 Boronate activation by ligand exchange

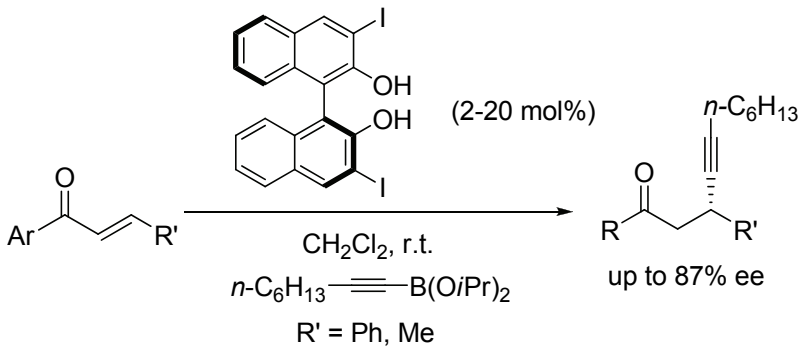
McCusker and co-workers first noticed the rapid exchange of alkoxy ligand in organoboronates in 1962 (Scheme 1.15). Upon mixing diisobutylmethoxyborane **1.36** and isobutyldiethoxyborane **1.37**, an equilibrium mixture of starting materials and diisobutylethoxyborane **1.38**, isobutyldimethoxyborane **1.39** and isobutylmethoxyethoxyborane **1.40** was found. NMR study showed that the equilibrium was reached within 30 seconds at room temperature.[65]



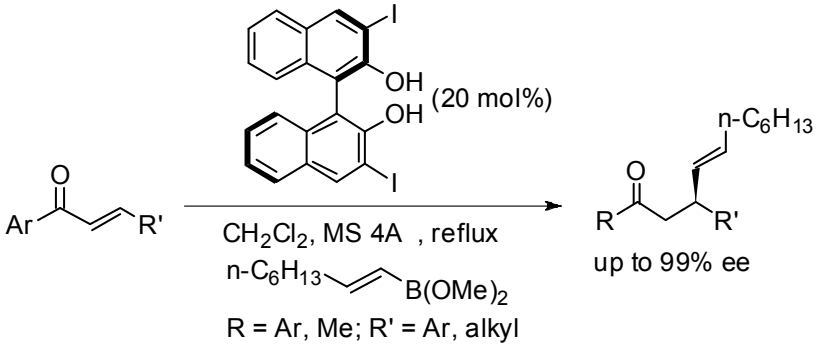
Scheme 1.15

To understand the relative stabilities of boronic esters, an extensive survey was done by Roy and Brown. Their goal was to find out which diols would make a catalytic version of Matteson homologation possible. Relative rates of transesterification of various diols and boronic esters were monitored. It is noteworthy that binaphthols and similar derivatives were *not* examined (vide infra). [66,67]

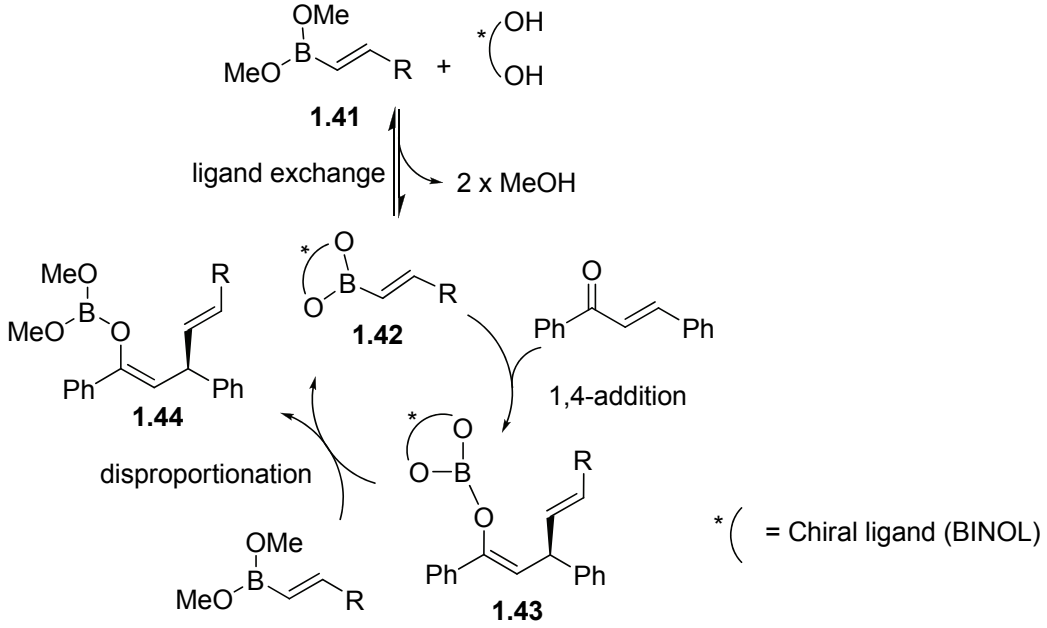
Our group first reported the use of a catalytic amount of a chiral binaphthol as an 'exchangable' chiral ligand on the boron in asymmetric conjugate addition of alkynylboronates and alkenylboronates (Scheme 1.16 and 1.17).[68,69] The use of substoichiometric amounts of binaphthols offers high synthetic utility.



Scheme 1.16



Scheme 1.17



Scheme 1.18

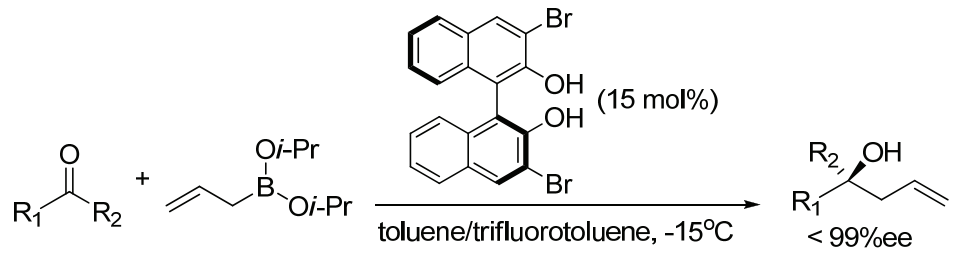
The proposed mechanism demonstrated that a fine balance of reactivity of each component is the key to stereodifferentiation (Scheme 1.18). The dimethoxyboronate undergoes ligand exchange with binaphthols to form a binaphthol-coordinated chiral boronate species **1.42**, followed by subsequent 1,4-addition. The chiral boron enolate **1.43** generated undergoes disproportionation with another dimethoxyboronate to regenerate the binaphthol-coordinated boronate **1.42**.[68,70]

High enantioselectivities can be accomplished because the background reaction between the dimethoxyboronate and the enone is slower than that between the chiral boronate species and the enone. In the dimethoxyboronate, the planar structure offers stabilization resulting from the effective donation of an oxygen lone pair to the vacant boron p orbital. In the binaphthol boronate **1.42**, the cyclic bidentate coordination prevents the two oxygen atoms and the boron atom to align on the same plane. Hence, the activation energy of the reaction is much lowered for the chiral boronate because of the decreased boron-oxygen conjugation.[71]

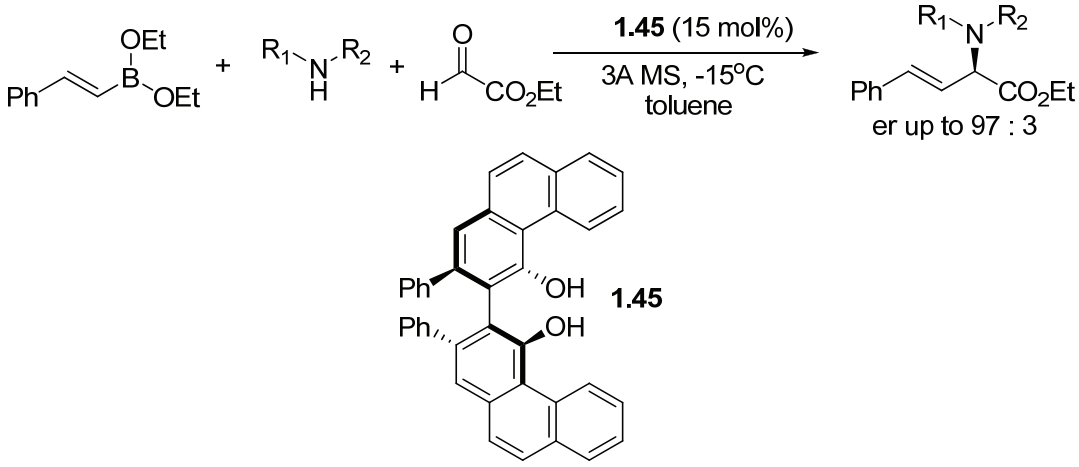
The proposed mechanism is supported by a theoretical study performed by the Goodman group.[71] The activation energy in a binaphthol-catalyzed reaction is favored by 19.7 kcal mol^{-1} compared to an uncatalyzed variant. The conjugate addition occurs via a six-membered transition state. An efficient catalyst turnover can be rationalized by an energetically favorable disproportionation. Similar results were reported on the alkynylation catalyzed by binaphthols.[72]

Later, the Schaus group applied the ligand-exchange concept to asymmetric allylboration of ketones (Scheme 1.19). Promoted by 3,3′-dibromo-BINOLs, both aliphatic and cyclic ketones generated allylic alcohols in good yields and high er's.

Unsaturated ketones gave only 1,2-products. Crotylboration of acetophenone using this method gave moderate yield but excellent dr and er.[73] Subsequent to our report on alkenylation, the Schaus group revealed the use of alkenylboronates for catalytic enantioselective Petasis-Mannich reactions (Scheme 1.20).[18]



Scheme 1.19



Scheme 1.20

In the catalytic allylboration reaction reported by the Schaus group, a Brønsted-acid assisted chiral-Lewis acid type (BLA) catalysis was suggested. Schaus and co-workers suggested that the hydrogen bonding of the isopropyl group activates the chiral diol and hence gives high selectivities. In their proposed transition state, the active allylboronate is resulted from the exchange of one of the two hydroxy groups in the chiral diol (Figure 1.5).[73] However, the latest computational study by the Goodman group does not support this argument. Their calculations suggest a cyclic Lewis-acid activated boronate is the only species that leads to the correct enantiomer.[74] In another study on the catalytic alkenylation of enone performed by Goodman and co-workers, computational results supported the cyclic Lewis-acid transition state proposed by Chong and co-workers (Figure 1.6).[70]

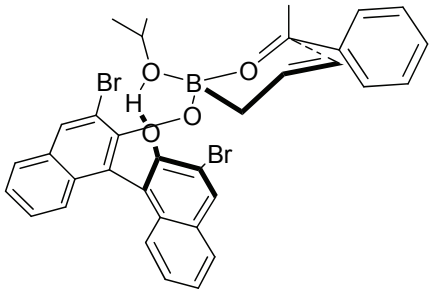


Figure 1.5 Schaus' Model

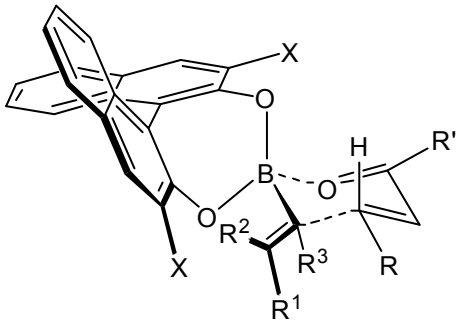
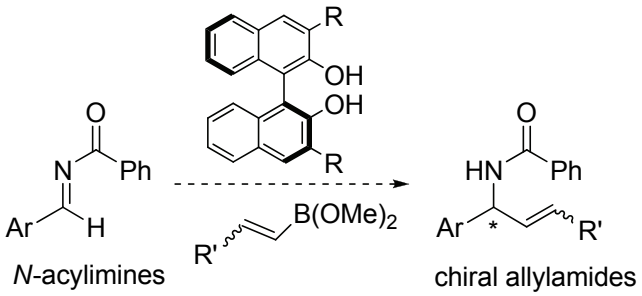


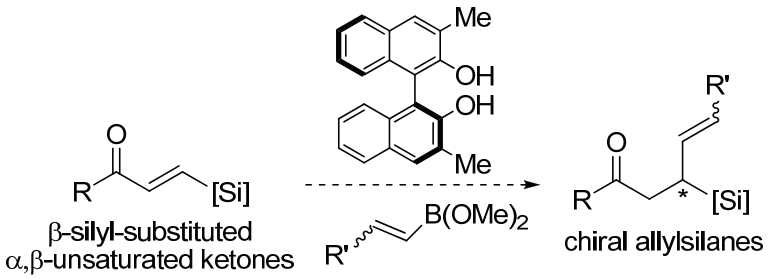
Figure 1.6 Chong's model

1.3 Purpose and scope of this thesis

Our group pioneered the activation of alkenylboronates through ligand exchange of binaphthols. This thesis mainly focuses on expanding the scope of alkenylation to *N*-acylimines and β-silyl-α,β-unsaturated ketones (Scheme 1.21 and 1.22). The resulting products, chiral allylamides and allylsilanes are valuable building blocks in natural product syntheses.



Scheme 1.21



Scheme 1.22

1.4 References:

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Chapter 2. Asymmetric conjugate addition of boronates to *N*-acylimines catalyzed by 3,3′-disubstituted binaphthols

2.1 Introduction

Chiral allylic amines/amides are synthetically valuable building blocks for pursuing biologically active compounds. A number of methods are available to synthesize allylamines, including allylic rearrangements,[1-4] amination of allylic electrophiles,[5-9] C—H activation,[10,11] hydroamination,[12,13] and addition of vinyl nucleophiles to imine derivatives.[14,15] Recently, our group found that chiral allylic amides can also be achieved by binaphthol-catalyzed reactions. The following will discuss some representative methods for preparing allylic amines/amides, as well as the results from our group.

2.2 Methods of synthesizing allylic amines/amides

2.2.1 Enantioselective Overman rearrangements

The Overman rearrangement is generally referred to as a [3,3] sigmatropic rearrangement of trichloroacetimidates. There are numerous palladium catalysts employed for this reaction, including Hayashi's phosphine-oxazoline and bisoxazoline complexes as well as Overman's diamine ligands,[16,17] cyclopalladated ferrocenyl amine catalysts and cyclopalladated ferrocenyl oxazoline catalysts.[18] Unfortunately, most of them do not give synthetically useful yields and enantioselectivities. The breakthrough came when Overman and his co-workers developed the use of cyclopentadienyl-cyclobutadienyl-cobalt palladacycle (COP-X, Figure 2.1). The COP catalysts convert achiral allylic alcohols to chiral allylic trifluoroacetamides in good selectivities. The resulting compounds can be easily transformed to enantioenriched primary amines.

COP-Cl is also able to catalyze the rearrangement of trichloroacetimidates in good yields and excellent stereoselectivities (Table 2.1). Unfortunately, these reactions can only be performed at low concentrations owing to the low solubility of COP-Cl in various solvents.[19] To address this issue, COP-acac and COP-hfacac were devised (Figure 2.1). These modified catalysts enable the rearrangement of trichloroacetimidates to be performed in solvents including CH_2Cl_2, THF, toluene, etc. Higher yields and stereoselectivities could be achieved when compared to COP-Cl.[20]

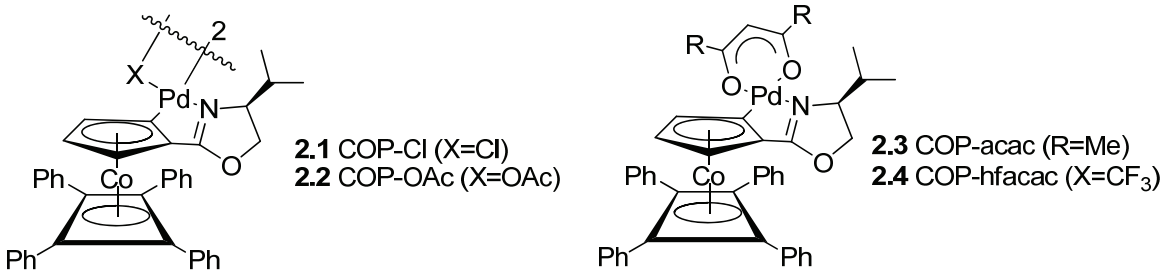
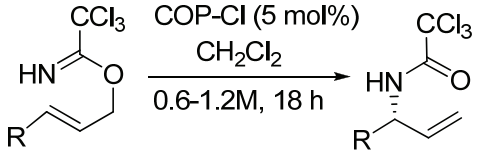
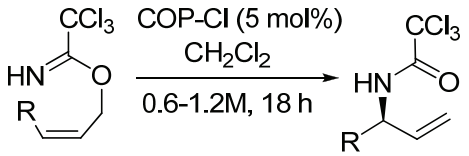


Figure 2.1 COP catalysts



entry	R	temp	yield (%)	ee(%)
1	*n*Pr	38	99	95
2	*i*Bu	38	92	98
3	Me	rt	84	92

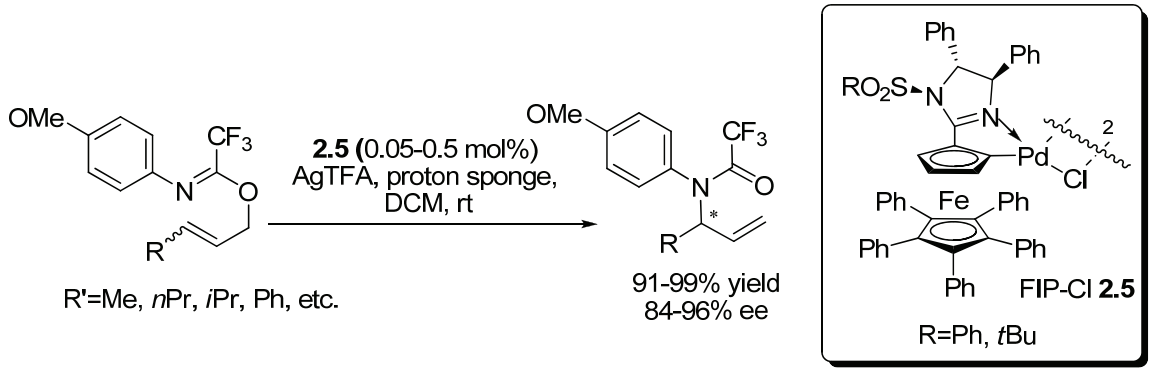
Table 2.1 Rearrangement of *trans*-trichloroimidates catalyzed by COP-Cl



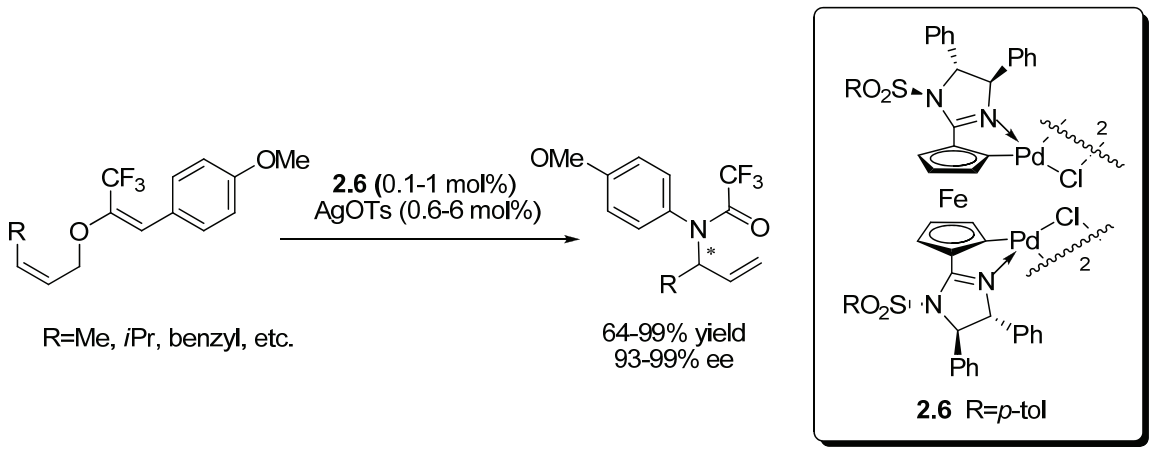
entry	R	temp	yield (%)	ee(%)
1	*n*Pr	38	17	71
2	*i*Bu	38	8	73

Table 2.2 Rearrangement of *cis*-trichloroimidates catalyzed by COP-Cl

The allylic rearrangements catalyzed by COP-Cl require a minimum catalyst loading of 5 mol%. Also, rearrangements of *cis*-imidates gave poor yields (Table 2.2). To improve the synthetic utility of the rearrangement reactions, Peters and co-workers reported ferrocenyl–imidazoline palladacycle catalysts. These highly activated catalysts **2.5** generated products with excellent ee's and enantioselectivities at a loading as low as 0.05% (Scheme 2.1).[21] In a subsequent publication, macrocyclic ferrocenyl–bismidazoline palladacycle dimers **2.6** were developed for the aza-Claisen rearrangement of *cis*-imidates in excellent yields and enantioselectivities (Scheme 2.2).[22]



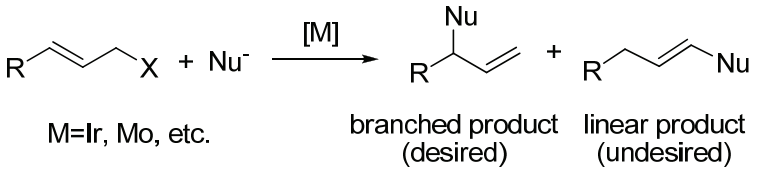
Scheme 2.1



Scheme 2.2

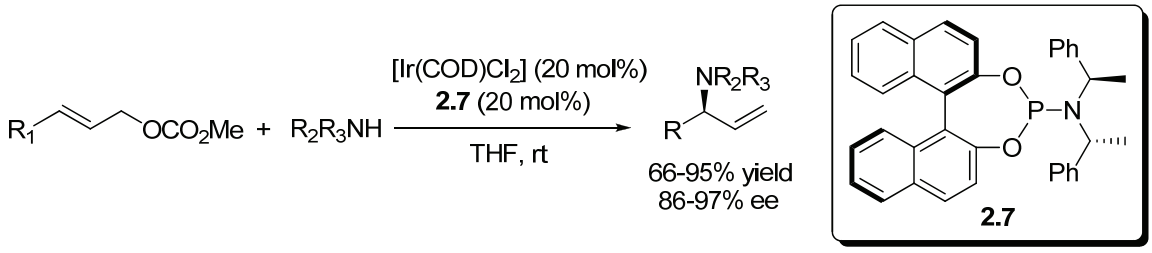
2.2.2 Metal-catalyzed allylic substitutions

Allylic substitutions involving nitrogen-containing nucleophiles are effective ways to access enantioenriched allylic amines. Transition metal complexes involving Ir, Mo and Ru normally prefer the formation of branched products over undesired linear allylic amines (Scheme 2.3).[23]

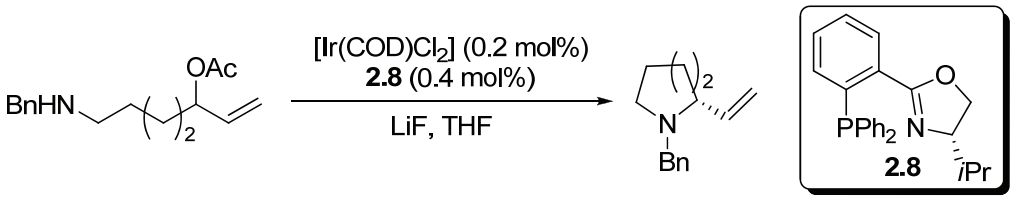


Scheme 2.3

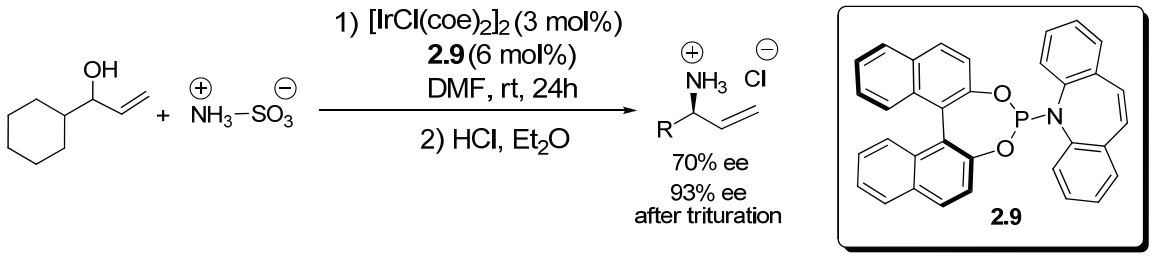
In 2002, Hartwig and co-workers exploited Feringa's phosphoramidite ligand in the iridium-catalyzed enantioselective reaction, affording branched allylic amines in high yields (66-95%) and enantiopurities (86-97% ee) (Scheme 2.4).[8] Later, the Helmchen group reported the use of Ir-complexes in asymmetric intramolecular allylic substitution to furnish cyclic amines in good yields and selectivities (Scheme 2.5).[24,25]



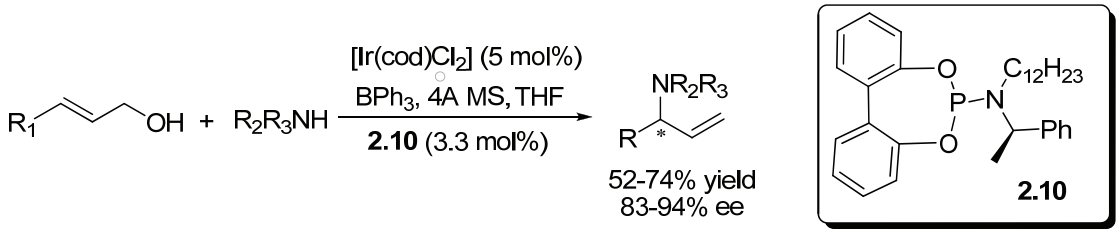
Scheme 2.4



Scheme 2.5



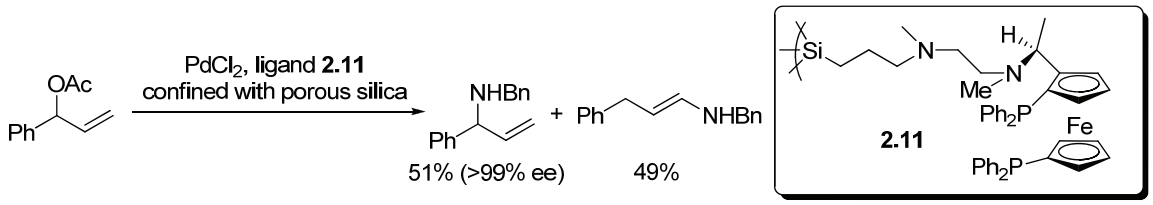
Scheme 2.6



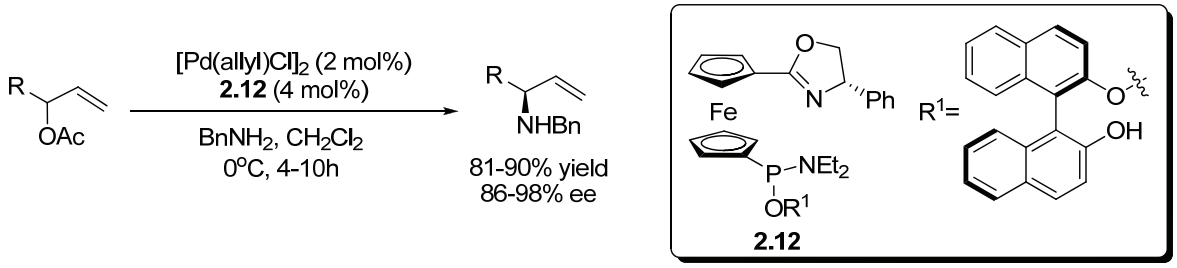
Scheme 2.7

Normally allylic substitution requires the use of allylic esters or carbamates because of their good leaving-group properties. As the hydroxyl group is a poor-leaving group, substitution of an allylic alcohol requires high temperatures. In 2007, the Carreira and Hartwig groups independently reported using allylic alcohols as substrates in asymmetric aminations (Scheme 2.6 and 2.7).[26,27] Both reactions were performed in mild conditions. Carreira's report was the first example to generate allylic primary amines using substitution methods (Scheme 2.6).

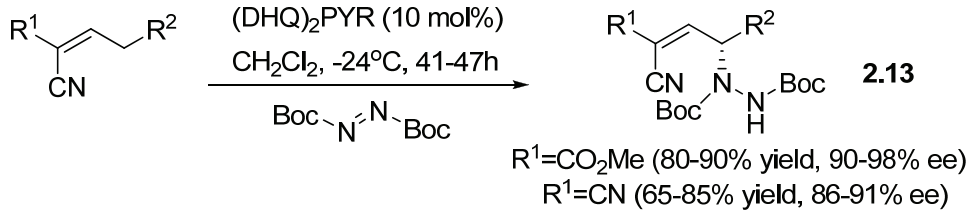
In palladium-catalyzed allylic substitution, formation of the undesired linear products is commonly observed. For instance, the use of palladium chloride and chiral ferrocene-based ligands **2.11** generated the desired amine in only 51% yield, albeit in high ee. The remaining 49% of product was found to be the linear product (Scheme 2.8). Nevertheless, specially designed catalysts allow allylic aminations to take place in high regioselectivities and stereoselectivities.[23] Scheme 2.9 shows an example using a catalyst developed by Dai.[9]



Scheme 2.8



Scheme 2.9



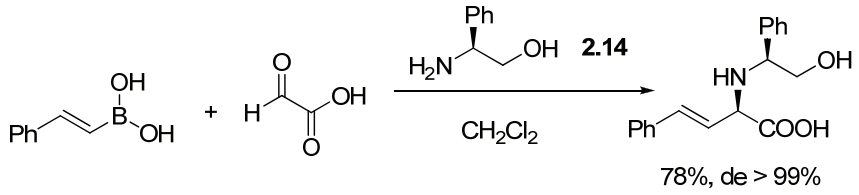
Scheme 2.10

Other than transition metal complexes, asymmetric allylic amination can also be catalyzed by organocatalysts. Jørgensen and co-workers exploited cinchona alkaloids to facilitate deprotonation of electron-poor α,β-unsaturated esters and nitriles, where a chiral ion-pair is formed.[28] Subsequent enantioselective addition of dialkyl azodicarboxylate results in product **2.13**. The reported yields and enantioselectivities are good (Scheme 2.10). Chiral allylic amines can be prepared from **2.13** by acetylation with acetic anhydride followed by reduction with SmI_2.

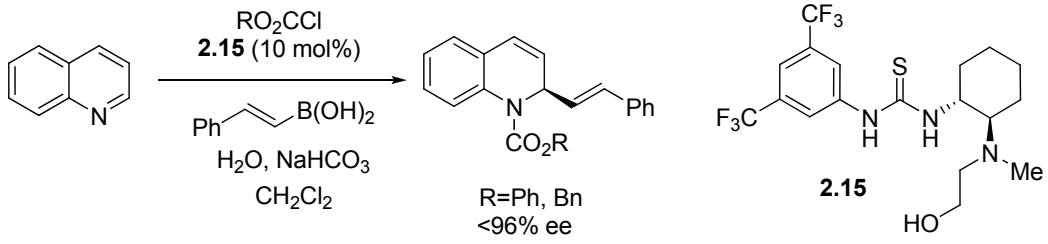
2.2.3 Petasis reactions

In 1997, the Petasis group reported the condensation of carbonyl compounds, amines and aryl/vinyl boronic acid derivatives in preparing unsaturated amino acids.[29] Good yields were observed for a wide range of substrates in the racemic reactions. Excellent diastereoselectivities were observed in using chiral amines,[30] chiral aldehydes[31] and aminoalcohol **2.14** (Scheme 2.11).[29]

While a few variations were reported,[32,33] there was no catalytic asymmetric process until the first enantioselective catalytic Petasis-like reaction revealed by Takemoto and co-workers in 2007 (Scheme 2.12).[32-34]



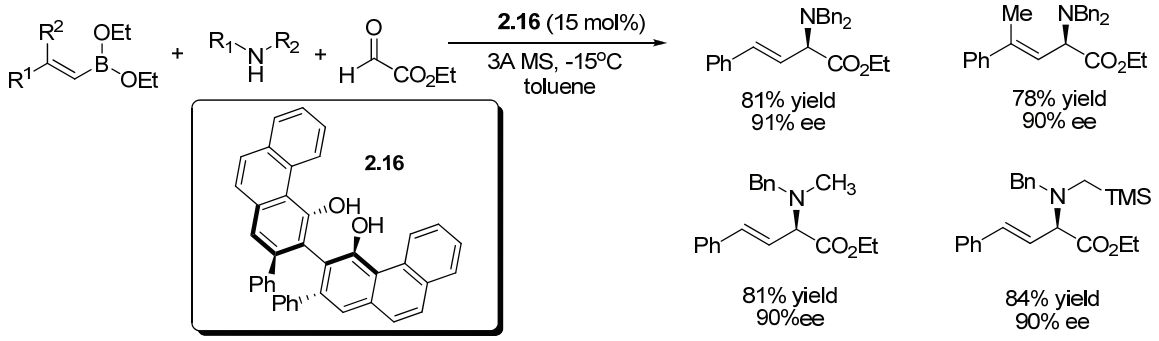
Scheme 2.11



Scheme 2.12

Earlier this year, Schaus and Lou reported the first asymmetric Petasis reaction catalyzed by chiral biphenols.[35] The optimized multicomponent reactions involving alkenylboronates, dibenzylamine and ethyl glyoxylate resulted in products with good ee's

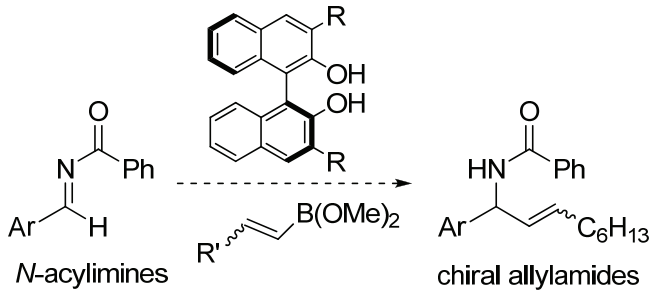
and yields. This protocol can be applied to substrates such as disubstituted alkenylboronates, benzyl- and allylamines. However, less nucleophilic ethyl aniline gave slight lower yields and selectivities (Scheme 2.13).



Scheme 2.13

2.3 Proposal

To complement the existing transition metal-catalyzed reactions, our group developed 1,4-additions of alkenylboronates and alkynylboronates onto enones. These metal-free reactions are catalyzed by 3,3′-binaphthol derivatives. Due to the structural similarity of enones and *N*-acylimines, alkynylation of *N*-acylimines was also developed.[37] Based on this previous work, alkenylboration of *N*-acylimines is proposed (Scheme 2.14).

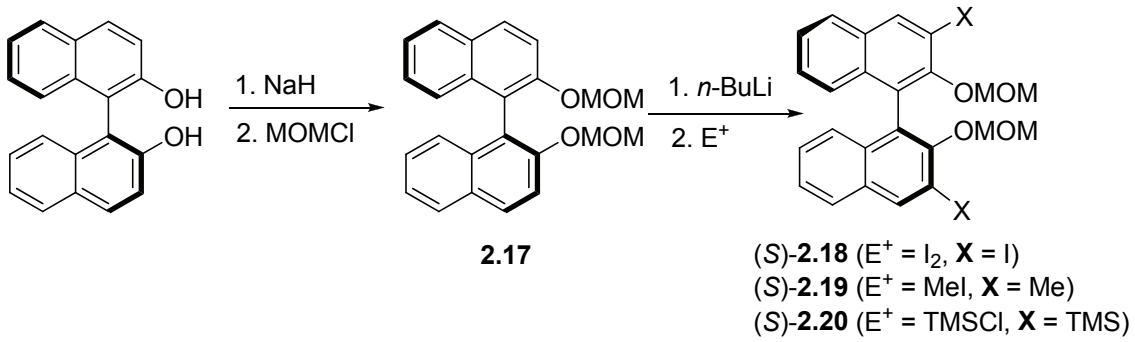


Scheme 2.14

2.4 Results and discussions

2.4.1 Preparation of 3,3′-disubstituted binaphthols[36,37]

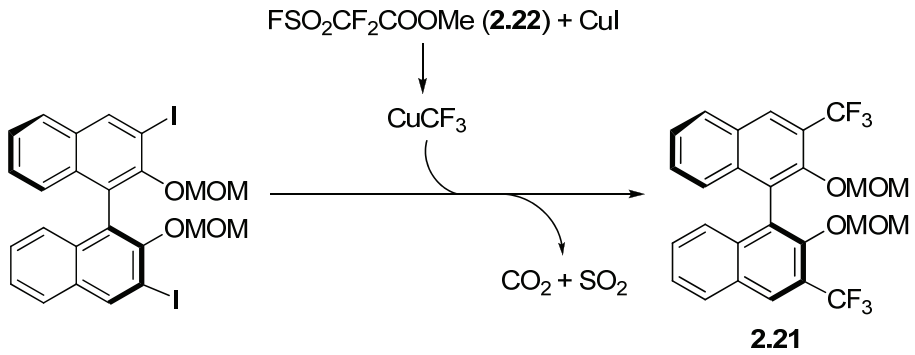
The steric and electronic properties of binaphthol catalysts can be easily fine-tuned by installing various substituents in 3,3′, 6,6′-, 7,7′- and 4,4′-positions.[38] In previous studies on alkenylation and alkynylation of organoboronates catalyzed by binaphthols, modifications at the 3,3′-positions significantly improved yields and selectivities of the reactions.[39-42] 3,3′-Disubstituted BINOLs were easily prepared from the MOM derivatives. **2.17**. o*rtho*-Metalation of **2.17** using *n*-butyllithium forms a dianionic species. Subsequent trapping of the dianion by the appropriate electrophiles afforded **2.18**-**2.20** in good yields (Scheme 2.15).



2.17

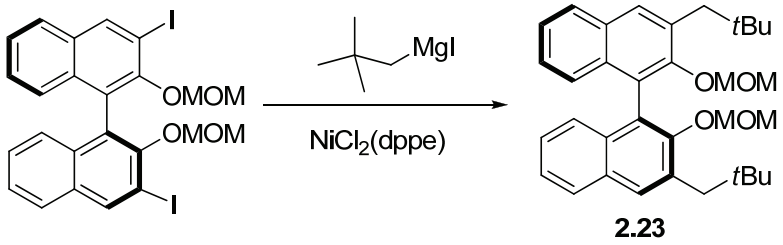
(*S*)-**2.18** ($E^+ = I_2$, **X** = I)
(*S*)-**2.19** (E^+ = MeI, **X** = Me)
(*S*)-**2.20** (E^+ = TMSCl, **X** = TMS)

Scheme 2.15



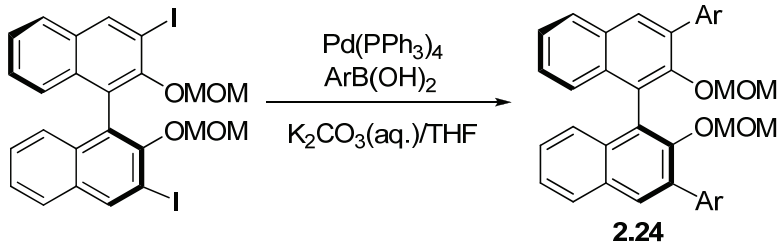
2.21

Scheme 2.16



2.23

Scheme 2.17

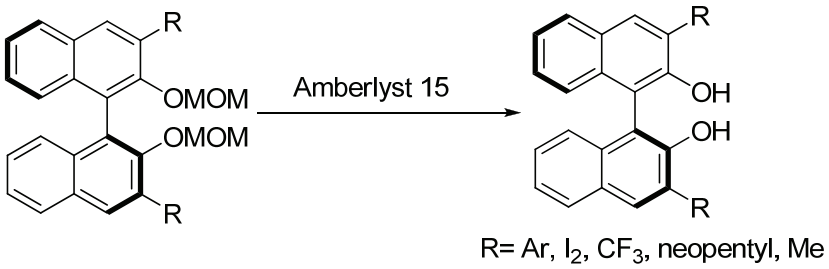


2.24

Scheme 2.18

Diiodo-substituted binaphthyl **2.18** can be further derivatized into CF_3, neopentyl and phenyl-disubstituted variants. The CF_3-disubsituted compound **2.21** was obtained by copper-mediated cross-coupling reaction between compound CuI and methyl fluorosulfonyldifluoroacetate **2.22** (Scheme 2.16).[43] It is believed that $CuCF_3$ is an intermediate in the reaction. The driving force of this reaction includes the formation of carbon dioxide and sulfur dioxide, which readily escape from the reaction. The neopentyl and phenyl groups were installed by nickel-catalyzed Kumada cross-coupling and palladium-catalyzed Suzuki cross-coupling to give **2.23** and **2.24**, respectively (Scheme 2.17 and 2.18).

Removal of the MOM group from derivatives can be accomplished by catalytic amount of Amberlyst 15 with nearly quantitative yields (Scheme 2.19). The exception to this procedure is the bis(trimethylsilyl)-substituted compound, where the desilylation product was obtained in the reaction. After extensive optimizations, pyridinium *p*-toluenesulfonate and methanol was found to be an effective acid catalyst system to remove the MOM without generating the undesired product. No column chromatography is needed for the deprotection. Recently, Feringa and co-workers developed another approach towards bis(trimethylsilyl)-BINOL using 6N HCl to remove the MOM group. In their preparation, column chromatography is required to get the pure chiral diol.[44]

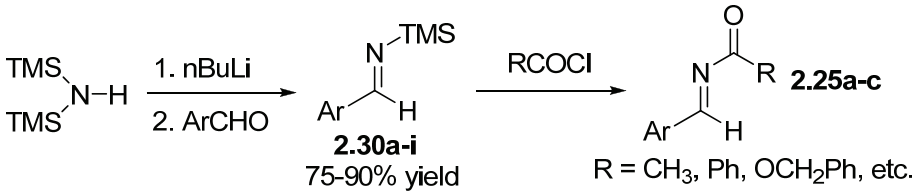


Scheme 2.19

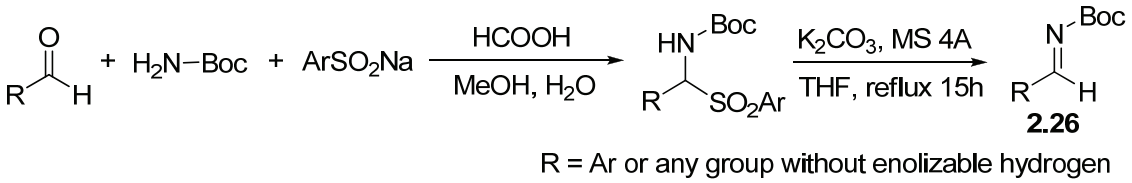
2.4.2 Preparation of *N*-acylimines

Most of the *N*-acylimines **2.25** were synthesized using Kupfer's procedure with slight modifications.[39,45] Acyl chlorides were reacted with *N*-TMS protected imines, which can be easily generated from the corresponding aldehyde (Scheme 2.20). Boc-protected imines were synthesized by elimination of α-phenylsulfonyl *N*-Boc-protected amines (Scheme 2.21).[46,47] Boc and Cbz protected imines were prepared because of the ease of carbamate cleavage to generate the corresponding amines, which could increase the synthetic utility of the methodology. While sulfinimines and tosylimines are commonly used in additions of imines, *N*-acylimines are utilized in this project because of the structural similarity to enones. Meanwhile, its enhanced electrophilicity relative to sulfinimines and tosylimines facilitates the addition of nucleophiles.[57]

N-acylimines, except for Boc-protected imines **2.26**, have to be freshly prepared from the *N*-TMS protected imines and have to be used immediately without further purification. Careful handling is essential in achieving good yields in subsequent alkenylations because *N*-acylimines are very moisture sensitive. Depending on the substituents on the aryl groups, TMS-imines can be stored from a week to a couple of months. TMS-imines with more electron-withdrawing substituents have shorter shelf-lives. The preparation of TMS-protected imines is limited to non-enolizable aldehydes; hence aliphatic *N*-acylimines cannot be made with the same method.[45] As a consequence, only aromatic or *α,β*-unsaturated aldehydes will be used in the preparation of the imines.



Scheme 2.20

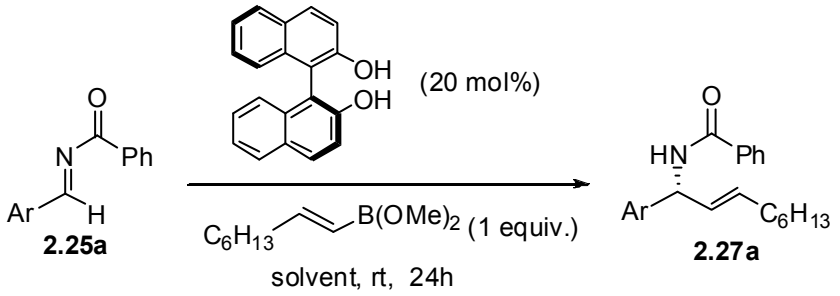


Scheme 2.21

2.4.3 Alkenylation of *N*-acylimines catalyzed by 3,3′-disubstituted binaphthols

2.4.3.1 Solvent screening

We initiated our study with 20 mol% of BINOL and one equivalent of (*E*)-octenylboronate relative to *N*-acylimines. The enantioselectivity of the reaction is relatively insensitive to the choice of solvents (Table 2.3). Methylene chloride gave the best results in terms of yields and stereoselectivities. In particular, in the presence of 4Å powdered molecular sieves, there is a slight increase in yield (entry 1 and 2, table 2.3). The use of 4Å sieves is to remove the methanol generated from the ligand exchange process as well as a small amount of water that might be present in the reaction adventitiously (vide infra). This is consistent with the previous observations by Chong and Wu.[37,41] Hexane does not solvate the binaphthol catalyst well. Hence the observed yield was much lower than with other solvents.



entry	solvent	yield (%)[a]	er[b]
1	**CH_2Cl_2 (with MS 4Å)**	**66**	**96.5 : 3.5**
2	CH_2Cl_2	61	96.8 : 3.2
3	THF	53	96.3 : 3.7
4	hexane	19	90.9 : 9.1
5	Et_2O	43	96.9 : 3.1

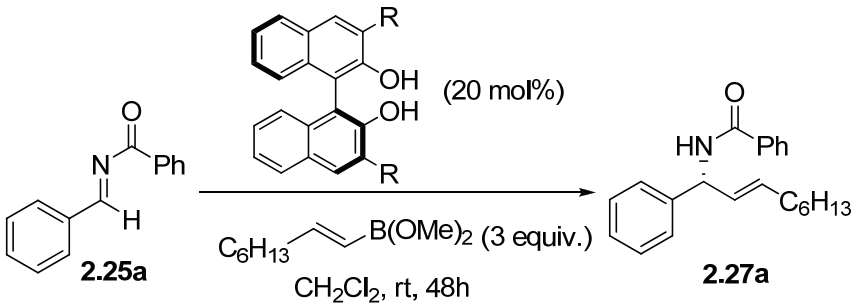
[a]isolated yields after flash chromatography
[b]determined by HPLC using a Chiralcel OD column

Table 2.3 The effect of solvents on alkenylation of *N*-acylimines

2.4.3.2 Ligand screening

Consistent with the previous studies in other binaphthol-catalyzed 1,4-additions of organoboranes, substitution in 3 and 3′ position of the catalyst results in products with higher enantiopurity (Table 2.4). Dimethyl- or dineopentyl-substituted BINOLs gave good yields and excellent stereoselectivities. Catalysts with more electron-withdrawing substituents tend to give lower yields (entry 1 and 3, table 2.4). Interestingly, a strong electron-donating substituent such as trimethylsilyl was found to give lower yields and enantioselectivity. Dimethyl-substituted BINOL was the ligand of choice for this reaction as it is easier to synthesize compared to the neopentyl counterpart.

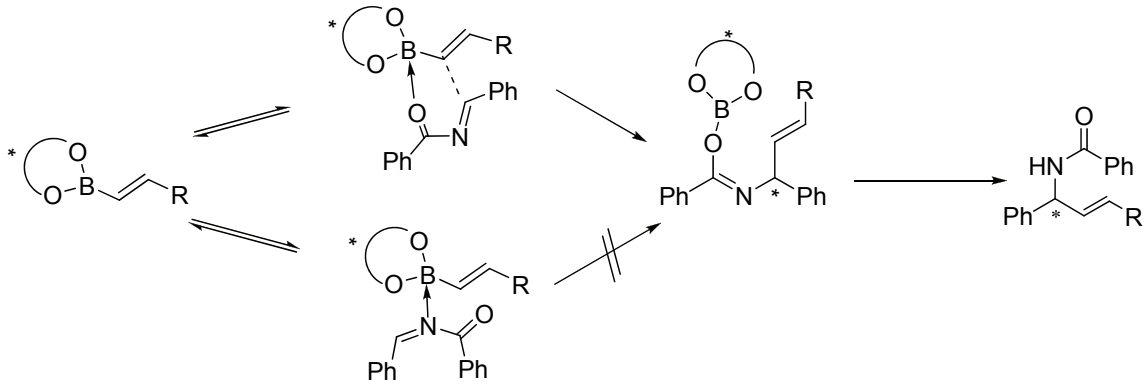
A possible rationale of low yields observed with electron-withdrawing ligands is the coordination of the nitrogen atom of the *N*-acylimines with the electron deficient boron atom in the boronate. This coordination prevents 1,4-addition, which is an essential step in generating the product (Scheme 2.22). For binaphthols with less electron-withdrawing 3 and 3′ substituents, the tendency for the nitrogen atom to coordinate with the slightly more electron-rich boron is lower. A similar ligand effect on yields was noted in alkynylation of *N*-acylimines.[39] However, the reason for TMS-substituted binaphthols giving such poor results is unknown.



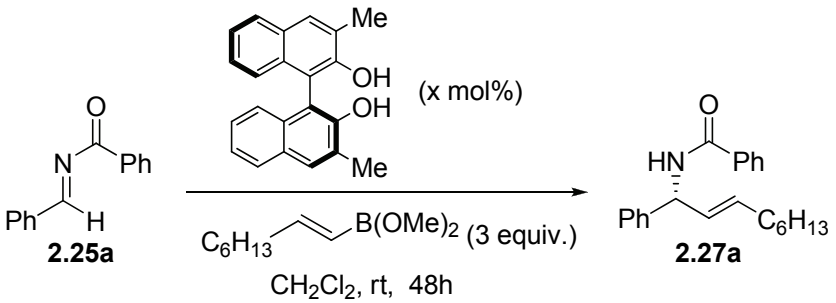
entry	R	yield (%)[a]	er[b]
1	I	59	99.2 : 0.8
2	**Me**	**74**	**99.3 : 0.7**
3	CF_3	57	99.1 : 0.9
4	Ph	59	94.9 : 5.1
5	TMS	52	77.7 : 22.3
6	Neo-pentyl (*R*)	75	0.7 : 99.3

[a]isolated yields after flash chromatography
[b]determined by HPLC using a Chiralcel OD column

Table 2.4 Effect of substituents on 3 and 3′ positions of the binaphthol catalysts



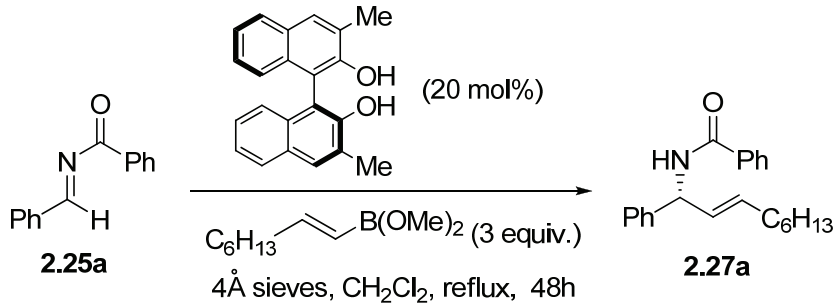
Scheme 2.22



entry	catalyst loading (x mol%)	yield (%)[a]	er[b]
1	5	21	79.1 : 20.9
2	10	28	87.4 : 12.6
3	20	75	99.3 : 0.7

[a]isolated yields after flash chromatography
[b]determined by HPLC using a Chiralcel OD column

Table 2.5 Effect of catalyst loading on alkenylboration of *N*-acylimines



trial no.	yield (%)[a]
1	69
2	74
3	75

[a]isolated yields after flash chromatography

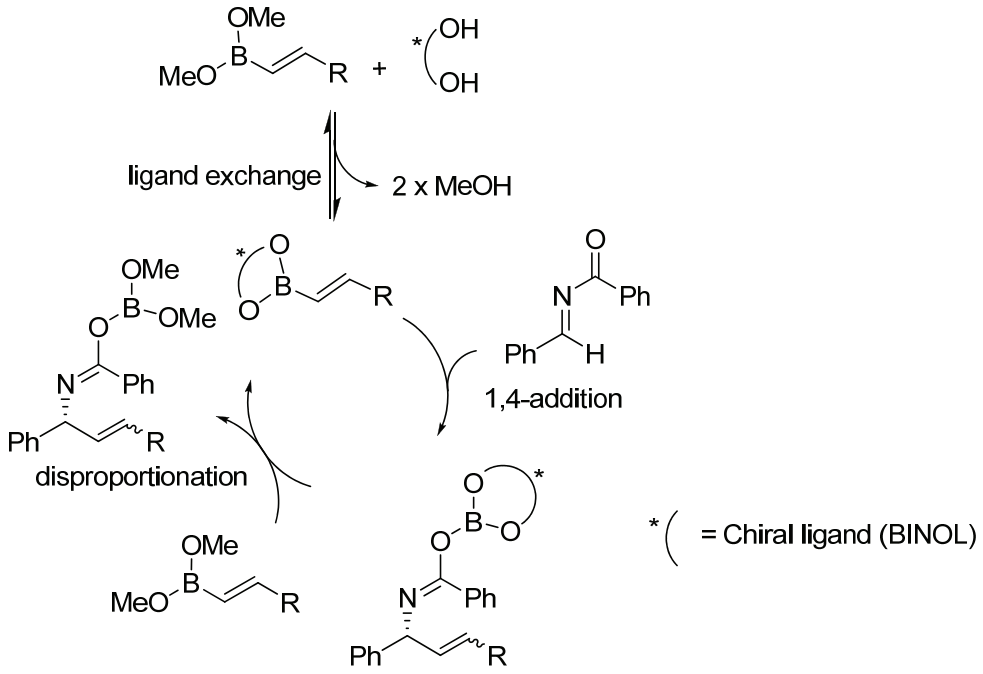
Table 2.6 Reproducibility of the alkenylation of N-acylimines

As for the catalyst loadings, 20 mol% of the catalyst offered the best yield and stereoselectivity. Reduction of loadings to 10 mol% resulted in dramatic decrease in yield and a slight decrease in er. Yields can be improved and be kept consistent when using Schlenk tubes instead of round-bottomed flasks as reaction vessels. In preparing *N*-acylimines, benzoyl chloride should be freshly distilled and added to the TMS-imines to ensure consistency in results. Under the optimized conditions of refluxing *N*-acylimines with three equivalents of boronates, 20 mol% of dimethyl-substituted binaphthol catalyst in the presence of sieves for 48 hours, the yields became rather reproducible (Table 2.6).

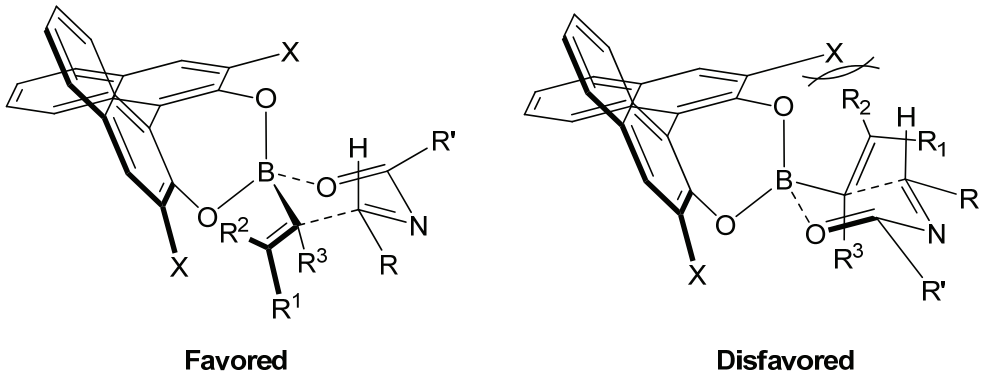
2.4.3.3 Proposed reaction mechanism and models

The proposed mechanism is similar to the one mentioned in Chapter 1. The alkenylboronate first undergoes ligand exchange with the chiral binaphthols, followed by an addition/disproportionation sequence (Scheme 2.23). Two diastereomeric transition states are formed in the 1,4-addition step, in which one of them is disfavored because of the steric interaction of the substrates with the 3 position of the BINOL catalyst. The favored pathway generates the product (Scheme 2.24).

The ligand exchange step gives off methanol as by-product, which may lower the yield of alkenylboration through methanolysis of *N*-acylimines. Using 4Å sieves can remove methanol from the solution phase and hence reduce the chance of methanolysis.



Scheme 2.23

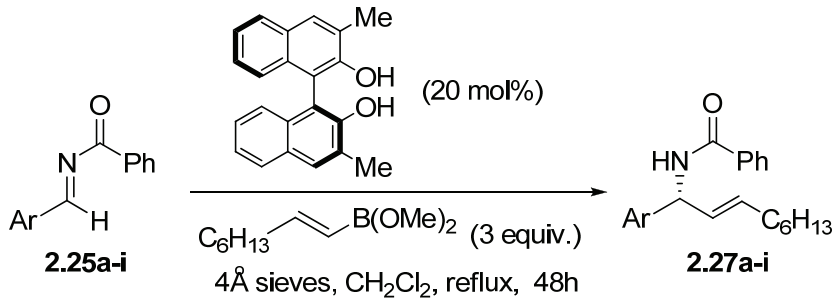


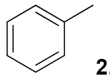
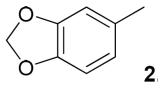
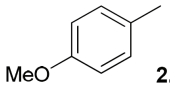
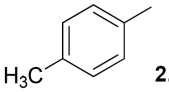
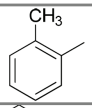
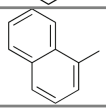
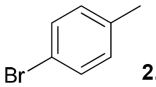
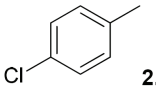
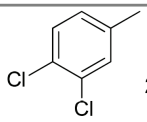
Scheme 2.24

2.4.4.4 Scope and limitations

A variety of *N*-acylimines were studied. Reactions involving *N*-benzoylimines all achieved excellent stereoselectivities. The imines with electron-donating groups on the β-aryl group gave higher yields than their counterparts with electron-withdrawing groups. (entry 1 & 2 vs. entry 7 & 8 in table 2.7) It is speculated that even though an electron-withdrawing group increases the reactivity of *N*-acylimines, these electron-deficient imines are more susceptible to methanolysis. If the increase in rate of methanolysis is higher than that for alkenylation, then a lower yields results. Most *N*-acylimines gave excellent stereoselectivities, regardless of the electron-donating abilities of the substituents (er>98:2). However, *p*-CH_3- and *p*-Br-substituted *N*-acylimines gave unexpectedly low er's, even after repeated trials.

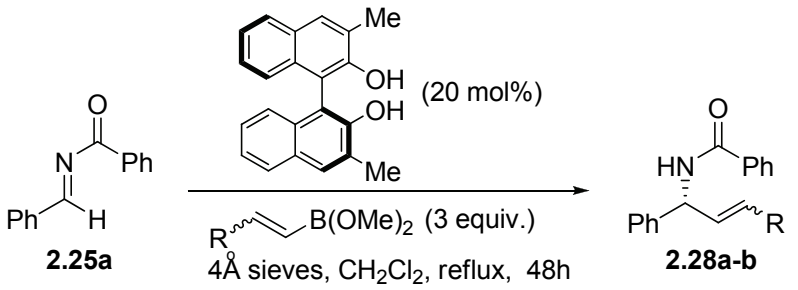
This reaction also proceeded smoothly on a gram-scale. Unlike small scale reactions, the large scale reactions tend to give a distinct purple color (instead of yellow) during alkenylation. However, the color change does not seem to affect the reaction.

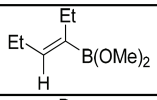
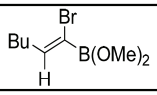
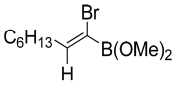


Ar	yield (%)[a]	er[b]
 2.25a	74	99.3 : 0.7
 2.25b	82	98.8 : 1.2
 2.25c	76	98.3 : 1.7
 2.25d	71	90.1 : 9.9
 2.25e	77	>99.5 : 0.5
 2.25f	64	98.7 : 1.3
 2.25g	65	96.4 : 3.6
 2.25h	48	99.2 : 0.8
 2.25i	46	99.5 : 0.5

[a]isolated yields after flash chromatography
[b]determined by HPLC using a Chiralcel OD column

Table 2.7 Effect of alkenylation of various substituents on the β-aryl group



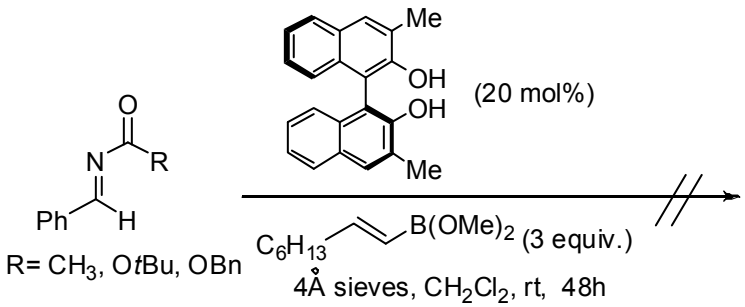
entry	boronate	yield (%) [a]	er [b]
1		87	77 : 23
2		31	>99.5 : 0.5
3		No desired product found	--

[a]isolated yields after flash chromatography
[b]determined by HPLC using a Chiralcel OD column

Table 2.8 Alkenylation of *N*-acylimines using different boronates

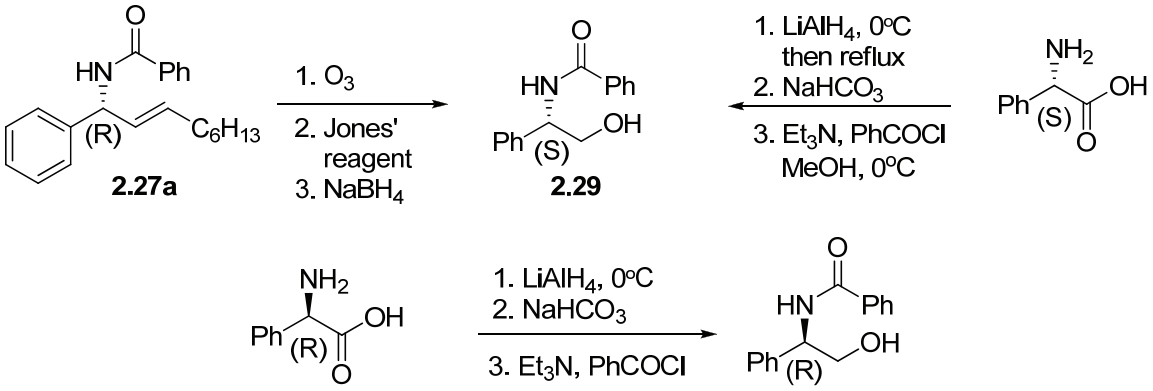
A diethylsubstituted boronate gave higher yields but lower er than the (*E*)-octenylboronate, probably because the former one is more electron rich and hence increased reactivity (entry 1 & 2, table 2.8). Unexpectedly, no desired product was found for a bromo-substituted octenylboronate (entry 3, table 2.8).

To improve the synthetic utility of the reactions, we explored other substituents on the carbonyl group, such as methyl, OBn and O*t*Bu. However, no product was isolated (Scheme 2.25).



Scheme 2.25

2.5 Correlation of absolute configurations



Scheme 2.26

To establish the absolute configurations, the alkenylation product **2.27a** was treated with ozone and worked up oxidatively to yield a carboxylic acid, followed by reduction using sodium borohydride to yield an alcohol **2.29′**. At the same time, the (*R*) and (*S*) enantiomers of compound **2.29** were synthesized separately from enantiomerically pure phenylglycine. The pair of enantiomers served as references on HPLC to find out the retention time of each enantiomer. The alcohol **2.29'** made from **2.27a** was subsequently subjected to HPLC analysis. After comparing the retention time of the reference enantiomers **2.29** and that of **2.29'**, it was determined that the alkenylation product has an (*R*) configuration.

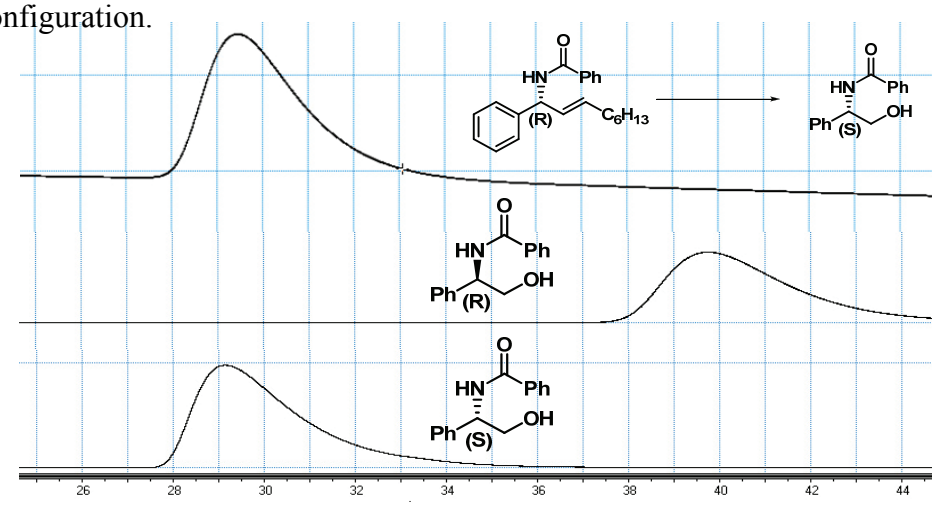


Figure 2.2 HPLC chromatogram in determining the absolute configuration of the alkenylation product

2.6 Conclusions

The alkenylation of *N*-acylimines was found to be catalyzed with 3,3′-disubstituted binaphthols in good yields and high selectivities. This is one of the few methods of synthesizing allylic amides without involving any transition metal catalysts.

2.7 Experimental

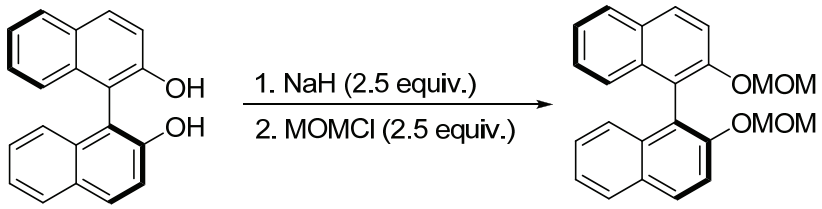
General Experimental

IR spectra were recorded on a Bomem MB-100 infrared spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 MHz and 75 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.

All reactions were performed using flame-dried Schlenk tubes under argon atmosphere. 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. $CHCl_3$ was freshly distilled from P_2O_5. Benzaldehyde was purified by passing through a basic alumina column. Benzoyl chloride was distilled under reduced pressure before use. 4Å Molecular sieves (powdered) were activated immediately prior to use by flame drying under vacuum. Chiral 3,3′-disubstituted binaphthols and alkenylboronates were synthesized using procedures from previous reports.[48,49]

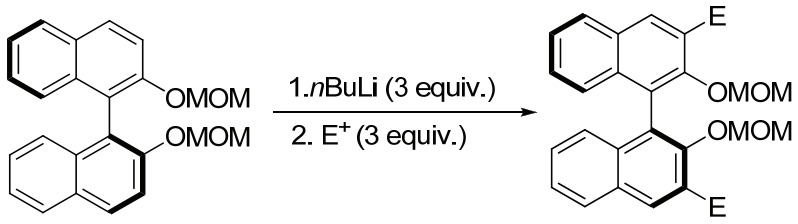
(*S*)-1,1′-Bi-2-naphthol was purchased from Wilmington Pharmatech Company. Methyl fluorosulfonyldifluoroacetate was purchased from SynQuest Laboratories and used without further purification. Unless otherwise noted, other chemicals were purchased from Aldrich Chemical Company. Chloromethyl methyl ether (MOMCl) was synthesized using a procedure established by Chong and Shen.[50]

Preparation of (±)- and (*S*)-2,2′-Bis(methoxymethoxy)-1,1′-binaphthyl **(2.17)**



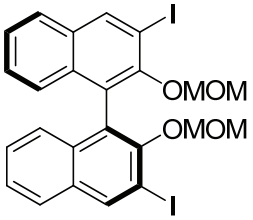
The preparation followed literature procedures with some modifications.[51] NaH (2.92 g, 60% in oil, 73.0 mmol) was mixed in dry THF (150 mL) in a 500 mL round-bottomed flask at 0 ^{o}C under an argon atmosphere. To the stirred mixture was added a solution of (±)-2,2′-dihydroxy-1,1′-binaphthyl (9.50 g, 33.2 mmol) in THF (50 mL) from 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 (±)-**2.17** in quantitative yield. ^{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 (CAr), 121.3 (C_{Ar}), 117.3 (C_{Ar}), 95.2 (OCH_2O), 55.7 (OCH_3); MS *m/e* (relative intensity): 374 (M^+, 100), 298 (90), 270 (71). (*S*)-2,2′-Dihydroxy-1,1′-binaphthyl was used to afford (*S*)-**2.17** in quantitative yield. The sample showed $[\alpha]_D^{25}$ = -94.0 (c = 1.0, THF).

General Procedure A: Preparation of 3,3′-Disubstituted-2,2′-bis(methoxymethoxy) -1,1′-binaphthyls (2.18-2.20)



The preparation of 3,3′-disubstituted binaphthyl compounds followed literature procedures with some modifications.[51] (±)- or (*S*)-2,2′-Bis(methoxymethoxy)-1,1′-binaphthyl (**2.17)** (1.0 equiv.) was dissolved in dry Et_2O (17 mL/1 mmol of **2.17**) in a round-bottomed flask under an argon atmosphere. To the stirred mixture, was added *n*-BuLi (3.0 equiv.) at room temperature by syringe injection. After 3 hours, THF (11 mL/1 mmol of **2.17**) was injected into the flask and then the mixture was stirred for 1 hour. The flask was cooled in an ice water bath for 5 minutes and 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 purification by column chromatography and recrystallization gave the product.

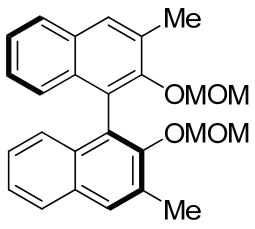
Preparation of (±)- and (*S*)-3,3′-Diiodo-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.18**)



(±)-2,2′-Bis(methoxymethoxy)-1,1′-binaphthyl (**2.18**) (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 resulting mixture was then stirred for 15 minutes, followed by the addition of $Na_2S_2O_3$. The mixture was stirred overnight for

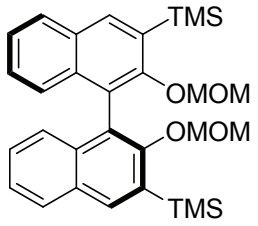
convenience. The crude product was extracted with ether. The solvent was then evaporated. The resulting mixture was dissolved with minimal amount of THF and purified by column chromatography (gradual elution using EtOAc/hexanes from 1/15 to 1/12.5, crude material/silica gel: 1/60 by weight) and crystallized from CH_2Cl_2/hexanes to give a white crystalline product (**2.18**) (9.60 g) in 89% yield. ^{1}H 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), 549 (100), 239 (46). The *S* enantiomer showed $[\alpha]_D^{25}$ +5.2 (c = 1.0, THF).

Preparation of (*S*)-3,3′-Dimethyl-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.19**)



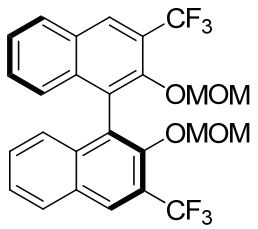
In a well-ventilated fumehood, (*S*)-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl [(*S*)-**2.13**] (2.0 g, 5.34 mmol) was treated with *n*-BuLi (10.0 mL of a 1.6 M solution in hexane, 16.0 mmol) at room temperature and the resulting mixture was quenched with iodomethane (1.0 mL, 16.0 mmol). The crude product was evaporated, dissolved in minimal amount of THF and then purified by column chromatography (EtOAc/hexanes: 1/12.5, crude material/silica gel: 1/60 by weight) and crystallized from CH_2Cl_2/hexanes to give a white crystalline product (*S*)-**2.16** (2.1 g) in 94% yield. ^{1}H 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); 13C 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(OCH_2O), 56.4 (OCH_3), 17.8 ($ArCH_3$); MS *m/e* (relative intensity): 402 (M^+, 30), 326 (100), 297 (50) . The sample showed $[\alpha]_D^{25}$ +84.7 (c = 1.0, THF).

Preparation of (*S*)-2,2′-Bis(methoxymethoxy)-3,3′-bis(trimethylsilyl)-1,1′-binaphthyl (**2.20**)[47]



(*S*)-2,2′-Bis(methoxymethoxy)-1,1′-binaphthyl [(*S*)-**2.17**] (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 a very pale yellow product (*S*)-**2.20** (2.80 g) in 97% 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). ^{13}C NMR ($CDCl_3$): δ158.0, 135.5, 134.3, 130.2, 128.2, 127.0, 126.0, 124.5, 122.3, 97.7, 56.6, -0.4.

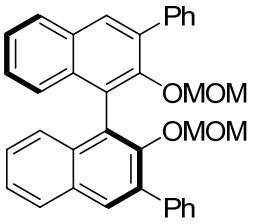
Preparation of (*S*)-3,3′-Bis(trifluoromethyl)-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.21**)



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 (*S*)-3,3′-diiodo-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.18**) (2.0 g, 3.19 mmol) in DMF (40 mL) was stirred under an argon atmosphere for 6 hours at 70 ^{o}C. 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.

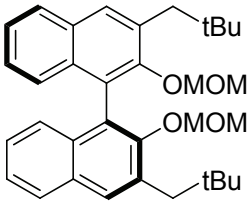
Purification was done by column chromatography (EtOAc/hexanes: 1/20) to give pure product **2.21** (91%). ^{1}H NMR ($CDCl_3$): δ 8.22-8.32 (H_{Ar}, 2H, m), 7.85-7.98 (H_{Ar}, 2H, m), 7.25-7.55 (H_{Ar}, 4H, m), 7.08-7.25 (H_{Ar}, 2H, m), 4.68 (OCH_2O, 2H, d, J = 5.5 Hz), 4.44 (OCH_2O, 2H, d, J = 5.5 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-C_{Ar}, q, J = 30.4 Hz), 123.6 (CF_3, q, J=272.7 Hz), 99.7 (OCH_2O), 56.2 (OCH_3); The sample showed $[\alpha]_D^{25}$ +57.0 (c = 1.0, THF).

Preparation of (*S*)-3,3′-Diphenyl-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.24**)



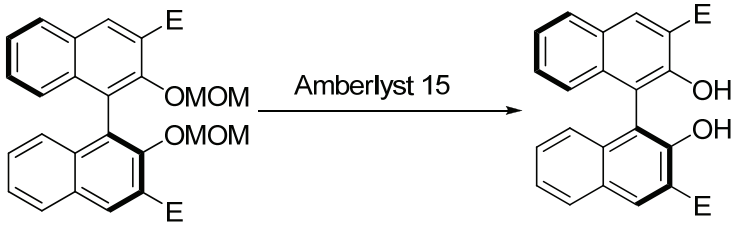
(*S*)-3,3′-Diiodo-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.18**) (1.0 equiv.) and $Pd(PPh_3)_4$ (10 mol%) were mixed in THF or DME in a round-bottomed flask at room temperature under an argon atmosphere. To the mixture, with stirring, were added phenylboronic acid (2.5-3.5 equiv.) and 2 M aqueous degassed K_2CO_3 (or Na_2CO_3) solution. The resulting mixture was stirred and heated to reflux for 24-48 hours (monitored by TLC), 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. Purification was carried out by column chromatography (EtOAc/hexanes: 1/10) to give a foamy product (*S*)-**2.20** (3.55 g) in 93% yield. ^{1}H NMR ($CDCl_3$): δ7.65-8.05 (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 ($CDCl_3$): δ139.0 (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 (OCH_2O), 55.8 (OCH_3).

Preparation of (*S*)-3,3′-Di-neopentyl-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.23**)



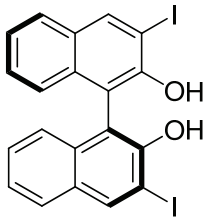
This compound was synthesized by Hendel and Chong.[52] Neopentyl iodide (3.67 g, 18.53 mmol, 11.6 equiv.) was added *via* syringe over 2 hours to Mg turnings (0.26 g, 10.9 mmol, 6.8 equiv.) in 20 mL of refluxing diethyl ether. After the addition, the mixture was stirred at room temperature for 1.5 hours. The resulting solution was transferred *via* cannula into a mixture of $NiCl_2$(dppe) (6.1 mg) and (*S*)-3,3′-diiodo-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl **2.18** (1.0 g, 1.6 mmol, 1.0 equiv.) in 20 mL of Et_2O 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 10% aqueous 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 solid in 85% yield. ^1H NMR ($CDCl_3$): δ7.81 (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 (CH_2t-Bu, 2H, d, *J* = 12.8 Hz), 3.01 (OCH_3, 6 H, s), 2.66 (CH_2t-Bu, 2H, d, *J* = 12.8 Hz), 0.99 (-CH_3, 18H, s).

General Procedure B: Preparation of 3,3′-Disubstituted-2,2′-dihydroxy-1,1′-binaphthyls (2.18a-2.24a)



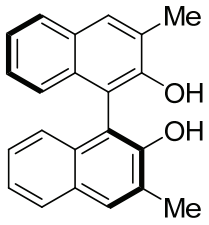
A mixture of 3,3′-disubstituted-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (2.0 mmol) and Amberlyst 15 resin (1.0 g) in THF/MeOH (1:1) was stirred and heated to reflux under an argon atmosphere for 15 hours, then cooled to room temperature. The resin was removed by filtration and the filtrate was concentrated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

Preparation of (*S*)-3,3′-Diiodo-2,2′-dihydroxy-1,1′-binaphthyl (**2.18a**)



(*S*)-3,3′-Diiodo-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.18**) (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 B. Purification was carried out by column chromatography (EtOAc/hexanes: 1/10), and by crystallization (EtOAc/hexanes) to afford a light yellow crystalline product (*S*)-**2.18a** (96%). ^{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 ($CDCl_3$): δ152.0, 140.4, 133.4, 130.7, 128.0, 127.3, 126.8, 125.2, 124.8, 124.4; The sample showed $[\alpha]_D^{25}$ -100.7 (c = 1.0, THF).

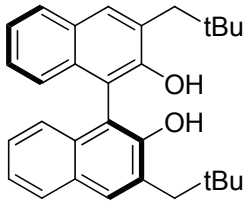
Preparation of (*S*)-3,3′-Dimethyl-2,2′-dihydroxy-1,1′-binaphthyls (**2.19a**)



(*S*)-3,3′-Dimethyl-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.19**) (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 B. Purification was carried out by column chromatography (EtOAc/hexanes: 1/10), and by crystallization (CH_2Cl_2/hexanes) to afford a slightly yellow crystalline product (*S*)-**2** (96%)**.**

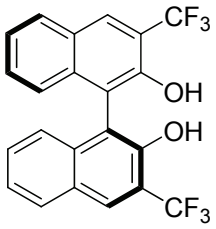
^{1}H NMR, and ^{13}C NMR were identical with the literature.[53]

Preparation of (*S*)-2,2′-Dihydroxy-3,3′-di-neopentyl-1,1′-binaphthyl (**2.23a**)



A mixture of (*S*)-**2.23** (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 a yellow foam (quantitative yield). ^{1}H NMR ($CDCl_3$): δ7.84 (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 ($CDCl_3$): δ152.5 (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 (CH_2*t*-Bu), 32.9 (CMe_3), 29.6 (CH_3). MS *m/e* (relative intensity): 627 (M^+, 1), 270 (100), 269 (30). The sample showed $[\alpha]_D^{25}$ +110 (c = 1.1, THF).

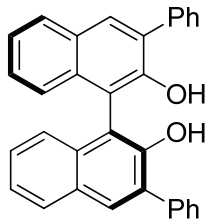
Preparation of (*S*)-3,3′-Bis(trifluoromethyl)-2,2′-dihydroxy-1,1′-binaphthyl (**2.21a**)



(*S*)-3,3′-Bis(trifluoromethyl)-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (**2.21**) (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 B. Purification was carried out by column chromatography (EtOAc/hexanes: 1:10), and by crystallization (CH_2Cl_2/hexanes) to afford a white crystalline product (*S*)-**2.21a** (94%). ^{1}H NMR ($CDCl_3$): δ8.30-8.48 (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,

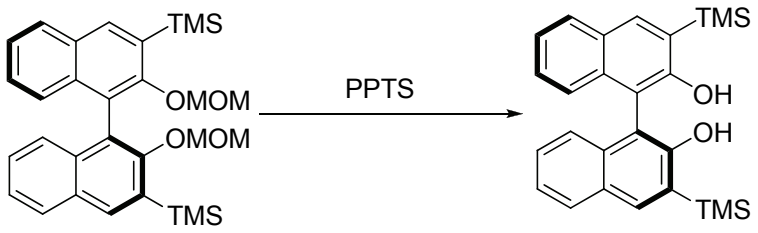
123.9, 123.3 (CF_3, q, J = 272.2 Hz), 118.9 (q, J = 30.9 Hz), 112.2; The sample showed $[\alpha]_D^{25}$ -100.3 (c = 1.0, THF).

Preparation of (*S*)-3,3′-Diphenyl-2,2′-dihydroxy-1,1′-binaphthyl (**2.24a**)



(*S*)-3,3′-Diphenyl-2,2′-bis(methoxymethoxy)-1,1′-binaphthol (**2.24**) (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 B. Purification was carried out by column chromatography (EtOAc/hexanes: 1/10), followed by crystallization (CH_2Cl_2/hexanes) to afford a white crystalline product (*S*)-**2.24a** (91%). ^{1}H NMR, ^{13}C NMR were identical to that of (±)-(**2.24a**) in the literature;[54] the sample showed $[\alpha]_D^{25}$ -135.2 (c = 1.0, THF).

Preparation of (*S*)-3,3′-bis(trimethylsilyl)-2,2′-dihydroxy-1,1′-binaphthyl

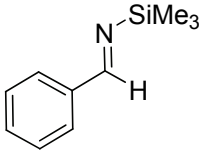


(*S*)-2,2′-Bis(methoxymethoxy)-3,3′-bis(trimethylsilyl)-1,1′-binaphthyl (1 g, 1.93 mmol) and PPTS (0.1 g, 0.4 mmol) was stirred at reflux in MeOH for 20 hours. A constant monitor by TLC is recommended to maximize the yield. Recrystallization gave the pure product in 87% yield. ^{1}H NMR ($CDCl_3$): δ8.07 (s, 2H), 7.89 (d, J = 7.9 Hz, 2H), 7.23-7.38 (m, 4H), 7.10 (d, J = 8.2 Hz, 2H), 5.22 (s, 2H), 0.41 (s, 18H).

Preparation of *N*-trimethylsilyl arylaldimines

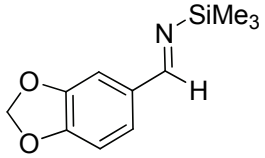
The preparation is modified from the preparation by Chong and Wu.[37] A 2-necked round-bottomed flask was equipped with a distillation apparatus and an addition funnel. It was charged with 4.59 mL (28.4 mmol) of 1,1,1,3,3,3-hexamethyldisilazane (HMDS), followed by the slow addition of 16.1 mL (25.8 mmol) of a 1.6 M hexane solution of *n*-butyllithium over a 5-min period at 0 ^{o}C. Solvents were removed *in vacuo* until a very small amount white precipitate appeared. The resulting suspension was cooled in an ice bath. Benzaldehyde (2.74 g, 25.8 mmol) was added over a 10-min period. Fractional distillation (0.25 torr, 50-60 ^{o}C) of the resulting solution gave the imine as a pale yellow liquid. *To improve the shelf-life of TMS-imines, it is strongly recommended to synthesize the imines on relatively dry days.*

Preparation of *N*-trimethylsilyl benzaldimine (**2.30a**)



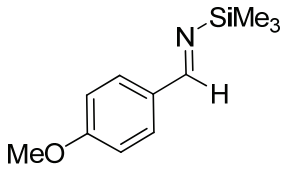
74% yield; ^{1}H NMR ($CDCl_3$): δ8.97 (1H, s), 7.77-7.79 (H_{Ar}, 2H, m), 7.41-7.43 (H_{Ar}, 3H, m), 0.25 (9H, s); ^{13}C NMR ($CDCl_3$): δ168.4, 138.7, 131.1, 128.4, 128.3, -1.3.

Preparation of *N*-trimethylsilyl piperonaldimine (**2.30b**)



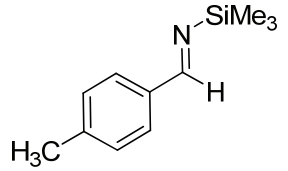
52% yield; ^{1}H NMR ($CDCl_3$): δ8.81 (1H, s), 7.38 (H_{Ar}, 1H, d, *J*=1.2 Hz), 7.19 (H_{Ar}, 1H, d, *J*=7.9Hz), 6.82 (H_{Ar}, 1H, d, *J*=7.9 Hz), 5.96 (2H, s), 0.2 (9H, s); ^{13}C NMR ($CDCl_3$): δ167.1, 150.3, 147.8, 134.1, 125.3, 107.6, 100.7, -1.2.

Preparation of *N*-trimethylsilyl anisaldimine (**2.30c**)



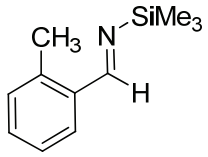
79% yield; ^{1}H NMR ($CDCl_3$): δ8.89 (1H, s), 7.75-7.72 (H_{Ar}, 2H, d, *J*=8.6 Hz), 6.93-6.91 (H_{Ar}, 2H, d, *J*=8.7 Hz), 3.82 (3H, s), 0.25 (9H, s); ^{13}C NMR ($CDCl_3$): δ167.6, 162.1, 132.1, 130.0, 113.8, 55.2, 0.5;

Preparation of *p*-methyl *N*-trimethylsilyl benzaldimine (**2.30d**)



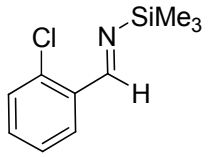
88% yield; ^{1}H NMR ($CDCl_3$): δ8.96 (1H, s), 7.71 (H_{Ar}, 2H, d, *J*=7.8 Hz), 7.24 (H_{Ar}, 2H, d, *J*=7.8 Hz), 2.39 (3H, s), 0.27 (9H, s); ^{13}C NMR ($CDCl_3$): δ168.4, 141.6, 136.4, 129.2, 128.4, 21.5, -1.1.

Preparation of *o*-methyl *N*-trimethylsilyl benzaldimine (**2.30e**)



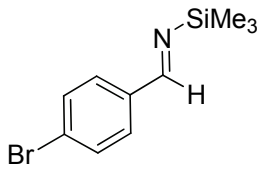
80% yield; ^{1}H NMR ($CDCl_3$): δ9.31 (1H, s), 7.87 (H_{Ar}, 2H, d, *J*=7.4 Hz), 7.23-7.33 (H_{Ar}, 2H, m), 7.15 (H_{Ar}, 1H, d, *J*=7.4 Hz), 2.56 (3H, s), 0.24 (9H, s). ^{13}C NMR ($CDCl_3$): δ167.8, 162.1, 132.1, 130.0, 113.8, 55.2, -1.2.

Preparation of *o*-chloro *N*-trimethylsilyl benzaldimine (**2.30f**)



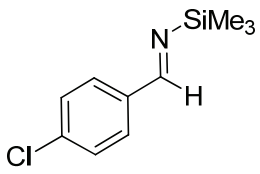
37% yield; ^{1}H NMR ($CDCl_3$): δ9.36 (1H, s), 8.02 (H_{Ar}, 1H, d, *J*=7.2 Hz), 7.26-7.35 (3H, m), 0.26 (9H, s); ^{13}C NMR ($CDCl_3$): δ165.3, 136.3, 135.0, 131.9, 129.7, 128.3, 127.0, -0.9.

Preparation of *p*-bromo *N*-trimethylsilyl benzaldimine (**2.30g**)



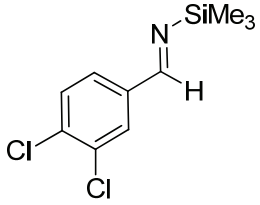
69% yield; ^{1}H NMR ($CDCl_3$): δ8.89 (1H, s), 7.64 (H_{Ar}, 2H, d, *J*=8.4Hz), 7.54 (H_{Ar}, 2H, d, *J*=8.4 Hz), 0.22 (9H, s); ^{13}C NMR ($CDCl_3$): δ166.8, 137.5, 131.7, 129.2, 125.7, -0.69.

Preparation of *p*-chloro *N*-trimethylsilyl benzaldimine (**2.30h**)



40% yield; ^{1}H NMR ($CDCl_3$): δ8.91 (1H, s), 7.72 (H_{Ar}, 1H, d, *J*=6.5 Hz) 7.39 (H_{Ar}, 1H, d, *J*=6.6Hz), 0.24 (9H, s); ^{13}C NMR ($CDCl_3$): δ166.7, 137.1, 129.9, 128.8, -0.9.

Preparation of 3,4-dichloro *N*-trimethylsilyl benzaldimine (**2.30i**)



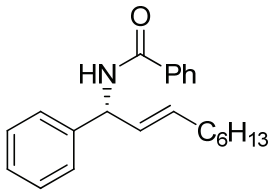
20% yield; ^{1}H NMR ($CDCl_3$): δ8.84 (1H, s), 7.87 (H_{Ar}, 1H, d, *J*=1.8 Hz), 7.57 (H_{Ar}, 1H, dd, *J*=1.8 Hz, 8.2 Hz), 7.47 (H_{Ar}, 1H, d, *J*=8.2 Hz), 0.23 (9H, s); ^{13}C NMR ($CDCl_3$): δ165.1, 138.5, 135.1, 133.0, 130.6, 130.0, 127.7, -0.9.

General procedure for the alkenylboration of *N*-acylimines:

To a mixture of activated powdered MS 4Å (0.03 g) and *N*-trimethylsilyl benzaldimine (0.7 mmol) in 3 mL of $CHCl_3$ was added benzoyl chloride (0.7 mmol). The resulting solution was brought to reflux for 3 hrs and then cool to -78 ^{o}C for 10 mins. The cool bath was removed. Volatiles were then removed under high vacuum *very* carefully to give the *N*-acylimine as a pale

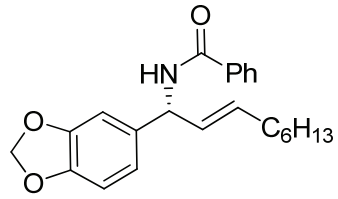
yellow oil. A chiral binaphthol catalyst (0.14 mmol) and an alkenylboronate (2.1 mmol) in 3 mL of CH_2Cl_2 were then added to the crude materials. The reaction was allowed to stir for 48 h. Workup was done by quenching the reaction with saturated aqueous NH_4Cl (4 mL). The organic phase was separated, the aqueous phase was extracted with CH_2Cl_2 (6 mL x 3). The combined organic layer was dried by $MgSO_4$. Column chromatography (hexane/EtOAc: 12/1) gave the desired allylic amides and the 3,3′-disubstituted binaphthol in pure form. The enantiomeric excess of products was determined by the HPLC (4.6 X 250 mm Chiralcel OD) analysis. Yields and er's are listed in Tables 2.7 and 2.8.

Preparation of *N*-(*E*)-(1-Phenyl-2-nonenyl)benzamide (**2.27a**)



IR (NaCl): 3331 (N-H), 1652 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ7.78 ($H_{Ar,}$ 2H, d, *J*=7.2 Hz), 7.07-7.51 ($H_{Ar,}$ 8H, m), 6.35 (1H, d, *J*=7.5 Hz), 5.62-5.80 (3H, m), 2.04-2.08 (2H, m), 1.26-1.38 (8H, m), 0.84-0.88 (3H, br); ^{13}C NMR ($CDCl_3$): δ166.2, 141.4, 134.4, 133.4, 131.4, 128.8, 128.6, 128.5, 127.4, 127.0, 126.9, 54.9, 32.2, 31.5, 28.9, 28.8, 22.5, 13.8; MS *m/e* (relative intensity): 321.3 (M^+, 100), 222.1 (55), 105.0 (100). The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH=95/5, flow rate= 1.0 mL/min), t_R=20.7 min (*R*). t_R=34.2 min (*S*). $[\alpha]_D^{25}$ -3.0 (98.8: 1.2 er, c=0.7, THF).

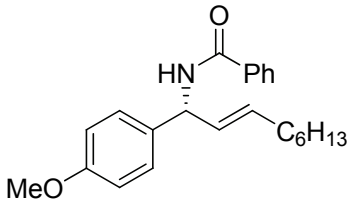
Preparation of *N*-(*E*)-(1-(3,4-methylenedioxyphenyl)-2-nonenyl)benzamide (**2.27b**)



IR(NaCl): 3438 (N-H), 1660 (C=O), 1265 (C-O)cm^{-1}; ^1H NMR ($CDCl_3$): δ7.77 (H_{Ar}, 2H, d, *J*=7.1Hz), 7.38-7.51 (H_{Ar}, 3H, m), 6.74-6.83 (3H, m), 6.28 (1H, d, *J*=7.1 Hz), 5.93 (2H, s), 5.63-

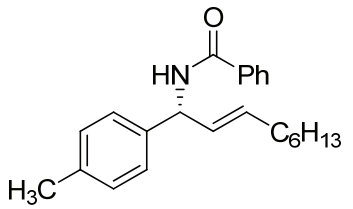
5.69 (3H, m), 2.02-2.09 (2H, m), 0.83-1.37 (8H, m), 0.83-0.88 (3H, m); ^{13}C NMR ($CDCl_3$): δ166.1, 147.8, 146.8, 135.4, 134.4, 133.2, 131.4, 128.8, 128.5, 126.8, 120.2, 108.2, 107.5, 100.9, 76.9, 54.7, 32.2, 31.5, 28.9, 28.8, 22.5, 13.9; MS *m/e* (relative intensity): 365.2 (M^+, 100), 266.1 (40), 105.0 (89). The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH=95/5, flow rate= 1.0 mL/min), t_R=33.6 min (R). t_R=50.9. $[\alpha]_D^{25}$ +5.9 (98.9: 1.1 er, c =1.0, THF).

Preparation of *N*-(*E*)-(1-(4-Methoxyphenyl)-2-nonenyl)benzamide (**2.27c**)



IR (NaCl): 3328 (N-H), 1647 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ7.76 (H_{Ar}, 2H, d, *J*= 7.1 Hz), 7.37-7.49 (H_{Ar}, 3H, m), 7.24-7.28 (H_{Ar}, 2H, m), 6.86 (2H, d, *J*= 8.7 Hz), 6.38 (2H, d, *J*= 7.6 Hz), 5.67-5.75 (3H, m), 3.78 (3H, s), 2.03-2.07 (2H, m), 1.26-1.37 (8H, m), 0.84-0.88 (3H, br); ^{13}C NMR ($CDCl_3$): δ166.1, 158.9,134.5, 133.5, 132.9, 131.4, 129.0, 128.4, 128.2, 126.8, 55.2, 54.3, 32.2, 31.5, 29.0, 28.8, 22.5, 14.0; MS *m/e* (relative intensity): 351 (M^+, 87), 266 (50), 105 (100) 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=32.1 min (*S*). $[\alpha]_D^{25}$ +147 (97.8: 2.2 er, c=0.4, THF).

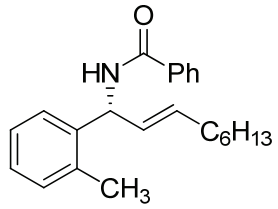
Preparation of *N*-(*E*)-(1-(4-Methylphenyl)-2-nonenyl)benzamide (**2.27d**)



IR (NaCl): 3332 (N-H), 1643 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ7.77 (H_{Ar}, 2H, d, *J*=7.7 Hz), 7.38-7.50 (H_{Ar}, 3H, m), 7.22-7.25 (H_{Ar}, 3H, m), 7.14 (H_{Ar}, 1H, d, *J*=8.0 Hz), 6.32 (2H, d, *J*= 7.1 Hz), 5.61-5.76 (3H, m), 2.33 (3H, s), 2.03-2.07 (2H, m), 1.26-1.37 (8H, m), 0.84-0.88 (3H, br); ^{13}C NMR ($CDCl_3$): δ166.2, 138.5, 137.0, 134.5, 133.0, 131.3, 129.3, 129.0, 128.4, 126.92, 126.89,

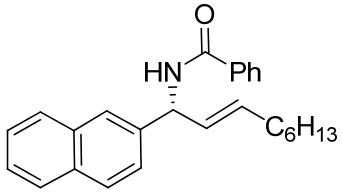
54.7, 32.2, 31.6, 29.0, 28.8, 22.5, 21.0, 13.9; MS *m/e* (relative intensity): 335 (M^+, 2), 143 (45), 105 (100). The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH=95/5, flow rate= 1.0 mL/min), t_R=14.4 min (*R*). t_R=22.7 min (*S*). $[\alpha]_D^{25}$ +10.0 (93.5: 6.5 er, c=0.6, THF).

Preparation of *N*-(*E*)-(1-(2-Methyl)phenyl-2-nonenyl)benzamide (**2.27e**)



IR (NaCl): 3304 (N-H). 1630 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ7.78 (H_{Ar}, 2H, d, *J*=7.0 Hz), 7.30-7.47 (H_{Ar}, 4H, m), 7.18-7.21 (H_{Ar}, 3H, m), 6.44 (1H, br), 5.92-5.97 (1H, m), 6.58-5.68 (2H, m), 2.41 (3H, s), 2.03-2.10 (2H, m), 1.27-1.37(8H, m), 0.85-0.89 (3H, br); ^{13}C NMR ($CDCl_3$): δ166.1, 139.4, 136.3, 134.4, 132.7, 131.4, 130.7, 128.6, 128.4, 126.9, 126.2, 126.1, 51.7, 32.2, 31.6, 29.0, 28.8, 22.5, 21.4, 19.2, 14.0; MS *m/e* (relative intensity): 335 (M^+, 2), 129 (20), 105 (100) The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH=95/5, flow rate= 1.0 mL/min), t_R=10.3 min (R). t_R=34.2 min (*S*). $[\alpha]_D^{25}$ -12.7 (>99.5: 0.5 er, c=1.1, THF).

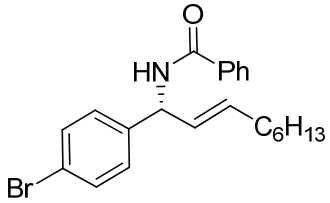
Preparation of *N*-(*E*)-(1-(2-Naphthyl)-2-nonenyl)benzamide (**2.27f**)



IR(NaCl): 3304 (N-H), 1630 (C=O)cm^{-1}; ^1H NMR ($CDCl_3$): δ8.17 (H_{Ar}, 1H, d, *J*=8.0 Hz), 7.74-7.87 (H_{Ar}, 3H, m), 7.35-7.54 (H_{Ar}, 7H, m), 6.54 (1H, m), 6.38-6.55 (1H, m), 5.75-6.35 (2H, m), 2.08-2.15 (2H, m), 1.26-1.39 (8H, m), 0.84-0.88 (3H, br); ^{13}C NMR ($CDCl_3$): δ166.1, 136.9, 134.3, 134.0, 132.7, 131.4, 131.2, 128.6, 128.50, 128.49, 128.46, 126.9, 126.5, 125.1, 124.6, 123.6, 51.1, 32.2, 31.6, 29.0, 28.8, 22.5, 14.0; MS *m/e* (relative intensity): 371.2 (M^+, 100), 272.1 (45), 105.0 (84). The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-

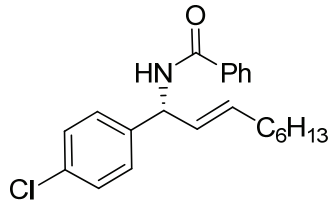
PrOH=95/5, flow rate= 1.0 mL/min), t_R=16.9 min (R). t_R=38.1 min (*S*). $[\alpha]_D^{25}$ +38.7 (98.7: 1.3 er, c =1.2, THF).

Preparation of *N*-(*E*)-(1-(4-Bromophenyl)-2-nonenyl)benzamide (**2.27g**)



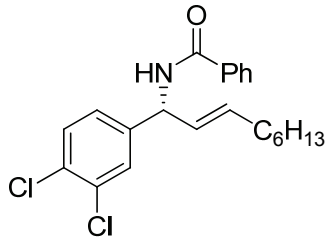
IR (NaCl): 3272 (N-H), 1633 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ7.77 (H_{Ar}, 2H, d, *J*=7.5 Hz), 7.38-7.49 (H_{Ar}, 5H, m), 7.20-7.22 (H_{Ar}, 3H, m), 6.42 (1H, d, *J*=7.2 Hz), 5.63- 5.71 (3H, m), 2.02-2.08 (2H, m), 1.26-1.36 (8H, m), 0.84-0.88 (3H, m); ^{13}C NMR ($CDCl_3$): δ 166.2, 140.5, 134.2, 131.64, 131.57, 128.7. 128.5, 128.3, 126.8, 121.2, 54.5, 32.2, 31.5, 28.9, 28.7, 22.5, 13.9; MS *m/e* (relative intensity): 401.2 (M^++2, 40), 399.2 (M^+, 40), 105 (100). The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH=95/5, flow rate= 1.0 mL/min), t_R=22.4 min (R). t_R=41.5 min (*S*). $[\alpha]_D^{25}$ -25.0 (98.0: 2.0 er, c=1.1, THF).

Preparation of *N*-(*E*)-(1-(4-Chlorophenyl)-2-nonenyl)benzamide (**2.27h**)



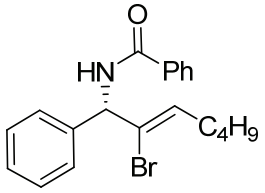
IR (NaCl): 3306 (N-H), 1649 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ7.77 (H_{Ar}, 2H, d, *J*=7.1Hz), 7.38-7.48 (H_{Ar}, 3H, m), 7.24-7.30 (H_{Ar}, 4H, m), 6.46 (2H, d, *J*=7.47 Hz), 5.63-5.74 (3H, m), 2.02-2.08 (2H, m), 1.25-1.58 (8H, m), 0.65-0.88 (3H, br); ^{13}C NMR ($CDCl_3$): δ166.4, 140.0, 134.2, 134.1, 133.1, 131.6, 128.7, 128.6, 128.5, 128.3, 126.9, 54.5, 32.2, 31.6, 28.9, 28.8, 22.5, 14.0; MS *m/e* (relative intensity): 355 (M^+, 2), 256 (5), 105 (100) The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH=95/5, flow rate= 1.0 mL/min), t_R=20.9 min (R). t_R=40.8 min (*S*). $[\alpha]_D^{25}$ -112.3 (99.2: 0.8 er, c=0.4, THF).

Preparation of (*E*)-(1-(3,4-Dichloro)phenyl-2-nonenyl)benzamide (**2.27i**)



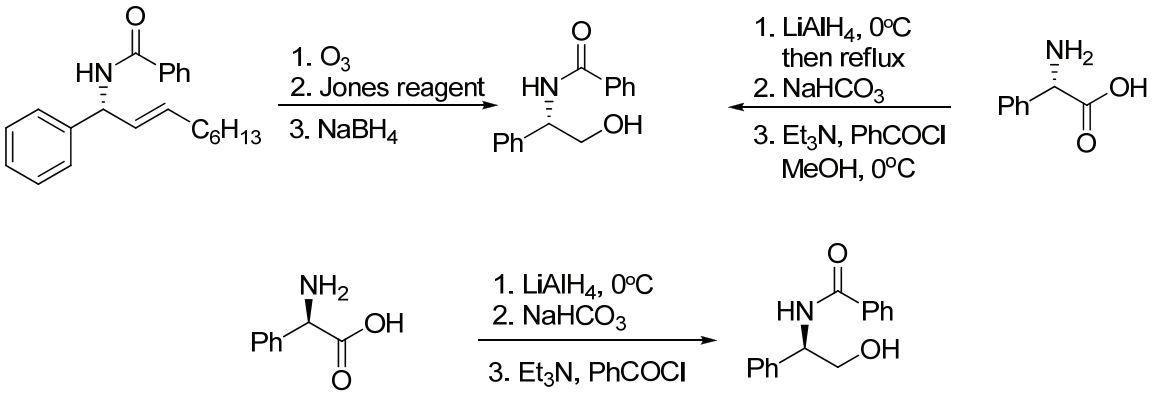
IR(NaCl): 3280 (N-H), 1635 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ7.78 (H_{Ar}, 2H, d, *J*=7.3 Hz), 7.37-7.55 (H_{Ar}, 5H, m), 7.17 (H_{Ar}, 1H, d, *J*=8.2 Hz), 6.41 (1H, d, *J*=7.2Hz), 5.56-5.75 (3H, m), 2.03-2.09 (2H, m), 1.25-1.37 (8H, m), 0.84-0.86 (3H, br); ^{13}C NMR ($CDCl_3$): δ166.4, 141.8, 134.9, 133.9, 132.6, 131.7, 131.3, 130.5, 128.8, 128.6, 127.9, 126.9, 126.4, 54.3, 32.2, 31.5, 28.8, 28.7, 22.5, 14.0 MS *m/e* (relative intensity): 389.2 (M^+, 48), 290.0 (27), 105.0 (100). The enantiomeric excess of the product was determined by HPLC (hexanes/*i*-PrOH=95/5, flow rate= 1.0 mL/min), t_R=20.9 min (R). t_R=51.2 min (*S*). $[\alpha]_D^{25}$ -26.8 (99.6 : 0.3 er, c=1.2, THF).

Preparation of *N*-(*Z*)-(1-Phenyl-2-bromo-2-hexenyl)benzamide (**2.28b**)



^1H NMR ($CDCl_3$): δ7.83 (H_{Ar}, 2H, d, *J*=7.1 Hz), 7.43-7.55 (H_{Ar}, 3H, m), 7.28-7.36 (H_{Ar}, 6H, m), 6.74 (2H, d, *J*=8.4 Hz), 6.19 (1H, t, *J*=6.9 Hz), 6.07 (1H, d, *J*=8.5 Hz), 2.21-2.28 (2H, m), 1.24-1.48 (4H, m), 0.88-0.93 (3H, br); ^{13}C NMR ($CDCl_3$): δ166.2, 138.7, 134.0,133.0, 131.7, 128.9, 128.6, 127.8, 127.0, 126.7, 126.6, 59.6, 30.6, 30.3, 22.2, 13.8.

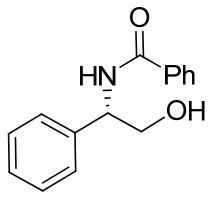
Correlation of Absolute Configurations



The procedure followed two literature methods.[55,56] To a suspension of lithium aluminum hydride (0.55 g, 14.5 mmol) in THF, L-phenylglycine (1 g, 0.66 mmol) was added slowly at 0 °C. The reaction was then stirred at reflux overnight and then cooled to room temperature. Saturated sodium carbonate (10 mL) was then added carefully. Subsequent filtration and evaporation of solvent gave the amino alcohol as yellow solid in quantitative yield. The amine group was then converted to the benzamide by adding Et_3N (0.2 mL) and benzoyl chloride (0.93 mL, 0.73 mmol) in MeOH (10 mL at 0 °C). The procedure was repeated for D-phenylglycine to obtain the reference compounds for HPLC analysis.

To determine the absolute configuration of the alkenylation, the product from the alkenylation reaction (0.05 g, 0.16 mmol) was dissolved in methanol (15 mL) and cooled in dry-ice/acetone bath. A stream of ozone in oxygen was then passed through until the solution became blue, indicating the presence of excess ozone. Argon was then flushed through the solution till it turned colorless. After warming to 0 °C, sodium borohydride was then added in very small portions until no effervescence was observed. The reaction was then stirred for 1 h, followed by addition of 2M hydrochloric acid until no effervescence observed. MeOH was then removed by rotary evaporator. The resulting mixture was then partitioned between EtOAc (5 mL) and water (5 mL). The aqueous layer was washed with EtOAc (5 mL x 3). The combined organic layer was then dried by $MgSO_4$ and filtered. Solvent was subsequently removed *in vacuo*. The residue is then purified

by column chromatography (1/15 EtOAc/hexane).



IR (NaCl): 3315 (N-H), 1631 (C=O), 1266 (C-O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ7.80 (2H, H_{Ar}, d, *J*=7.2 Hz), 7.27-7.53 (8H, m), 6.83 (1H, m), 5.27 (1H, q, *J*=4.8 Hz), 4.00-4.21 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ167.8, 138.8, 134.0, 131.7, 131.7, 129.0, 128.6, 128.0, 127.0, 126.6, 66.7, 56.2. $[\alpha]_D^{25}$ +40.6 (>99.5: 0.5 er, c=0.7, THF).

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Chapter 3 Catalytic asymmetric conjugate addition (ACA) of alkenylboronates to β-silyl-α,β-unsaturated ketones

3.1 Introduction

A silicon group attached to a stereogenic carbon center is a key moiety in asymmetric synthesis. It is most often used as a synthetic equivalent of a hydroxyl group, through oxidative degradation under mild reaction conditions. Tamao/Fleming oxidation reactions readily convert a carbon-silicon bond to a carbon-oxygen bond. These oxidations proceed through retention of configuration with high stereochemical fidelity.[1-5] In addition, the steric bulkiness of a silyl group is able to provide good stereocontrol in diastereoselective reactions.[6]

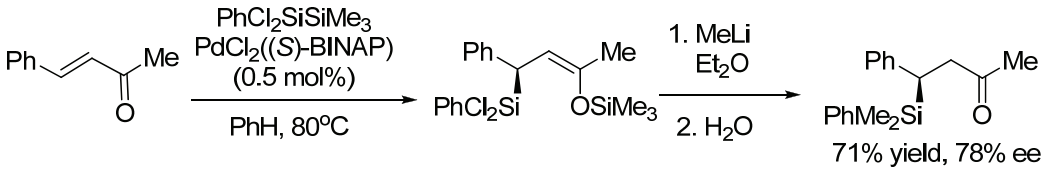
Chiral β-silylcarbonyls can act as an aldol product surrogate, a synthetically versatile intermediate in natural product synthesis. After Hayashi's pioneering research in the late 1980s, this area remained dormant.[7] In recent years publications targeting chiral silylcarbonyl compounds have resurged. The following summarizes the main routes to these organosilicon compounds. It should be noted that at the time this chapter was drafted, 1,4-addition onto β-silyl-α,β-unsaturated enones could only be accomplished using transition metal catalysts. This chapter reports the first binaphthol-catalyzed additions onto this type of silyl compound without any heavy metals.

3.2 Enantioselective synthesis of β-silylcarbonyl derivatives

3.2.1 Synthesis of β-silylcarbonyls by asymmetric 1,4-addition

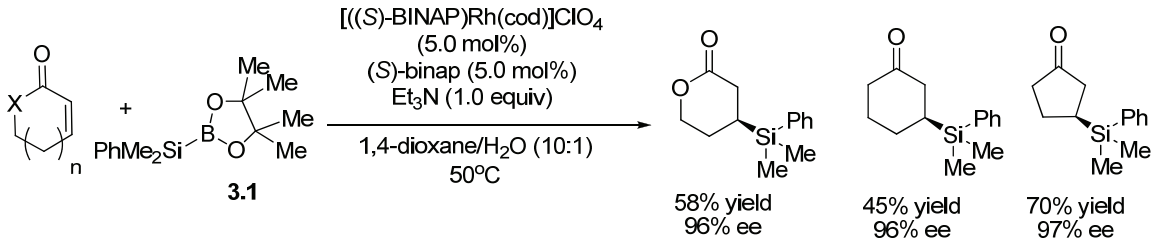
In 1988, the Hayashi group described the first catalytic enantioselective synthesis of β-silyl carbonyl compounds using palladium-catalyzed 1,4-disilylation of acyclic α,β-unsaturated ketones.[7] Dichlorophenyl silanes, generated from a disilylation promoted by a Pd-BINAP complex, were treated with MeLi followed by water to give

dimethylphenylsilyl ketones with up to 92% ee. An example is shown in Scheme 3.1. This asymmetric reaction was not extended to cyclic enones, which appeared to be the more challenging substrates in racemic reactions compared to aliphatic enones. When catalyzed by $Pd(PPh_3)_4$, disilylation of cyclic enones only furnished products in moderate yields.



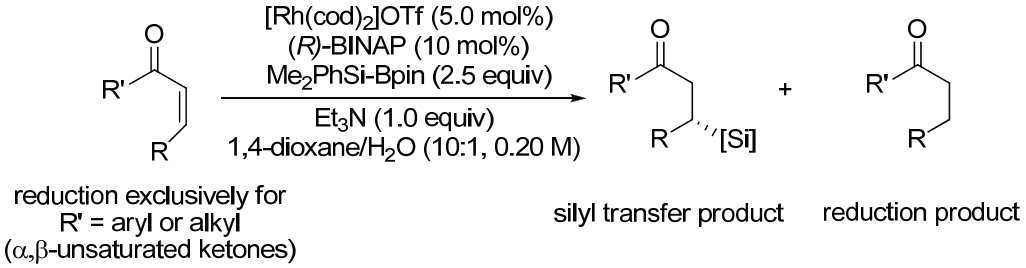
Scheme 3.1

Apart from the catalytic addition of Si-Si bonds onto α,β-unsaturated acceptors, addition of Si-B bonds to these Michael acceptors is a novel approach for accessing β-silyl carbonyls, discovered by Oestreich and coworkers.[8] A silyl boronic ester was utilized as a silyl anion source to undergo conjugate silyl transfer onto cyclic enones and lactones with excellent stereoinduction (Scheme 3.2). It is noteworthy that cyclic enones were not exploited in the asymmetric version of Hayashi's disilylation; so far, this is the only reported method of synthesizing chiral β-silyl in cyclic carbonyl derivatives.[9] In the presence of BINAP, addition of silyl pinacol boronate **3.1** yielded products above 90% ee. When the ring size of the carbonyl compound was increased, the yield was found to be decreased significantly. Addition onto an unsaturated lactone gave moderate yield (Scheme 3.2).[8]

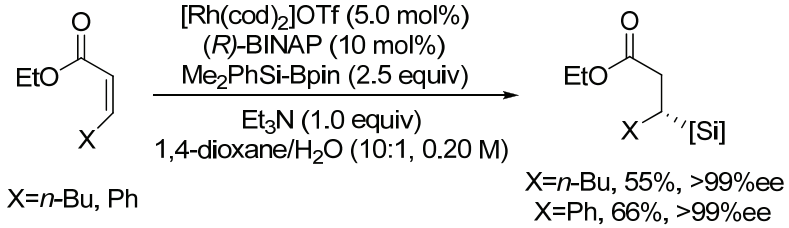


Scheme 3.2

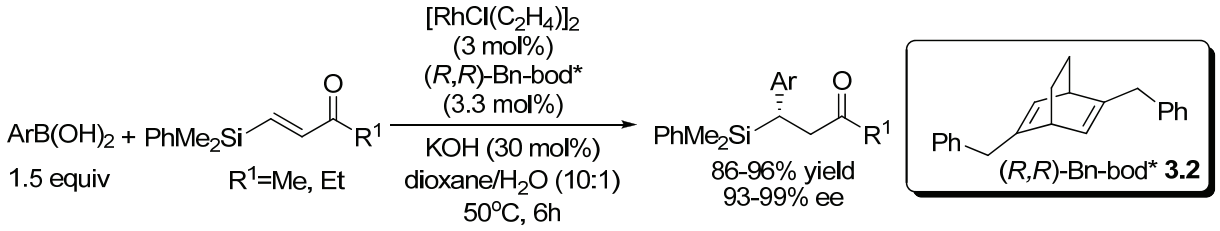
When the silyl transfer reaction was applied to acyclic enones and enoates, isomerization and 1,4-reduction were found to be the side reactions (Scheme 3.3).[10] Despite the modest yields, Oestreich's protocol produced very high stereoselectivites in both β-aryl and alkyl-substituted enoates (Scheme 3.4).



Scheme 3.3



Scheme 3.4

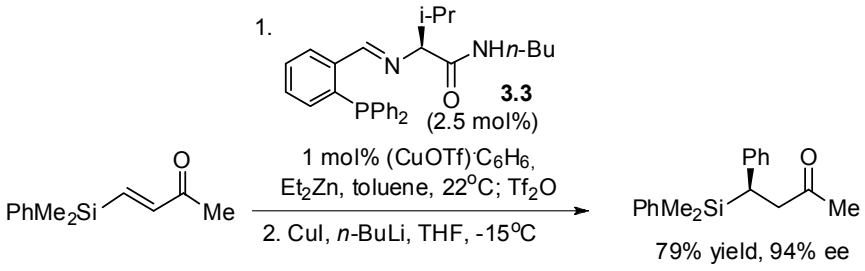


Scheme 3.5

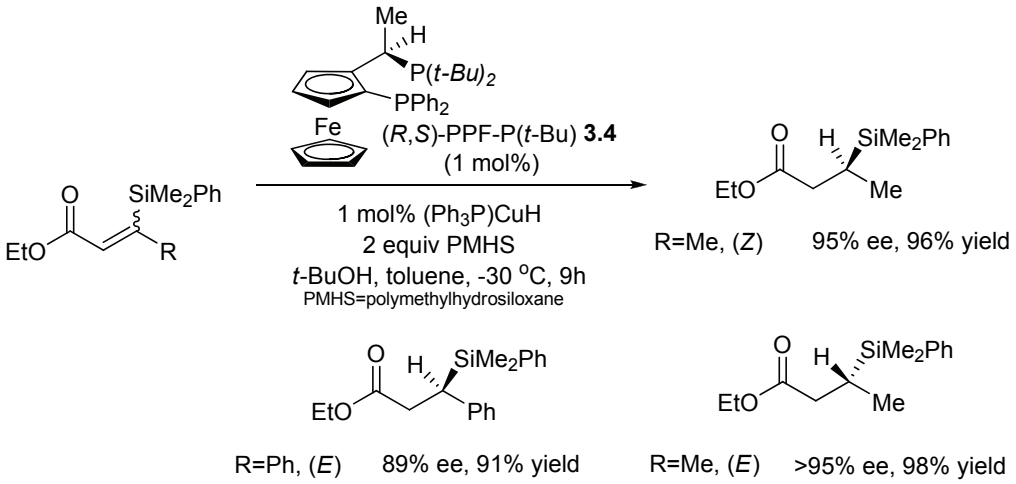
There was no report on stereoselective conjugate additions onto β-silyl α,β-unsaturated carbonyl derivatives until 2005. The reactivity of these silyl compounds might cause difficulties in developing new synthetic methodologies. While cuprates are effective reagents in the 1,4-additions, piperidone anions are found to be problematic in the transformations.[11] The first successful example was disclosed by the Hayashi group,

through rhodium-catalyzed 1,4-additions of arylboronic acids.[12] Excellent enantioselectivities were achieved by exploiting (*R,R*)-Bn-bod* **3.2** as a ligand (Scheme 3.5). Arylboronic acids with electron-donating and withdrawing substituents furnished high yields and stereoselectivities with various β-dimethylphenylsilyl enones. Enoates gave slightly lower yields but enantiomeric excesses remained above 90%.

A copper-catalyzed ACA of zinc reagents was reported by the Hoveyda group.[13] Catalyzed by chiral amino acid-based phosphines, dialkyl- and diarylzinc reagents were added onto β-silyl enones with good stereoinduction (Scheme 3.6). Enones with dimethylphenylsilyl groups generally provide better yields when compared to the TMS counterparts. It was noted that commercial available catalysts such as **3.3** can be used without further purification.



Scheme 3.6

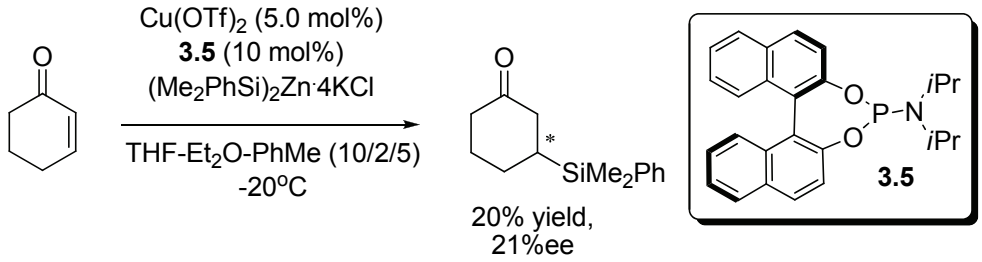


Scheme 3.7

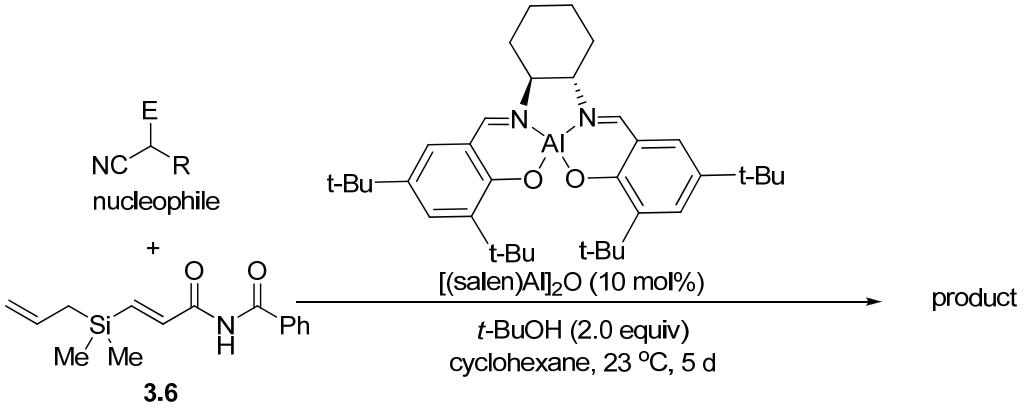
Enantioenriched β-silyl carbonyls can also be synthesized by asymmetric hydrosilylations of β-silyl enoates using copper catalysts. Lipshutz and coworkers revealed the use of (*R*, *S*)-PPF-P(*t*-Bu) ligand **3.4** afforded products with >90% yields and ee's at a relatively high substrate-to-ligand ratio (100:1) (Scheme 3.7). This 1,4-hydride reduction works well in both (*E*) and (*Z*)-enoates, as well as β-alkyl or β-aryl silyl enoates.[14]

Copper-catalyzed ACA of a silicon-containing organozinc reagent was attempted by the Oestreich group. Unfortunately, the yield and enantiopurity of the product was low (Scheme 3.8).[15] Only one example was given in the paper.

Jacobsen and coworkers exploited aluminum-salen complexes in enantioselective 1,4-addition to α,β-unsaturated β-silyl imides.[16] Various aminocyanoacetates such as **3.6** can be used as nucleophiles to afford silanes in high enantio- and diastereoselectivities, offering a one-step approach to chiral γ-lactams (Table 3.1). In the total synthesis of (+)-lactacystin, Michael addition of the cyanoacetate to imide **3.6** and subsequent nucleophilic attack of the PMB-protected amine to the imide gives lactam **3.7** as the intermediate in the synthetic route.



Scheme 3.8



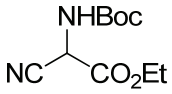
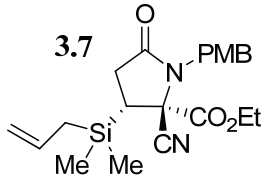
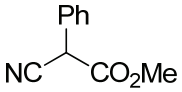
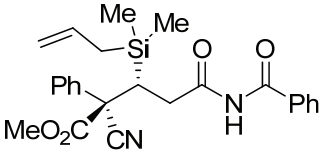
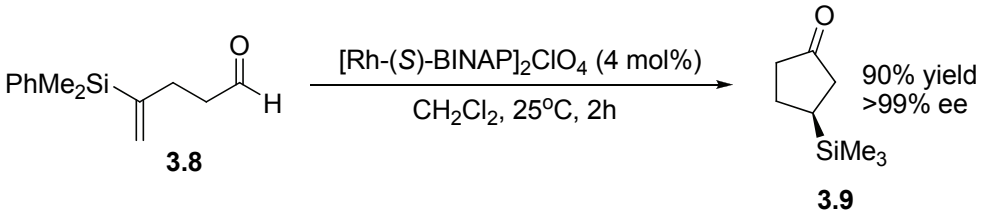
nucleophile	product	yield (%)	ee(%)/dr
	 **3.7**	81	99/15:1
		73	92/4:1

Table 3.1 Aluminum-salen catalyzed enantioselective 1,4-addition to α,β-unsaturated β-silyl imides

3.2.2 Synthesis of β-silylcarbonyls by hydroacylation and isomerization reactions

Rhodium-catalyzed hydroacylation and isomerization reactions are effective routes to enantioenriched β-silyl cyclopentanones. The Bosnich group reported the first asymmetric intramolecular hydroacylation of 4-pentenals.[17] Utilizing 4 mol% of Rh-BINAP as catalyst, aldehyde **3.8** can be transformed to the cyclic chiral silane **3.9** in >99% ee and 90% yield. Alkyl, aryl and keto-groups at the γ-position of the unsaturated aldehyde are tolerated in the reaction condition (Scheme 3.9).

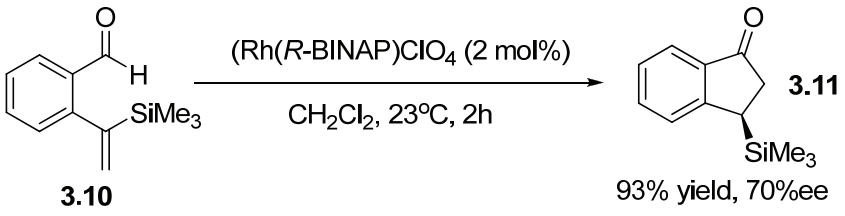
The application of the Bosnich method was demonstrated by Morehead in enantioselective syntheses of indanones. 2-(1-trimethylsilylethenyl)benzaldehyde (**3.10**) was transformed to indanone **3.11** by 2 mol% of Rh-BINAP in 70% ee.[18] The enantiopurity observed is the lowest among the substrates investigated. When the trimethylsilyl group was replaced by an alkyl, an aryl or an ester, the enantiopurities of the products exceed 95% ee (Scheme 3.10).



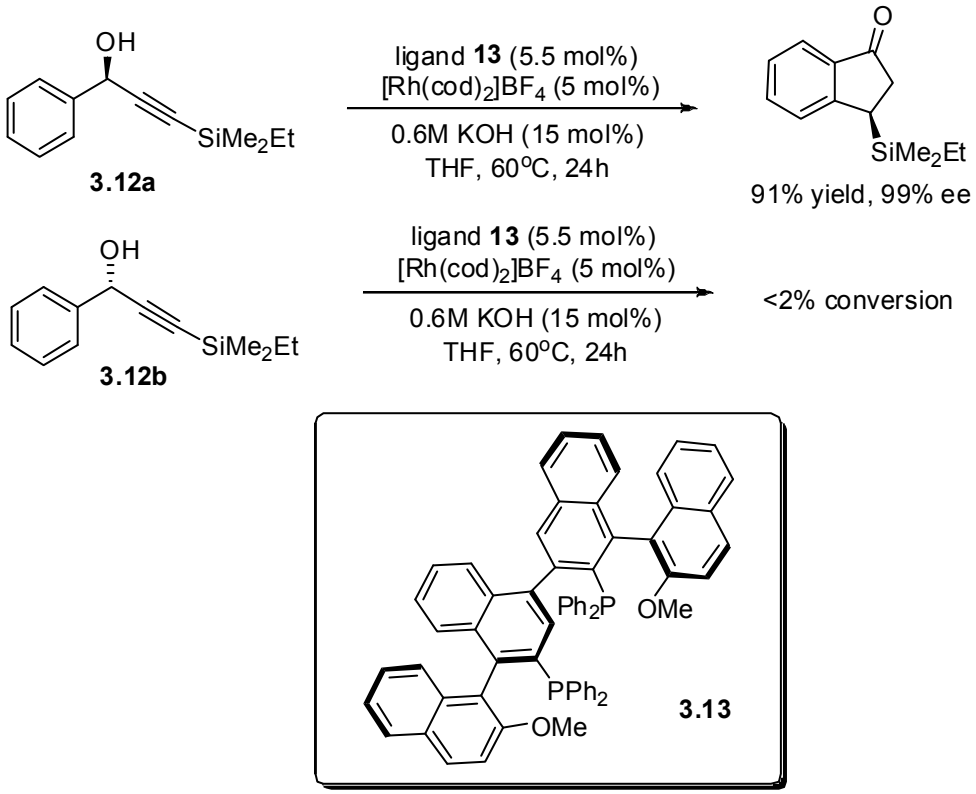
3.8 **3.9**

Scheme 3.9

Hayashi and coworkers synthesized β-chiral indanones via isomerization of racemic α-arylpropargyl alcohols **3.12a** and **3.12b**.[19] One of the enantiomers of the alcohol was selectively converted into chiral indanones very efficiently with high stereoinduction (Scheme 3.11). $SiMe_2Et$ offers higher stereocontrol than TMS group in the reaction.



Scheme 3.10

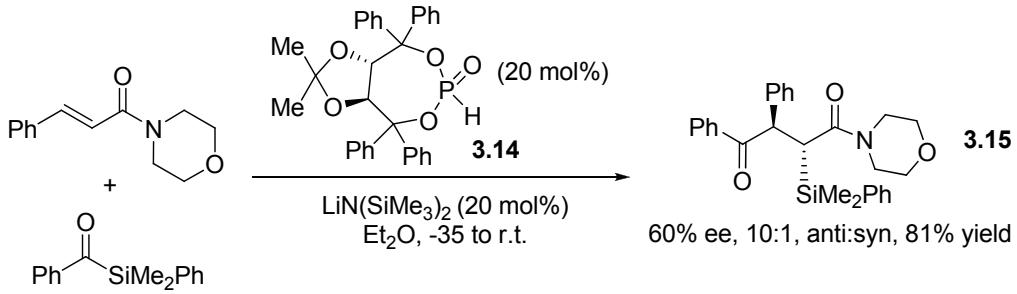


Scheme 3.11

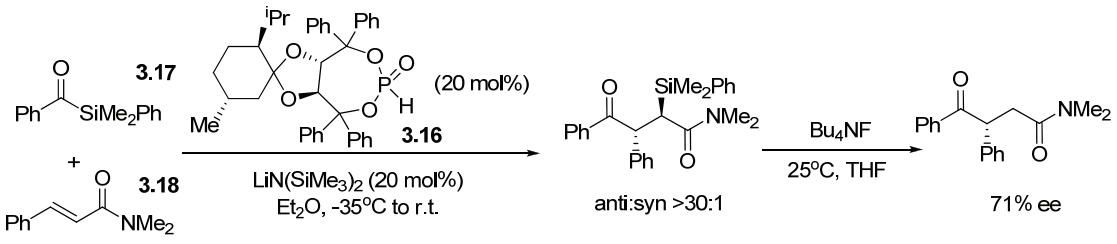
3.2.3 Other approaches of chiral β-silyl carbonyls

Johnson and coworkers disclosed another approach to chiral β-silyl carbonyl compounds by asymmetric addition of acylsilanes to α,β-unsaturated amides. The TADDOL phosphite catalyst **3.14** initiates [1,2] Brook rearrangement/conjugate addition/retro-[1,4] Brook rearrangement sequence to afford the silicon-containing dicarbonyl compound **3.15** in 60% ee, 10:1 *anti*:*syn* and 81% yield (Scheme 3.12).[20]

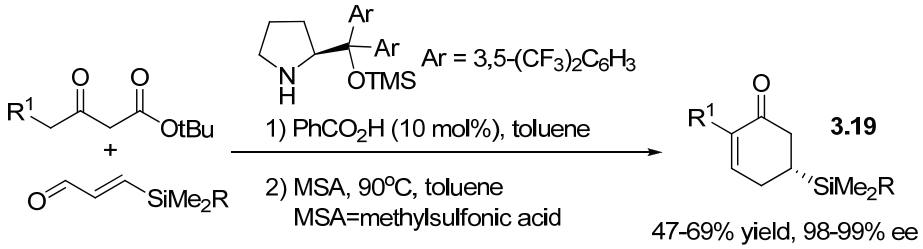
After further ligand screening, the Johnson group found an *l*-menthone derived TADDOL phosphite **3.16** offered higher enantiomeric and diastereomeric control than previously described. The addition of acyl silane **3.17** to amide **3.18** in the presence of sub-stoichiometric amounts of **3.16** generated the organosilicon compound in >30:1 anti:syn. Subsequent removal of the silyl group gave product of 71% ee. However, relatively high catalyst loading is essential for an efficient transformation.[21]



Scheme 3.12



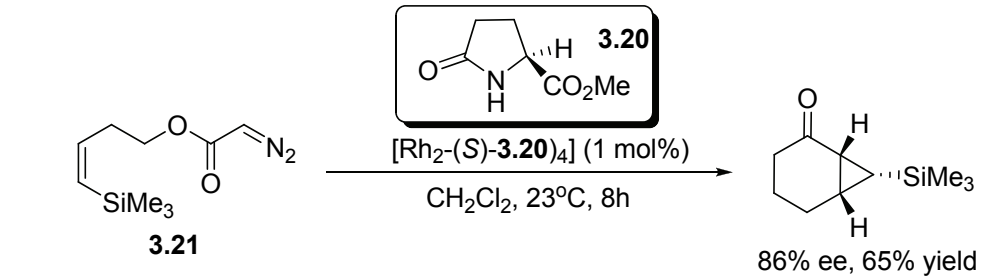
Scheme 3.13



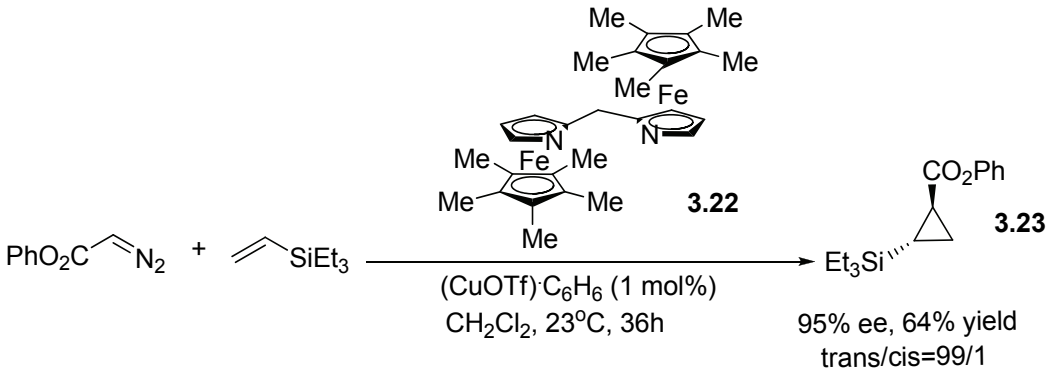
Scheme 3.14

The first organocatalytic approach to chiral 5-(trialkylsilyl)cyclohex-2-enones was revealed by the Jørgensen group in 2008.[22] These enones can be produced by carboxylation-aldol reaction of β-ketoesters with α,β-unsaturated aldehydes. Compounds **3.19** generated from aliphatic, allylic or aromatic β-ketoesters were produced in excellent ee's (Scheme 3.14).

Enantioselective cyclopropanation reaction can also generate chiral β-silyl carbonyls. Martin and coworkers reported Rh_2-(*S*)-**3.20** (also called Rh_2(5*S*-MEPY)$_4$) as an efficient catalyst in intramolecular cyclopropanation of homoallylic diazoacetates. Vinylsilane **3.21** was transformed to give β-silyl carbonyl in 86% ee (Scheme 3.15).[23,24] In 1998, Fu and coworkers developed chiral bisazaferrocene catalyst **3.22** and applied in Cu(I) catalyzed cyclopropanation of olefins. *Trans* cyclopropane **3.23** was formed in 95% ee (Scheme 3.16).[25]



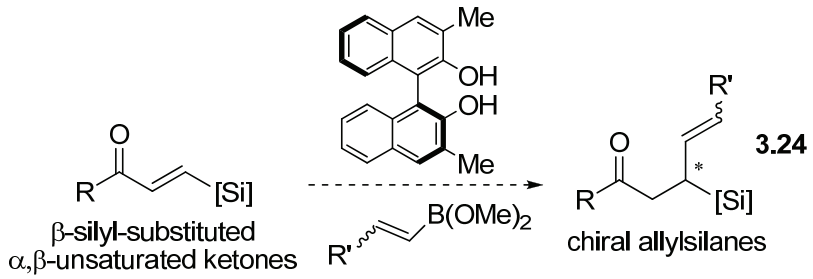
Scheme 3.15



Scheme 3.16

3.3 Proposal

Our group reported catalytic alkenylation of α,β-unsaturated ketones recently. We hope to extend the methodology to silyl enones (Scheme 3.17).[26] Chiral allylsilane **3.24** can be generated in this proposed reaction. It should be noted that currently there is no report on *non-transition metal catalyzed* additions to β-silyl-substituted α,β-unsaturated enones.

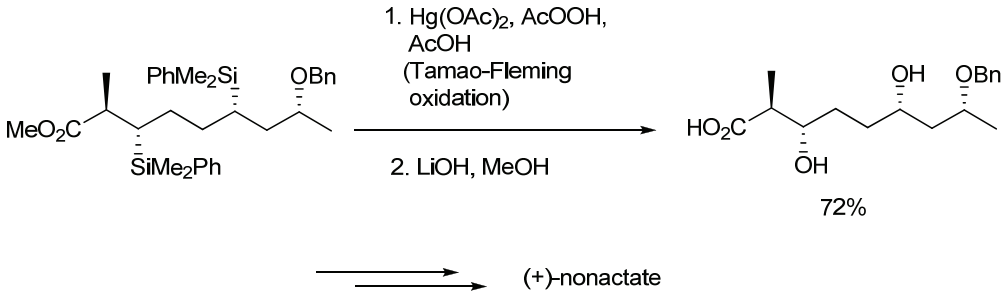


Scheme 3.17

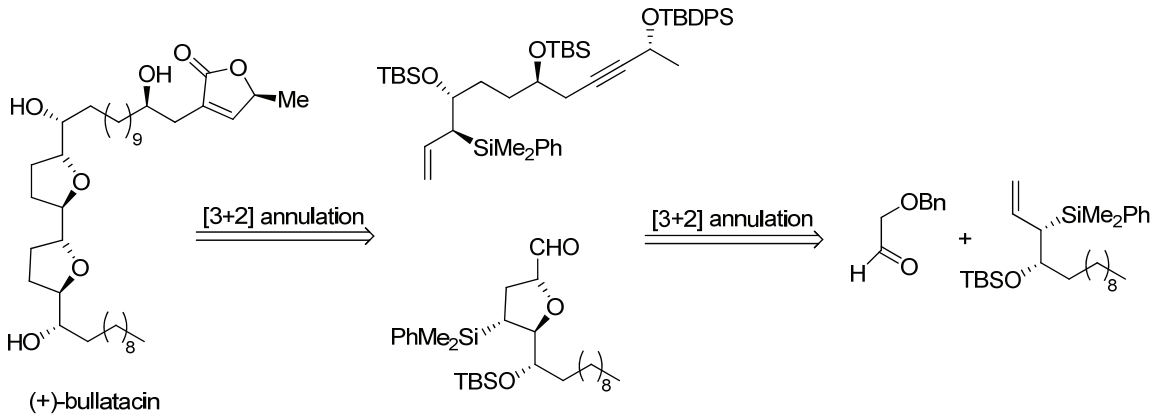
The following accounts for the versatility of chiral allylsilanes:

1) This structural motif can be converted to chiral alcohols under in mild conditions in high stereochemical fidelity. For instance, Fleming and co-workers demonstrated the use of the oxidation in the synthesis of (+)-nonactate, retention of configuration was observed (Scheme 3.18).[27]

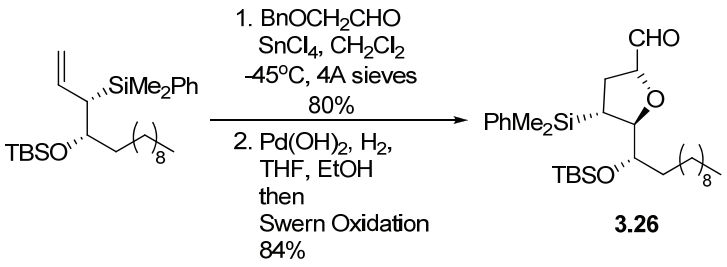
2) Silyl groups often exert high diastereomeric control in a number of organic reactions due to their steric bulkiness, as exemplified by the total synthesis of (+)-bullatacin (**3.25**) by the Roush group.[28] Two diastereoselective chelation-controlled [3+2] annulation reactions were employed in pursuing the natural product (Scheme 3.19). The *erythro* stereochemistry of C(23)-C(24) of the aldehyde **3.26** relies on the use of a *syn*-β-silyloxy allylsilane (Scheme 3.20).



Scheme 3.18



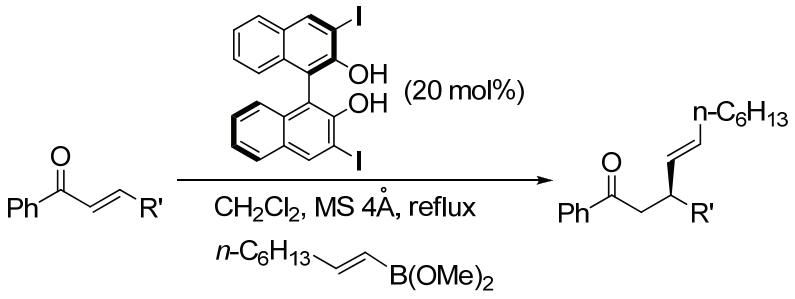
Scheme 3.19



Scheme 3.20

One of the challenges in working with β-silyl α,β-unsaturated ketones is envisaged to be the low reactivity associated with these compounds. Silyl groups are often strongly electron-donating; thus the silyl enones are more electron-rich than simple enones. In alkenylation of ketones, more electron-rich substrates gave lower yield and took longer time to react; this could be an indication of lower reactivity associated with more electron-donating substituents (Table 3.2). More vigorous reaction condition might be

needed, e.g. elevated reaction temperature. However, increased temperature often leads to lower stereoselectivity. Hence, optimization of this reaction aims at achieving an efficient reaction without compromising enantioselectivity.



R′	time (h)	yield (%)
4-ClC_6H_4	36	96
Ph	36	93
4-$MeOC_6H_4$	48	86

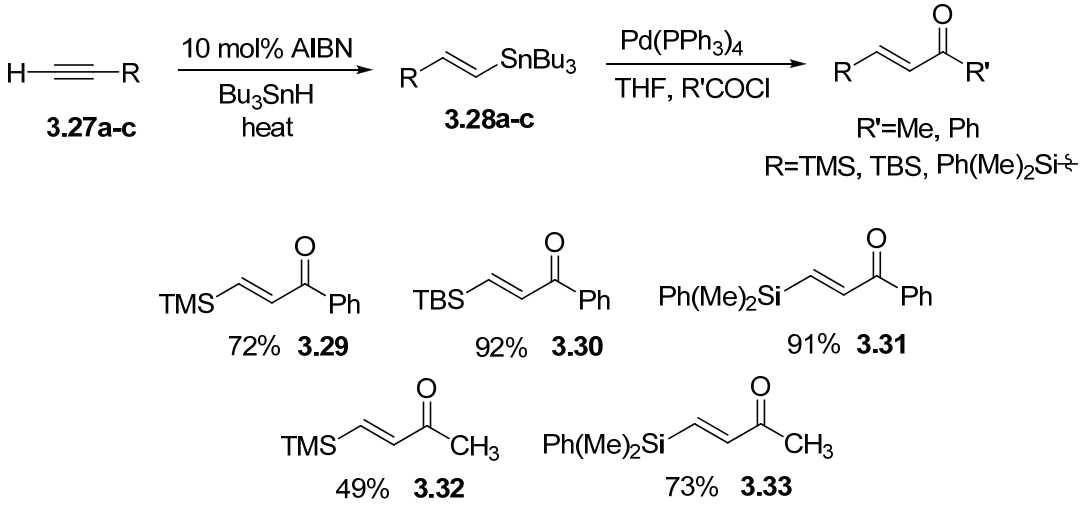
Table 3.2 Effect of electron-donating substituents on enones

3.4 Results and discussions

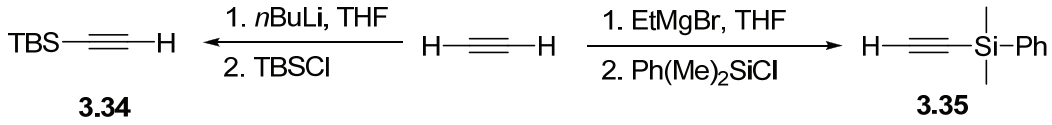
3.4.1 Synthesis of β-silyl-α,β-unsaturated ketones

Existing methods of synthesizing the unsaturated β-silyl ketones require at least two steps from commercially available materials and column chromatography twice.[12,13,29] Our group devised a more convenient strategy to access these carbonyl compounds. Hydrostannation of an alkyne followed by Stille coupling of an acyl chloride affords the silyl enone with only a single column chromatography operation (Scheme 3.21). Dimethylphenylsilyl acetylene **3.35** and *tert*-butyldimethylsilyl acetylene **3.34** were synthesized from acetylene because of the cost of the commercially available materials

(Scheme 3.22). In making the dimethylphenylsilyl alkyne **3.35**, using a Grignard reagent instead of an alkyllithium for deprotonation significantly reduced the amount of impurities generated, and hence increased the yield (<50% vs 85%). The Denmark procedure was found to be the most efficient in synthesizing alkyne **3.35** (Scheme 3.22).[30]



Scheme 3.21

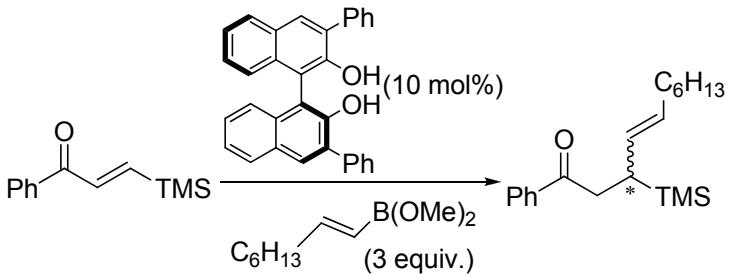


Scheme 3.22

3.4.2 Alkenylation of β-silyl-α,β-unsaturated ketones

Lang performed a pilot study in the alkenylation reaction (Scheme 3.23).[31] No products were isolated from reactions in refluxing dichloromethane (40 ^{o}C), dichloroethane (83 ^{o}C) and α,α,α-trifluorotoluene (109 ^{o}C). A serendipitous breakthrough came from an accidental evaporation of a reaction mixture at high temperature. When the reaction was heated to dryness, the desired product was isolated. This result led us to realize that

running the alkenylation reaction neat (without solvents) may be a good starting point. This is consistent with our expectation that the silyl enones are less reactive than enones such as chalcone.



Scheme 3.23

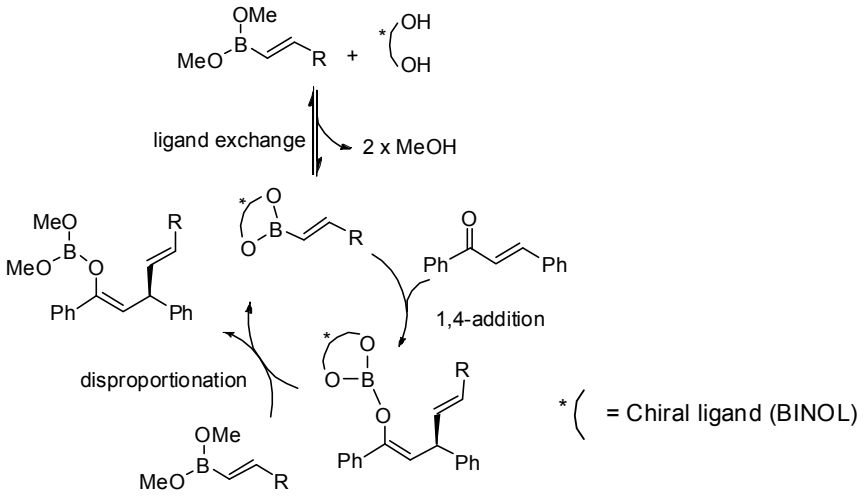
3.4.2.1 Optimization

Because of the expected low reactivity of the silyl enones, we first tried the reaction under rather harsh conditions: 220 ^{o}C with microwave irradiation for 3 hours. In attempting to improve the enantioselectivity of the reaction, the temperature was further tuned down by using a silicone oil bath. To our delight, the er went up from 92.8:7.2 to 94.5:5.5 (entry 1 vs 2 in Table 3.3). An increase in the amount of boronate from three to eight equivalents (relative to the amount of silyl enone used) slightly increased the yield but substantially reduced stereoselectivity. A background reaction was suspected to be the "culprit". Indeed, without any binaphthol catalyst, the yield was 37% when 5.3 equivalent of boronate was used! In contrast, in the alkenylation of simple enones, the reaction proceeds smoothly without any background reaction observed at 40 ^{o}C. In the case of a silyl enones, increase in the reaction temperature promotes not only the alkenylation reaction but also the background reactions as well.

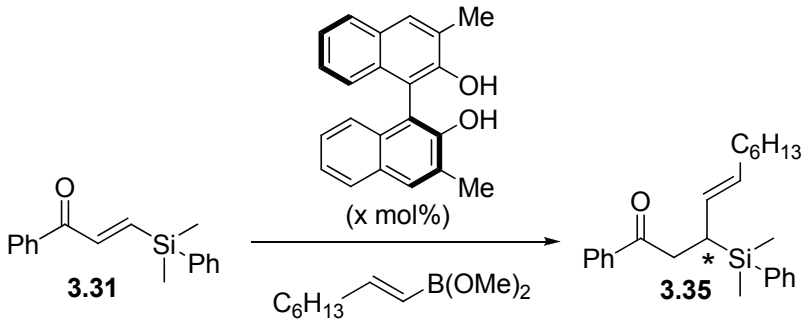
Other than the amount of the boronate used, the catalyst loading has a significant effect on both yield and stereoselectivity (entry 5 vs 6 in Table 3.3). When the loading was

increased from 5 to 10%, the er went up from 86.1:13.9 to 94.0:6.0.

Various binaphthol ligands were screened (Table 3.4); 3,3′-diiodo-substituted binaphthol offered the best enantioselectivity and yield. Diols with electron-withdrawing CF_3 and electron-donating TMS gave slightly inferior enantioselectivities. The yield obtained from the TMS-substituted binaphthol-catalyzed reaction is much lower than that from other diols, despite repeated trials. It is speculated that the electron-donating TMS group might stabilize the electron-deficient boron center, thereby reducing the reactivity of the chiral boron species after the ligand exchange (Scheme 3.24). In alkenylboration and alkynylboration, the ligand exchange of a dimethoxyboronate with a binaphthol in the catalytic cycle activates the boron species by reducing electron-donation to the boron atom.[26,32] With TMS group, the boron may not be electronically activated enough or is too sterically hindered to react. Please refer to Chapter 1, Section 1.2.1.3 for details.



Scheme 3.24



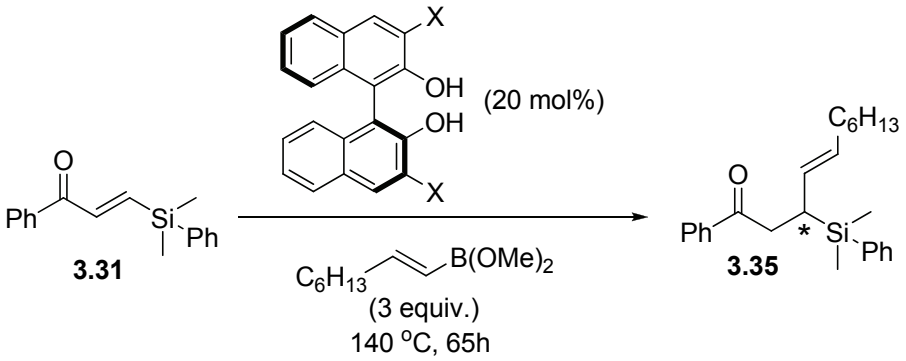
entry	temp (^{o}C)	time (h)	equivalents of boronates	catalyst loading (x mol%)	yield (%)[a]	er[b]
1	220 (MW)	3	3	20	50	92.8: 7.2
2	140	65	3	20	83	94.5 : 5.5
3	140	36	8	20	89	81.0 : 19.0
4	140	65	2	10	73	94.0 : 6.0
5	140	65	2	5	67	86.1 : 13.9
6	140	65	1	5	30	87.6 : 12.4
7	140	65	5.3	0	37	50 : 50

[a]isolated yields after flash chromatography
[b]determined by HPLC using a Chiralcel OD column

Table 3.3 Effect of catalyst loading and equivalents of boronate relative to the enones on alkenylation of the silyl enone 3.31

3.4.2.2 Possibility of Lewis-acid catalyzed reaction?

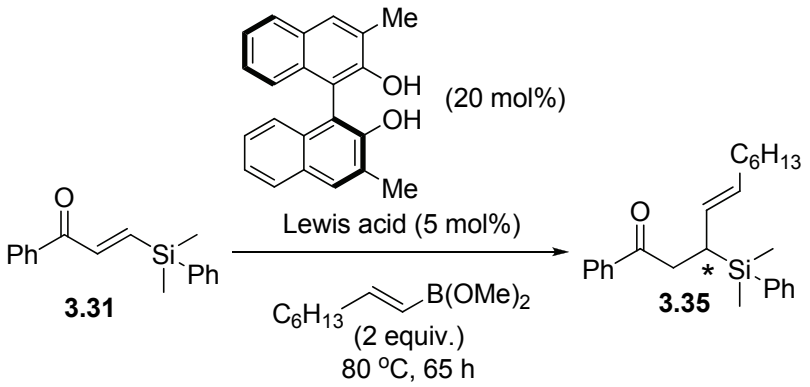
Inspired by the Lewis-acid promoted allylation reaction, we speculated that Lewis acids might accelerate the alkenylation reaction (Scheme 1.10 in Chapter 1). It was anticipated that if this reaction can be promoted at lower temperatures, an increase in enantioselectivity would be possible. Initially, the trials were performed at 140 ^{o}C for easy comparison with the data obtained. However, Lewis acids such as scandium triflate and copper(II) triflate decomposed. The temperature was then decreased to 80 ^{o}C, at which the yield of binaphthol-catalyzed reaction is around 24%; hence the effects created by various Lewis-acids would be easier to be observed. Unfortunately, these Lewis acid catalysts are found to *inhibit* the reaction (Table 3.5). The Lewis acid might coordinate with the carbonyl oxygen of the silyl enone more readily than the boronate. Hence, a six-membered closed transition state, which is crucial for the 1,4-addition to proceed, might not be able to form. As a result, no product was found in these reactions.



entry	X	yield (%)[a]	er[b]	equiv. of boronate
1	CF_3	78	71.4 : 28.6	5.3
2	I	91	98.3 : 1.7	5.3
3	TMS	43	84.3 :15.7	5.7
4	Me	83	94.5 : 5.5	5.3
5	Ph	58	98.2 : 1.8	5.3

[a]isolated yields after flash chromatography
[b]determined by HPLC using a Chiralcel OD column

Table 3.4 Effect of ligands on the alkenylation reaction



entry	Lewis acid	Remarks
1	$Sc(OTf)_3$	No product found in crude ^1H NMR or TLC
2	$Cu(OTf)_2$	
3	$B(OiPr)_3$	
4	None	24% yield[a]

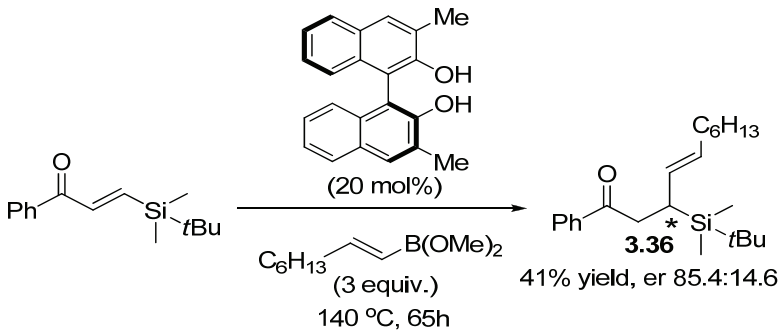
[a]isolated yields after flash chromatography

Table 3.5 Effect of Lewis Acids on alkenylation reactions

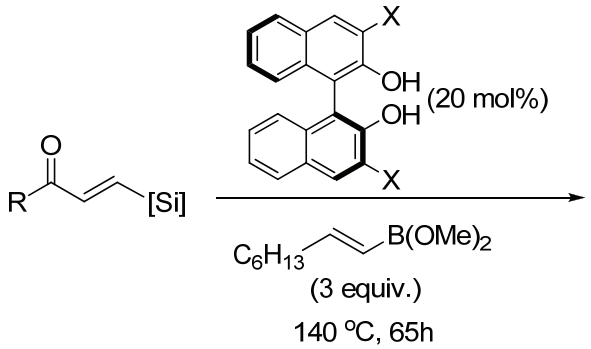
3.4.2.3 Scope and limitations

So far, this methodology works well with β-silyl-α,β-unsaturated enones with Ph attached to the carbonyl group. When a methyl group is attached, no product was obtained or isolated under these reaction conditions (Table 3.6).

The dimethylphenylsilyl group offers high yields and stereoselectivities. Alternatively, a TBS group could be used but with lower yield and er, probably because of its steric bulkiness (Scheme 3.25). When a TMS group was used, only trace amount of product was found by TLC or crude NMR spectra. In addition, a number of signals were found near 0 ppm, suggesting the TMS group might be labile under the reaction conditions (Table 3.6).



Scheme 3.25



entry	R	X	[Si]	Remark
1	CH_3	H	-$SiMe_2Ph$	No product found in crude ^1H NMR or TLC
2	CH_3	Me	-$SiMe_2Ph$	
3	CH_3	H (racemic)	-$SiMe_3$	
4	CH_3	Me	-$SiMe_3$	
5	CH_3	I	-$SiMe_3$	
6	Ph	Me	-$SiMe_3$	Trace amount (<5%) of product was found

Table 3.6 Alkenylation reaction on various substrates

This methodology can potentially be applied to a range of natural products if the procedure can be modified such that the scope can be extended to alkyl group adjacent to the carbonyl group. In the latter case, it is possible to transform the alkenylation product using well-established methods in enolate chemistry, such that synthesis of macrolides would be plausible.

3.5 Future directions

A two-step approach to a chiral 1,3,5-triol would be feasible using binaphthol-catalyzed alkenylation, followed by hydroboration.[33] The structural moiety is commonly found in natural products such as the antifungal agents filipin and mycoticin A (Figure 3.1).[34]

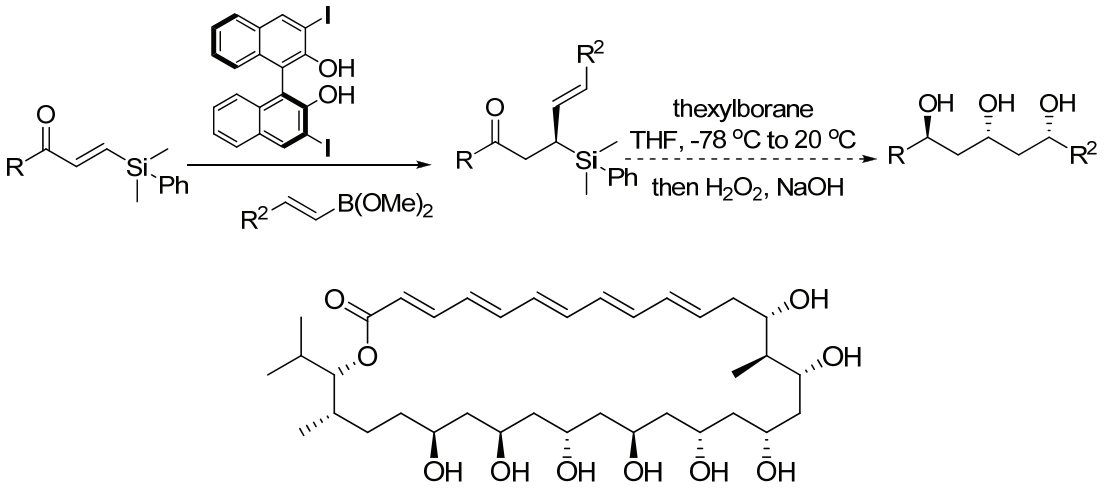


Figure 3.1 Mycoticin A

3.6 Summary

Alkenylation of β-silyl-α,β–unsaturated ketones offered chiral silanes in 89% yield and 94.5 : 5.5 enantiomeric ratio using catalytic amount of 3,3′-dimethylsubstituted binaphthol. The reaction is relatively insensitive to moisture; it proceeds without any solvent. Further optimization, such as adding activated molecular sieves, may improve yields and stereoselectivities.

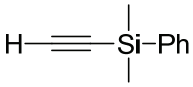
3.7 Experimental

General Experimental

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 MHz and 125 MHz, respectively, unless otherwise specified. All reactions were performed under argon atmosphere with flame-dried glassware; the alkenylation reactions are the exceptions. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were dried by distillation from sodium/benzophenone. Dimethylphenylchlorosilane and *tert*-butyldimethylchlorosilane were purchased from Gelest, Inc. Acetylene gas and trimethylsilylacetylene were purchased from Praxair and GFS Chemicals respectively.

Representative preparation of silicon-containing acetylene

Preparation of (dimethylphenylsilyl)acetylene (**3.27a**)



Reaction A: (Dimethylphenylsilyl)acetylene was prepared using Denmark's procedure with a slight modification.[30] To a two-necked round-bottomed flask fitted with a reflux condenser and a addition funnel, Mg (3.6 g, 148 mmol) was added. The setup was then flame-dried. A crystal of I_2 was introduced. EtBr (16.14 g, 148 mmol) in 24 mL of THF was added dropwise. When the reaction vessel was warm, a ice-water bath was placed underneath the flask. After the addition was complete, the resulting mixture was then refluxed for an hour.

Reaction B: To a separate three-necked round-bottomed flask equipped with a reflux condenser, was added 120 mL of dry THF. The solution was cooled to -78 ^{o}C and saturated with acetylene (passed through -78 ^{o}C dry-ice/acetone trap) for at least 30 min then warmed to 0 ^{o}C. The acetylene flow was maintained. EtMgBr generated from reaction A was then cannulated into reaction B in at least six portions. It was best to transfer contents of reaction A when it was still warm to avoid the mixture getting too viscous to be transferred. The reaction was then warmed to room temperature. Dimethylphenylchlorosilane (10.7 g, 125 mmol) was then added dropwise.

After complete addition, the acetylene flow was stopped. The reaction mixture was then refluxed under argon for 36 hours. To quench the reaction, 110 mL of water was added after the reaction was cooled down. The mixture was then extracted with Et_2O (2 x 220 mL). Each extract was washed with water (1 x 220 mL) and brine (1 x 220 mL) and dried with Na_2SO_4. The crude material was then filtered, concentrated and purified by fractional distillation (~60-65 ^oC/3-4 Torr).

85% yield; ^1H NMR($CDCl_3$):δ7.66-7.67 (H_{Ar}, m, 2H), 7.40-7.43 (H_{Ar}, m, 3H), 2.5 (C≡C$\underline{H}$, 1H s), 0.48 (Si(C$\underline{H_3}$)$_2$, 6H, s); ^{13}C NMR ($CDCl_3$): δ136.2 (*ipso*-C_{Ar}), 133.6 (C_{Ar}), 129.6 (C_{Ar}), 127.8 (C_{Ar}), 94.8 (C≡C), 88.2 (C≡C), -1.1 (SiPh(C$\underline{H_3}$)$_2$).

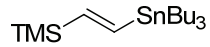
Preparation of (*tert*butyldimethylsilyl)acetylene (**3.27b**)

TBS—≡—H

The procedure was modified from de Meijere's protocol.[35] At -78 ^oC, to a flame-dried three-necked round-bottomed flask with 150 mL of THF saturated with acetylene, was added *n*BuLi (47.3 mL of a 1.6 M solution in hexane, 78 mmol) over a 25 min. The reaction was then stirred for an hour at -78 ^oC. *tert*-Butyldimethylchlorosilane (9.1 g, 60 mmol) in 30 mL THF was then introduced over a 30 min period. The cooling bath was removed and the mixture was then stirred at room temperature for at least 24 hours. The reaction was then quenched with water (25 mL). It was then partitioned with pentane (40 mL x 4). The combined organic layer was dried with Na_2SO_4 and purified by fractional distillation (~50-55 ^oC/3-4 Torr). 71% yield; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.32 (C≡C$\underline{H}$, 1H, s), 0.92 (C(C$\underline{H_3}$)$_3$, 9H, s), 0.11 (Si(*t*Bu)CH_3, 6H, s); ^{l3}C NMR ($CDCl_3$, 75MHz): δ 93.7 (C ≡ C), 88.2 (C ≡ C), 25.7 (C$\underline{(CH_3)_3}$), 16.3 (C(*C*H_3)$_3$), -4.78 (Si(CH_3)$_3$).

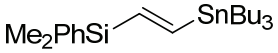
Representative procedure for preparation of silylvinylstannane

(*E*)-2-(trimethylsilylethenyl)tributylstannane (**3.28a**)



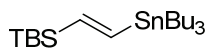
The procedure follows the protocol reported by Darwish and Chong.[36] Trimethylsilylacetylene (0.61 g, 6.27 mmol) was added to tributyltinhydride (1.82 g, 6.27 mmol) under argon. Then AIBN (0.102 g, 0.627 mmol) was added. The reaction mixture was then heated with an internal temperature of 50 °C for 24 hours. The mixture was diluted with ether (3 x 30 mL) and washed with water (2 x 30 mL). The combined organic layer was then dried with $MgSO_4$ and concentrated. This material was used in the subsequent Stille coupling without any further purification. 95% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ6.85 ($H_{C=C}$, AB, q, Δv=140Hz, J=22.6 Hz, 2H with J_{Sn-H}=104, 101 Hz), 1.23-1.56 (12H, m), 0.85-0.95 (15H, s), 0.04 (9H, s).

(*E*)-2-(Dimethylphenysilylethenyl)tributylstannane (**3.28b**)[30]



97% yield; ^{1}H NMR ($CDCl_3$, 300MHz): δ 7.56-7.59 (H_{Ar}, m, 2H), 7.38-7.43 (H_{Ar}, m, 2H), 6.94 ($H_{C=C,}$ AB, q, Δv= 168 Hz, J = 22.6 Hz, 2 H with J_{Sn-H}= 100, 95 Hz) , 1.23-1.57 (12 H, m), 0.8-1.05 (15H, m), 0.35 (6H, s); ^{13}C NMR ($CDCl_3$, 125 MHz): δ152.8 (C=C), 152.2 (C_{Ar}), 139.1 (*ipso*-C_{Ar}), 134.0 (C_{Ar}), 128.8 (C=C), 127.7 (C_{Ar}), 29.1 ($\underline{C}H_2CH_2CH_2CH_3$), 27.3 ($CH_2\underline{C}H_2CH_2CH_3$), 13.7 ($CH_2CH_2\underline{C}H_2CH_3$), 9.5($CH_2CH_2CH_2\underline{C}H_3$), -2.8 (Si($\underline{C}H_3)_3$).

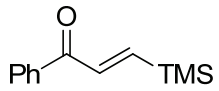
(*E*)-2-(Dimethyl(*tert*-butyl)silylethenyl)tributylstannane (**3.28c**)[37]



93% yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ6.75 ($H_{C=C}$, AB, q, Δv=148Hz, J=22.7 Hz, 2H with J_{Sn-H} =100, 104 Hz), 1.31-1.57 (14H, m), 0.93 (9H, s) 0.87-0.9 (14H, m); ^{13}C NMR ($CDCl_3$): 152.2 (C=C), 151.6 (C=C), 29.5 ($\underline{C}(CH_3)_3$), 29.1 ($\underline{C}H_2CH_2CH_2CH_3$), 27.3 ($CH_2\underline{C}H_2CH_2CH_3$), 26.5 ($C(\underline{C}H_3)_3$), 13.7 ($CH_2CH_2\underline{C}H_2CH_3$), 9.5 ($CH_2CH_2CH_2\underline{C}H_3$), -6.5 (Si(*t*Bu)($\underline{C}H_3)_2$).

Representative preparation of β–silyl–α,β–unsaturated ketone

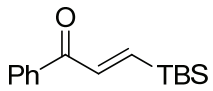
(*E*)-1-Phenyl-3-(trimethylsilyl)-2-propen-1-one (**3.29**)[12]



(*E*)-2-(trimethylsilylethenyl)tributylstannane **3.28a** (2.0 g, 4.43 mmol) was mixed with benzoyl chloride (0.806 g, 5.76 mmol) in 60 mL of THF under an argon atmosphere. $Pd(Ph_3P)_2Cl_2$ (0.040 g, 0.0415 mmol) was added. The reaction was refluxed at 65 °C for 6-8 hours. If $Pd(Ph_3P)_4$ was used, the reflux time was increased to 10-12 h. The progress of the reaction was monitored by ^1H NMR. When there was no starting material detected, the reaction mixture was then cooled down and diluted with saturated aqueous KF (20 mL) and stirred for 30 min. The reaction was extracted with Et_2O (2 x 50 mL) and water (2 x 50 mL). The aqueous phase was back extracted with ether (1 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resulting residue was passed through a silica plug (with water suction) prior to column chromatography. (hexane/Et_2O: 10/1) to yield the pure product in 72% yield.

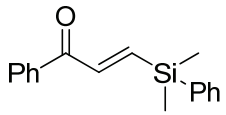
^1H NMR ($CDCl_3$): δ7.96-7.97 (H_{Ar}, m, 2H), 7.60 (H_{Ar}, dt, 1H, *J*=7.5, 1.3 Hz), 7.51 (H_{Ar}, appl. triplet, 2H, *J*=7.8 Hz), 7.31 ($H_{C=C}$, AB, 2H, *J*=18.7 Hz), 0.24 ($Si(CH_3)_3$, 9H, s); ^{13}C NMR ($CDCl_3$): δ190.6 (C=O), 149.8 (C=C), 138.1 (C_{Ar}), 137.5 (C_{Ar}), 132.8 (C=C), 128.8 (C_{Ar}), 128.6 (C_{Ar}), -1.7 ($Si(\underline{C}H_3)_3$).

(*E*)-1-Phenyl-3-(dimethyl-*tert*-butylsilyl)-2-propen-1-one (**3.30**)[12]



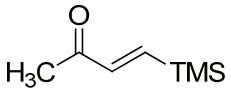
92% yield; ^1H NMR ($CDCl_3$): δ7.97 (H_{Ar}, 2H, dd, *J*=7.1, 1.1 Hz), 7.59 (H_{Ar}, dt, 1H, *J*=7.4, 1.09Hz), 7.51 (H_{Ar}, 2H, triplet, *J*=7.39 Hz), 7.32 ($H_{C=C}$, AB, 2H, *J*=18.8 Hz), 0.97 ($C(CH_3)_3$, 9H, s), 0.18 ($Si(tBu)(C\underline{H}_3)_2$, 6H, s); ^{13}C NMR ($CDCl_3$): δ190.3 ($\underline{C}$=O), 147.6 (C=C), 139.4 (C_{Ar}), 137.6 (*ipso*-C_{Ar}), 132.8 (C=C), 128.8 (C_{Ar}), 128.6 (C_{Ar}), 26.4 ($C(\underline{C}H_3)_3$), 16.7 $\underline{C}(CH_3)_3$, -6.3 ($Si(tBu)(\underline{C}H_3)_2$).

(*E*)-1-Phenyl-3-(dimethylphenylsilyl)-2-propen-1-one (**3.31**)[12]



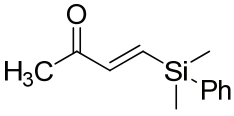
91% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ7.89-7.93 (H_{Ar}, m, 2H), 7.53-7.58 (H_{Ar}, m, 3H), 7.46 (H_{Ar}, t, 2H, *J*=7.8 Hz), 7.41 ($H_{C=C}$, d, 1H, *J*=18.8 Hz), 7.41-7.36 (H_{Ar}, m, 3H), 7.28 ($H_{C=C}$, d, 1H, *J*=18.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ190.4 (C=O), 147.4 (C_{Ar}), 139.4 (C_{Ar}), 137.4 (C_{Ar}), 136.6 (C=C), 133.9 (C_{Ar}), 132.8 (C=C), 129.5 (C_{Ar}), 128.8 (C_{Ar}), 128.6 (C_{Ar}), 128.0 (C_{Ar}), -3.0 ($SiPh(CH_3)_2$).

(*E*)-4-(trimethylsilyl)-3-buten-2-one (**3.32**)[13]



49% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.00 ($H_{C=C}$, AB, d, 1H, *J*=19.4 Hz), 6.42 ($H_{C=C}$, AB, d, 1H, *J*=19.4 Hz), 3.26 ((O=C)CH_3, 3H, s), 0.13 (9H, s, ($Si(CH_3)_3$);); ^{13}C NMR ($CDCl_3$): δ198.8 (C=O), 147.7 (C=C), 143.0 (C=C), 26.2 ((C=O)CH_3), -1.9 ($Si(CH_3)_3$).

(*E*)-4-(dimethylphenylsilyl)-3-buten-2-one (**3.33**)[13]

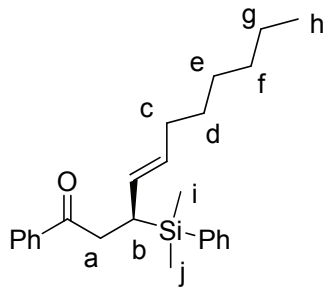


73% yield; ^{1}H NMR ($CDCl_3$): δ7.53-7.54 (H_{Ar}, 2H, m), 7.39-7.44 (H_{Ar}, 3H, m), 7.14 ($H_{C=C}$, 1H, *J*=19.2 Hz), 6.51 ($H_{C=C}$, 1H, *J*=19.2 Hz), 2.31 ((O=C)CH_3, 3H, s), 0.46 ($SiPh(CH_3)_2$, 6H, s); ^{13}C NMR ($CDCl_3$): δ198.6 (C=O), 145.6 (C=C), 144.2 (C_{Ar}), 136.3 (C=C), 133.8 (C_{Ar}), 129.6 (C_{Ar}), 128.1 (C_{Ar}), 26.4 (CH_3), -3.2 ($SiPh(CH_3)_2$).

General procedure for alkenylation of β–silyl–α,β–unsaturated ketone

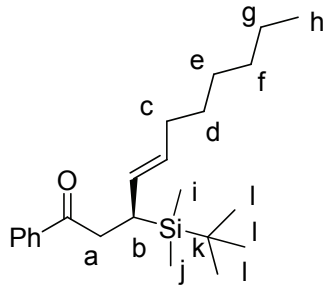
To 0.050 g (0.186 mmol) of (*E*)-1-phenyl-3-(dimethylphenylsilyl)-2-propen-1-one, 0.020 g (0.037 mmol) of (*S*)-3,3′-diiodo-2,2′-dihydroxy-1,1′-binaphthyl and 0.034 g (0.986 mmol) of (*E*)-octenylboronate was added to a Schlenk-type tube and the tube was sealed. The reaction was put into a 140 ^{o}C silicone oil bath for 65 hours. The reaction was then cooled and diluted with methanol and solvent was then evaporated. The crude material was purified by column chromatography (hexane/ether: 20/1) to give product as a very-pale yellow viscous liquid.

(E)-1-phenyl-3-dimethylphenylsilyl-4-undecen-1-one (**3.35**)



^{1}H NMR ($CDCl_3$): δ7.81 (H_{Ar}, m, 2H), 7.52-7.57 (H_{Ar}, m, 3H), 7.38-7.44 (H_{Ar}, m, 5H), 5.26 ($H_{C=C}$, AA′B, 2H), 2.91-3.01 (H_a, AB, 2H), 2.42 (H_b, dt, 1H, *J*=9.3, 4.2 Hz), 1.92-1.95 (H_c, 2H, m), 1.26-1.30 (8H, m), 0.90 (H_h, 3H, t), 0.37 ($H_{i\ or\ j}$, 3H, s), 0.35 ($H_{i\ or\ j}$, 3H, s); ^{13}C NMR ($CDCl_3$): δ200.1 (C=O), 137.3 (C_{Ar}), 134.1 (C_{Ar}), 132.7 (C=C), 129.7 (C_{Ar}), 129.2 (C_{Ar}), 129.0 (C_{Ar}), 128.5 ($C_{Ar,}$ br), 128.1 (C=C), 127.8 (C_{Ar}), 38.3 (C_a), 32.8 (C_c), 31.7 (C_f), 29.8 (C_d), 28.3 (C_e), 28.1 (C_b), 22.7 (C_g),14.1 (C_h), -4.2 (C_i), -5.2 (C_j). The enantiomeric excess of the product was determined by HPLC on a Chiralcel OD column (hexanes/*i*-PrOH=99.75/0.25, flow rate= 0.8 mL/min); two retention time are 27.6 min and 32.3 min.

(*E*)-1-phenyl-3-dimethyl*tert*butyllsilyl-4-undecen-1-one (**3.36**)



^{1}H NMR ($CDCl_3$): δ7.47-7.62 (H_{Ar}, m, 5H), 5.27 ($H_{C=C}$, AA′B, 2H), 2.87-3.13 (H_a, AB, 2H), 2.38 (H_b, dt, 1H, *J*=10.0, 3.8 Hz), 1.89-1.92 (H_c, 2H, m), 1.22-1.27 (8H, m), 0.97 (H_h. 3H, t), 0.19($H_{i\ or\ j}$, 3H, s), 0.03 ($H_{i\ or\ j}$, 3H, s); ^{13}C NMR ($CDCl_3$): δ200.4 (C=O), 137.6 (C_{Ar}), 132.6 (C=C), 130.2 (C_{Ar}), 129.2 (C=C), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.0 (C_{Ar}), 39.2 (C_a), 32.7 (C_c), 31.7 (C_f), 29.6 (C_d), 28.8 (C_k), 27.2 (C_e), 26.6 (C_l), 22.6 (C_g), 17.7 (C_b), 14.1 (C_h), -6.73 (C_i), -7.05 (C_j). The enantiomeric excess of the product was determined by HPLC on a Chiralcel AD-H column (100% hexane, flow rate= 1.0 mL/min); two retention times are 12.5 min and 16.6 min.

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