Asymmetric Alkenylation of Enones and Other α,β-Unsaturated Carbonyl Derivatives Using Chiral 3,3′-Disubstituted Binaphthols and Boronates

by

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A thesis

presented to the University of Waterloo

in fulfillment of the

thesis requirement for the degree of

Master of Science

in

Chemistry

Waterloo, Ontario, Canada, 2009

AUTOHR'S DECLARATION FOR ELECTRONIC SUBMITTION OF A THESIS

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Abstract

Various α,β-unsaturated carbonyl compounds and derivatives were explored in order to expand the range of substrates for the 1,4-addition of alkenylboronates using 3,3′-disubstituted binaphthols. Enones **2.60** were examined and found to be suitable for conjugate addition under our proposed reaction conditions.

The asymmetric 1,4-additions of alkenylboronates to enones **2.60** using catalytic amounts of 3,3′-disubstituted binaphthols was shown to occur with moderate to good yields and high enantioselectivities. The chiral products could serve as enantioenriched substrates for further transformation such as asymmetric reduction, which was performed with good yield and selectivity. The absolute configuration for the alkenylation of enones was also confirmed to be the (*R*) enantiomer using (*S*)-3,3′-disubstituted binaphthols via X-ray crystallographic analysis.

Investigations into selective Baeyer-Villiger oxidation of 1,4-addition products of enones was also examined. Although the desire ester products were not obtained, intriguing informative findings were still obtained from the investigation.

Acknowledgements

I extend my deepest gratitude to Prof. Michael Chong for his immense guidance and support throughout my graduate studies. I do appreciate his patience in giving us the chance to learn at our own pace. It was a pleasure and a great experience working with Mike.

I am very grateful to my advisory committee members, Prof. Gary Dmitrienko and Prof. Eric Fillion for their commitment and time in evaluating and reading my thesis. Also, special thanks to Ms. Jan Venne for her NMR assistance and Cathy Van Esch for her assistance with general faculty problems especially finance.

I like to thank the past and current members of our Group: Alla (for the overall lab experience), Alice, Minh, Heather, Rosie, John, Felicia and Hope for the constant motivation and support. I would also like to thank members of neighboring groups: Jarrod Johnson for his sarcastic remarks as well as taking his time to proofread my thesis; Glen for his help with NMR spectroscopy; Aaron Dumas for the chemistry related suggestion and entertaining movies; and the other members of the Fillion and Dmitrienko Labs for their informative, technical and moral support. I also acknowledge the University of Waterloo for providing funding throughout my masters program

Finally, I want to thank my parents for their never-ending motivation and support. Without them, I would not be here today.

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List of Abbreviations

Ac	acetyl
acac	acetylacetonato
Acc	acceptor
aq	aqueous
Ar	aryl
BINOL	1,1′-bi-2,2′-naphthol
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Bn	benzyl
BTP	bis(trimethylsilyl)peroxide
Bu	butyl
BV	Baeyer-Villiger
cat.	catalytic
CBS	Corey-Bakshi-Shibata
cod	cycloocta-1,5-diene
coe	cyclooctene
CuTC	copper(I) thiophene-2-carboxylate
d	doublet
DA	*trans*-1,2-(diamino)cyclohexane
DFT	density functional theory
dr	diastereomeric ratio

DMAP	4-dimethylaminopyridine
DMSO	dimethyl sulfoxide
E^+	electrophile
ee	enantiomeric excess
equiv	equivalent
er	enantiomeric ratio
Et	ethyl
EWG	electron withdrawing group
h	hour
HMPA	hexamethylphosphoric amide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectra
Hz	Hertz
i-Pr	isopropyl
J	spin coupling constant
m	meta
m	multiplet
M	metal
Me	methyl
min	minute
mL	milliliter

mmol	millimole
MMT	montmorillonite
MS	molecular sieves
MOM	methoxymethyl
MSDS	material safety data sheet
MTBE	methyl *tert*-butyl ether
m/z	mass to charge ratio
nbd	norbornadiene
n-BuLi	*n*-butyllithium
NMR	nuclear magnetic resonance
Nu	nucleophile
o	ortho
OXB	oxazaborolidines
p	para
Ph	phenyl
pyr	pyridine
q	quartet
R_f	retention factor
rt	room temperature
t-Bu	*tert*-butyl
THF	tetrahydrofuran

TLC	thin layer chromatography
TMS	trimethylsilyl
tol	tolyl
t_R	retention time

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CHAPTER 1

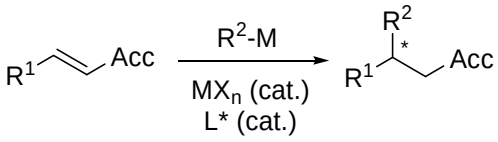
Introduction

1.1 Asymmetric Conjugate Additions

1.1.1 General

The asymmetric formation of carbon-carbon bonds via the 1,4-conjugate addition has been a theme of great interest and development over the past few decades. In 2001, a review by Krause and Hoffmann-Röder[1] focused on the recent advancement in the field of catalytic enantioselective Michael additions. In 2007, a group led by Christoffers[2] also reviewed these asymmetric conjugate additions with complete emphasis on the metal-catalyzed frontier. Exploring ways to apply these intriguing methods to new and synthetically applicable substrates has become a fascinating way to investigate the industrial and medicinal application of these carbon-carbon bond formations. The stereoselective formation of carbon-carbon bonds includes enantio- and diastereoselective reactions, in which covalently bound chiral auxiliary[3] or a stoichiometric chiral ligand coordinating to the nucleophile's cationic counterion results in an optically active electrophilic olefin or nucleophile.

Henceforth, investigation into the establishment of a generalized method for performing 1,4-conjugate additions by exploring the properties of various carbonyl derivatives seems promising (with excellent stereoselective results) (Scheme 1.1).[1]



Metal (M)	Mg, Zn, Al, La, Rh, B, etc.
R^2	Carbon nucleophile (alkenes, alkynes, etc.)
Acceptor (Acc)	COR, CO_2R, $CONR_2$, CN, COSR, etc.

Scheme 1.1

1.1.2 Enantioselective Conjugate Additions

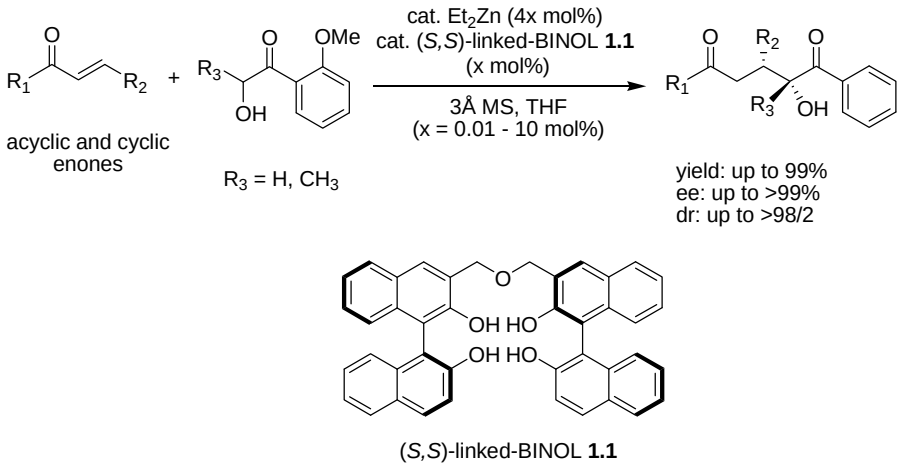
Over the past couple of years, various organocatalytic techniques have been developed for asymmetric 1,4-conjugate additions of carbon nucleophiles to Michael acceptors.[4] Amongst the various Michael acceptors that were investigated are α,β-unsaturated carbonyl compounds,[5-8] nitroolefins,[9] vinyl sulfones,[10] and other capable acceptors.

The focus of this discussion is to place emphasis on previous investigations and findings on the asymmetric conjugate additions of carbon nucleophile to α,β-unsaturated carbonyl compounds. Most of the successful reports involve the application of chiral catalysts.[3] Review of some of the recent and flourishing advances in the field of catalyzed asymmetric 1,4-conjugate additions is discussed in the following section.

1.1.2.1 Zinc-Linked-BINOL Catalyzed Asymmetric 1,4 Addition

Among the different linked-BINOL ligands developed by Shibasaki and co-workers, Et_2Zn/(*S*,*S*)-linked BINOL ligand **1.1** was reported to have been effectively applied in the 1,4-

addition of 2-hydroxy-2'-methoxyacetophenone to *β*-substituted enones to afford products of high yield (up to 90%) and enantiomeric purity (up to 96% ee). In addition, *β*-substituted enones also worked well and gave good diastereoselectivity (up to 99% dr) and high enantioselectivity (up to 99% ee) (Scheme 1.2).[11] The Et_2Zn/(*S*,*S*)-linked BINOL **1.1** complex was determined to be effective in shielding one of the enantiotopic faces of the enolate generated from the hydroxyketone, giving a useful method of providing *syn*-1,2-dihydroxyketones through the aldol reaction of the 2-hydroxy-2′-methoxyacetophenone with various aldehydes.[12] As a beneficial side effect, the linking of the two BINOL moieties facilitated recovery and reuse of these chiral ligands.

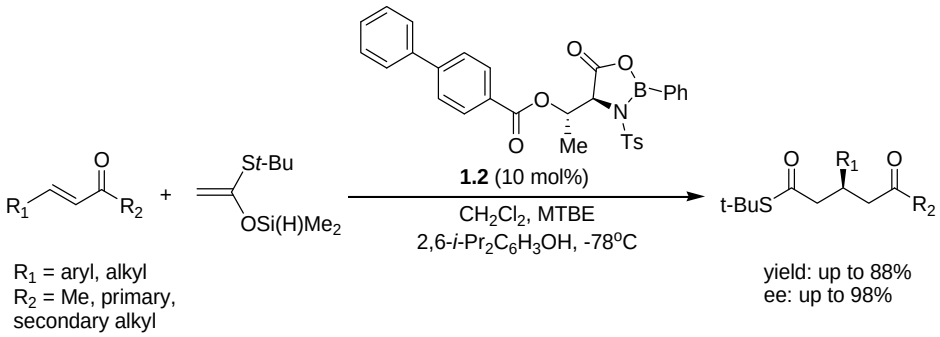


Scheme 1.2

1.1.2.2 Oxazaborolidinone Catalyzed Asymmetric 1,4-Conjugate Addition

Investigations by Harada and coworkers have shown that oxazaborolidinones (OXB) such as **1.2** are promising as Lewis acidic catalysts.[13] Their use as efficient catalysts was first shown in the asymmetric Diels-Alder reaction of unsaturated aldehydes[14,15] and in aldol reaction.[16,17] This was of great interest because the chiral OXB catalyst **1.2** was reported to effectively promote the asymmetric Mukaiyama-Michael reaction on acyclic enones.[18-20] This

was done in the presence of 2,6-diisopropylphenol in order to effectively retard the undesired Me_3Si^+-catalyzed racemic pathway which tends to compete with the desired chiral Lewis acid catalyzed enantioselective pathway and degrade the overall selectivity. Under these conditions, the use of dimethylsilanyl ($Me_2Si(H)$) ketene *S,O*-acetal as a nucleophile,[21] rather that the conventional TMS derivative, was found to increase the enantioselectivity of OXB-catalyzed asymmetric Michael reactions as well as expand the variety of enone structures that could be used in the reaction (Scheme 1.3).[22] Observations also showed that the effect of the additive 2,6-diisopropylphenol was enhanced when combined with methyl *tert*-butyl ether (MTBE); as a second additive.[19] Enantioselectivity was improved to 98% *ee*.

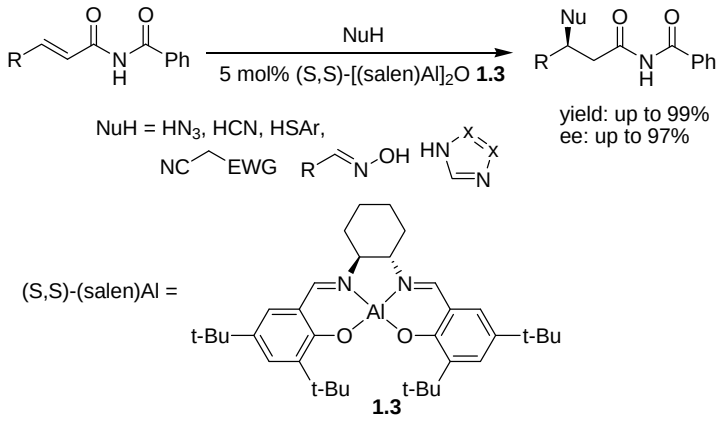


Scheme 1.3

1.1.2.3 Salen-Aluminum Catalyzed Asymmetric 1,4-Conjugate Addition

The introduction of chiral metal (III)-salen complexes as Lewis acidic catalysts by the Jacobsen group for the catalyzed asymmetric conjugate addition of carbon, oxygen and nitrogen nucleophiles to α,β-unsaturated imides has been reported (Scheme 1.4).[23,24] With the aid of dinuclear μ-oxo-aluminum-salen complexes such as compound **1.3**, they were able to perform addition of *N*-heterocyclic compounds like purine and benzotriazole to the α,β-unsaturated imides with excellent stereoselectivities (95% ee and 99% ee, respectively).[25] Although, with the

addition of both purine and benzotriazole, regioisomeric addition were also obtained as addition products (Figure 1.1) in 5:1 ratio for the purine addition (**N1** and **N2**), and 3:1 ratio for the benzotriazole addition (**N3** and **N4**).



Scheme 1.4

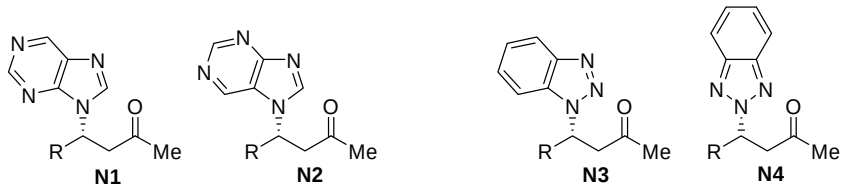
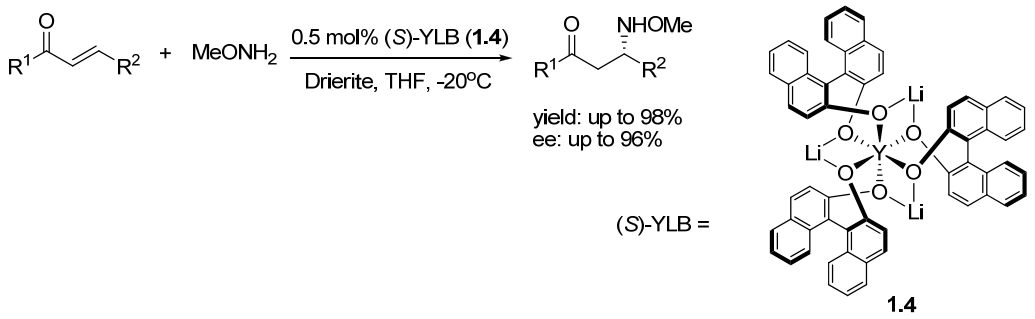


Figure 1.1: Regioisomeric addition products of salen-aluminum catalyzed addition of N-heterocyclic compounds

1.1.2.4 Heterobimetallic BINOLate Catalyzed Asymmetric 1,4- Addition

Shibasaki *et al*. have also successfully developed the asymmetric Michael reactions to enones using heterobimetallic BINOLate complex such as the aluminum-lithium-BINOLate (ALB),[26] and the yttrium-lithium-BINOLate (YLB).[27] The former was most efficient for asymmetric 1,4-addition of malonates to cycloalkenones, while the latter turned out to be an proficient catalyst for the asymmetric 1,4-addition reaction of hydroxylamine derivatives to enones (Scheme 1.5).[28]



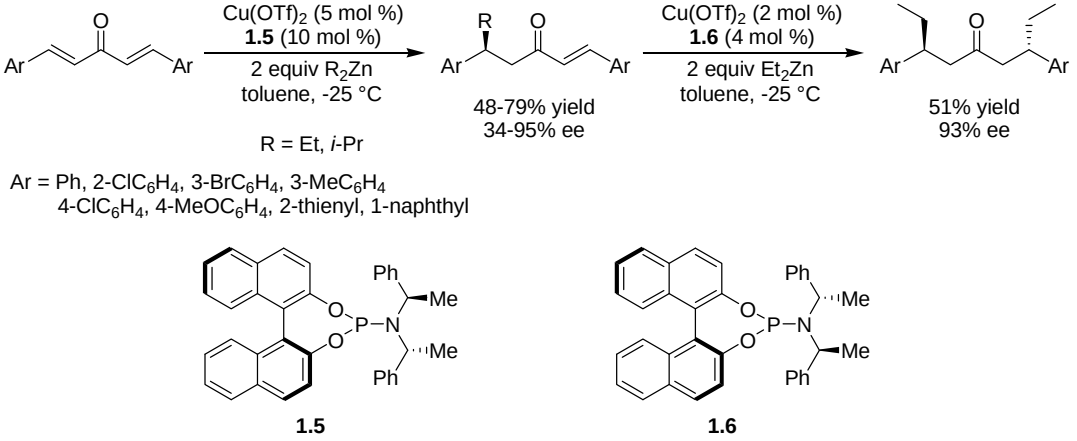
Scheme 1.5

1.1.2.5 Copper Catalyzed Asymmetric 1,4- Addition

A comprehensive literature review by Feringa and coworkers shows the recent advances in enantioselective copper-catalyzed 1,4-additions of organometallic reagents to α,β-unsaturated compounds.[29] In 1988, pioneering work on copper-catalyzed 1,4-addition of Grignard reagents to cycloalkenones by Lippard using chiral copper(I) tropinone complexes resulted in selectivities up to 78% ee.[30] Further investigations with a wide variety of chiral ligands and metal complexes have generally resulted in only modest enantioselectivities.

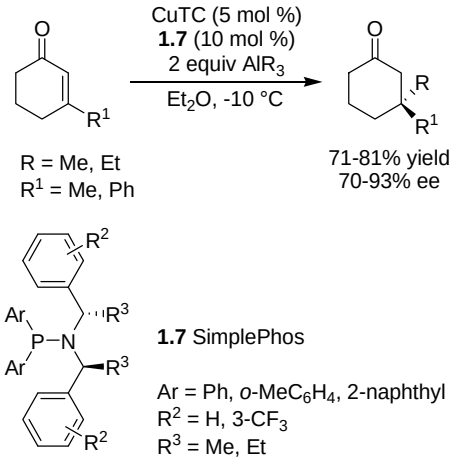
The use of phosphoramidites as chiral ligands have shown exceptional selectivity and versatility in 1,4-addition.[31-35] Recent investigations involving the use of catalytic copper sources combined with phosphoramidite ligands in asymmetric conjugate additions of dialkylzincs to a large variety of substrates have yielded good results, hence increasing versatility of the catalytic system. An intriguing case involves the 1,4-addition of dialkylzinc reagents to dienone derivatives since they would be subjected to two consecutive conjugate addition reactions (Scheme 1.6).[36] First addition step in the presence of ligand **1.5** resulted in good to high yield and enantioselectivities up to 95% ee. The subsequent addition of diethylzinc gave reasonable yield

with high enantioselectivity (93% ee). However, the diastereoselectivity was modest since 28% of the achiral *meso*-analogue was obtained as well.



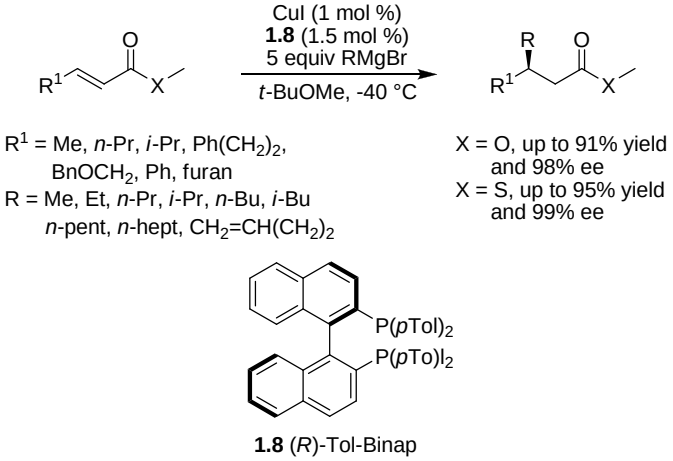
Scheme 1.6

Also, the use of trialkylaluminum compounds as alkylating agents rather than dialkylzinc compounds presents new opportunities in copper-catalyzed 1,4-addition. An example involves the use of ligand **1.7** in the efficient addition of trialkylaluminum to *β*-substituted cyclohexenones, hence the 1,4-adduct possessed a quaternary stereogenic centre with high yields and enantioselectivities up to 93% ee (Scheme 1.7).



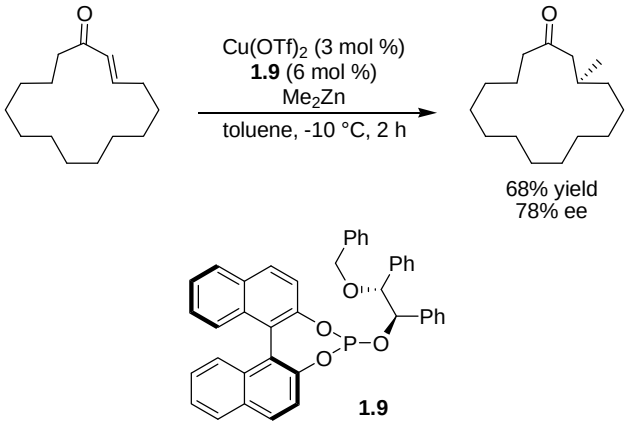
Scheme 1.7

Using phosphine ligands, the binap-type phosphine ligands can be seen as a typical example of which only three examples of copper-catalyzed 1,4-addition of Grignard reagents have been reported so far. Scheme 1.8 depicts one of such examples in which Loh and coworkers described the conjugate addition of a broad range of Grignard reagents to α,β-unsaturated esters and thioesters using (*R*)-Tol-Binap **1.8** to afford highly enantioenriched corresponding β-substituted esters (up to 94% ee) and thioesters (up to 99%) in good yields (80-91%).[37-39]



Scheme 1.8

In 1997, the early studies of copper-catalyzed 1,4-addition of diethylzinc to 2-cyclohexenone conducted by Alexakis involved the use of phosphate ligands derived from tartrate.[40] This led to the successful asymmetric synthesis of (*R*)-(-)-muscone, the key odor component of musk, in 2003. This synthetic application was achieved using the conjugate addition of dimethylzinc to (*E*)-cyclopentadec-2-en-1-one using chiral phosphite ligand **1.9** in combination with $Cu(OTf)_2$ as the copper source to afford the desired product in 68% yield and 78% ee (Scheme 1.9).[41]



Scheme 1.9

Furthermore, the Christoffers group has reviewed some other fascinating metal-catalyzed asymmetric conjugate additions that have proven to be of great success over the past few decade.[2] This includes the use of other metal complex catalyst involving transition metals such as scandium,[42] lanthanum,[43] samarium,[44] gadolinium,[45] ruthenium,[46] nickel,[8] palladium,[5] rhodium[47] and others. All these metal catalysts have displayed very good yields and enantioselectivities. However, these metal catalysts have some disadvantages such as high toxicity, air and moisture sensitivity, as well as being quite expensive.

Palladium and rhodium complexes have also been used to catalyze various asymmetric 1,4-addition reactions in which boronic acids or esters were used as the nucleophilic sources. Work by Hayashi and Miyaura in the rhodium-catalyzed additions of aryl and alkenyl boronic acids have emerged as important methodologies in this field of organic synthesis as discussed in the next chapter.

1.2 Boronic Acids and Esters

1.2.1 General

The unique properties of boronic acids as mild Lewis acids and their mitigated reactivity profile coupled with their stability and ease of handling, makes boronic acids a particularly attractive class of synthetic intermediates.[48] Moreover, because of their low toxicity and their ultimate degradation into environmentally friendly boric acid, boronic acids can be regarded as "green" compounds. Several factors contribute to the stability of boronic acids and their esters. However, thermodynamic consideration makes the exchange of hydroxyl substituents of boronic acids with other ligands quite unfavorable. In the case of the esters, by losing the hydrogen bond donor capability of the hydroxyl groups, they are less polar and even easier to handle. Substitution with alcohols or diols to form the corresponding boronic esters usually requires dehydration techniques to drive the reaction forward. The synthesis of boronic esters from their boronic acids and alcohols or diols is straightforward with the overall process being in equilibrium as shown on the equation below.

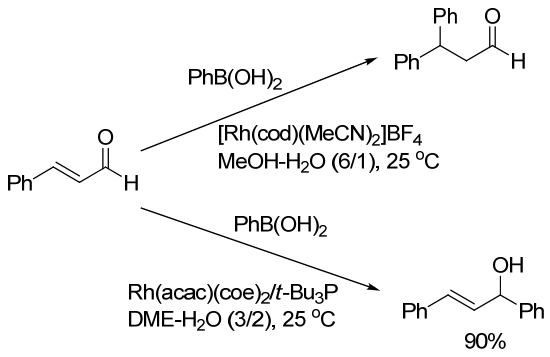
$$RB(OH)_2 + 2\,R'OH \rightleftharpoons RB(OR')_2 + 2\,H_2O$$

In terms of applications, boronic acids and esters are used extensively in organic synthesis. This includes their use in Suzuki coupling, [49] Chan-Lam coupling,[50,51] Liebeskind-Srogl coupling,[52-54] homologation,[55] electrophilic allyl shift,[56] arene borylation,[57-61] and conjugate addition (discussed in the next section).

1.2.2 Boronic Acids and Esters in Conjugate Additions

The 1,4-conjugate addition of aryl- and 1-alkenylboronic acids to α,β-unsaturated ketones/enones,[62] esters, and amides was reported by Miyaura and coworkers to proceed

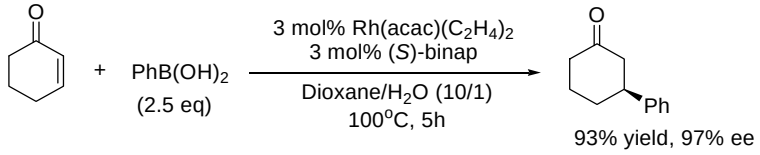
smoothly using rhodium-catalyzed systems. Also, they reported the 1,2-addition of arylboronic acids to aldehydes such as cinnamaldehyde in preference to the usual 1,4-addition with the addition of a *t*-Bu_3P complex with a chemoselectivity of 90% (Scheme 1.10).[63] However, with the use of rhodium(I)-binap complex alongside boronic acids, similar procedures have been extended to the asymmetric conjugate addition of the aryl- and 1-alkenylboronic acids to 1-alkenylphosphonates (in this case, boroxine – the boronic acid trimers were used)[64] and α,β-unsaturated carbonyl compounds in general.[65-67] Unlike the copper-catalyzed asymmetric conjugate reaction which is effective in the formation of C-C bonds with sp^3 carbon, rhodium-catalyzed reactions using organoboronates was determined to be an efficient technique for the addition of sp^2 carbon (aryl and vinyl groups) with respect to C-C bond formation.



Scheme 1.10

Since the earliest report on the rhodium-catalyzed addition of aryl and alkenyl boronic acids and other organometallic reagents to activated alkenes by Hayashi and Miyaura in 1998 (Scheme 1.1),[44] it has emerged as a very valuable methodology in the field of organic synthesis. This was mainly due to the fact that it had several advantages over other 1,4-addition reactions.[47] This includes: (1) the stability of organoboronic acids to moisture and oxygen, allowing the reaction to be performed using protic solvents or even aqueous solution; (2) the diminished reactivity of organoboronic acids towards enones in the absence of a rhodium catalyst unlike

other organometallic counterpart so far used, and no 1,2-addition in the presence or absence of the catalyst; (3) the catalyzed reaction using transition-metal complexes coordinated with phosphine ligands, based on the extensive studies done on transition-metal-catalyzed asymmetric reactions and accumulated knowledge gathered on chiral auxiliaries such as chiral phosphine ligands. Hence, this led to the development of asymmetric 1,4-addition of aryl and alkenyl boronic acids with high enantioselectivities in the presence of a chiral phosphine-rhodium catalysts.[68]



Scheme 1.11

Nevertheless, rhodium-catalyzed asymmetric 1,4-addition of boronic acids would be discussed in greater detail in the following chapter.

1.3 Purpose and Scope of this Thesis

With recent advancement in asymmetric conjugate additions, the utilization of boron reagents and binaphthol-based ligands has become an intriguing field of study. Quite recently, asymmetric conjugate additions using binaphthol-modified boron reagents were established by our group.[69] This thesis capitalizes on this previous profound development in the adaptive uses of 3,3′-disubstituted binaphthols and boron reagents especially boronic acids and boronates in asymmetric 1,4-additions.

This thesis focuses on the asymmetric 1,4-addition of alkenyl boronates to enones and the possibilities of extending this methodology to other potential substrates. This comes with the

intention of creating potential applications for the 1,4-addition products. Another approach explored was the possible Baeyer-Villiger oxidation of the 1,4-addition products in order to obtain synthetically applicable carboxylic acid-derived handles.

CHAPTER 2

Catalytic Asymmetric Conjugate Alkenylation of Enones and Other Carbonyl Derivatives

2.1 Introduction

Courtesy of the explosive interest and development involved in the formation of carbon-carbon bonds via 1,4-conjugate addition over the years, discovery of compatible substrates for these methods seems to be a viable approach to broaden the synthetic and industrial applications. A majority of the carbon-carbon bond formation have been catalyzed by transition-metal complexes, which allowed the introduction of carbon nucleophiles to the *β*-position of the electron-deficient olefins comprising mainly of *α,β*-unsaturated ketones and esters.[1] However, recent progress has seen the expansion of the various substrates using rhodium-based catalysts in asymmetric 1,4-addition of organoboron reagents to electron-deficient olefins such as *α,β*-unsaturated ketones,[2-4] esters,[5,6] amides,[7,8] phosphonates,[9] nitroalkenes,[10] sulfones[11] and even oxanorbornene[12,13] derivatives. This section discusses various substrates that have been used in metal-catalyzed 1,4-addition reactions with major emphasis on those involving the use of boron reagents.

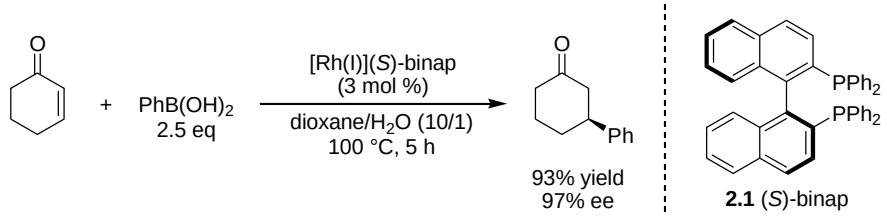
2.1.1 Rhodium-Catalyzed

2.1.1.1 α,β-Unsaturated Ketones

2.1.1.1.1 Addition of Boronic Acids

Advances have been made since Miyaura first reported, in 1997,[2] the use of a rhodium catalyst generated from $Rh(acac)(CO)_2$ and 1,4-bis(diphenylphosphino)butane (dppb) in the first nonasymmetric 1,4-addition of aryl- and alkenylboronic acids to enones. Asymmetric rhodium-

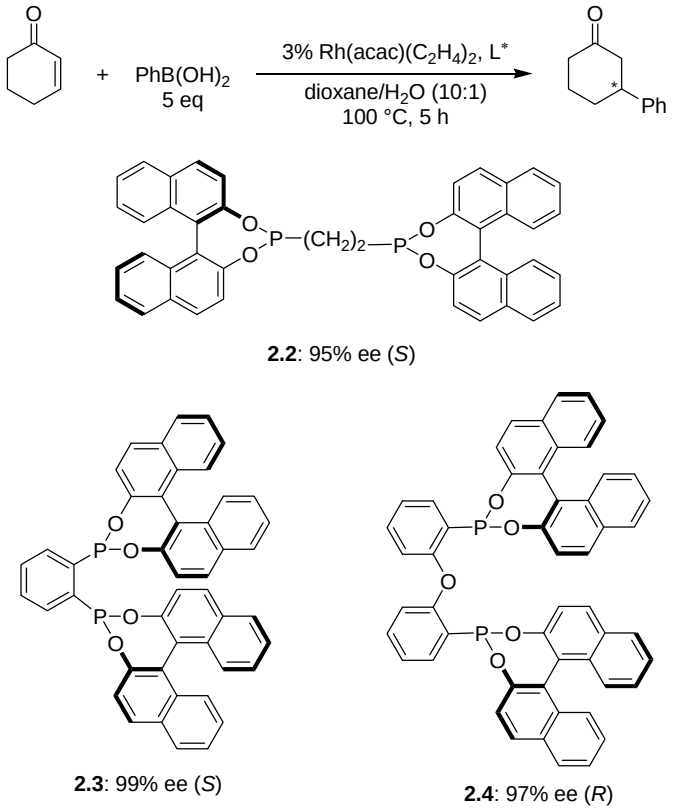
catalyzed conjugate addition was later reported by Hayashi and Miyaura in 1998[3] following some modifications of the initial protocol described by Miyaura. The notable modifications that favored high catalytic activity and high enantioselectivity included the use of $Rh(acac)(C_2H_4)_2$ as a rhodium catalyst precursor, binap as a chiral ligand, high reaction temperature of about 100 °C, and a 10:1 mixture of dioxane and water as solvent.[14] Scheme 2.1 shows a typical example of the reaction involving 2-cyclohexenone and 2.5 equiv of phenylboronic acid in the presence of 3 mol % of $Rh(acac)(C_2H_4)_2$ and (*S*)-binap **2.1** in the dioxane/H_2O (10:1) at 100 °C for 5 h, which gave 93% yield of (*S*)-3-phenylcyclohexanone in 97% enantiomeric purity.[15]



Scheme 2.1

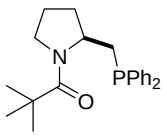
Under these standard conditions, with slight variations in the amount of boronic acids used, rhodium-catalyzed asymmetric 1,4-additions were carried out successfully with high yields and enantioselectivity for both cyclic and linear enones accompanied with a variety of arylboronic acids.[15]

Aside from binap, other chiral ligands have shown high enantioselectivity for various types of enones and boronic acids. Amongst these are the 1,1′-binaphthol-based diphosphonites (**2.2**, **2.3** and **2.4**) reported by Reetz to be strongly dependent on their achiral backbone.[16] Thus, using the same standard conditions mentioned earlier with variations in ligand used, high selectivities similar to those obtained with the use of binap were also observed (Scheme 2.2).



Scheme 2.2

Tomioka also showed that bidentate amidomonophosphine ligand **2.5** derived from L-proline was a good ligand for asymmetric addition to cyclic enones (Figure 2.1).[17] This was attributed to its behaviour as a hemilabile ligand with the phosphorus atom strongly bound to rhodium(I) and the amide carbonyl oxygen coordinatively labile.

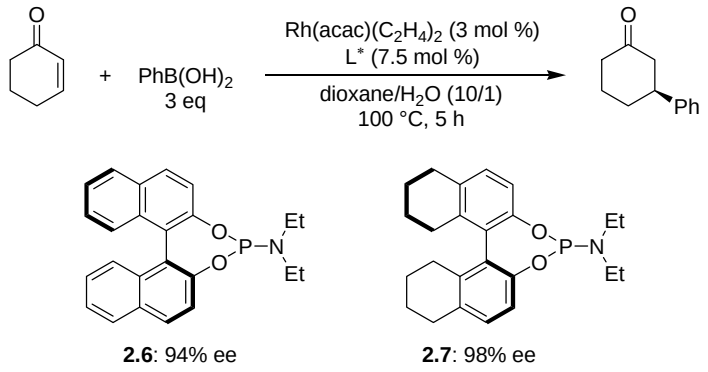


2.5: 96% ee

Figure 2.1 Bidentate Amidomonophosphine Ligand **2.5**

Subsequently, Feringa reported the high efficiency and enantioselectivity of rhodium-catalyzed conjugate addition of arylboronic acids to cyclic enones with the aid of monodentate phosphoramidites (Scheme 2.3).[18] Screening and temperature-dependent studies proved that the

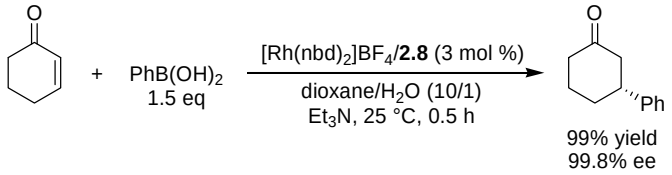
catalyst based on phosphoramidite **2.7** was the most enantioselective with high levels up to 98% ee even at high temperatures in polar solvents. Despite these harsh conditions (dioxane, H_2O, and 100 °C for 5 h), the rhodium-bound phosphoramidites were found to possess remarkable stability.[19]

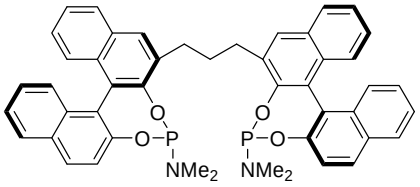


2.6: 94% ee **2.7**: 98% ee

Scheme 2.3

Further studies by Yamamoto and Miyaura on rhodium(I)-chiral phosphoramidite complexes have resulted in the development of chiral bidentate phosphoramidites, which were synthesized from Shibasaki's linked-(*R*)-BINOL[20,21] and $P(NMe_2)_3$ as a ligand for rhodium-catalyzed asymmetric conjugate addition of arylboronic acids to various enones (Scheme 2.4).[22] A complex between ligand **2.8** and $[Rh(nbd)_2]BF_4$ in the presence of Et_3N aided the fast addition to cyclic enones with 2 h (or even less) at room temperature with yields up to 99% and selectivities between 96-99.8% ee. Although with acyclic enones, yields and selectivities were widely varied ranging from 62-98% yield and 66-94% ee, respectively.



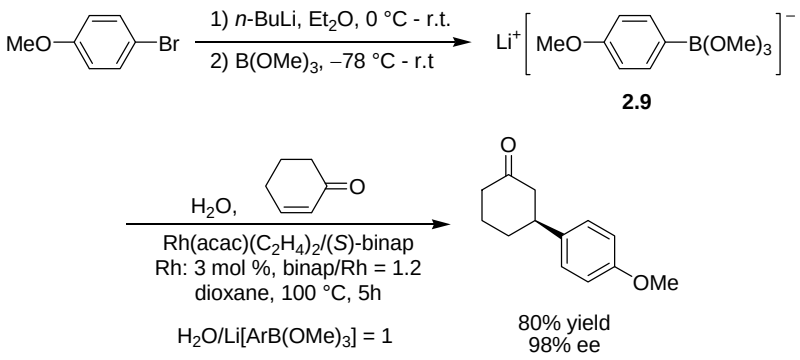


2.8

Scheme 2.4

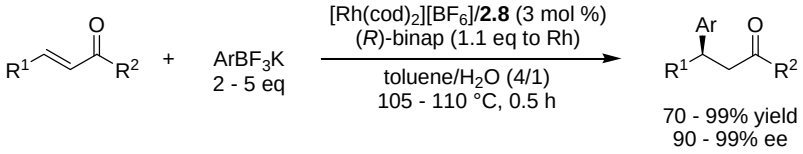
2.1.1.1.2 Addition of Other Organoboranes

Further investigation into the use of organoboron reagents has given rise to various options aside from boronic acids. Hayashi reported the use of lithium trimethyl arylborates (e.g. **2.9**) which were generated *in situ* by the treatment of aryl bromides with *n*-butyllithium and trimethoxyborane for the asymmetric conjugate addition to enones (Scheme 2.5).[23] This one-pot reaction provided an alternative way of obtaining higher yields than those obtained with arylboronic acids because studies of the reaction condition indicated that the amount of water had an effect on the overall yield but left enantioselectivity unaffected. Hence, the highest yield was observed with 1:1 ratio of water to **2.9** with 80% yield and 98% ee. However, an intriguing case was observed involving the use 2-bromonaphthalene, in which 0.1 mol% catalyst loading gave a yield of 96% and 99% enantiomeric purity.



Scheme 2.5

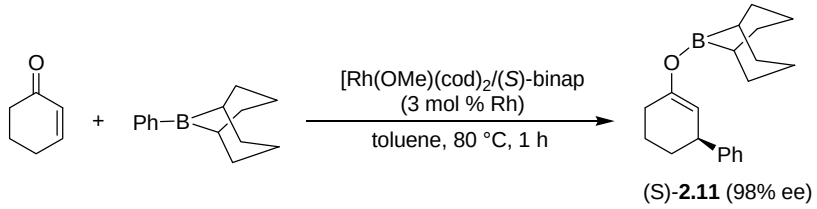
Compared to organoboronic acids, potassium organotrifluoroborates **2.10** which are generally more stable were shown by Darses and Genet to favor the asymmetric rhodium-catalyzed 1,4-addition (Scheme 2.6).[24] The conjugate addition reaction of aryltrifluoroborates such as phenyltrifluoroborate to enones such as 2-cyclohexenone proceeded at 105–110 °C in the presence of a cationic rhodium catalyst generated from $[Rh(cod)_2][PF_6]$ and (*R*)-binap, to give high yield and 98% ee of desired product. Due to the poor catalytic nature of the neutral rhodium complex generated from $Rh(acac)(C_2H_4)_2$ for the reaction organotrifluoroborates, $[Rh(cod)_2][PF_6]$ was employed. Also, enantioselectivity was seen to be strongly dependent on the solvent used.



Scheme 2.6

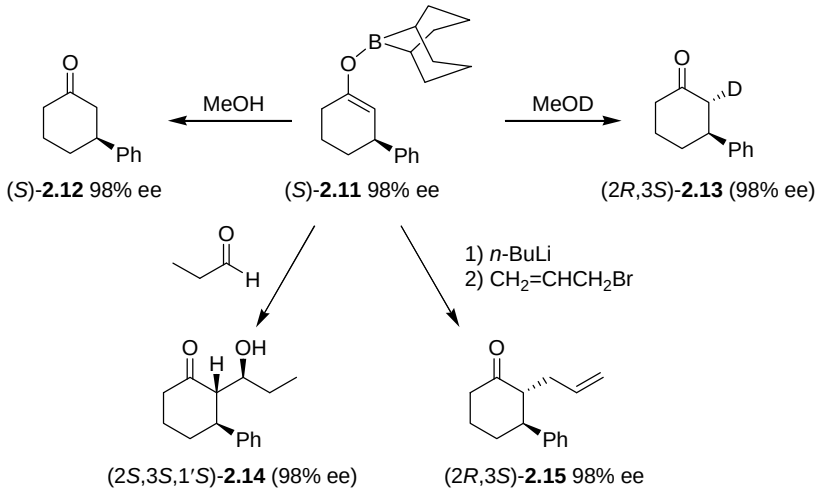
In 2003, Hayashi and coworkers were able to report the generation of chiral boron enolates by rhodium-catalyzed asymmetric conjugate addition of 9-aryl-9-borabicyclo[3.3.1]nonanes (*B*-Ar-9BBN) to α,β-unsaturated ketones (Scheme 2.7).[25] This reaction proceeded with high enantioselectivity (98% ee) in toluene at 80 °C in the presence of a

rhodium catalyst generated from $[Rh(OMe)(cod)]_2$ and (*S*)-binap to give a high yield of the boron enolate (S)-**2.11**.



Scheme 2.7

They were also able to show examples of interesting reactions **2.11** could undergo with various electrophiles such as methanol-*d*, propanal, and allyl bromide to give the corresponding 2-substituted (3*S*)-3-phenylcyclohexanones with perfect regio- and diastereoselectivities (Scheme 2.8).

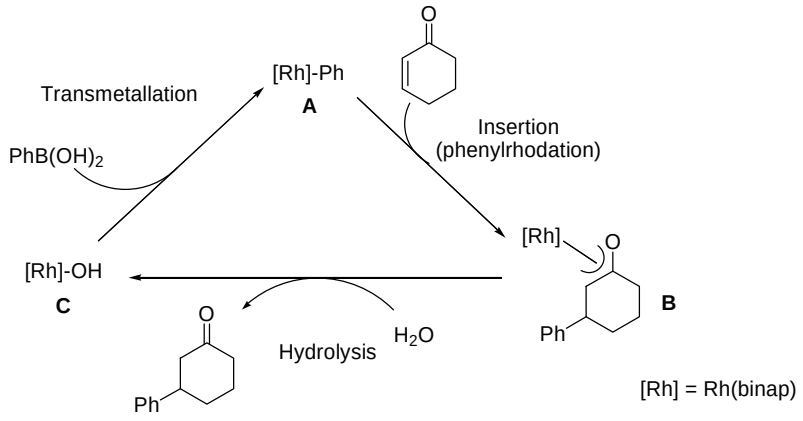


Scheme 2.8

2.1.1.1.3 Catalytic and Stereochemical Pathways

By characterizing the different intermediates involved in the rhodium-catalyzed 1,4-additions using $RhPh(PPh)_3(binap)$ as a key intermediate, Hayashi and coworkers were able to elucidate the catalytic cycle of the reaction between phenylboronic acid and 2-cyclohexenone

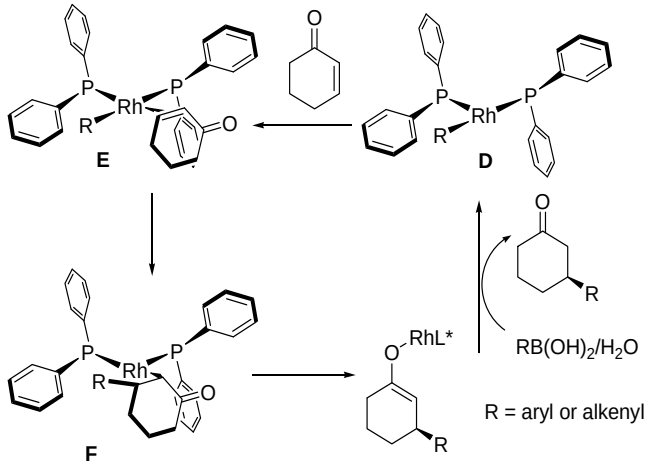
(Scheme 2.9).[26] The reaction was observed to proceed through three intermediates, phenylrhodium **A**, hydroxorhodium **B**, and oxa-π-allylrhodium **C** complexes. The reaction of 2-cyclohexenone with **A** gave **B** via the insertion of the carbon-carbon double bond of the enone into the phenyl-rhodium bond followed by isomerization into the thermodynamically stable complex. Complex **B** then undergoes immediate conversion into **C** through the hydrolytic addition of water, liberating the phenylation product, 3-phenylcyclohexanone. Regeneration of phenylrhodium **A** was aided by the transmetalation of phenyl group from boron to rhodium by the addition of phenylboronic acid.



Scheme 2.9

Focusing on the stereochemical pathway in the reaction catalyzed by the rhodium complex coordinated to (*S*)-binap shown in Scheme 2.10, the absolute configurations of all the 1,4-addition products were predicted by this unique stereocontrol model. For obtaining the *S* absolute configuration using (*S*)-binap, the (*S*)-binap-rhodium intermediate **D** was shown to possess an open space at the lower part of the coordination site, with the upper part being blocked by one of the phenyl rings of binap ligand. This leaves the olefinic double bond of 2-

cyclohexenone to coordinate to rhodium with its *αsi* face forming **E**. A migratory insertion can then be anticipated to form a stereogenic carbon center in **F**.



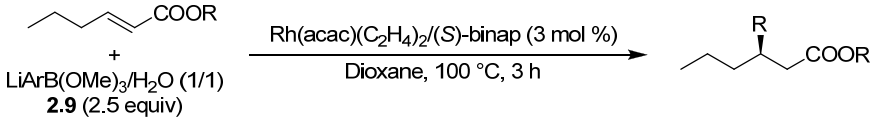
Scheme 2.10

Aside from the already mentioned rhodium-catalyzed conjugate additions, there have been many other reported asymmetric 1,4-addition reactions that involved the use of rhodium catalyst and boronic acids (or their derivative such as boronates and boroxines) or other organoboron reagents.[27-33]

2.1.1.2 α,β-Unsaturated Esters

Work on the conjugate addition of organboron reagents to *α,β*-unsaturated esters using rhodium catalysts have shown them to be good substrates with some high enantioselectivities reported. Just like their enone counterparts,[23] they gave better results when reacted with lithium arylborates rather than the corresponding arylboronic acids (Scheme 2.11).[5] The poor results obtained from the addition of phenylboronic acid to esters of large alcohols (i.e. isopropyl ester and *tert*-butyl ester) were attributed to the competitive deboronation of the phenylboronic acid resulting in consumption of the nucleophile prior to reaction with the reacting ester.[34] A brief

summary of the observed trends obtained by arylation of (*E*)-hexenoate esters in the presence of $Rh(acac)(C_2H_4)_2$/(*S*)-binap catalyst is shown in Table 2.1.



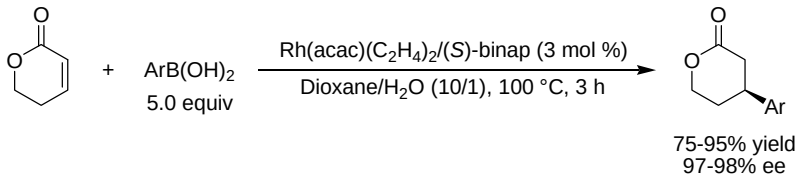
Scheme 2.11

Table 2.1 Asymmetric 1,4-Addition of Arylboron Reagents **2.9** to *α,β*-Unsaturated Esters Catalyzed by (*S*)-Binap-Rhodium (Scheme 2.11)[5]

entry	ester (R)	borates (Ar)	product	
			yield (%)	% ee (*R*)
1	Me	Ph	>99	89
2	Et	Ph	>99	91
3	*i*-Pr	Ph	96	95
4	*t*-Bu	Ph	92	96
5	*i*-Pr	4-MeC_6H_4	88	97
6	*i*-Pr	4-$CF_3C_6H_4$	98	96
7	*i*-Pr	4-ClC_6H_4	95	97
8	*i*-Pr	2-naphthyl	96	93

The yields of 3-phenylhexanoates showed decreases upon addition of lithium phenylborate to esters of sterically bulky alcohols. However, the enantioselectivity increased as the steric bulkiness of the ester moiety increased (entries 1-4). Also, with substituted phenyl and 2-naphthyl groups introduced at the *β* position of isopropyl ester, high enantioselectivities between 93% and 97% ee were obtained in high yields using the corresponding lithium arylborates (entries 5-8).

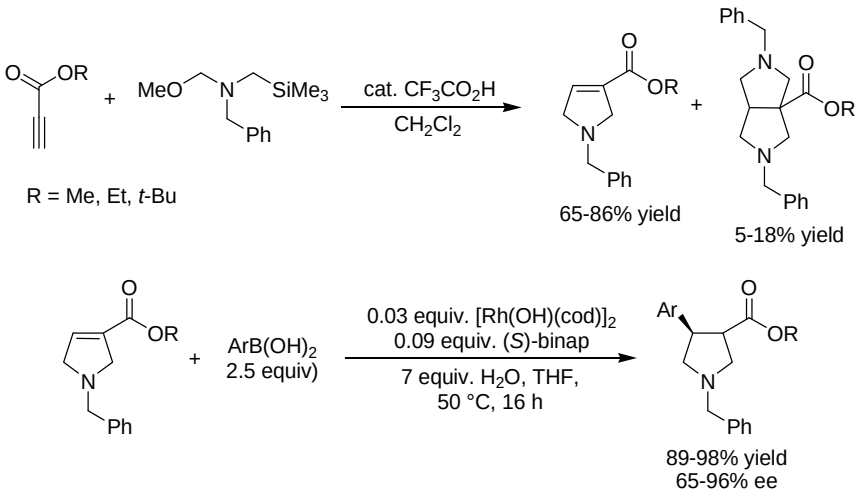
In the same report,[5] cyclic esters were shown to undergo 1,4-addition with arylboronic acids in the presence of the rhodium catalyst to afford the desired arylation products in high yields and enantioselectivities (Scheme 2.12).



Scheme 2.12

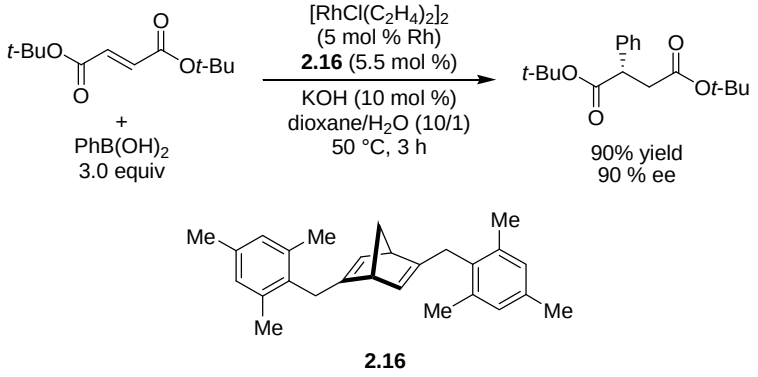
An independent report by Miyaura and coworkers also showed similar results for the asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated esters (in this case crotonate esters) in the presence of rhodium catalysts with good enantioselectivities.[6]

Scheme 2.13 shows a reported synthetic approach to obtaining asymmetric 1,3,4-trisubstituted pyrrolidines via rhodium-catalyzed 1,4-arylation of an intermediate pyrroline with arylboronic acids.[35] The provides a good application in which conjugate addition to α,β-unsaturated esters affords highly enantioselective trisubstituted pyrrolidine products. Prior to the rhodium-catalyzed 1,4-addition reaction, the substituted pyrroline esters were prepared by acid catalyzed 1,3-dipolar cycloaddition conditions using *N*-benzyl-*N*-(methoxymethyl)-trimethylsilylmethylamine as the azomethine source and propiolate esters as dipolarophiles (Scheme 2.13).[36]



Scheme 2.13

Esters such as fumaric acid diesters were also investigated as substrates for rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids using chiral norbornadiene **2.16** as an effective ligand since other phosphorus-based chiral ligands failed to induce high stereoselectivity (Scheme 2.14)[37]

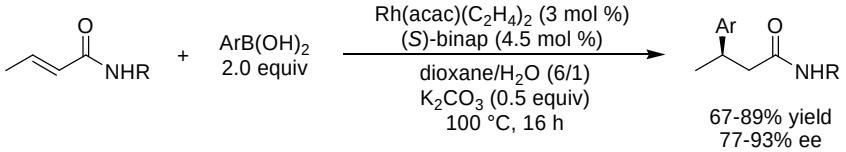


Scheme 2.14

However, continuous discovery of new and useful *α,β*-unsaturated esters, effective chiral ligands and reactive organoboron reagents, have led to reports of synthetically applicable rhodium-catalyzed 1,4-addition.[22,38-40] However, some still need improvement in terms of their yields and selectivities.

2.1.1.3 α,β-Unsaturated Amides

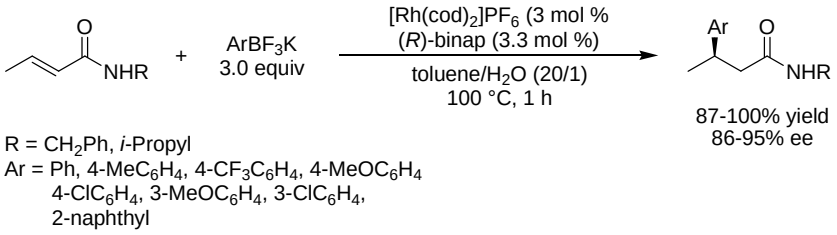
The first use of *α,β*-unsaturated amides in the asymmetric addition of arylboronic acids was performed by Miyaura.[7] Unlike enones, they suffered from poor reactivity and yields but were later found to react with complete conversion upon the addition of an aqueous base such as potassium carbonate. Hence, improved yield and enantioselectivity comparable to that of their corresponding esters were observed (Scheme 2.15).



R = CH_2Ph, *c*-Hex, H, Ph
Ar = Ph, 4-MeC_6H_4, 4-$CF_3C_6H_4$, 4-$MeOC_6H_4$

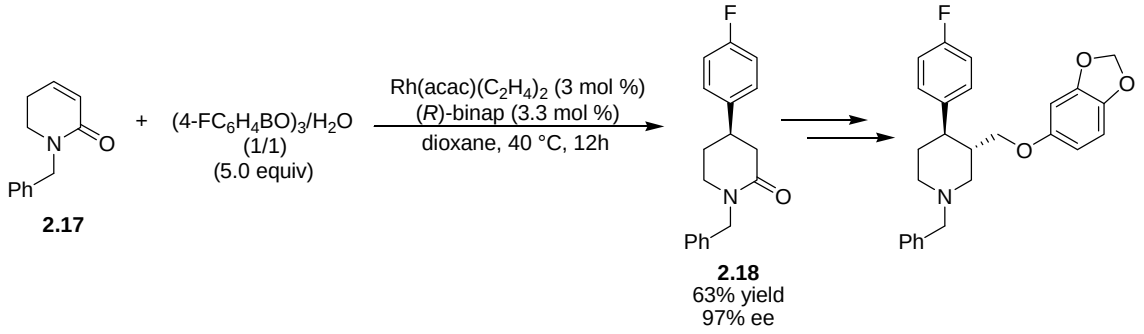
Scheme 2.15

Using previously described reaction condition for 1,4-addition to enones[24] and *α,β*-unsaturated esters,[39] Darses and Genêt reported the synthesis of chiral *β*-arylamides from the 1,4-addition of potassium aryltrifluoroborates to crotonamides by refluxing in toluene/water (20:1) in the presence of a chiral catalyst generated *in situ* from $[Rh(cod)_2]PF_6$ and (*R*)-binap (Scheme 2.16).[41] This afforded the desired 1,4-adducts in high yields and enantioselectivities. They were also able to show that unlike that rhodium-catalyzed 1,4-addition of arylboronic acids to enamides describe by Miyaura,[7] the addition of base had no influence on conversions but rather resulted in the decrease of the enantioselectivities.



Scheme 2.16

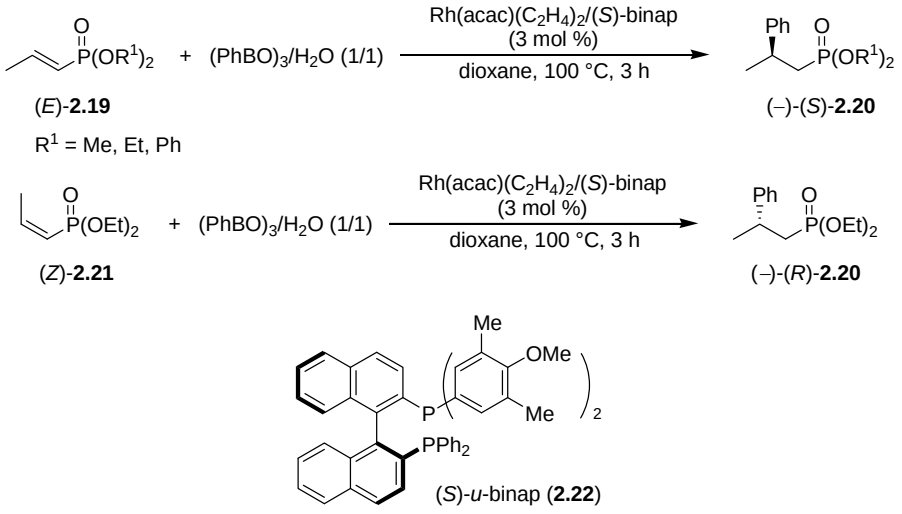
Asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated lactams facilitated the production of enantiomerically enriched 4-aryl-2-piperidinones (Scheme 2.17).[8] However, this procedure required slight modifications as seen by the absence of water and the reduction in temperature when compared with the typical protocols for acyclic α,β-unsaturated amides. In order to synthesize (-)-paroxetine, the 1,4-addition of a 4-fluorophenyl nucleophile to lactam **2.17** was envisioned since it can provide a useful intermediate. When the reaction was initially performed under standard conditions for enones using **2.17** and 4-$FC_6H_4B(OH)_2$, the 1,4-adduct **2.18** was obtained in 17% yield and 92% ee. Further investigation showed that the low yield was due to the instability of the 4-fluorophenyl rhodium(I) intermediate towards protonolysis resulting in consumption of the arylboronic acid prior to complete reaction with **2.17**. The problem was solved by running the reaction at 40 °C instead of 100 °C as well as using (4-$FC_6H_4O)_3$ with 1 equiv of water with respect to boron. Hence, a 63% yield and 97% ee of **2.18** was obtained.



Scheme 2.17

2.1.1.4 α,β-Unsaturated Phosphonates

The asymmetric 1,4-addition to *α,β*-unsaturated phosphonates was first reported by Hayashi and coworkers,[9] in which they found that the conjugate addition of arylboronic acids under the standard conditions previously reported for enones gave poor yield. For example, 44% yield was obtained for addition of phenylboronic acid to diethyl (*E*)-1-propenylphosphonate **2.19** (Table 2.2, entry 1). This was attributed to similar loss in catalytic activity as a result of large amounts of water as a co-solvent deactivating the catalyst. The reaction was improved by using arylboroxines in place of arylboronic acid and 1 equiv (to boron) of water in dioxane (Scheme 2.18). The effectiveness of the reaction was explained by the equilibration of boroxine and water with boronic acid under the reaction conditions.[42] Hence, the addition of one equiv of water is essential for obtaining high yield since almost no reaction (only 5% yield) takes place in the absence of water (entry 3).



Scheme 2.18

Table 2.2 Asymmetric 1,4-Addition of Arylboroxine to *α,β*-Unsaturated Phosphonates Catalyzed by (*S*)-Binap-Rhodium[9,42]

entry	phosphonates	$(ArBO)_3$	yield (%)	% ee
1[a]	(*E*)-**2.19**	$PhB(OH)_2$	44	84 (*S*)
2[b]	(*E*)-**2.19**	$(PhBO)_3$	94	96 (*S*)
3[c]	(*E*)-**2.19**	$(PhBO)_3$	5	
4[d]	(*E*)-**2.19**	$(PhBO)_3$	99	94 (*S*)
5[b]	(*Z*)-**2.21**	$(PhBO)_3$	96	89 (*R*)
6[d]	(*Z*)-**2.21**	$(PhBO)_3$	98	92 (*R*)

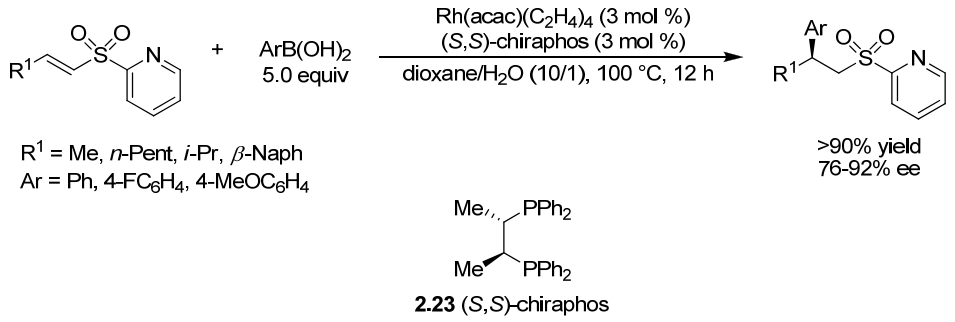
[a] The reaction of $ArB(OH)_2$ in dioxane/H_2O (10/1). [b] The reaction was carried out under conditions described in Scheme 2.18 using (*S*)-binap. [c] The reaction was carried out without the addition of H_2O. [d] (*S*)-*u*-binap **2.22** was used in place of (*S*)-binap.

It was also observed that the asymmetric phenylation of diethyl (*Z*)-propenylphosphonate **2.21** with phenylboroxine gave the *R* isomer of the 1,4 adduct in 96% yield and 89% ee (entry 5). The observation of the opposite absolute configuration of products **2.20** showed that the dialkoxyphosphinyl moiety on the 1-alkenylphosphonate played a key role in the enantioface selection. They were also able to show that unsymmetrical substituted binap ligand such as (*S*)-*u*-binap **2.22**, could slightly increased the enantioselectivities and yield (entry 4 and 6).

2.1.1.5 *α,β-Unsaturated Sulfones*

Recently, Carretero reported the successful enantioselective rhodium-catalyzed conjugate addition of arylboronic acids to acyclic *α,β*-unsaturated sulfones (Scheme 2.19).[11] Interestingly, 2-pyridylsulfonyl group was essential for achieving the catalyzed conjugate addition in *α,β*-unsaturated sulfones because of the key coordination of rhodium catalyst with the appropriately

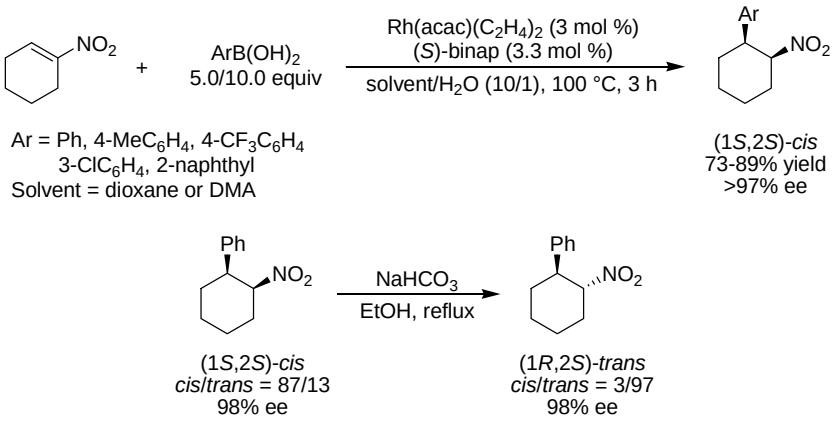
placed nitrogen atom in the substrates.[43] This substrate also allowed for its basic elimination via Julia-Kociensky olefination reaction,[44-46] hence providing a practical alternative for creating a carbon-carbon double bond (i.e. allylic substituted alkenes). Ligand screening placed ligand **2.23** as the best suited catalytic ligand for the conjugate addition besides binap and tol-binap affording complete conversion with high yield (>90%) and high enantioselectivities (76-92% ee).



Scheme 2.19

2.1.1.6 1-Nitroalkenes

Another good group of substrates reported by Hayashi for rhodium-catalyzed 1,4-addition of organoboronic acid are nitroalkenes in which addition to 1-nitrocyclohexene for example, proceeded with high diastereoselectivity to afford the thermodynamically less stable *cis* isomer preferentially (Scheme 2.20). Using 1-nitrocyclohexene which is a commercial available 1-nitroalkene, the reaction was performed following the standard conditions[15] for enones for 3 h to give 89% yield. Although the main 1,4-addition product was the *cis* isomer (*cis*/*trans* = 87/13), both isomers had 98% enantiomeric purity. *Cis*-*trans* equilibration was obtained by treatment of the *cis*-rich mixture with sodium bicarbonate in refluxing ethanol to obtain the thermodynamically more favorable *trans*-isomer (*trans*/*cis* = 97/3) without loss of its enantiomeric purity. The preferential formation of the *cis* isomer was tied to the equatorial protonation of a rhodium nitronate intermediate in the catalytic cycle (Figure 2.2).



Scheme 2.20

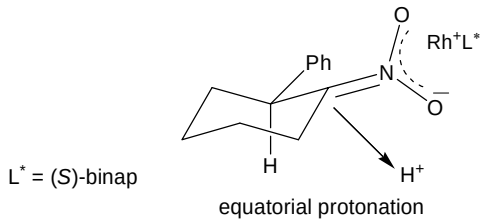
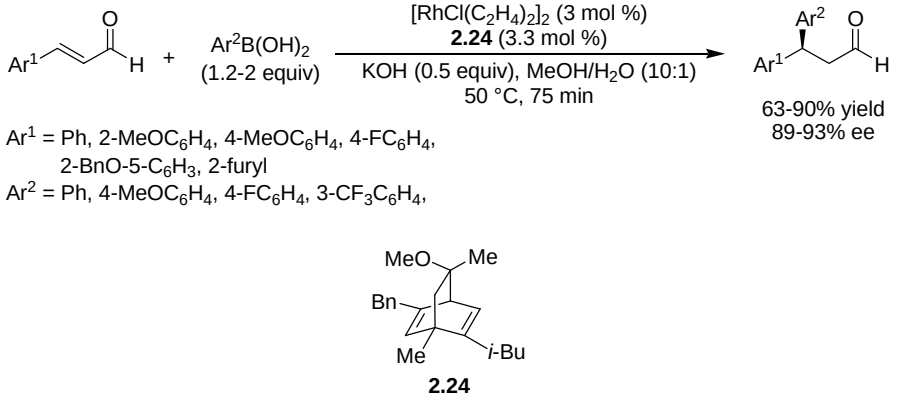


Figure 2.2 Nitronate Intermediate for Phenylation of 1-Nitrocyclohexene

In 2003, further investigation into the effects of combination of chiral monodentate phosphoramidite ligands in rhodium-catalyzed 1,4-addition of boronic acids to enones and nitroalkenes as substrates were performed by Feringa and coworkers.[47] Since the catalytically active species contains two monodentate ligands, a mixture of two different phosphoramidites (Lx and Ly) will lead to the formation of two homo-complexes, $Rh(Lx)_2$ and $Rh(Ly)_2$, and the hetero-complex Rh(LxLy) simultaneously. They were actually able to establish that catalysts based on hetero-combinations of ligands which represents a new catalyst, were more effective than the homo-combinations.

2.1.1.7 α,β-Unsaturated Aldehydes

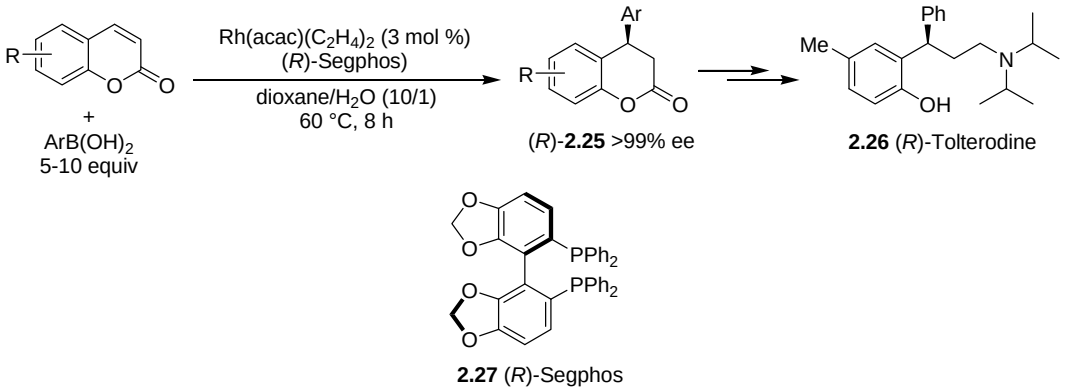
Earlier reports on the use of unsaturated aldehydes as substrates for asymmetric 1,4-addition resulted in either the formation of racemic product,[48] or the formation of modest yields of 3-alkyl-3-arylpropanal.[29] The competition between the 1,2-addition pathway and the 1,4-addition pathway has placed serious complication in developing a notable conjugate addition to unsaturated aldehydes (discussed in chapter 1). However, work by Carreira and coworkers have seen to the development of a noteworthy means of performing asymmetric 1,4-addition of arylboronic acids to cinnamaldehyde derivatives using chiral dienes (substituted bicyclo[2.2.2]octadiene) as ligands (Scheme 2.21).[49] The screening of various ligands via a systematic variation of pseudo-C_2 symmetric ligand scaffold places ligand **2.24** as the best candidate providing optically enriched 3,3-diarylpropanals in 63-90% yield and 89-93% ee. This method proved to be both chemoselective (unsaturated aldehydes rather than saturated) and regioselective (1,4-addition rather than 1,2).



Scheme 2.21

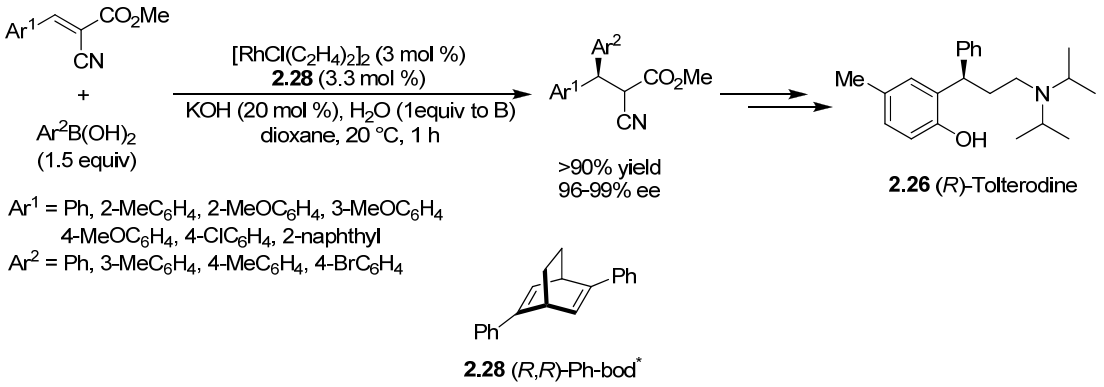
2.1.1.8 Other Substrates

Other substrates have been found to be suitable for 1,4-addition because of the applications and ability to create structural motifs often found in pharmaceutical. One of these cases was the reported use of coumarin[50] derivatives in the rhodium-catalyzed 1,4-addition of arylboronic acid to give 4-arylchroman-2-nones **2.25** in good yield and excellent enantioselectivities (>99% ee) (Scheme 2.22).[51] Amongst the various ligands which were successful for asymmetric addition, (*R*)-Segphos **2.27**[52] gave the best results for both yield and enantioselectivity. This provided an efficient route for arriving at an enantiomerically enriched intermediate used in asymmetric synthesis of (*R*)-tolterodine **2.26**,[53,54] an important urological drug.



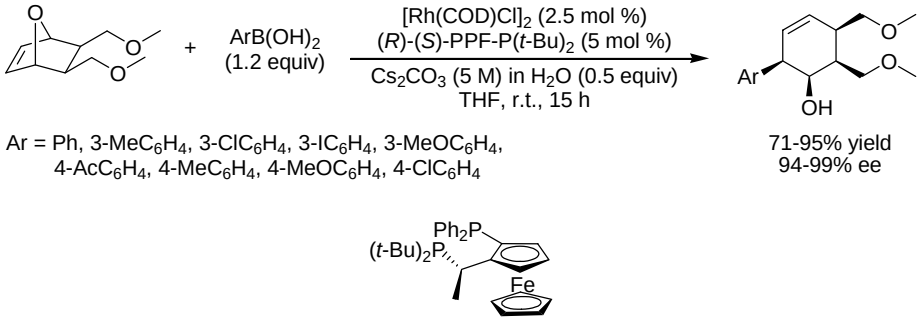
Scheme 2.22

Methyl (*E*)-2-cyano-3-arylpropenoates were also shown to be useful substrates for the asymmetric conjugate addition of arylboronic acids in the presence of rhodium catalysts to give high yields (90-99%) of the corresponding methyl 3,3-diaryl-2-cyanopropanoates with high enantioselectivity (96-99% ee) (Scheme 2.23).[55] This was accomplished with the aid of a chiral diene ligand, (*R*,*R*)-Ph-bod* **2.28**.[49,56] This was also shown as a key step in the sequential five-step synthesis of (*R*)-tolterodine starting from its corresponding cyanoacetate derivative.



Scheme 2.23

Related to conventional 1,4-addition substrates, Lautens and coworkers were able to report the first rhodium-catalyzed asymmetric addition of organoboronic acid to oxabicyclic alkenes (oxanorbornene derivatives) resulting in an asymmetric ring opening reaction with high yields (71-95%), enantioselectivity (94-99% ee) and diastereoselectivity (Scheme 2.24).[13] This reaction proceed under very mild conditions in the presence of catalytic $[Rh(COD)Cl]_2$ and PPF-P*t*-Bu_2 **2.29** system.

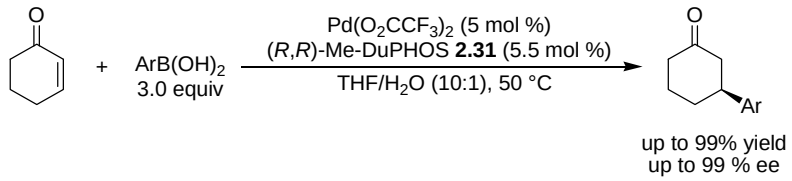


Scheme 2.24

2.1.2 Palladium-Catalyzed

In 2005, Minnaard and coworkers reported the first palladium-catalyzed 1,4-addition of arylboronic acids to α,β-unsaturated ketones, aldehydes and esters (Scheme 2.25).[57] Using 2-

cyclohexenone because of its commercial availability as the benchmark reaction, they were able to establish that fast Pd-C bond cleavage was necessary to avoid the competing *β*-hydride elimination which led to the formation of Heck-type products.[58,59]



Scheme 2.25

Figure 2.3 depicts three bidentate ligands **2.30-32** that were tested and showed successful conversion. However, (*R*,*R*)-Me-DuPHOS **2.31** gave the best results with complete conversion of the starting material, 2-cyclohexenone to product within 12 h with good yield and 98% ee; exclusive of any 1,2 addition product or Heck coupling product. While exploring the scope of arylboronic acids, they noted that electron poor arylboronic acids such as *m*-nitrophenylboronic acid, lacked reactivity.

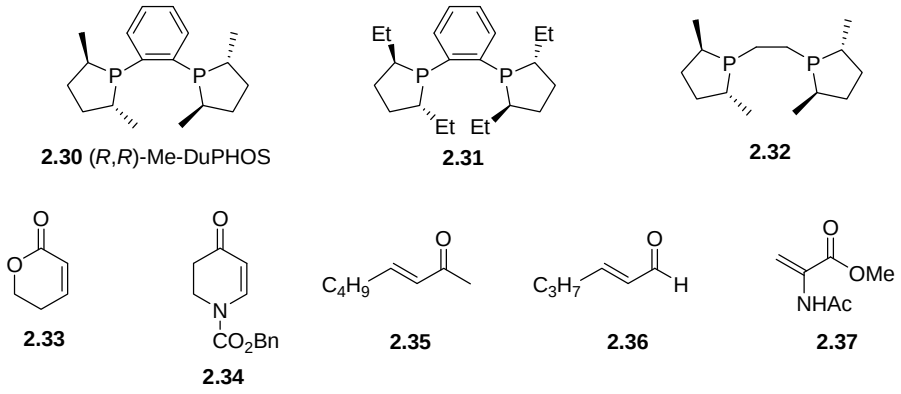
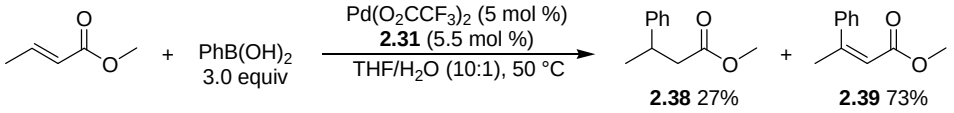


Figure 2.3 Bidentate Ligands and Substrates tested in Pd-Catalyzed 1,4-Addition

Substrates such as lactone **2.33** and dihydropyridone **2.34** underwent full conversion with high enantioselectivities of 94% ee and >99% ee respectively. On the other hand, linear substrates such as ketone **2.35** and aldehyde **2.36** showed incomplete conversion with reasonable (60% ee for **2.35**) to moderate (49% ee for aldehyde **2.36**, without 1,2-addition product)

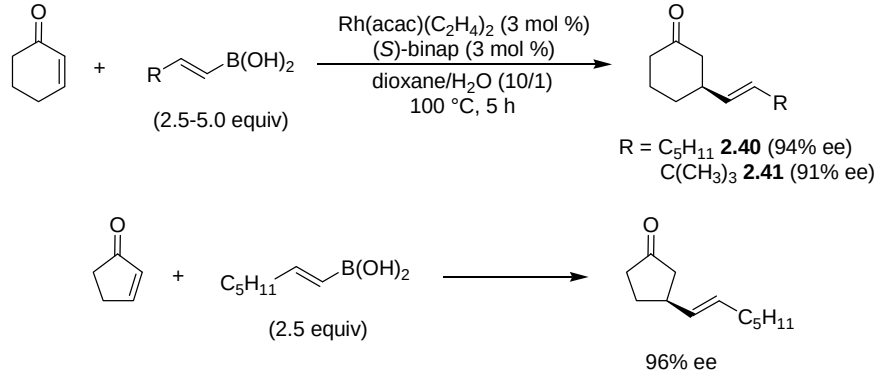
enantioselectivities. The use of acrylate **2.37** showed no reaction. An attempt to perform the addition to methyl *E*-crotonate resulted in the formation of a dominant Heck coupling product **2.39** over the desired 1,4-adduct **2.38** (Scheme 2.26).



Scheme 2.26

2.2 Alkenylation of Enones

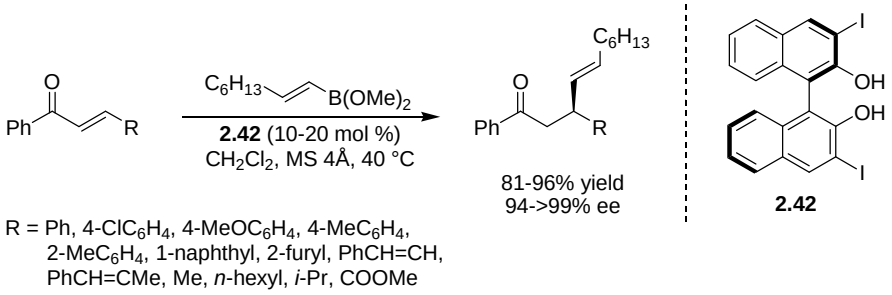
Initial work on the asymmetric conjugate addition of organoboronic acids to enones described by Hayashi also involved the addition of alkenylboronic acids aside from the previously mention arylboronic acids.[14,60] Scheme 2.27 shows examples of the initial 1,4-addition of alkenylboronic acids (**2.40** and **2.41**) to cyclic enones in the presence of catalyst generated from $Rh(acac)(C_2H_4)_2$ and (*S*)-binap to afford the respective 1,4-adduct in high enantioselectivities.[60] This high selectivity was partly attributed to the lack of reactivity of the alkenylboronic acids towards enones in the absence of catalysts.



Scheme 2.27

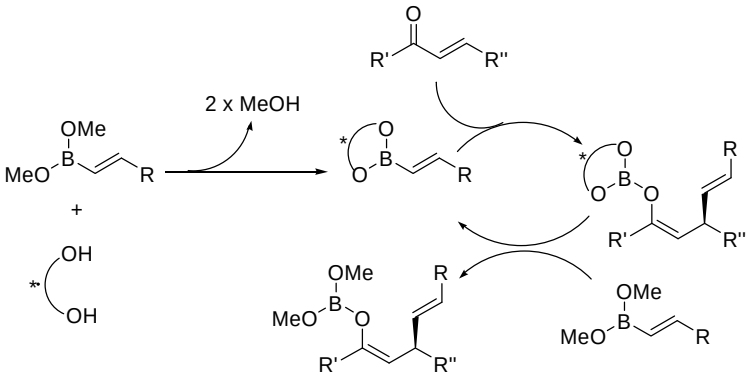
Besides the use of boron for asymmetric transfer of alkenyl groups, alkenyl transfer has also been accomplished using Si,[61,62] Sn,[63] and Zr[64] derivatives in the presence of rhodium catalysts.

Without the dependence of a heavy metal, Chong and coworkers reported the catalytic asymmetric alkenylation of enones using boronates in the presences of catalytic amounts of 3,3′-disubstituted binaphthols **2.42** with good yields and excellent enantioselectivities (up to >99% ee) (Scheme 2.28).[65]



Scheme 2.28

Due to previous work on the asymmetric 1,4-addition of alkynylboronates to enones,[66] they reasoned that activation of the enone could be obtained by esterification with a suitable chiral diol. During the investigation, it was gathered that no alkenylation product is obtained in the absence of binaphthol and that water or methanol inhibit the reaction. Hence, the addition of appropriate molecular sieves was introduced to alleviate the problem. This was factored into the proposed catalytic mechanism wherein catalysis of the reaction involved the transesterification of dimethyl boronate with binaphthol to produce a more Lewis acidic/reactive boronate accompanied by the displacement of methanol (Scheme 2.29). This has been supported by recent theoretical work by Goodman and Pelligrinet using density functional theory (DFT) studies to prove that binaphthol-derived alkenylboronate obtained from the reversible exchange of methoxy ligand was highly Lewis acidic and strongly coordinated to the enone's carbonyl oxygen in a reversible fashion.[67] This lowered the energy barrier for the subsequent conjugate addition.



Scheme 2.29

The high selectivities obtained in these conjugate addition reactions were explained by invoking the formation of a six-membered chair-like transition state with the option of two possibilities (Figure 2.4). Amongst the two possibilities, one (disfavored transition state) experiences destabilization due to steric interaction between the alkenyl group and the binaphthol when the *β*-substituent of the enone is pseudo-equatorial. Thus, the reaction was thought to proceed via the other (favored) transition state to yield the observed enantiomer. Using the (*R*)-3,3′-disubstituted BINOL and following the favored transition state as illustrated in Figure 2, the (*S*) enantiomer of the 1,4-addition product should be the major enantiomer formed regardless of the alkenylboronate used (*trans* or *cis*). This corresponds to the observed results reported by Chong and coworkers.[65] Whereas, if the disfavored transition state was followed, the (*R*) enantiomer would have been the major enantiomer formed.

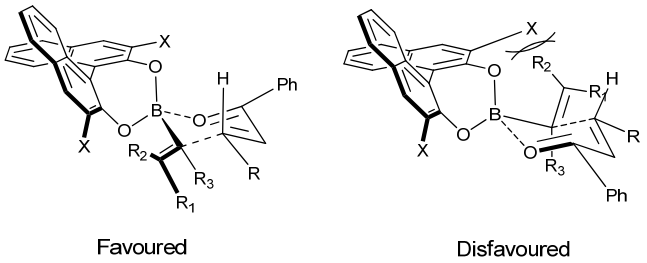
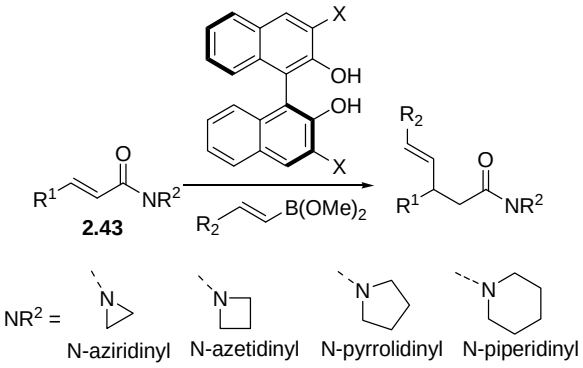


Figure 2.4 Proposed Transition States for Alkenylation of Enones

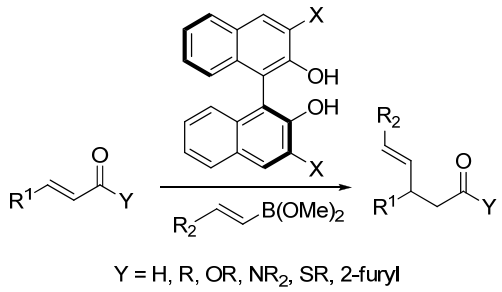
2.3 Proposal

As already mentioned in the previous section, work in our group has successfully developed asymmetric addition of alkenylboronates to enones using chiral 3,3′-disubstituted binaphthols (Scheme 2.28).[65] In order generalize the use of 3,3′-disubstituted binaphthols as catalysts in the asymmetric 1,4-addition of alkenylboronates to *α,β*-unsaturated carbonyl compounds, reactions using *α,β*-unsaturated amides **2.43** were proposed (Scheme 2.30).



Scheme 2.30

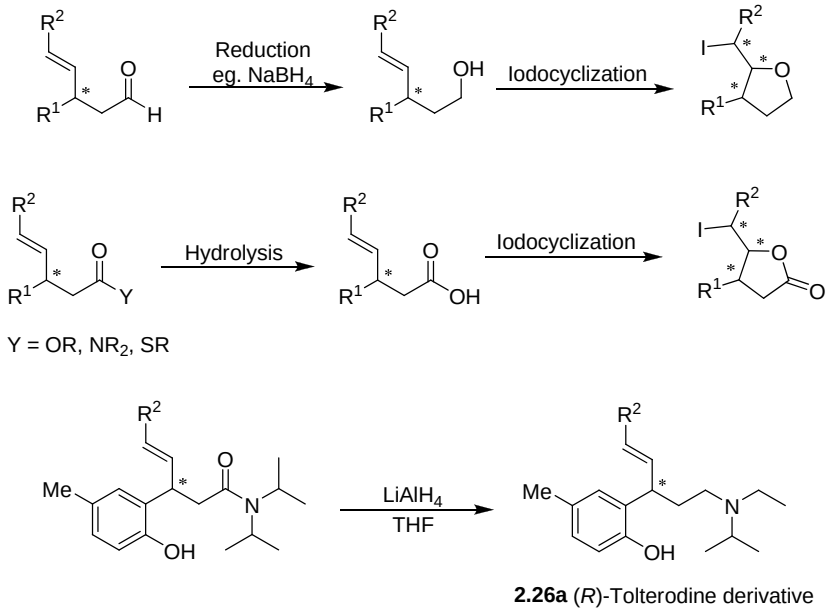
This would pave the way for further investigation into a proposed metal-free 3,3′-disubstituted binaphthol-catalyzed alkenylboration of other *α,β*-unsaturated carbonyl compounds as portrayed in Scheme 2.31 and other possible derivatives.



Scheme 2.31

The use of these *α,β*-unsaturated carbonyl compounds would aid in obtaining useful enantiomerically enriched substrates for further transformations (Scheme 2.32). For instance, the

use of α,β-unsaturated aldehydes in the asymmetric alkenylboration would yield enantiomerically enriched 1,4-addition products which can then undergo a simple reduction into primary alcohols followed by subsequent cyclization to afford disubstituted tetrahydrofuran (THF) compounds. A similar transformations could also be drawn for 1,4-addition products of α,β-unsaturated amides, esters and thioesters which could undergo hydrolysis and cyclization to obtain lactones. The synthesis (*R*)-tolterodine **2.26** or closely related compounds **2.26a** using 1,4-adducts of α,β-unsaturated amides would also pose as an interesting application.



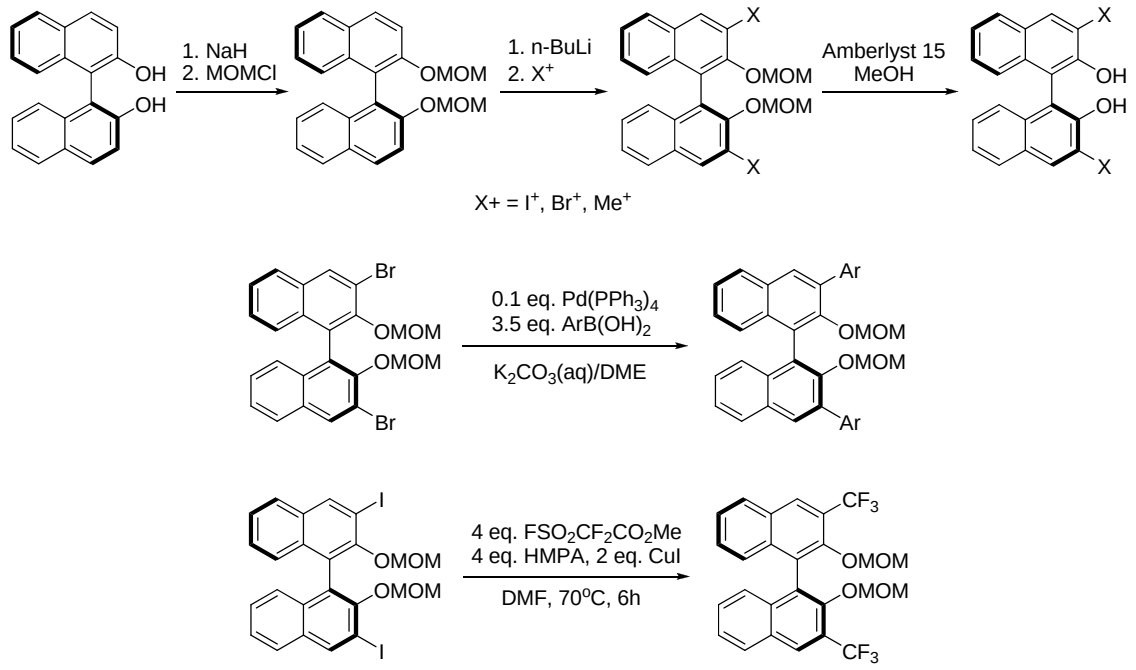
Scheme 2.32

2.4 Results and Discussion

2.4.1 Preparation of 3,3′-Disubstituted Binaphthols

Based on the previous research in our group, chiral binaphthols (BINOLs) with different substituents on the 3- and 3′- positions have been found to exert high degrees of reactivity and enantioselectivity in catalytic 1,4-addition reactions.[65,66,68-71] Reported work on the catalytic asymmetric allylation[72] and Petasis[73] reactions by Schaus and coworkers have also shown these

chiral BINOL-derived catalysts as good catalytic promoters in highly enantioselective reactions. Although some of these chiral BINOLs are commercially available, they were conveniently synthesized from their unsubstituted binaphthol precursors. This involved the consecutive methoxymethyl (MOM)-protection of the hydroxyl group on the BINOL, *o*-metalation (*o*-lithiation), substitution of the appropriate electrophile (X^+) on the 3- and 3′- positions, and the subsequent deprotection of the hydroxyl group with the help of acidic resins (Scheme 2.33). In order to obtain 3,3′-disubstituted binaphthol with aryl and CF_3 substituents using the MOM-protected BINOLs, extended procedures were required. The aryl-substituted BINOLs were obtained by Suzuki coupling, while the CF_3-substituted BINOL was obtained via reaction with methyl fluorosulfonyldifluoroacetate[74] using a 3,3′-dihalo BINOL as starting material.



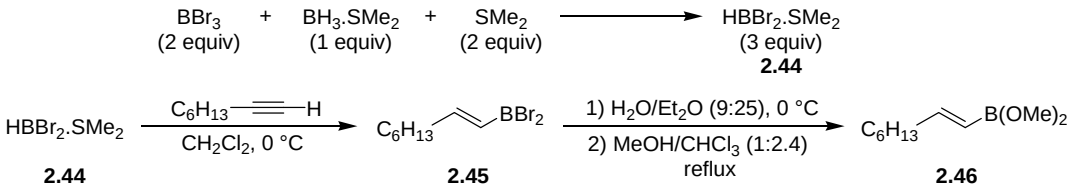
Scheme 2.33

However, due to the remarkable high yield and enantioselectivity observed when 3,3′-diiodobinaphthol **2.42** was used for alkenylation of enones,[65] more emphasis were placed on its use as the best candidate for the asymmetric 1,4-addition to *α,β*-unsaturated carbonyl compounds

and derivatives. Its high reaction rate was tied to the electron-withdrawing capacity of the iodide, hence creating a more activated and better Lewis acidic BINOL-boronate species. The excellent enantioselectivity was attributed to the bulky nature of the iodide substituent, which reduces the chance of forming the disfavored enantiomer as shown in Figure 2.4.

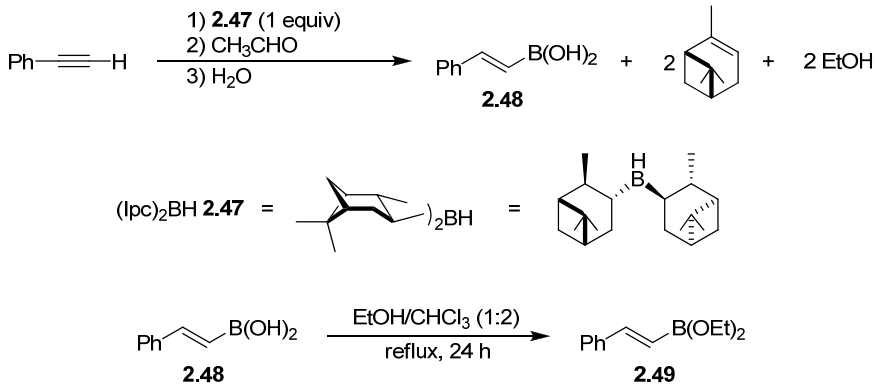
2.4.2 Preparation of Alkenylboronates

Since boronic esters (boronates) proved to be more reactive and afforded better yield and selectivity than their corresponding boronic acids,[65,72] much emphasis was placed on the synthesis of potential alkenylboronates. Scheme 2.34 shows the synthesis of (*E*)-dimethyl 1-octenylboronate **2.46** by a method developed by Brown.[75-78] This method involved the redistribution reaction between boron tribromide, dimethyl sulfide and the readily available borane-dimethyl sulfide complex to generate dibromoborane-dimethyl sulfide complex **2.44**. Due to the reactivity of this haloborane adduct,[75] it proved to be a convenient reagent for hydroboration, hence it was applied in the hydroboration of terminal alkynes. Due to convenience and commercial availability, 1-octyne was mainly used. Dibromoborane-dimethyl sulfide **2.44** was then used for direct hydroboration of 1-octyne to afford 1-alkenyldibromoborane **2.45**.[76] Reaction of **2.45** with a mixture of water and ether (9:25) resulted in the formation of the corresponding boronic acid and subsequent reflux in an azeotropic mixture of methanol and chloroform (1:2.4) gave the desired boronate **2.46**. In order to favor the formation of the boronate **2.46** (i.e the forward reaction), which is in equilibrium with its corresponding boronic acid, 3Å molecular sieves were incorporated into the reaction to facilitate the removal of water formed.



Scheme 2.34

Although most of the boronic acids could be obtained via hydroboration, some boronic acids required a different hydroboration approach. In the process of synthesizing (*E*)-styrylboronic acid, hydroboration was accomplished with the aid of diisopinocampheylborane (Ipc_2BH) **2.47**, followed by oxidative dealkylation using acetaldehyde to afford the diethyl boronic ester. Subsequent *in situ* treatment with water gave the desired boronic acid **2.48** (Scheme 2.35).[73] Esterification of **2.48** in an azeotropic mixture of ethanol and chloroform (1:2) afforded diethyl boronate **2.49**.[79] It was also realized that 3Å molecular sieves were very crucial during the esterification of **2.48**.



Scheme 2.35

2.4.3 Preparation of *α,β*-Unsaturated Carbonyl Compounds and Derivatives

2.4.3.1 Preparation of α,β-Unsaturated N-Acylaziridine

Our first and crucial *α,β*-unsaturated *N*-amide analyzed, *α,β*-unsaturated *N*-acylaziridine, was chosen based on its arguable structural similarities to enones. Unlike other amides, *N*-

acylaziridines possess unique characteristics that lead to increased reactivity and usefulness in organic synthesis. These unique characteristics were attributed to the hybridization of the nitrogen. This was as a result of the much greater *s*-character of the *N*-acylaziridine nitrogen's lone pair (sp^3-orbital) as compared to typical amides. The lone pair of the nitrogen is thought to interact very poorly with the adjacent carbonyl group.[80,81] Hence, this minimizes the usual electron delocalization experienced by typical amides as shown in Figure 2.5. Therefore, in *α,β*-unsaturated *N*-acylaziridine, species ***a*** tends to be the most favorable resonance contributor aside from the major contributor ***b*** since it has similar a electron system when compared with enones. The *s*-character of the *N*-acylaziridine nitrogen's lone pair also implies that the nitrogen atom inverts very slowly.[82]

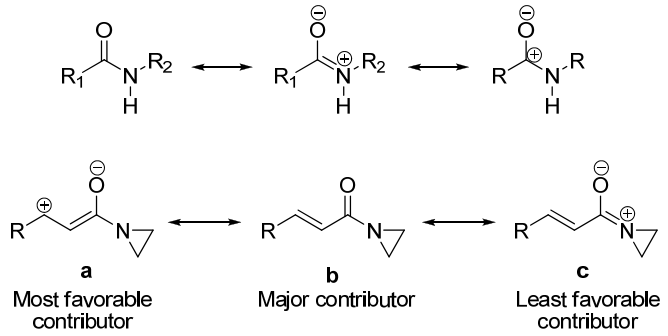
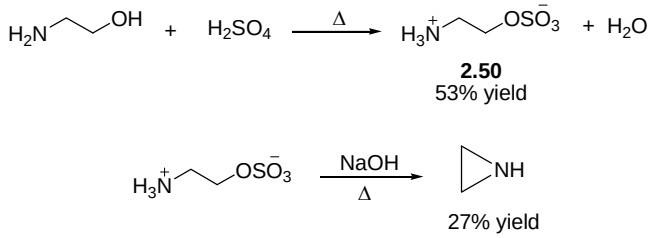


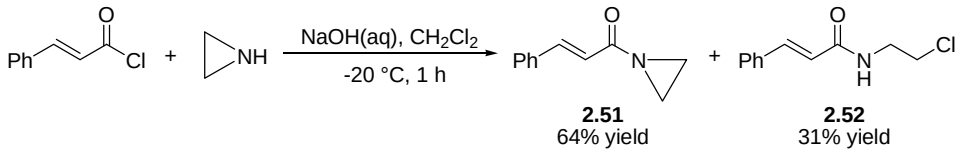
Figure 2.5 Compared Resonance Structures of Typical Amides and *N*-Acylaziridine

Based on the modified Wenker's methodology, aziridine was synthesized by the reaction of ethanolamine and sulfuric acid under reduced pressure to give a moderate yield of 2-aminoethyl hydrogen sulfate salt **2.50**.[83-85] This salt **2.50** was then used to obtain the aziridine by flash distillation in the presence of sodium hydroxide. Separation of the top layer and subsequent re-distillation was required for obtaining pure aziridine product in modest yield (Scheme 2.36).

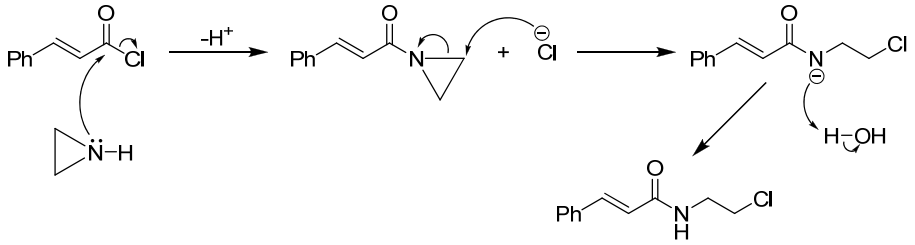


Scheme 2.36

The aziridine was reacted with cinnamoyl chloride in the presence of a stoichiometric amount of aqueous sodium hydroxide at -20 °C for afford *N*-cinnamoyl aziridine **2.51** in moderate yield (64%) and a side product **2.52** in a 31% yield (Scheme 2.37).[86] The formation of compound **2.52** was attributed to ring opening of the aziridine by a nucleophilic attack of free chloride anions. These chloride anions were formed upon nucleophilic attack of the carbonyl group on cinnamoyl chloride by aziridine; hence resulting in the displacement of chloride anion as shown in Scheme 2.38.



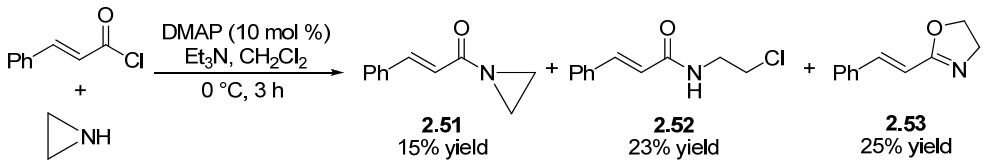
Scheme 2.37



Scheme 2.38

Prior to developing the methodology shown in Scheme 2.37 for preparing *N*-cinnamoyl aziridine **2.51**, another protocol was explored. This involved the reaction of cinnamoyl chloride with aziridine in the presence of triethylamine and catalytic amount of 4-dimethylaminopyridine

(DMAP). However, this resulted in the formation of a mixture of two side products, **2.52** and **2.53** as well as the desired product in very poor yield (Scheme 2.39). The observed side products were confirmed by ^{1}H and ^{13}C NMR spectroscopy. Compound **2.53** was speculated to have been formed via intramolecular cyclization of amide **2.52**.



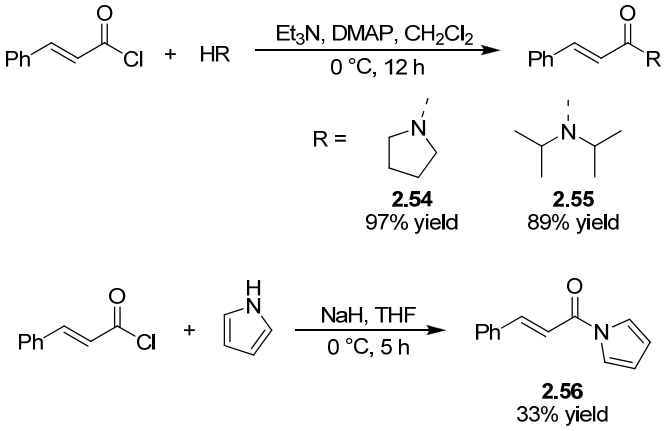
Scheme 2.39

2.4.3.2 Preparation of Other α,β-Unsaturated Amides

Aside from compound **2.51**, other amides were made in order to investigate their potential in undergoing the 1,4-addition reaction proposed in Scheme 2.30. The amides made involved the incorporation of cyclic and bulky amines to cinnamoyl chloride with the intention that the bulky nature of the amides would favor the 1,4-addition via the proposed six-member ring chair transition state (coordination to the carbonyl oxygen) rather than an unfavorable coordination with the nitrogen on the amide.

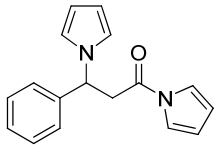
Amides **2.54** and **2.55** were synthesize from their corresponding amines by reacting with cinnamoyl chloride and triethylamine in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) at 0 °C to give 97% and 89% yield, respectively (Scheme 2.40).[87] Amide **2.56** was synthesized using a different approach. This involved the reaction of pyrrole with cinnamoyl chloride using sodium hydride as base at 0 °C to obtain **2.55** in a quite modest yield (33%).[88,89] Compared to other amines, the aromaticity of pyrrole makes amide **2.56** a suitable substrate for 1,4-addition reaction using the proposed reaction conditions. The aromaticity of pyrrole allows amide **2.56** to possess close structural and electronic similarities to enones such as chalcone owing to their comparable resonance structures. However, being an

amide, 1,4-addition to compound **2.56** would serve as way of creating substrates for useful synthetic transformations as mentioned in Scheme 2.32.



Scheme 2.40

Prior to obtaining a 33% yield for amide **2.56**, a even lower yield (15%) was obtained. ^{1}H NMR spectroscopy confirmed that this lower yield was due to the formation of a 1,4-addition side product **2.57** (Figure 2.6). The 15% yield was obtained as a result of addition of cinnamoyl chloride to an ice-cooled mixture of pyrrole and sodium hydride, and allowing the reaction mixture to warm up to room temperature while stirring over a prolonged period of 24 h. It could be inferred that deprotonation of pyrrole, with sodium hydride creates a nucleophile that is capable of performing both nucleophilic acyl substitution and 1,4 addition. The yield was increase to 33% by slight modification of the previous protocol. This involved the addition of a mixture of pyrrole and sodium hydride in THF to an ice-cooled solution of cinnamoyl chloride in THF, and stirring this reaction mixture over a period of 5 h. Therefore, the improved result was achieved by inverting the addition process and reducing the reaction time, assuming that the nucleophilic acyl substitution product, **2.56** is the kinetic favorable product and the 1,4-addition product, **2.57** formed in a subsequent step.



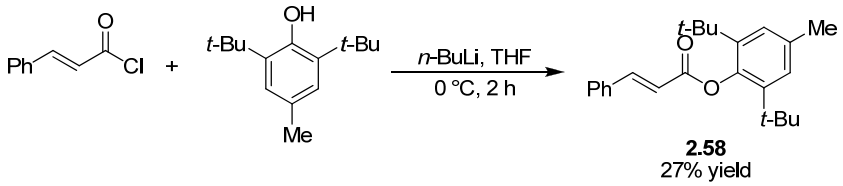
2.57
20% yield

Figure 2.6 Side Product from Synthesis of Compound **2.56**

2.4.3.3 Preparation of Other α,β-Unsaturated Esters

Only one ester was used in this investigation. Ester **2.58** used was thought to be useful in the investigation of the asymmetric 1,4 addition of organoboronates because the bulkiness of the ester substituent. It was reasoned that given the bulky nature of the ester, competitive coordination of the boron to the oxygen adjacent to the carbonyl group would be disfavored; hence favoring selective coordination to only the carbonyl oxygen, which leads to the proposed six membered transition state.

Although a poor yield was obtained for this synthetic protocol, ester **2.58** was synthesized from the reaction of cinnamoyl chloride and 2,6-di-*tert*-butyl 4-methylphenol using *n*-butyllithium as the base at -78 °C (Scheme 2.41).



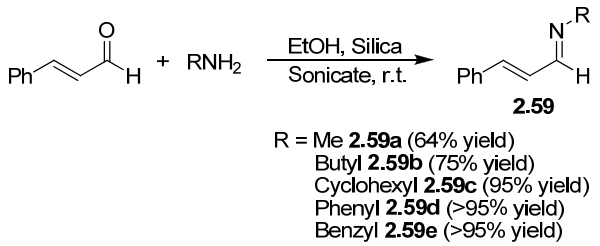
2.58
27% yield

Scheme 2.41

2.4.3.4 Preparation of α,β-Unsaturated Imines

All the imines used in this investigation were derived from cinnamaldehyde. Due to the fact that cinnamaldehyde was found to be too reactive because of its self-addition and possible

oligomerization, the idea of using less reactive imines looked promising. The imines were made by the sonic irradiation of a mixture of cinnamaldehyde and the required amine in ethanol at room temperature to give moderate to excellent yields of the respective imines **2.59** (Scheme 2.42).[90,91]



Scheme 2.42

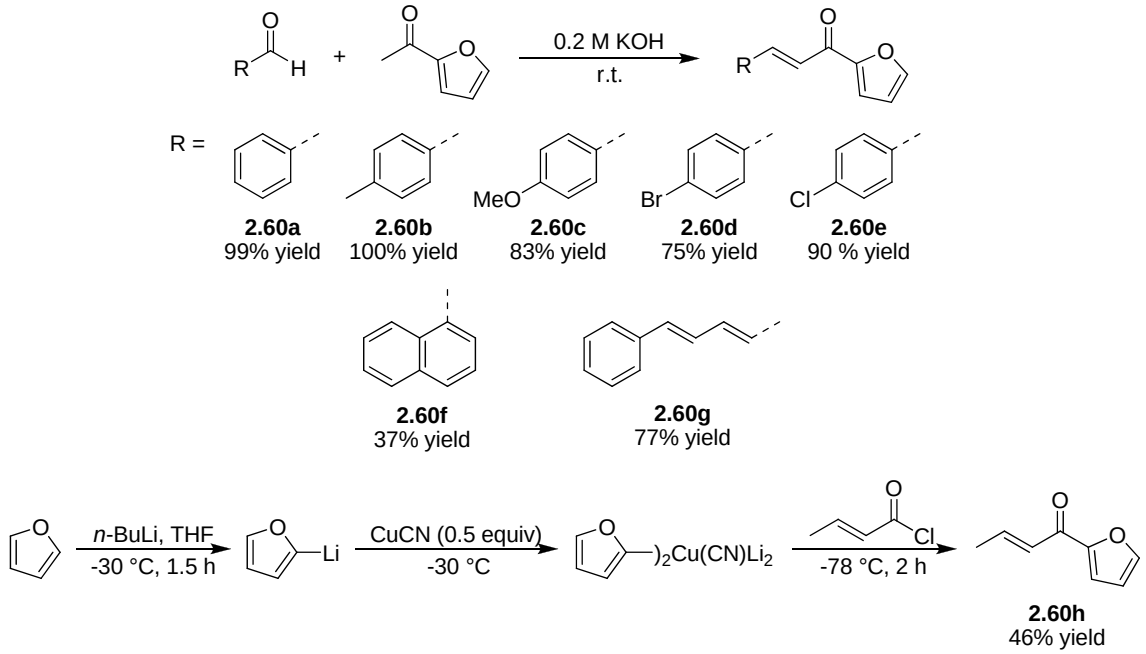
The imines prepared, **2.59a-e** tend to show varying stabilities in the presence of air and moisture, with imine **2.59d** (Schiff base) being the most stable. The less stable imines, **2.59a-c** tend to readily hydrolyze or oligomerize on exposure to oxygen or moisture, while imine **2.59d** is quite stable to water or moisture because of stabilization by delocalization of electron between the phenyl group and the carbon-nitrogen double bond. Imine **2.59e** showed reasonable stability slightly comparable to **2.59d**. Therefore, it was necessary to investigate the reactivity of the individual imines in our proposed 1,4-addition reaction.

2.4.3.5 Preparation of Enones 2.60

Compared to the conventional enones previously explored and reported by our group,[65] enones **2.60** may be more useful substrates due to the presence of an adjacent furyl ring to the carbonyl carbon. This would be of great importance since the furyl ring can play the role of a good surrogate handle and also possesses aromaticity similar to phenyl rings. Furyl rings have been reported to undergo oxidative opening using mild conditions to afford their respective enedione systems.[92,93] The surrogate ability of the furyl ring was also tied to its susceptibility of

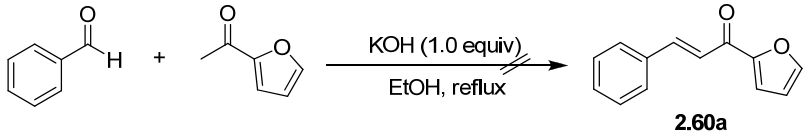
undergoing oxidative cleavage to afford a carboxylic acid which can be used for many synthetic applications. Most reported oxidative cleavage of furyl rings included methodologies involving ozonolytic cleavage of the furyl ring.[94-97] The convenience of using enones **2.60** was based on the fact that they were expected to undergo asymmetric 1,4-addition of alkenylboronates already reported for standard enones due to their complete electronic similarities. Also, the furyl ring has been shown to be stable in compounds that experience transformation of the adjacent carbonyl group to alcohols.[98] This would pose as a useful trait for 1,4-adducts of enones **2.60** during the process of obtaining a suitable starting material for cyclization via asymmetric (CBS) reduction.

Nevertheless, enones **2.60** were observed to be quite heat sensitive, and therefore relied on a mild synthetic protocol for preparation via base-catalyzed aldol condensation reactions. This procedure involved the stirring of a mixture of 2-acetylfuran and the appropriate aldehyde in the presence of catalytic amount of aqueous potassium hydroxide at room temperature (Scheme 2.43).[99] However, this process was only applicable for cases involving aromatic aldehydes. Thus, for the synthesis of enones **2.60** with aliphatic groups at the *β*-position, a different methodology was devised. This was facilitated by the lithiation of furan, then the formation of difuranyl cyanocuprate and the subsequent reaction with the desired *α*,*β*-unsaturated acyl chloride (crotonoyl chloride) to give the desire enone (Scheme 2.43).[100]



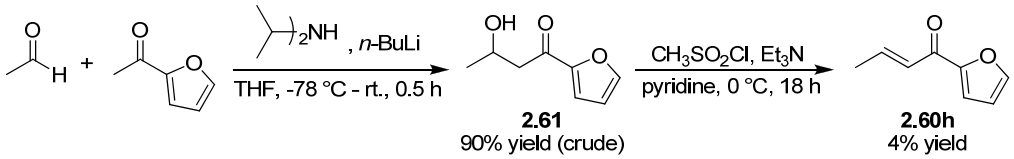
Scheme 2.43

Scheme 2.44 shows a methodology that was performed in an attempt to synthesize enones **2.60a**. However, this procedure was unsuccessful due to the decomposition of the 2-acetylfuran under the harsh reaction condition such as heat.[101] We can therefore deduce that furan ring is quite sensitive to harsh reaction conditions such as high heated temperatures.



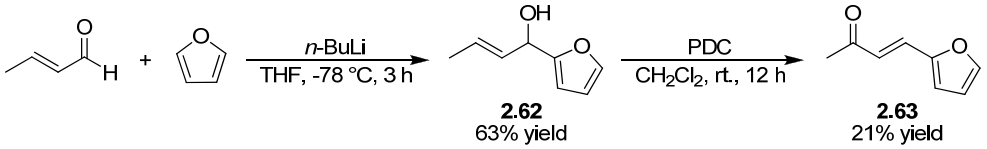
Scheme 2.44

Also, in the process of synthesizing compound **2.60h**, other protocols were explored. One of such protocols was the aldol condensation reaction of 2-acetylfuran and acetaldehyde (Scheme 2.45).[102] Although the aldol intermediate **2.61** was formed in good yield (90%), the subsequent condensation reaction using methanesulfonyl chloride gave very poor yield (4%). Hence, the procedure was deemed unsuitable for the synthesis of enone **2.60h**.



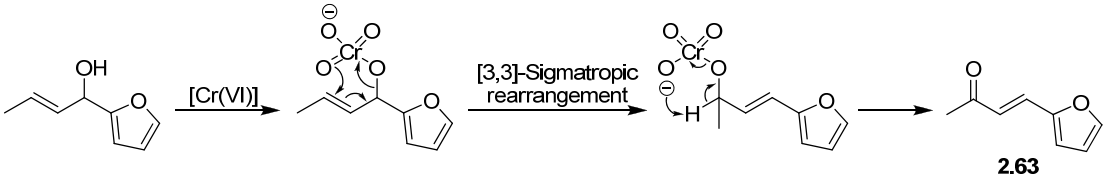
Scheme 2.45

The other procedure used in an attempt to synthesize enone **2.60h** involved the lithiation of furan followed by the nucleophilic attack of crotonaldehyde by the lithiated furan to afford alcohol **2.62** in moderate yield.[103] However, the subsequent oxidation of alcohol **2.62** with pyridinium dichromate (PDC) afforded the unexpected enone **2.63** (Scheme 2.46).[104]



Scheme 2.46

A reasonable rationale for the formation of enone **2.63** can be attributed to the possible [3,3]-sigmatropic rearrangement that occurs during the PDC oxidation of allylic alcohols as shown in Scheme 2.47. Hence, this method was also unsuitable for obtaining the desired enone **2.60h**.



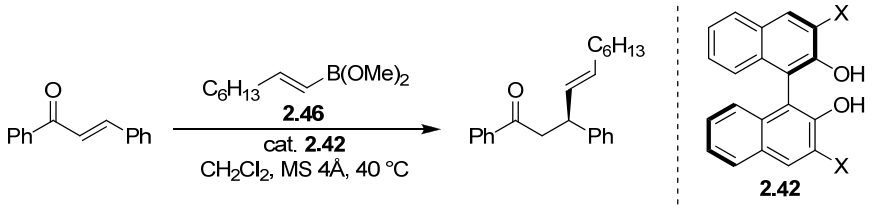
Scheme 2.47

2.4.4 Studies on Catalytic Alkenylation of *α,β*-Unsaturated Carbonyl Compounds

Due to previous studies performed on the effect of 3,3′-disubstituted BINOLs on the alkenylation of chalcone with boronate **2.46** (Table 2.3),[65] our group was able to observe that the

highest reaction rates occurred with BINOL ligands bearing electron-withdrawing substituents on the 3- and 3′-positions (entries 2, 5 and 6). However, 3,3′-diiodoBINOL **2.42f** (entry 6) also gave excellent yield and enantioselectivity, and was chosen as the best candidate for investigating the catalytic alkenylation of *α,β*-unsaturated carbonyl derivatives. It is also one of the easiest 3,3′-disubstituted BINOLs to make.

Table 2.3 Effect of BINOLs on the Alkenylation of Chalcone with Boronate **2.46**[65]



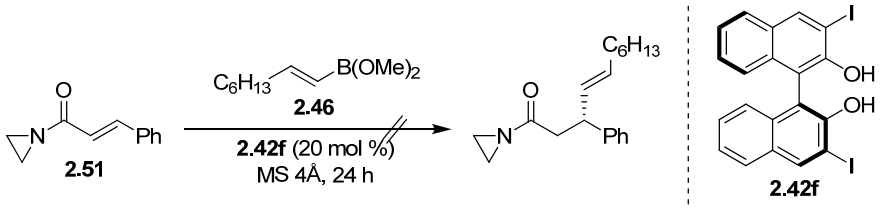
entry	X (ligand **2.42**)	catalyst loading (mol%)	time (h)	yield[a] (%)	er[b]
1	Me (**a**)	20	36	25[c]	98.6:1.4
2	CF_3 (**b**)	20	12	90	98.6:1.4
3	Ph (**c**)	20	36	75[c]	97.1:2.9
4	3,5-$(CF_3)C_6H_3$ (**d**)	20	36	>95[c]	98.7:1.3
5	Br (**e**)	20	12	92	98:2
6	I (**f**)	20	12	92	98.7:1.3
7	I (**f**)	10	36	93	98.6:1.4

[a] Isolated yield after purification. [b] Determined by chiral HPLC analysis. [c] Conversion by ^{1}H NMR analysis.

As proposed, our investigation on potential substrates for catalytic asymmetric 1,4-addition of alkenylboronates started with the use of amide **2.51** (Table 2.4). However, using the already developed standard procedure developed by our group for the alkenylation of enones

(entry 2), no reaction was observed. This led to the exploration of components such as solvent (entries 3 and 4) and temperature (entries 1, 3, and 4) that could favor any possible reaction; but there was no observable addition reaction since starting material (amide **2.51**) was either recovered (entry 2) or decomposed at high temperature (entries 3 and 4). Under neat condition (i.e. without the presence of solvent), no observable reaction occurred between 50 °C and 90 °C (entry 1). Heating above 90 °C resulted in the decomposition of amide **2.51**. Hence, in all cases, no desired reaction was observed.

Table 2.4 Effects of Solvent and Temperature in the Alkenylation of *N*-acylaziridine **2.51** with Boronate **2.46**

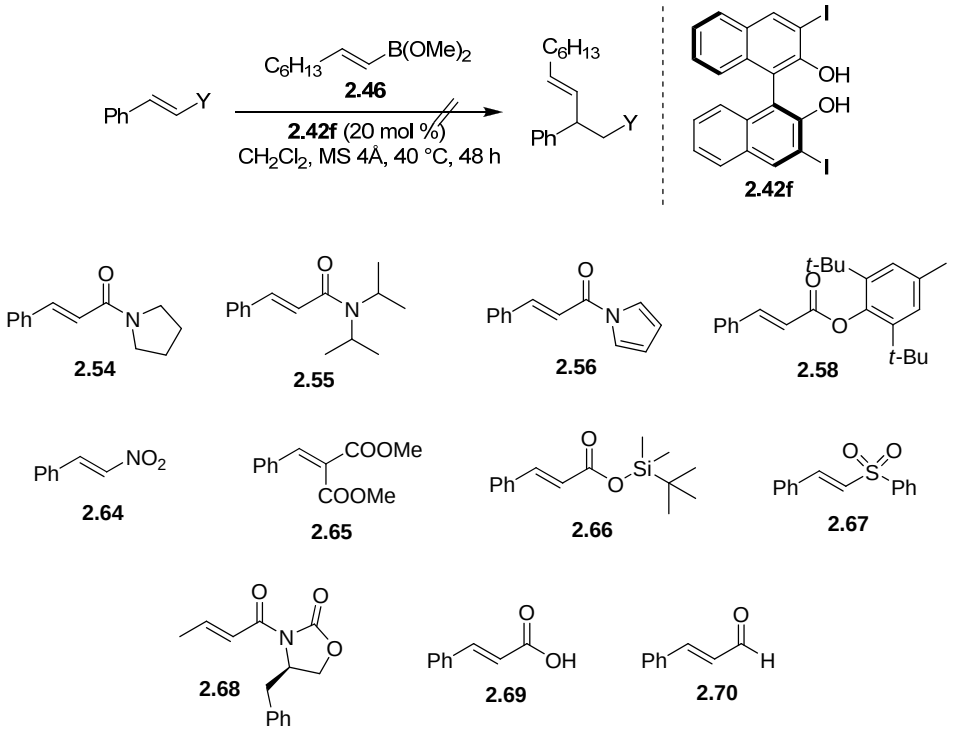


entry	solvent	temperature (°C)	results[c]
1	neat[a]	50-90[b]	nr
2	CH_2Cl_2	40	nr
3	$C_6H_5CF_3$	100	decompose
4	C_6H_5Br	150	decompose

[a] Molecular sieves were absent. [b] Results were gradually monitored with periodic increase in temperature. [c] Results were determined by TLC and ^{1}H NMR analysis and 'nr' implies 'no desired reaction' .

Due to the lack of beneficial results from the reactions involving amide **2.51**, other amides (amides **2.54**, **2.55** and **2.56**) were explored (Scheme 2.48). However, no reaction was also observed even when other reaction conditions similar to those tried for **2.51** on Table 2.4 were implemented. Rather, the starting materials were recovered. This then implies that

regardless of the steric and electronic compatibility of the different amide substituents, amides were just not suited for 1,4-addition under our proposed conditions. Thus, lack of reactivity could be tied to the possible coordination of the boron on the chiral alkenylboronate to the nitrogen of the amide rather than the proposed coordination to the carbonyl oxygen which forms a six-membered ring transition state (Figure 2.7).



Scheme 2.48

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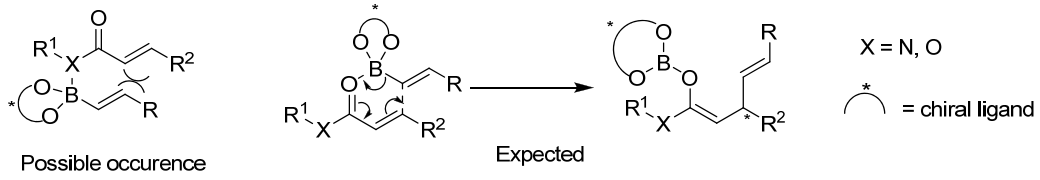
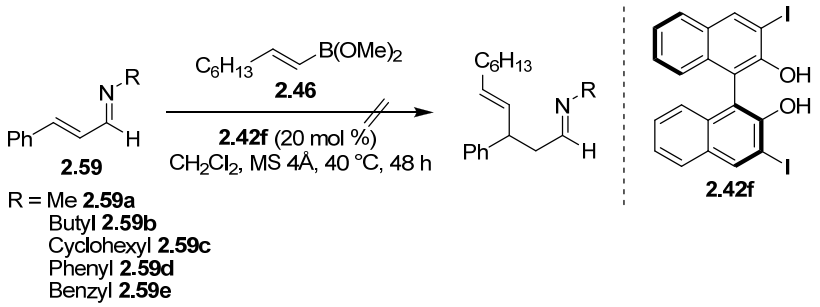


Figure 2.7 Possible and Expected Outcomes of Alkenylation Process

Further exploration led to trials of the different substrates in Scheme 2.48 (**2.58**, **2.64-2.69**) with no substantial results obtained (Scheme 2.48). Investigations with ester **2.58** were

performed under proposed reaction condition shown on Scheme **2.48** and under neat (without methylene chloride solvent) reaction condition at 120 °C. In both cases, no reaction was observed with complete recovery of starting material. Similar investigations were performed using silyl ester **2.66** as substrate. Although the neat reaction was performed at 55 °C, no reaction was observed under both reaction conditions but rather, the starting materials were recovered. This lead to tests using nitroalkene **2.64,** due to reports of this substrate being an excellent Michael-acceptor and the wide applicability of nitro compounds to organic transformations.[105,106] Under the proposed reaction conditions on Scheme 2.48, starting material was completely recovered. Reaction using *α*,*α*,*α*-trifluorotoluene as a high boiling solvent (110 °C) also showed no reaction with recovery of starting material. Neat reaction at 110 °C also resulted in the recovery of starting substrate. In an attempt to explore better activated systems, malonate **2.65** was made.[107] However, reaction under the proposed reaction condition and under neat reaction condition at 65 °C showed no observable reaction but the presence of unreacted starting materials. Other studies with sulfone **2.67**, oxazolidinone **2.68** and cinnamic acid **2.69** under the proposed reaction condition and neat reaction condition at 95-100 °C showed no observable reactions but rather, the presence of unreacted starting substrates. However, cinnamaldehyde **2.70** showed an intriguing reactivity as observed by ^{1}H NMR analysis. The ^{1}H NMR showed a mix of 1,4-addition reaction as well as self-addition (aldol condensation) reactions, hence displaying a very messy NMR spectra. This supported our previous speculations of cinnamaldehyde being too reactive. Thus, imines **2.59** were used for further investigation (Scheme 2.49).

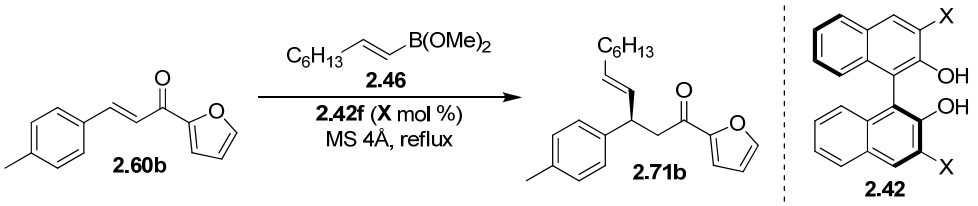


Scheme 2.49

However, the studies performed on imines **2.59** showed no desired 1,4-addition reaction. Under the proposed reaction conditions as shown on Scheme 2.49, imines **2.59a-c** were observed to have completely decomposed, while **2.59e** experienced partial decomposition after 48 h. **2.59d** was unreactive under the proposed reaction conditions after 48 h. Attempts to replace the solvent (methylene chloride) with a high boiling solvent such as *α*,*α*,*α*-trifluorotoluene resulted in complete decomposition of imine **2.59e** and possible oligomerization was observed for **2.59d**. Therefore, we were led to presume that imines **2.59a-c** and **2.59e** were either not reactivity enough to undergo 1,4-addition reactions and were not stable under the reaction conditions. Imine **2.59d** behave in the same way as cinnamaldehyde **2.70**.

Since other carbonyl derivatives seem to be unable to undergo 1,4-addition under our proposed reaction conditions, we decided to fall back to enones which had already been reported to undergo asymmetric conjugate alkenylation under the proposed catalytic conditions. Accordingly, we explored the use of enones **2.60** which possess a furyl group directly adjacent to the carbonyl group. We were able to perform the exact same asymmetric conjugate alkenylation to these enones using catalytic amounts of 3,3′-disubstituted BINOL **2.42f**.

Table 2.5 Effects of Solvent and Ligands on the Alkenylation of Enone **2.60b** with Boronate **2.46**



entry	solvent	time (h)	ligand (X)	catalyst loading (X mol %)	% conversion[a]	er[b]
1	CH_2Cl_2	24	I	20	22	97.6:2.4
2	CH_2Cl_2	48	I	20	61	97.4:2.6
3	CH_2Cl_2	72	I	20	85	97.5:2.5
4	CH_2Cl_2	96	I	20	100	97.5:2.5
5	$CHCl_3$	48	I	20	100[c]	95.9:4.1
6	$ClCH_2CH_2Cl$	12	I	20	100[d]	97.3:2.7
7	CH_2Cl_2	96	I	10	80	97.5:2.5
8	CH_2Cl_2	48	CN	20	100	88.4:11.6

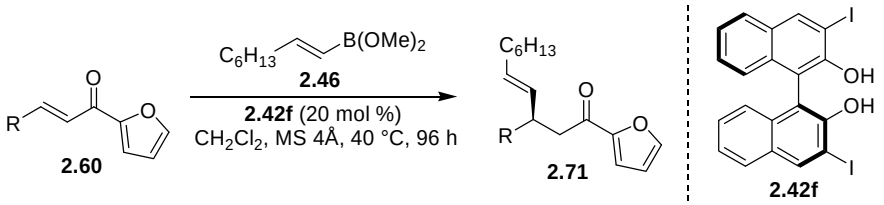
[a] Determined by ^{1}H NMR analysis. [b] Determined by chiral HPLC analysis. [c] An inseparable 14% side product was formed. [d] An inseparable 17% side product was formed.

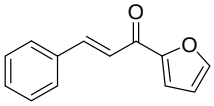
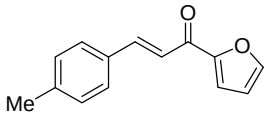
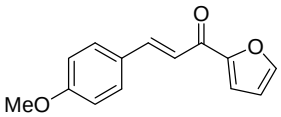
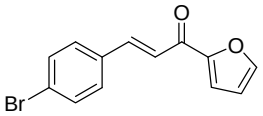
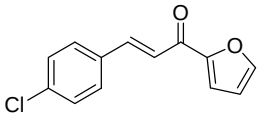
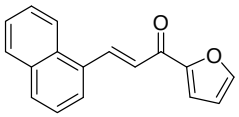
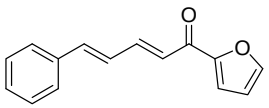
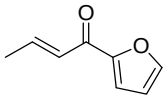
After some experimentation, it was found that the 1,4-alkenylation of enone **2.60b** using dimethyl boronate **2.46** could be achieved using catalytic amounts of BINOL **2.42f** (Table 2.5). Under the proposed reaction conditions, using catalytic 3,3′-diiodoBINOL **2.42f**, 1,4-adduct **2.71b** was obtained with highest enantioselectivity using dichloromethane as solvent, 20 mol % catalyst loading for 96 h. Heating the reaction mixture in higher boiling solvents such as chloroform and 1,2-dichloroethane resulted in relatively higher reaction rates with high

enantioselectivities (entries 5 and 6). However, an inseparable side product was formed which accounted for significant amount of the isolated yield. It was observed to account for 14% of the isolated yield with chloroform as the solvent, and 17% of the isolated yield with 1,4-dichloroethane as solvent. Therefore, with increase in reaction temperature, more of the inseparable side product was formed regardless of the increased rate of reaction. Reduction in the catalytic loading resulted in reduced reaction rate but no significant effect on the selectivity (entry 7). Exploration of 3,3′-dicyano BINOL as a ligand for the reaction resulted in a relatively high reaction rate but low enantioselectivity (entry 8).

Further investigation of this new reaction process showed that high selectivities could be obtained for virtually all enones studied (Table 2.6). Thus heating a mixture of boronate **2.46** and enones **2.60** with a catalytic amount of diol **2.42f** afforded the desired 1,4-addition product with high enantioselectivities ranging from 95:5 to 99.5:0.5. Although, low reaction rates (% conversion) were observed for relatively large aryl groups and conjugated dienone (alkenyl group) in the *β*-position (entries 6 and 7), consistent high selectivities were still maintained. Enones bearing electron donating groups on the *para*- position of the phenyl group (entries 2 and 3) were observed with high enantioselectivities up to 98.5:1.5 er. Even higher selectivities up to 99.5:0.5 er were observed with enones bearing electron withdrawing groups (entries 4 and 5). With an enone possessing a methyl group on the *β*-position (entry 8), good yield (89%) and enantioselectivity (96.8:3.2 er) were obtained. The overall high selectivities observed could be naively attributed to the exact same six-membered chair-like transition states previously proposed by our group (Figure 2.4). Therefore, reaction via the favored transition state led to the observed enantiomer which is supported by the X-ray crystallographic analysis discussed in the next section.

Table 2.6 Alkenylation of Enones **2.60** with Boronate **2.46**

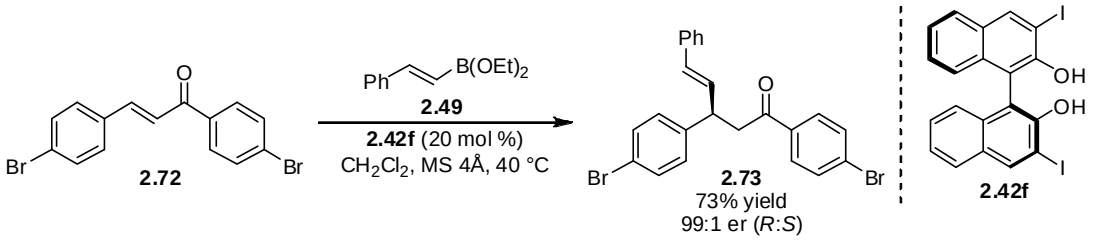


entry	substrates	% yield[a] (**2.71**)	er[b] (*R*:*S*)
1		83 (**2.71a**)	95:5
2		81 (**2.71b**)	98.5:1.5
3		78 (**2.71c**)	98:2
4		79 (**2.71d**)	98.5:1.5
5		65 (**2.71e**)	99.5:0.5
6		29[c] (**2.71f**)	97.9:2.1
7		37[c] (**2.71g**)	97.5:2.5
8		89 (**2.71h**)	3.2:96.8

[a] Isolated yields obtained after purification. [b] Determined by chiral HPLC analysis. [c] ^{1}H NMR analysis showed about 60% conversion after 96 h.

2.4.5 Confirmation of Absolute Configuration

Earlier investigations in our group have been able to determine the absolute configuration of the asymmetric alkenylation of enones based on the optical correlation to compounds synthesized and characterized by other groups.[4,64] To verify our assignment, the absolute configuration was determine by a more reliable X-ray structure of the 1,4-addition product (Figure 2.8). Enone **2.72** and boronate **2.49** were designed for this process because of their potential to produce a crystalline 1,4-addition product **2.73** as a result of their bulky nature of the boronate and the polarized dispersion of X-rays scattered by bromine atoms.[108] The 1,4-addition product **2.73** was obtained in good yield (73%) and excellent selectivity (99:1 er) (Scheme 2.50).



Scheme 2.50

In order to obtain an X-ray structure, recrystallization of the white **2.73** solid was performed. The monoclinic crystals were slowly grown from a mixture of dichloromethane and hexane by slow evaporation. The slow evaporation helped in the nucleation of the crystallite. Care was taken to prevent fast evaporation which results in the formation of a shower of small crystallite with the aid a hypodermic needle. X-ray crystallographic analysis was performed and indicated that the absolute configuration was (*R*) (Appendix). This is consistent with anticipated configuration derived from the proposed transition state.

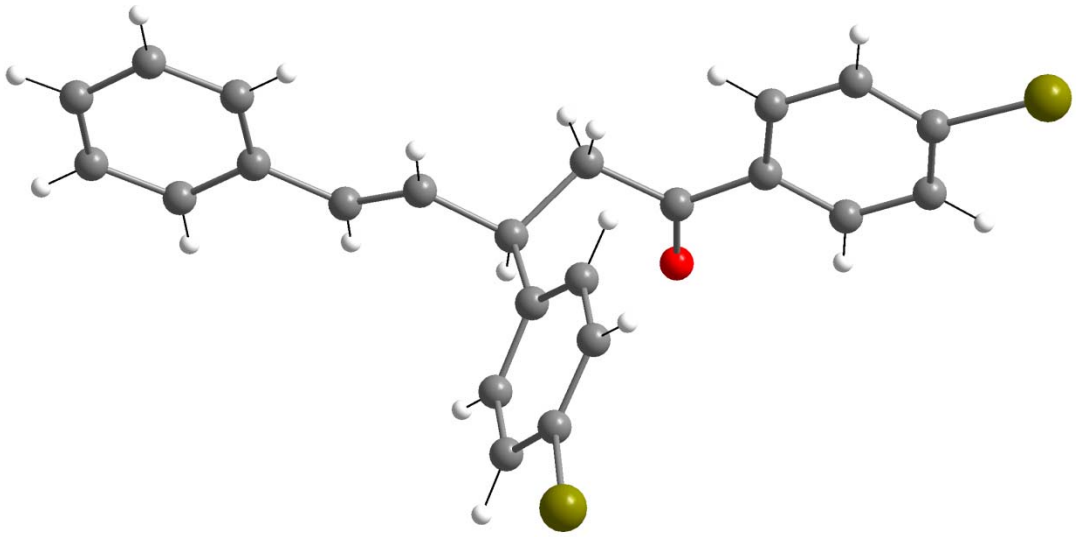
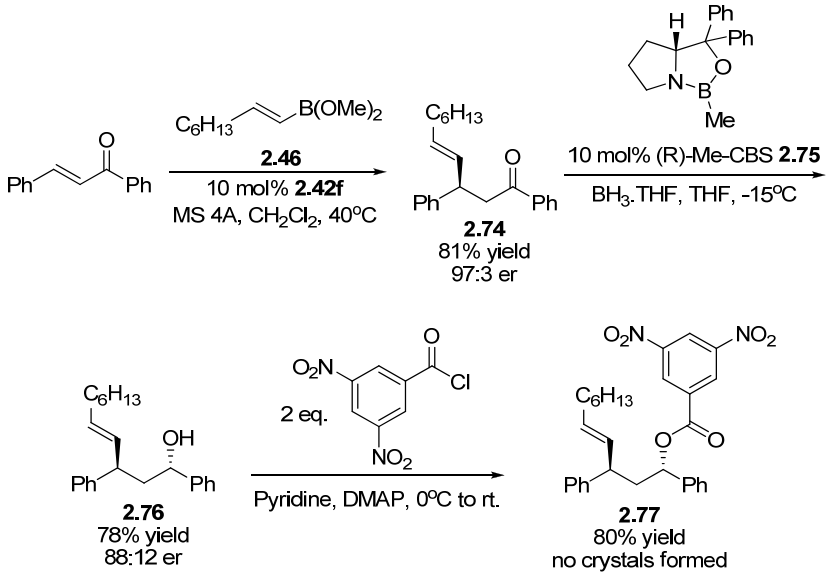


Figure 2.8 Absolute Configuration of Asymmetric 1,4-Adduct **2.73**

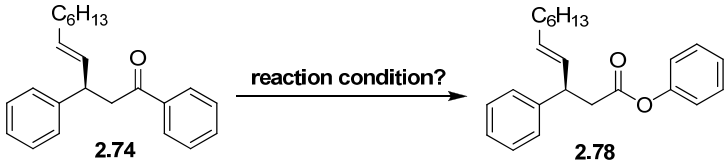
An initial attempt to obtain the absolute configuration of 1,4 addition products using BINOL **2.42f** involved the alkenylation of chalcone with boronate **2.46** followed by the asymmetric reduction of the 1,4-adduct **2.74** using CBS catalyst **2.75** (Scheme 2.51). The obtained alcohol **2.76** was then used to synthesize the bulky ester **2.77** via reaction with 3,5-dinitrobenzoyl chloride with the intention of obtaining a crystalline ester **2.77**. The use of 3,5-dinitrobenzoyl chloride was tied to its ability to induce crystallization in compounds such as amino acids.[109] However, ester **2.77** was not a crystalline product but rather an oil.



Scheme 2.51

2.4.6 Baeyer-Villiger Oxidation of 1,4-Adducts of Enones

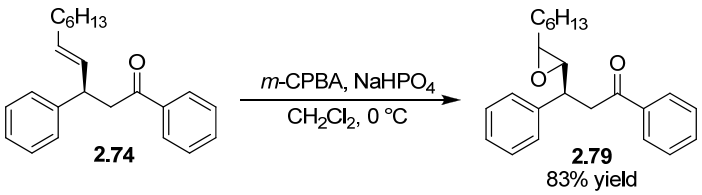
Since addition to acid derivatives such as esters did not produce 1,4-addition products, investigations with the Baeyer-Villiger (BV) oxidation of the 1,4-adducts from enones were conducted. This led to the examination of different protocols that have been used to perform BV oxidation (Scheme 2.52).[110,111]



Scheme 2.52

Our first attempt was the exploration of the commonly used *meta*-chloroperbenzoic acid (*m*-CPBA) which gave no desired oxidation product (ester). Rather, epoxidation of the alkenyl group was observed in good yield as a mixture of diastereomers (Scheme 2.53). Hence, indicating that the epoxidation process occurs at a much faster rate than the Baeyer-Villiger

oxidation. Since the alkenyl group was already expected to be a problem and we focused on selective BV oxidation that have been developed. Reported studies on the possible role of Lewis acidity have been used to investigate and support this rationale.[112]

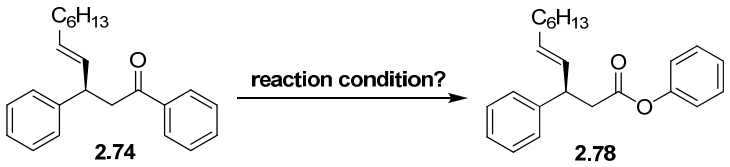


Scheme 2.53

Table 2.7 shows a summary of the results obtained from the study. Initial attempts focused on exploring other reported BV protocols. This included the hydrogen peroxide and trifluoroacetic anhydride mixture (entry 1), hydrogen peroxide, iodine and acetic acid mixture (entry 2), and sodium borate monohydrate and acetic/trifluoroacetic acid mixture (entries 3 and 4).[113,114] The first four tests (entries 1-4) were performed in order to determine whether other BV reaction conditions could drive the oxidation of ketone **2.74** towards the formation of a BV product. Peroxytrifluoroacetic acid has been found to be a remarkably efficient reagent for oxidation of ketones to the corresponding esters.[115] Using trifluoroacetic anhydride in conjunction with hydrogen peroxide helps generate peroxytrifluoroacetic acid *in situ* (entry 1).[116,117] However, this resulted in the complete decomposition of the ketone implying that reaction condition was probably too harsh. Therefore, we considered the use of a milder reaction condition involving catalytic amounts of molecular iodine and hydrogen peroxide in acetic acid at room temperature (entry 2).[118] In this case, no reaction was observed but rather the starting material was recovered after 48 h. Due to the reported use of sodium borate monohydrate as a source of 'active oxygen' in various oxidation reactions,[98] we felt the need to investigate its use in BV oxidation of ketone **2.74**. It was then used with acetic acid and heated to 70 °C (entry 3).

Partial decomposition of ketone **2.74** was observed with recovery of some starting material. By changing the reaction solvent to trifuoroacetic acid and heating to 60 °C, complete decomposition of the starting substrate **2.74** was observed. A repeat of some of the reactions showed unidentifiable products with loss of the alkenyl group as observed by ^{1}H NMR analysis (entries 2 and 3).

Table 2.7 Reaction Conditions for Baeyer-Villiger Oxidations



entry	reaction conditions	results[a]
1	30% H_2O_2, $(CF_3CO)_2O$, Na_2HPO_4, 0 °C	nr
2	30% H_2O_2, I_2, AcOH, r.t.	nr
3	$NaBO_3.H_2O$, AcOH, r.t - 70 °C	nr
4	$NaBO_3.H_2O$, CF_3COOH, 60 °C	nr
5	BTP, DA, $SnCl_4$, Na_2SO_3, 4Å MS, 0 °C	nr
6	30% H_2O_2, Sn-MMT, Dioxane, 90 °C	nr
7	30% H_2O_2, Sn-MCM-41, Dioxane, 90 °C	nr
8	30% H_2O_2, Sn-MCM-41, isoamyl alcohol, 90 °C	nr

[a] Results were confirmed by TLC and ^{1}H NMR analysis. 'nr' implies 'no desired reaction'.

The other approaches comprised of the application of tin as a Lewis acid catalyst which would coordinate to the carbonyl oxygen, hence activating the carbonyl group for further oxidation by various oxidants. The first approach was the use of tin(IV)-chloride as the Lewis acid catalyst, bis(trimethylsilyl)peroxide (BTP) as the oxidant, and *trans*-1,2-

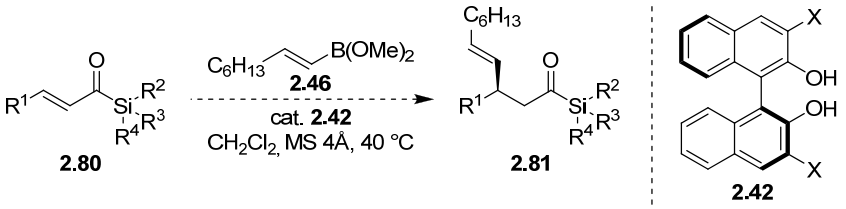
(diamino)cyclohexane (DA) as a ligand (entry 5).[119] Although the rationale behind this approach seems promising, no observable reaction occurred with complete recovery of starting substrate. The next attempt was the use of tin(II) catalyst supported by montmorillonite (Sn-MMT) and hydrogen peroxide (entry 6).[120] However, only starting material **2.74** was recovered. The final non-productive approach involved the use of hydrogen peroxide in the presence of mesoporous tin(IV)-Lewis acid, Sn-MCM-41 (entries 7 and 8).[121-123] Hence, from these investigations, we could presume that tin was unable to sufficiently activate the carbonyl group for the BV oxidation to occur.

2.5 Future Work

Regardless of the good results obtained from the catalytic asymmetric 1,4-alkenylation of enones **2.60**, further optimization studies still need to be conducted to achieve a more efficient reaction. This includes:

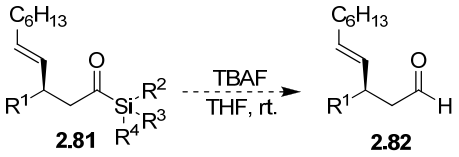
1. Further screening of 3,3′-disubstituted BINOL ligands that improve the reactivity of the reaction, hence reducing the reaction time as well as maintaining or even increasing selectivity.
2. Further analysis into the effect of higher temperature in the formation of the desired product and the inseparable side product that resulted in the reduced enantioselectivities.

Although we have been able to find substrates that do not undergo asymmetric 1,4-alkenylation under our proposed reaction conditions, there are still room for further exploration. This includes the use of α,*β*-unsaturated acylsilanes **2.80**[124,125] as potential substrates (Scheme 2.54).



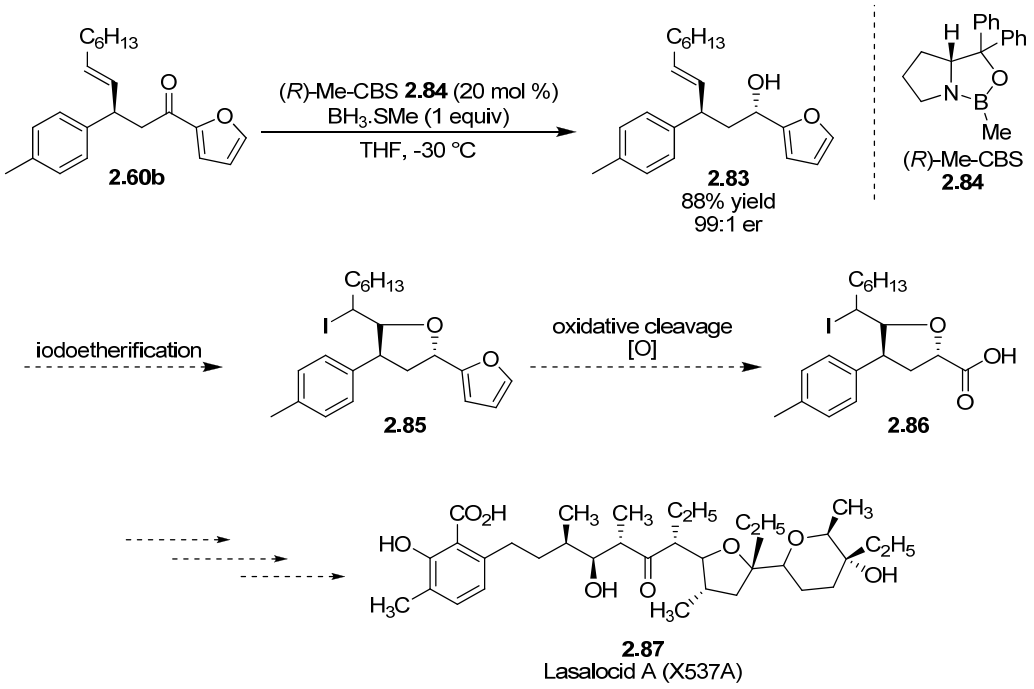
Scheme 2.54

α,*β*-Unsaturated acylsilanes **2.80** would be an ideal substrate because the 1,4-addition products **2.81** can be easily desilylated to the corresponding aldehydes **2.82** (Scheme 2.55),[126] which can then be used for further synthetic transformations.



Scheme 2.55

Many natural products with tetrahydrofuran skeletal units have received a great deal of attention in the synthetic community not merely for their various biological activities but also for their structural complexities.[127,128] Therefore, investigation into the use of the 1,4-addition products **2.71** to obtain these tetrahydrofuran skeletal units seems very promising. This would involve the asymmetric reduction of ketone(s) **2.83** via CBS reduction (CBS named after *C*orey, *B*akshi, and *S*hibata) which helps to establish a specific stereochemistry for the resulting alcohol **2.83**.[129-131] This alcohol can then undergo cyclization by iodoetherification to obtain a trisubstituted tetrahydrofuran ring with three chiral centers.[124,125] Even further experimentation could be performed to obtain a suitable chiral handle for intriguing synthetic applications. This would involve the oxidative cleavage of the furan ring to obtain a carboxylic acid (Scheme 2.56). Potential use in the synthesis of natural compounds such as lasalocid A (**2.87**),[132] a potent ionophoric polyether antibiotic also seems promising.



Scheme 2.56

As illustrated in Scheme 2.56, we were already able to perform a successful asymmetric reduction of the ketone **2.71b** with good yield (88%) and excellent selectivity (98% ee) of alcohol **2.83**.

2.6 Conclusion

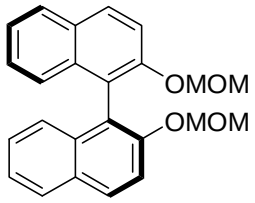
With more room for improvement and further investigation, we have successfully extended the asymmetric conjugate alkenylation of carbonyl derivatives to enones **2.60** with the aid of alkenylboronates using catalytic amount of 3,3′-disubstituted BINOL. In these reactions, it was possible to attain reasonable to good yields with excellent enantioselectivities. In that same light, we were able to confirm the absolute configuration of the alkenylation product via X-ray crystallographic analysis.

2.7 Experimental

2.7.1 General Experimental

^{1}H and ^{13}C NMR spectra were recorded using $CDCl_3$ at 300 MHz and 75 MHz, respectively, with a Brüker AVANCE 300 spectrometer unless otherwise noted. Mass spectra were recorded on a Kratos MA890 mass spectrometer using electron impact (EI, 70 eV) ionization. Optical rotations were performed in 10 cm path length cells on a Perkin-Elmer 241 digital polarimeter. X-ray studies were carried out by Dr. Jalil Assoud of the Department of Chemistry, University of Waterloo, and using a Bruker AXS X-ray single crystal diffractometer. All reactions involving air or moisture sensitive reagents were performed under argon on the bench or fume hood using standard Schlenk techniques. All round-bottom flasks used for the various reactions were flamed dried. Where necessary, reactions were monitored by thin-layer chromatography (TLC) by commercial glass backed TLC plates (silica gel 60A, F254). 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 (CaH_2). $CHCl_3$ was dried by distilling from phosphorus pentoxide (P_2O_5). (*S*)-1,1′-Bi-2-naphthol was purchased from Wilmington Pharmatech Company. Chiral 3,3′-disubstituted binaphthols and alkenylboronates were synthesized using procedures from previous reports.[75,133] Chloromethyl methyl ether (MOMCl) was synthesized using a procedure previously developed by Chong and Shen.[134] Unless otherwise stated, other chemicals were purchased from Aldrich Chemical Company. The enantiomeric excess of various stereoselective products was determined by the HPLC (4.6 × 250 mm Chiralcel OD) analysis.

2.7.2 Synthesis of (±) and (*S*)-2,2'-Bis(methoxymethoxy)-1,1'-binaphthyl (1)



Synthesis of this compound was performed according to previous procedures[68,135] with little modification.

To a flame dried 250 mL round bottom flask fitted with a magnetic stir bar and placed under argon, NaH (1.47 g, 60% in oil, 36.7 mmol) was mixed with freshly distilled THF (75 mL) at 0 °C. Through a dropping funnel, (*S*)-2,2′-dihydroxy-1,1′-binaphthyl (4.76 g, 16.6 mmol) dissolved in THF (25 mL) was added while stirring at 0 °C. After an hour of continuous stirring at 0 °C, the mixture was allowed to warm up to room temperature. Before subsequent addition of chloromethyl methyl ether, the reaction mixture was re-cooled to 0 °C. This was performed slowly with the aid of a dropping funnel and the reaction mixture was allowed to slowly warm up to room temperature overnight. Saturated aqueous NH_4Cl (50 mL) was added to the reaction mixture, which was then followed by the removal of the solvent *in vacuo*. The residue was extracted with CH_2Cl_2 (25 mL × 3). The combined organic layer was washed with brine (25 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc: 10/1) and crystallized from CH_2Cl_2/hexane to afford a white crystalline product (*S*)-**2** in 65% yield (4.06 g). ^{1}H NMR ($CDCl_3$): δ 7.93 (ArH, 2 H, d, AB, J_{AB} = 9.0 Hz), 7.85 (ArH, 2 H, d, AB, J_{AB} = 8.2 Hz), 7.55 (ArH, 2 H, d, AB, J_{AB} = 9.0 Hz), 7.33-7.12 (ArH, 6 H, m), 4.95, 5.06 (OCH_2O, 4 H, d, AB, J_{AB} = 6.7 Hz), 3.12 (OCH_3, 6 H, s); ^{13}C NMR ($CDCl_3$): δ 152.6 (ArC), 130.0 (ArC), 129.9 (ArC), 129.3 (ArC), 127.8 (ArC), 126.3 (ArC), 125.5 (ArC), 124.0 (ArC), 121.3 (ArC), 117.3 (ArC), 95.2 (OCH_2O), 55.7 (OCH_3); MS *m/e*

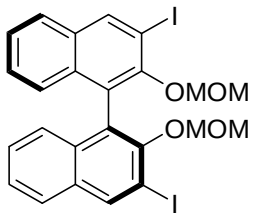
(relative intensity): 374 (M^+, 100), 298 (90), 270 (71). The sample showed $[\alpha]_D^{25}$ = -94.0 (c = 1.0, THF).

2.7.3 General Preparation of 3,3′-Disubstituted-2,2′-bis(methoxymethoxy)-1,1′-binaphthyls

The various 3,3′-disubstituted binaphthyl compounds were prepared following modified literature procedures.[68]

(±) or (*S*)-2,2′-Bis(methoxymethoxy)-1,1'-Binaphthyl (**1**) (1 equiv) was dissolved in dry Et_2O (17 mL/1 mmol of **1**) in a flame dried round bottom flask under an argon atmosphere. While stirring the mixture at room temperature, *n*-BuLi (3 equiv) was added via syringe injection. After allowing the reaction mixture to stir at room temperature for 3 h, THF (11 mL/1 mmol of **1**) was added to the flask and stirred for 1 h. This was followed by cooling the flask in an ice bath for 5 min, and then the quick addition of the appropriate electrophile (3 equiv). The reaction mixture was stirred for 15 min, quenched with saturated aqueous $Na_2S_2O_3$, followed by addition of saturated aqueous NH_4Cl and water. The two phases were separated and the aqueous layer was extracted with Et_2O twice. All organic layers were combined, washed with brine, dried over anhydrous Na_aSO_4 and concentrated. Further work-up and purification gave the desired product.

2.7.3.1 Synthesis of (*S*)-3,3′-Diiodo-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (2)[68]

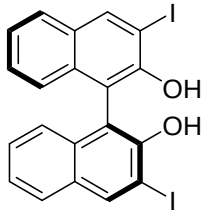


(*S*)-2,2′-Bis(methoxymethoxy)-1,1'-Binaphthyl (**1**) (13.08 g, 34.9 mmol) was reacted with *n*BuLi (92 mL of a 1.51 M solution in hexane, 139.6 mmol) at room temperature and allowed to react for 3 h. Iodine (35.43 g, 139.6 mmol) was dissolved in THF (250 mL) and used to quench the resulting reaction mixture. The crude product was purified via column chromatography (hexane/EtOAc: 10/1) and crystallized from CH_2Cl_2/hexane to afford a white crystalline product (**2**) in 55% yield (12.05 g). ^{1}H NMR ($CDCl_3$): δ 8.50-8.62 (ArH, 2 H, m), 7.70-7.85 (ArH, 2 H, m), 7.10-7.54 (ArH, 6 H, m), 4.81, 4.69 (OCH_2O, 4 H, d, AB, J_{AB} = 5.7 Hz), 2.59 (OCH_3, 6 H, s); ^{13}C NMR ($CDCl_3$): δ 152.2 (ArC), 140.0 (ArC), 133.8 (ArC), 132.8 (ArC), 132.2 (ArC), 127.1 (ArC), 126.7 (ArC), 126.5 (ArC), 126.2 (ArC), 125.8 (ArC), 99.4 (ArC), 92.5 (OCH_2O), 56.5 (OCH_3).

2.7.4 General Preparation of 3,3′-Disubstituted-2,2′-dihydroxy-1,1′-binaphthyls[68]

To a mixture of 3,3′-disubstituted-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (2.0 mmol) and Amberlyst 15 resin (1.0 g) in a flame dried round bottom flask, THF/MeOH (1:1) was added, stirred and heated to reflux under argon for 15 h. The reaction mixture was then cooled to room temperature followed by removal of the resin by filtration and concentration of the crude product *in vacuo*. Subsequent purification gave the desired product.

2.7.4.1 Synthesis of (*S*)-3,3′-Diiodo-2,2′-dihydroxy-1,1′-binaphthyl (2.42f)[68]

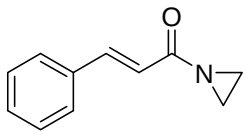


(*S*)-3,3′-Diiodo-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (1.00 g, 1.6 mmol) was treated with Amberlyst 15 (1.00 g) in THF/MeOH (60 mL, 1:1) following the above General Preparation. Purification by column chromatography (hexane/EtOAc: 10:1) was performed, and then crystallization (hexane/EtOAc) to give 0.80 g (93%) of a light yellow crystalline solid. ^{1}H NMR ($CDCl_3$): δ 8.40-8.60 (ArH, 2H, m), 7.70-7.90 (ArH, 2H, m), 7.02-7.50 (ArH, 6H, m), 5.41 (OH, 2H, s); ^{13}C NMR ($CDCl_3$): δ 152.0 (ArC), 140.4 (ArC), 133.4 (ArC), 130.7 (ArC), 128.0 (ArC), 127.3 (ArC), 126.8 (ArC), 125.2 (ArC), 124.8 (ArC), 124.4 (ArC).

2.7.5 Synthesis of α,*β*-Unsaturated Carbonyl Compounds and Derivatives

The various α,*β*-unsaturated carbonyl derivatives used were obtained commercially, prepared according to literature methods or prepared by modification of similar literature protocols.

2.7.5.1 Synthesis of (*E*)-1-(Aziridin-1-yl)-3-phenylprop-2-en-1-one (2.51)



The preparation of **(***E*)-1-(aziridin-1-yl)-3-phenylprop-2-en-1-one **2.51** was accomplished by consecutive preparation of 2-aminoethyl hydrogen sulfate,[83] ethylenimine (by flash distillation),[84,85] and then the desired product.[86a]

Ethanolamine (151 mL, 2.5 moles) and H_2SO_4 (133 mL, 2.5 moles) were dissolved in 80 mL and 70 mL of water, respectively, and cooled in an ice bath. In a 500-mL 3-neck round bottom flask fitted with a thermometer, glass beads and a magnetic stir bar, both solutions were slowly combined. The setup was placed under reduced pressure with the aid of a water aspirator

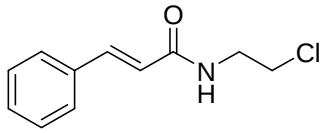
and heated until most of the water had been removed (at about 184 °C). After cooling the reaction mixture to room temperature, the viscous liquid was diluted in ethanol (150 mL), forming a crystalline salt. The solid was filtered and dried to give 184.63 g (53%) of 2-aminoethyl hydrogen sulfate salt.

To a 1-L 3-neck round bottom flask fitted with a dropping funnel, a magnetic stir bar and a condenser (set for distillation), 18 mL of 14% NaOH solution was added. The condenser was also connected to a 500-mL 2-neck flask partially immersed in an ice-salt bath and fitted with another condenser for the purpose of cooling only. To the attached dropping funnel, 2-aminoethyl hydrogen sulfate (0.5 moles, 70.58 g) was dissolved in a cold solution NaOH (42 g) and water (300 mL). The 1-L flask was heated until distillation proceeded at a rapid rate, after which the alkali solution of 2-aminoethyl hydrogen sulfate was added at a rate that kept the volume of mixture in the 1-L flask constant. Distillate was collected at about 97 °C. After distillation was completed, it was salted out by adding 150 g of NaOH while stirring and cooling in an ice bath. The mixture was allowed to settle; the top layer containing ethylenimine was separated and redistilled between 55-58 °C to give pure ethylenimine in 21% yield (4.6 g). ^{1}H NMR ($CDCl_3$): δ 1.23 (4 H, s), 0.20 (N<u>H</u>, 1 H, s).

To cinnamoyl chloride (1.33 g, 8.0 mmol) dissolved in CH_2Cl_2 (6.0 mL), a mixture of ethylenimine (0.35 g, 8.0 mmol), CH_2Cl_2 (2.0 mL), NaOH (0.32 g, 8.0 mmol), and H_2O (2.0 mL) was added at -20 °C while stirring. After 2 h, the reaction was stopped at -5 °C and diluted with CH_2Cl_2 (6.0 mL). The crude material was extracted with CH_2Cl_2 (3 × 5 mL), washed with brine, dried over Na_2SO_4 and concentrated. Purification was performed by flash column chromatography using CH_2Cl_2/EtOAc (10:1) to give the desired product **2.51** in 0.89 g (64%; R_f = 0.72, CH_2Cl_2/EtOAc: 3:1) and a side product **2.52** in 0.43 g (31%; R_f = 0.56, CH_2Cl_2/EtOAc:

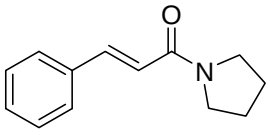
3:1) yield. IR (Film on NaCl): 1675 (C=O), 1626, 1450, 1349, 1123, 769 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.68 (C(O)CH=C<u>H</u>, 1 H, d, *J* = 16.0 Hz), 7.58-6.95 (ArH, 5 H, m), 6.64 (C(O)C<u>H</u>=CH, 1 H, d, *J* = 16.0 Hz), 2.27 (C<u>H</u>$_2$C<u>H</u>$_2$, 4 H, s); ^{13}C NMR ($CDCl_3$): δ 178.5 (C=O), 143.6 (C(O)CH=<u>C</u>H), 134.5 (ArC), 130.3 (ArC), 128.9 (ArC), 128.1 (ArC), 120.8 (C(O)<u>C</u>H=CH), 25.3 (CH_2CH_2); MS (EI) *m/z* (relative intensity): 181 (6), 131 (M^+-NC_2H_4, 29); HRMS *m/z* Calcd: for $C_{14}H_{12}O_3$ (M^+): 173.0841. Found: 173.0837.

Side Product: N-(2-chloroethyl)cinnamamide (**2.52**)



^{1}H NMR ($CDCl_3$): δ 7.63 (C(O)CH=C<u>H</u>, 1 H, d, *J* = 15.6 Hz), 7.53-6.98 (ArH, 5 H, m), 36.66 (N<u>H</u>, 1 H, s), 6,49 (C(O)C<u>H</u>=CH, 1 H, d, *J* = 15.6 Hz), 3.79-3.57 (NHC<u>H</u>$_2$C<u>H</u>$_2$Cl, 4 H, m); ^{13}C NMR ($CDCl_3$): δ 166.3 (C=O), 141.5 (C(O)CH=<u>C</u>H), 134.6 (ArC), 129.8 (ArC), 128.8 (ArC), 127.8 (ArC), 120.3 (C(O)<u>C</u>H=CH), 43.9 , 41.5 (NHC<u>H</u>$_2$C<u>H</u>$_2$Cl). This compound has been previously reported. [86b]

2.7.5.2 Synthesis of Pyrrolidin-1-yl)prop-2-en-1-one (2.54)

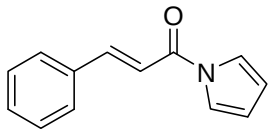


(*E*)-3-phenyl-1-(pyrrolidin-1-yl)prop-2-en-1-one was prepared following a procedure described by Ito and coworkers.[87]

In a flame dried round bottom flask charged with a magnetic stir bar and argon inlet, pyrrolidine (0.80 mL, 9.6 mmol) and triethylamine (1.67 mL, 12.0 mmol) were added to a solution of cinnamoyl chloride (1.333 g, 8.0 mmol) and *N*, *N*-dimethylaminopyridine (DMAP;

98 mg, 0.8 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The reaction was allowed to stir for 12 h and then diluted with H_2O (12 mL). Extraction was performed with EtOAc (3 × 12 mL), organic phase washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified via column chromatography (hexane/EtOAc: 7:3-3:7) to give 1.56 g (97%) of pure product. ^{1}H NMR ($CDCl_3$): δ 7.70 (C(O)CH=C<u>H</u>, 1 H, d, *J* = 15.6 Hz), 7.56-7.46 (ArH, 2 H, m), 7.41-7.32 (ArH, 3 H, m), 6.80 (C(O)C<u>H</u>=CH, 1 H, d, *J* = 15.6), 3.64 (4 H, m), 2.04-1.95 (2 H, m), 1.96-1.84 (2 H, m); ^{13}C NMR ($CDCl_3$): 164.5 (C=O), 141.5 (C(O)CH=<u>C</u>H), 135.2 (ArC), 129.4 (ArC), 128.6 (ArC), 127.7 (ArC), 118.8 (C(O)<u>C</u>H=CH), 46.7, 46.1, 26.3, 24.5.

2.7.5.3 Synthesis of (*E*)-3-Phenyl-1-(1H-pyrrol-1-yl)prop-2-en-1-one (2.56)

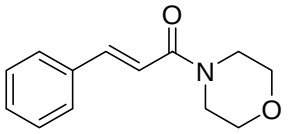


The preparation of (*E*)-3-phenyl-1-(1H-pyrrol-1-yl)prop-2-en-1-one was performed according to the literature protocol for a similar compound.[88,89]

To an ice-cold suspension of NaH (60% dispersion in mineral oil; 320 mg, 8.0 mmol) in dry THF (50 mL), pyrrole (0.56 mL, 8.0 mmol) dissolved in dry THF (15 mL) was slowly added through a dropping funnel while stirring at 0 °C. The mixture was slowly cannulated into another dry round bottomed flask containing cinnamoyl chloride (1.35 g, 8.1 mmol) dissolved in THF (15 mL) while stirring at 0 °C. The reaction mixture was then allowed to stir at room temperature for 4.5 h followed by cooling of the reaction setup to 0 °C before quenching with H_2O (35 mL). Both layers were separated and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic phase was washed with brine (50 mL), dried over Na_2SO_4 and concentrated. The crude material was purified by column chromatography (hexane/EtOAc: 30:1 to 20:1) to

give a moderate yield of the product (0.51 g, 33%). ^{1}H NMR ($CDCl_3$): δ 7.98 (C(O)CH=C<u>H</u>, 1 H, d, *J* = 15.5 Hz), 7.79-7.53 (pyrroleH, 2 H, m), 7.53-7.33 (ArH, 5 H, m), 7.14 (C(O)C<u>H</u>=CH, 1 H, d, *J* = 15.5) 6.73-6.28 (pyrroleH, 2 H, m); ^{13}C NMR ($CDCl_3$): 162.9 (C=O), 147.5 (C(O)CH=<u>C</u>H), 134.2, 130.9, 129.0, 128.3 (ArC), 119.2 (pyrrole-2C), 115.7 (C(O)<u>C</u>H=CH), 113.3 (pyrrole-3C).

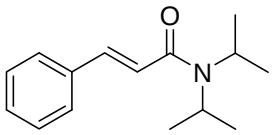
2.7.5.4 Synthesis of (*E*)-1-Morpholino-3-phenylprop-2-en-1-one



Procedure was performed exactly as described by Scheidt and coworkers.[136]

To a flame dried 50-mL 2-neck round bottomed flask, morpholine (2.62 mL, 30 mmol) was added to a dissolved mixture of cinnamoyl chloride (1.67 g, 10 mmol) in CH_2Cl_2 (10 mL) at 0 °C while stirring under argon atmosphere. The reaction mixture was allowed to warm up to room temperature, diluted with EtOAc and continuously stirred for 30 minutes. The mixture was then washed with 1 M HCl, Saturated aqueous $NaHCO_3$, and brine, after which the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was crystallized to afford white crystalline solid in high yield (2.17 g, 99%). ^{1}H NMR ($CDCl_3$): δ 7.67 (C(O)CH=C<u>H</u>, 1 H, d, *J* = 15.4 Hz), 7.58-7.29 (ArH, 5 H, m), 6.82 (C(O)C<u>H</u>=CH, 1 H, d, *J* = 15.4), 3.70 (morpholine-H, 8 H, s); ^{13}C NMR ($CDCl_3$): 165.6 (C=O), 143.2 (C(O)CH=<u>C</u>H), 133.1, 129.7, 128.8, 127.8 (ArC), 116.6 (C(O)<u>C</u>H=CH), 66.8 (morpholine-C).

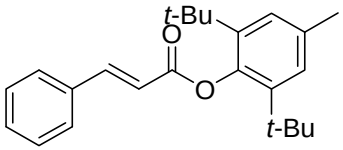
2.7.5.5 Synthesis of *N*,*N*-Diisopropylcinnamamide (2.55)[137]



N,*N*-diisopropylcinnamamide was prepared following the procedure described for preparation of (*E*)-3-phenyl-1-(pyrrolidin-1-yl)prop-2-en-1-one **2.54** above.

Diisopropylamine (1.35 mL, 9.6 mmol) and triethylamine (1.69 mL, 12.0 mmol) were added to a solution of cinnamoyl chloride (1.333 g, 8.0 mmol) and *N*, *N*-dimethylaminopyridine (DMAP; 98 mg, 0.8 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The reaction was allowed to stir for 12 h and then diluted with H_2O (15 mL). Extraction was performed with EtOAc (3 × 20 mL), organic phase washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified via column chromatography (CH_2Cl_2/EtOAc: 10:1) to give 1.64 g (89%) of pale yellow solid product. Mp: 37-39 °C; IR (Film on NaCl): 1645 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.56 (C(O)CH=C<u>H</u>, 1 H, d, *J* = 15.4 Hz), 7.52-7.25 (ArH, 5 H, m), 6.81 (C(O)C<u>H</u>=CH, 1 H, d, *J* = 15.4 Hz), 4.18-3.76 (2 H, m), 1.34 (12 H, s); ^{13}C NMR ($CDCl_3$): δ 166.0 (C=O), 140.7 (C(O)CH=<u>C</u>H), 135.6, 129.1, 128.6, 127.4 (ArC), 120.6 (C(O)<u>C</u>H=CH), 47.9, 45.8, 21.5, 20.6.

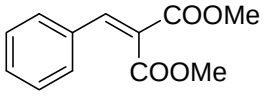
2.7.5.6 Synthesis of 2,6-Di-tert-butyl-4-methylphenyl cinnamate (2.58)



To a flame dried 250-mL 3-neck round bottomed flask fitted with a magnetic stir bar, a dropping funnel and an argon inlet adapter, 2,6-di-tert-butyl-4-methylphenol (1.763 g, 8.00 mmol) was dissolved in dry THF (50 mL) and cooled to -78 °C for 5 minutes. A solution of *n*-BuLi (6.01 mL of a 1.49 M solution in hexane, 8.96 mmol) was slowly added and allowed to stir

for 30 minutes at -78 °C. To the dropping funnel, cinnamoyl chloride (1.813 g, 10.90 mmol) dissolved in THF (15 mL) was added dropwise to the orange reaction mixture in the round-bottom flask while stirring and allowed to warm up to room temperature over 2 h. The reaction was quenched with H_2O (20 mL), extracted with Et_2O (3 × 30 mL), washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (hexane/EtOAc: 15:1) to afford a white solid in poor yield (0.746 g, 27%). Mp: 141-142 °C; IR (Film on NaCl): 1732 (C=O), 1632, 1598, 1449, 1140, 766 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.85 (C(O)CH=C<u>H</u>, 1 H, d, *J* = 16.0 Hz), 7.73-7.51 (ArH, 2 H, m), 7.51-7.32 (ArH, 3 H, m), 7.13 (ArH, 2 H, s), 6.70 (C(O)C<u>H</u>=CH, 1 H, d, *J* = 16.0 Hz), 2.32 (Me, 3 H, s), 1.33 (*t*-Bu, 18 H, s); ^{13}C NMR ($CDCl_3$): δ 167.3, 146.6, 145.7, 142.2, 134.5, 134.2, 130.7, 129.0, 128.4, 127.0, 118.6, 35.3, 31.6, 21.6; MS (EI) *m/z* (relative intensity): 331 (2), 131 (M^+-$C_{15}H_{23}O$, 82); HRMS *m/z* Calcd. for $C_{14}H_{12}O_3$ (M^+): 350.2246. Found: 350.2242.

2.7.5.7 Synthesis of Dimethyl 2-Benzylidenemalonate (2.65)



The procedure for the preparation of dimethyl 2-benzylidenemalonate was performed according to the protocol described in literature.[107,138]

A mixture of benzaldehyde (2.415 g, 2.30 mL, 22.8 mmol) and proline (0.262 g, 2.82 mmol) dissolved in dry DMSO (15 mL) was stirred for 5 minutes followed by the addition of dimethyl malonate (6.013 g, 5.20 mL, 45.5 mmol) which was then stirred overnight at room temperature. The reaction mixture was diluted with EtOAc (25 mL) and washed with H_2O (2 × 25 mL). The organic phase was dried over Na_2SO_4, concentrated and purified by column chromatography (hexane/EtOAc: 20:1) to afford 3.984 g (80%) of impure product. Distillation at

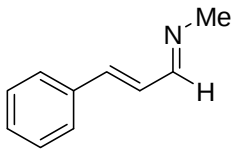
156 °C/0.08 mmHg) was used to further purify the impure product to give 1.640 g (33% overall) of pure product. ^{1}H NMR ($CDCl_3$): δ 7.74 (PhC<u>H</u>=C, 1 H, s), 7.57-7.27 (ArH, 5 H, m), 3.81 (C(O)OMe, 6 H, s); ^{13}C NMR ($CDCl_3$): δ 169.3, 164.3, 142.7, 132.6, 130.6, 129.2, 128.8, 125.4, 52.5.

2.7.5.8 General Procedure: Synthesis of *α,β*-Unsaturated Imines (2.59)

The eco-friendly procedure used for the preparation of the various *α,β*-unsaturated imines was performed according to the general procedure described in literature.[90,91]

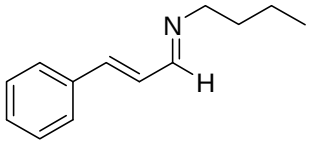
A mixture of trans-cinnamaldehyde (1 equiv), appropriate amine (1 equiv), silica (300 mg/1 mmol of cinnamaldehyde) and ethanol (5 mL/3 mmol of cinnamaldehyde) were placed in a dry round bottom flask and irradiated in the water of a sonicator at room temperature for 10-15 minutes. The mixture was then filtered to remove silica, concentrated under reduced pressure and distilled in some cases to improve the purity of the synthesized imines.

2.7.5.8.1 (*E*)-*N*-((*E*)-3-Phenylallylidene)methanamine (2.59a)[90]



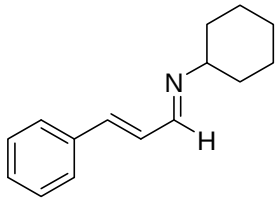
Yield: 64% (purified via distillation at 82 °C/0.8 mmHg to give a yellow oil); ^{1}H NMR ($CDCl_3$): δ 8.01 (1 H, d, J = 7.1 Hz), 7.73-7.09 (5 H, m), 7.09-6.71 (2 H, m), 3.42 (Me, 3 H, s); ^{13}C NMR ($CDCl_3$): δ 163.9 (H<u>C</u>=NR), 140.9, 135.7, 128.9, 128.7, 128.2, 127.1 (PhCH=CH), 48.1 (N<u>C</u>H$_3$).

2.7.5.8.2 (*E*)-*N*-((*E*)-3-Phenylallylidene)butan-1-amine (2.59b)[90]



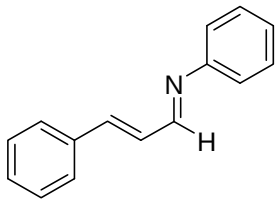
Yield: 99%; ^{1}H NMR ($CDCl_3$): δ 8.50-7.72 (HC=NR, 1 H, m), 7.72-7.07 (5 H, m), 7.07-6.71 (2 H, m), 3.50 ($NCH_2CH_2CH_2CH_3$, 2 H, t), 1.78-1.50 ($NCH_2CH_2CH_2CH_3$, 2 H, m), 1.50-1.19 ($NCH_2CH_2CH_2CH_3$, 2 H, m), 0.93 ($NCH_2CH_2CH_2CH_3$, 2 H, t); ^{13}C NMR ($CDCl_3$): δ 162.3 (HC=NR), 141.0, 135.7, 129.1, 128.7, 128.2, 127.1 (PhCH=CH), 61.2 ($NCH_2CH_2CH_2CH_3$), 32.9 ($NCH_2CH_2CH_2CH_3$), 20.3 ($NCH_2CH_2CH_2CH_3$), 13.8 ($NCH_2CH_2CH_2CH_3$).

2.7.5.8.3 (*E*)-*N*-((*E*)-3-Phenylallylidene)cyclohexanamine (2.59c)[90]



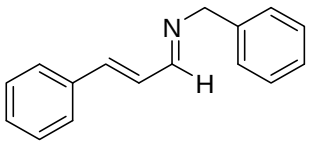
Yield: 95%; ^{1}H NMR ($CDCl_3$): δ 8.13-7.90 (HC=NR, 1 H, m), 7.47-7.09 (5 H, m), 7.09-6.74 (2 H, m), 3.17-2.89 (NCH, 1 H, m), 1.91-1.08 ($CH_2CH_2CH_2CH_2CH_2$, 10 H, m); ^{13}C NMR ($CDCl_3$): δ 160.3 (HC=NR), 141.1, 135.8, 69.6, 34.4, 25.5, 24.8.

2.7.5.8.4 (*E*)-*N*-((*E*)-3-Phenylallylidene)benzenamine (2.59d)[91]



Yield: 99%; ^{1}H NMR ($CDCl_3$): δ 8.37-8.15 (HC=NR, 1 H, m), 7.64-7.06 (12 H, m); ^{13}C NMR ($CDCl_3$): δ 161.7 (HC=NR), 144.1, 135.6, 129.6, 129.2, 128.9, 128.6, 127.5, 126.1, 120.9

2.7.5.8.5 (*E*)-Phenyl-*N*-((*E*)-3-Phenylallylidene)methanamine (2.59e)[91]

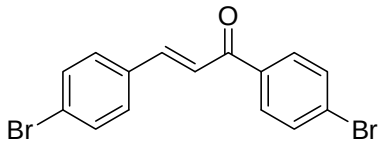


Yield: 91%; ^{1}H NMR ($CDCl_3$): δ 8.25-8.02 (HC=NR, 1 H, m), 7.59-7.11 (10 H, m), 7.11-6.87 (2 H, m), 4.72 (NCH_2, 2 H, s); ^{13}C NMR ($CDCl_3$): δ 163.4 (HC=NR), 141.9, 139.1, 135.6, 129.1, 128.8, 128.5, 128.1, 128.0, 127.2, 127.0, 65.2 (NCH_2)

2.7.5.9 Synthesis of Enones

The various enones used were obtained commercially, prepared according to literature methods or prepared by modification of similar literature protocols.

2.7.5.9.1 Synthesis of (*E*)-1,3-Bis(4-bromophenyl)prop-2-en-1-one (2.72)



(*E*)-1,3-bis(4-bromophenyl)prop-2-en-1-one was prepared following a procedure described in literature with slight modifications.[66]

A mixture of 4-bromoacetophenone (3.66 g, 18.4 mmol), 4-bromobenzaldehyde (3.40 g, 18.4mmol) and NaOH (73.6 mg, 1.84 mmol) in water (20 mL) and MeOH (20 mL) were heated to reflux in a 100-mL round bottomed flask overnight. After cooling the reaction mixture to

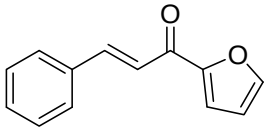
room temperature, 6 M HCl (0.32 mL, 1.92 mmol) was added to neutralize the NaOH. Extraction was then carried out with CH_2Cl_2 (3 × 75 mL), and the combined organic layer was washed with saturated aqueous $NaHCO_3$ (100 mL), brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated to give a yellow solid. The crude product was crystallized with hexane/EtOAc to afford 5.92 g (88%) yellow crystalline product. ^{1}H NMR ($CDCl_3$): δ 7.86 (ArH, 2 H, d, *J* = 8.5 Hz), 7.73 (C(O)CH=C<u>H</u>, 1 H, d, *J* = 15.7 Hz), 7.63 (ArH, 2 H, d, *J* = 8.5 Hz), 7.55 (ArH, 2 H, d, *J* = 8.5 Hz), 7.50-7.41 (3 H, m); ^{13}C NMR ($CDCl_3$): δ 189.0, 143.9, 136.7, 133.6, 132.3, 132.0, 130.0, 129.8, 128.1, 125.1, 121.9.

2.7.5.9.2 General Procedure for the Synthesis of Enones 2.60

The preparation of the various enones was performed according to procedure described by literature.[99]

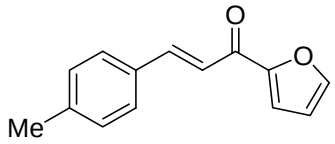
Aqueous KOH solution (100 mg in 10 mL of H_2O) was added to a stirred mixture of aryl-aldehyde (1 equiv.) in H_2O (2 mL per mmol) at room temperature. After 15 minutes of stirring at room temperature, 2-acetylfuran (1.33 equiv.) was quickly added and the reaction mixture was allowed to stir at room temperature overnight (more than 12 h). The reaction was monitored by TLC to check for completion. The mixture was then acidified with 1 M H_2SO_4 (2 mL), extracted with Et_2O, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude products were purified by flash chromatography (hexane/Et_2O: 5:1).

2.7.5.9.2.1 (*E*)-1-(Furan-2-yl)-3-phenylprop-2-en-1-one (2.60a)



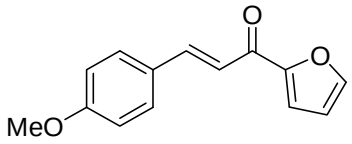
Yield: 99%. White solid; mp: 87-88°C; ^{1}H NMR ($CDCl_3$): δ 7.86 (C(O)CH=C<u>H</u>, 1 H, d, *J* = 15.8 Hz), 7.74-7.54 (3 H, m), 7.54-7.28 (5 H, m), 6.69-6.48 (1 H, m); ^{13}C NMR ($CDCl_3$): δ 178.0, 153.7, 146.5, 144.0, 134.7, 130.6, 128.9, 128.5, 121.2, 117.5, 112.5; MS (EI) *m/z* (relative intensity): 199 (30), 197 (M^+, 20), 181 (5); HRMS *m/z* Calcd. for $C_{13}H_{10}O_2$ (M^+): 198.0681. Found for $C_{13}H_9O_2$ (M^+-1) 197.0597.

2.7.5.9.2.2 (*E*)-1-(Furan-2-yl)-3-p-tolylprop-2-en-1-one (2.60b)



Yield: 99% (83% crystallized from hexane/CH_2Cl_2). White solid; mp: 111-112°C; ^{1}H NMR ($CDCl_3$): δ 7.88 (C(O)CH=C<u>H</u>, 1 H, d, *J* = 15.8 Hz), 7.76-7.51 (3 H, m), 7.51-7.13 (5 H, m), 6.71-6.51 (1 H, m), 2.41 (C<u>H</u>$_3$, 3 H, s); ^{13}C NMR ($CDCl_3$): δ 178.1, 153.8, 146.3, 144.0, 141.2, 132.1, 129.7, 128.6, 120.2, 117.2, 112.5, 21.5; MS (EI) *m/z* (relative intensity): 231 (4), 213 (31), 197 (M^+-CH_3, 77); HRMS *m/z* Calcd. for $C_{14}H_{11}O_2$ (M^+-1): 211.0759. Found for $C_{14}H_{11}O_2$ (M^+-1): 211.0765.

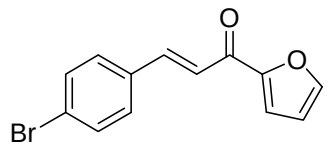
2.7.5.9.2.3 (*E*)-1-(Furan-2-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (2.60c)



Yield: 83% (71% crystallized from hexane/CH_2Cl_2). Pale yellow solid; mp: 111-112°C; ^{1}H NMR ($CDCl_3$): δ 7.88 (C(O)CH=C<u>H</u>, 1 H, d, *J* = 15.7 Hz), 7.76-7.50 (3 H, m), 7.50-7.13 (2 H, m), 7.07-6.85 (2 H, m), 6.72-6.50 (1 H, m), 3.88 (OC<u>H</u>$_3$, 3 H, s); ^{13}C NMR ($CDCl_3$): δ 178.1, 161.8, 153.9, 146.2, 143.8, 130.3, 127.6, 118.9 117.0, 114.4, 112.4, 55.4; MS (EI) *m/z* (relative

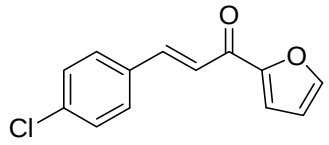
intensity): 231 (3), 228 (M^+, 10); HRMS *m/z* Calcd. for $C_{14}H_{12}O_3$ (M^+): 228.0786. Found: 228.0788.

2.7.5.9.2.4 (*E*)-3-(4-Bromophenyl)-1-(furan-2-yl)prop-2-en-1-one (2.60d)



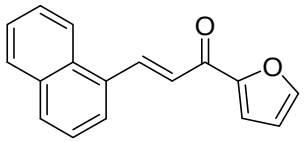
Yield: 75%. Pale yellow solid; mp: 130-131°C; ^{1}H NMR ($CDCl_3$): δ 7.78 (C(O)CH=C<u>H</u>, 1 H, d, *J* = 15.8 Hz), 7.70-7.59 (1 H, m), 7.59-7.28 (6 H, m), 6.69-6.48 (1 H, m); ^{13}C NMR ($CDCl_3$): δ 177.7, 153.5, 146.6, 142.5, 133.6, 132.1, 129.8, 124.9, 121.6, 117.6, 112.6; MS (EI) *m/z* (relative intensity): 280 (2), 277 (6), 276 (M^+, 71); HRMS *m/z* Calcd: for $C_{13}H_9{}^{79}BrO_2$ (M^+): 275.9786. Found: 275.9791.

2.7.5.9.2.5 (*E*)-3-(4-Chlorophenyl)-1-(furan-2-yl)prop-2-en-1-one(2.60e)



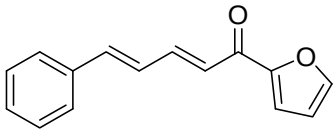
Yield: 77% (67% crystallized from hexane/CH_2Cl_2). White solid; mp: 135-137°C; ^{1}H NMR ($CDCl_3$): δ 7.80 (C(O)CH=C<u>H</u>, 1 H, d, *J* = 15.8 Hz), 7.71-7.49 (3 H, m), 7.49-7.27 (4 H, m), 6.69-6.48 (1 H, m); ^{13}C NMR ($CDCl_3$): δ 177.7, 153.6, 146.6, 142.5, 136.5, 133.2, 129.7, 129.2, 121.6, 117.6, 112.6; MS (EI) *m/z* (relative intensity): 233 (16), 232 (M^+, 89), 231 (1); HRMS *m/z* Calcd. for $C_{13}H_9{}^{35}ClO_2$ (M^+): 232.0291. Found: 232.0291.

2.7.5.9.2.6 (*E*)-1-(Furan-2-yl)-3-(naphthalen-1-yl)prop-2-en-1-one (2.60f)



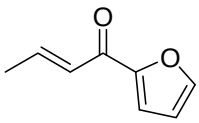
Yield: 37%. Yellow solid; mp: 87-88°C; ^{1}H NMR ($CDCl_3$): δ 8.72 (C(O)CH=C<u>H</u>, 1 H, d, J = 15.5 Hz), 8.27 (1 H, d, *J* = 8.3 Hz), 8.02-7.76 (3 H, m), 7.76-7.44 (5 H, m), 7.44-7.30 (1 H, m), 6.71-6.56 (1 H, m); ^{13}C NMR ($CDCl_3$): δ ; MS (EI) *m/z* (relative intensity): 269 (1), 249 (38), 232 (M^+, 95); HRMS *m/z* Calcd. for $C_{17}H_{12}O_2$ (M^+): 248.0837. Found: 248.0839.

2.7.5.9.2.7 (2*E*,4*E*)-1-(Furan-2-yl)-5-phenylpenta-2,4-dien-1-one (2.60g)



Yield: 77% (59% crystallized from hexane/CH_2Cl_2). Yellow solid; mp: 110-111°C; ^{1}H NMR ($CDCl_3$): δ 7.78-7.55 (2 H, m), 7.55-7.42 (2 H, m), 7.42-7.15 (4 H, m), 7.10-6.86 (3 H, m), 6.66-6.46 (1 H, m); ^{13}C NMR ($CDCl_3$): δ 178.0, 153.7, 146.4, 143.9, 142.1, 136.0, 129.2, 128.8, 127.3, 126.7, 124.6, 117.2, 112.4; MS (EI) *m/z* (relative intensity): 231 (3), 224 (M^+, 12); HRMS *m/z* Calcd. for $C_{15}H_{12}O_2$ (M^+): 224.0837. Found: 224.0832.

2.7.5.9.2.8 (*E*)-1-(Furan-2-yl)but-2-en-1-one (2.60h)



Rather than the conventional aldol condensation reaction previously used to prepare the aryl enones **2.60a-g**, this specific enone was prepared by a different technique described by Campbell and Lipshutz with minor adjustments.[100]

To a 2-neck 250-mL dried round bottom flask fitted with a magnetic stir bar, rubber septum and an argon inlet, a mixture of furan (6.81 g, 7.27 mL, 100 mmol) in THF (100 mL) and *n*-BuLi (55.56 mL of a 1.80 M solution in hexane, 100 mmol) was stirred at -30 °C. The homogeneous solution was allowed to warm up to about 0 °C over 1.5 h. In another dry 3-neck 500-mL round bottom flask fitted with a magnetic stir bar, rubber septum, argon inlet and a thermometer, a suspension of CuCN (4.48 g, 50 mmol) in THF (15 mL) was cooled to -30 °C. The homogeneous lithiated solution was then added to the suspension via cannulation (or syringe) at -30 °C. The cooling bath was removed and the reaction mixture was allowed to warm up gradually while stirring until the mixture became homogeneous. The homogeneous difuranyl cyanocuprate solution was cooled to -78 °C and crotonoyl chloride (10.45 g, 9.58 mL, 100 mmol) was added. The reaction was monitored by TLC. The reaction was quenched with saturated aqueous NH_4Cl (250 mL) after 2 h at -70 °C, diluted with Et_2O (200 mL) and allowed to warm up to room temperature overnight. The top organic layer was separated, washed with NaCl (2 × 300 mL), dried over Na_2SO_4, concentrated under reduced pressure and purified by flash column chromatography on silica gel (hexane/Et_2O: 9:1) to afford the desired product in 46% yield (31% crystallized from hexane). Pale yellow solid; mp: 59-61°C; IR (film on NaCl): 1668 (C=O), 1616, 1560, 1396, 1467, 1396, 1255; ^{1}H NMR ($CDCl_3$): δ 7.69-7.49 (1 H, m), 7.34-6.98 (2 H, m), 6.93-6.67 (1 H, m), 6.65-6.42 (1 H, m), 1.96 (3 H, dd, J = 6.9, 1.5 Hz); ^{13}C NMR ($CDCl_3$): δ 178.1, 153.3, 146.4, 144.3, 126.5, 117.4, 112.3, 18.5; MS (EI) *m/z* (relative intensity): 136 (M^+, 83); HRMS *m/z* Calcd: for $C_8H_8O_2$ (M^+): 136.0524. Found: 136.0522.

2.7.6 General Procedure for the Alkenylboration of Enones

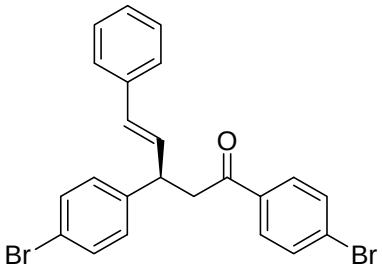
The procedure for the synthesis of the various 1,4-addition products were according to protocol used in previous literature with little additional modifications.[65]

To a mixture of activated 4Å molecular sieves (400 mg), appropriate enone (1 equiv, 0.30 mmol) and chiral diol **2.42f** (0.2 equiv, 0.06 mmol) in CH_2Cl_2 (6 mL), the required alkenylboronate (3 equiv, 0.90 mmol) was added at room temperature. The mixture was then refluxed over a period of time while monitoring completion by TLC. Upon completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (6 mL), filtered through celite, concentrated under reduced pressure and purified via flash column chromatography on silica gel (hexane/Et_2O: 9:1 ~ 4:1) to afford the addition product.

However, in some cases, TLC showed an overlap of the addition product and the chiral diol used (R_f = ~0.55). Hence, a basic workup was used to facilitate separation. The diluted reaction mixture with was then washed with 1 M NaOH (12 mL), H_2O (2 × 12mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified as previously mentioned to give the desired addition product.

The enantiomeric purities of the product were determined with the aid of HPLC analysis (4.6 × 250 mm ChiralCel OD or ChiralPak AD-H, hexanes/*i*-PrOH = 99.75/0.25 ~ 96.75/3.25 v/v).

2.7.6.1 (*R*,*E*)-1,3-Bis(4-bromophenyl)-5-phenylpent-4-en-1-one (2.73)



Yield: 78%. Colorless solid; mp.: 135-141°C; ^{1}H NMR ($CDCl_3$): δ 7.89-7.67 (ArH, 2 H, m), 7.67-7.50 (ArH, 2 H, m), 7.50-7.34 (ArH, 2 H, m), 7.34-7.05 (ArH, 7 H, m), 6.50-6.18 (C<u>H</u>=C<u>H</u>, 2 H, m), 4.23 (C<u>H</u>-CH=CH, 1 H, m), 3.59-3.24 (C(O)C<u>H</u>$_2$, 2 H, m); ^{13}C NMR ($CDCl_3$): δ 196.6, 141.9, 136.7, 135.6, 131.9, 131.7, 131.6, 130.5, 129.5, 129.4, 128.4, 128.3, 127.4, 126.1, 120.4, 44.1, 43.2; the enantiomeric purity was determined by HPLC analysis: (ChiralCel OD, hexane/*i*-PrOH = 99/1, flow rate = 0.5 mL/min) t_R = 7.59 min (*R*), t_R = 14.01 min (*S*); X-ray quality crystals were grown by recrystallization from CH_2Cl_2/hexane to give crystalline product of 99:1 er;

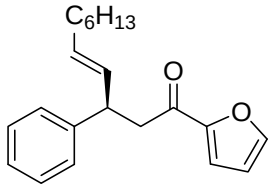
2.7.6.1.1 X-ray Crystallographic Analysis of 2.73[i]

The resulting precipitated solid product was recrystallized from CH_2Cl_2/hexane to give suitable crystalline product for x-ray diffraction studies. A single crystal measuring 0.50 × 0.23 × 0.10 mm was chosen. Intensity data was collected at 200(2) K with the exposure time 30 s/frame using 0.3° in ω scan in four groups of 600 at ϕ = 0°, 90°, 180° and 270°. The data were corrected for Lorentz and polarization effects. Absorption corrections were based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements using APEX II software. The lattice parameter indicated a monoclinic crystal system and the systematic

[i] Crystal data was obtained by Dr. Jalil Assoud of the Department of Chemistry, University of Waterloo.

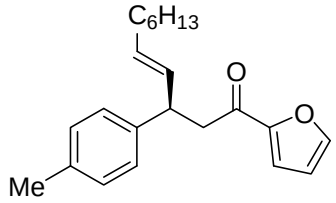
absences pointed toward the non-centrosymmetric space group $P2_1$. The structure was solved by direct methods using SHELXTL program package and refined through full matrix least-squares calculations, anisotropically for non-hydrogen atoms and isotropically for hydrogen atoms, to a final R = 2.57% and R_w = 6.65%. Crystal system: monoclinic. Space group: $P2_1$. Lattice parameters: a = 8.0749(13) Å, b = 5.9244(10) Å, c = 20.580(3) Å, β = 99.916(3) °. An absolute configuration of *R* was readily apparent (Appendix).

2.7.6.2 (*R*,*E*)-1-(Furan-2-yl)-3-phenylundec-4-en-1-one (2.71a)



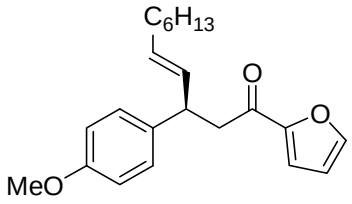
$[\alpha]_{589}^{25}$ -2.7 (95:5 er, c = 0.60, THF); yield: 83%. Yellow oil; IR (neat): 1677 (C=O), 1569, 1467, 1081, 968, 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.54 (1 H, s), 7.40-7.01 (6 H, m), 6.58-6.38 (1 H, m), 5.59 (1 H, dd, *J* = 15.3, 7.1 Hz), 5.43 (1 H, dt, *J* = 15.3, 6.4 Hz), 4.02 (1 H, m), 3.24 (1 H, dd, *J* = 15.4, 8.1 Hz), 3.13 (1 H, dd, *J* = 15.4, 6.7 Hz), 2.05-1.80 (2 H, m), 1.34-1.10 (8 H, m), 0.84 (3 H, t, *J* = 6.9); ^{13}C NMR ($CDCl_3$): δ 187.8, 153.0, 146.2, 143.8, 131.8, 131.3, 128.4, 127.5, 126.3, 117.0, 112.1, 44.6, 44.0, 32.4, 31.6, 29.2, 28.7, 22.5, 14.0; MS (EI) *m/z* (relative intensity): 331 (2), 95 (M^+-$C_{16}H_{23}$, 22); HRMS *m/z* Calcd: for $C_{21}H_{26}O_2$ (M^+): 310.1933. Found: 310.1934; the enantiomeric purity determined by HPLC analysis: (ChiralCel OD, hexane/*i*-PrOH = 98/2, flow rate = 0.5 mL/min) t_R = 18.95 min (*R*), t_R = 23.79 min (*S*).

2.7.6.3 (*R*,*E*)-1-(Furan-2-yl)-3-p-tolylundec-4-en-1-one (2.71b)



$[\alpha]_{589}^{25}$ -13.5 (98.5:1.5 er, c = 1.40, THF); yield: 81%. Yellow oil; IR (neat): 1678 (C=O), 1569, 1514, 1468, 1085, 1012, 969, 761 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.53 (1 H, s), 7.14-7.06 (5 H, m), 6.59-6.37 (1 H, m), 5.57 (1 H, dd, *J* = 15.3, 7.1 Hz), 5.42 (1 H, dt, *J* = 15.3, 6.5 Hz), 3.98 (1 H, m), 3.26-3.07 (2 H, m), 2.28 (3 H, s), 1.96-1.89 (2 H, m), 1.27-1.20 (8 H, m), 0.84 (3 H, t, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$): δ 187.8, 153.0, 146.1, 140.8, 135.7, 132.0, 131.0, 129.1, 127.3, 116.9, 112.1, 44.6, 43.5, 32.3, 31.6, 29.1, 28.6, 22.5, 20.9, 14.0; MS (EI) *m/z* (relative intensity): 331 (2), 198 (M^+-C_9H_{18}, 71); HRMS *m/z* Calcd: for $C_{22}H_{28}O_2$ (M^+): 324.2089. Found: 324.2093; the enantiomeric purity was determined by HPLC analysis: (ChiralCel OD, hexane/*i*-PrOH = 99/1 flow rate = 0.5 mL/min) t_R = 17.82 min (*R*), t_R = 20.79 min (*S*).

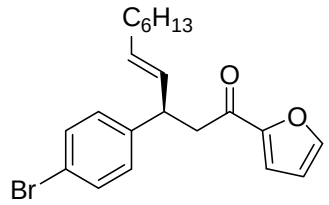
2.7.6.4 (*R*,*E*)-1-(Furan-2-yl)-3-(4-methoxyphenyl)undec-4-en-1-one (2.71c)



$[\alpha]_{589}^{25}$ -10.6 (95:5 er, c = 1.26, THF); yield: 78%. Yellow oil; IR (neat): 1677 (C=O), 1611, 1569, 1468, 1179, 1037, 970, 762 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.53 (1 H, s), 7.16-7.10 (3 H, m), 6.80 (2 H, d, *J* = 8.6 Hz), 6.48 (1 H, m), 5.56 (1 H, dd, *J* = 15.3, 7.0 Hz), 5.41 (1 H, dt, *J* = 15.3, 6.6 Hz), 3.97 (1 H, m), 3.75 (3 H, s), 3.24-3.06 (2 H, m), 1.96-1.89 (2 H, m), 1.34-1.09 (8 H, m), 0.84 (3 H, t, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$): δ 187.9, 158.0, 153.0, 146.2, 135.9, 132.1,

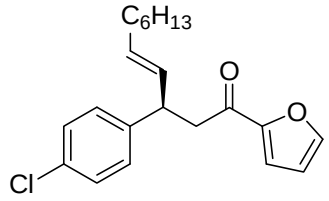
130.9, 128.4, 117.0, 113.8, 112.1, 55.2, 44.7, 43.1, 32.4, 31.6, 29.2, 28.7, 22.5, 14.0; MS (EI) *m/z* (relative intensity): 331 (2), 231 (M^+-$C_6H_5O_2$, 99); HRMS *m/z* Calcd: for $C_{22}H_{28}O_3$ (M^+): 340.2038. Found: 340.2034; the enantiomeric purity was determined by HPLC analysis: (ChiralCel OD, hexane/*i*-PrOH = 98/2, flow rate = 0.5 mL/min) t_R = 22.98 min (*S*), t_R = 28.50 min (*R*).

2.7.6.5 (*R*,*E*)-3-(4-Bromophenyl)-1-(furan-2-yl)undec-4-en-1-one (2.71d)



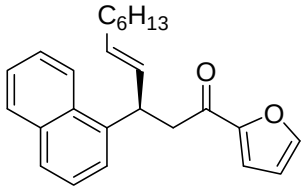
$[\alpha]_{589}^{25}$ -28.4 (98.5:1.5 er, c = 1.43, THF); yield: 79%. Yellow oil; IR (neat): 1678 (C=O), 1569, 1488, 1468, 1074, 1011, 969, 760 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.54 (1 H, s), 7.37 (2 H, d, *J* = 8.1 Hz), 7.11-7.08 (3 H, m), 6.49 (1 H, m), 5.54 (1 H, dd, *J* = 15.5, 6.7 Hz), 5.42 (1 H, dt, *J* = 15.5, 6.3 Hz), 3.98 (1 H, m), 3.24-3.07 (2 H, m), 1.92 (2 H, m), 1.20 (8 H, m), 0.83 (3 H, t, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$): δ 187.4, 152.9, 146.3, 142.8 131.7, 131.5, 131.4, 129.3, 120.1, 117.0, 112.2, 44.3. 43.2, 32.4, 31.6, 29.1, 28.7, 22.5, 14.0; MS (EI) *m/z* (relative intensity): 381 (2), 95 (M^+-$C_{16}H_{22}{}^{79}Br$, 56); HRMS *m/z* Calcd: for $C_{21}H_{25}{}^{79}BrO_2$ (M^+): 388.1038. Found: 388.1036; the enantiomeric purity was determined by HPLC analysis: (ChiralCel OD, hexane/*i*-PrOH = 98/2, flow rate = 0.5 mL/min) t_R = 20.40 min (*R*), t_R = 22.87 min (*S*).

2.7.6.6 (*R*,*E*)-3-(4-Chlorophenyl)-1-(furan-2-yl)undec-4-en-1-one (2.71e)



$[\alpha]_{589}^{25}$ -21.4 (99.5:0.5 er, c = 1.40, THF); yield: 65%. Yellow oil; IR (neat): 1678 (C=O), 1569, 1491, 1469, 1091, 1014, 969, 759 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.53 (1 H, s), 7.24-7.11 (5 H, m), 6.48 (1 H, m), 5.54 (1 H, dd, *J* = 15.4, 6.8 Hz), 5.42 (1 H, dt, *J* = 15.4, 6.4 Hz), 4.00 (1 H, m), 3.24-3.07 (2 H, m), 1.97-1.89 (2 H, m), 1.35-1.10 (8 H, m), 0.83 (3 H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$): δ 187.4, 152.9, 146.3, 142.2, 132.0, 131.6, 131.4, 128.9, 128.5, 117.0 112.2, 44.3, 43.2, 32.4, 31.6, 29.1, 28.7, 22.5, 14.0; MS (EI) *m/z* (relative intensity): 344 (M^+, 3), 95 (M^+-$C_{16}H_{22}{}^{35}Cl$, 25); HRMS *m/z* Calcd: for $C_{21}H_{25}{}^{35}ClO_2$ (M^+): 344.1543. Found: 344.1544; the enantiomeric purity was determined by HPLC analysis: (ChiralCel OD, hexane/*i*-PrOH = 98/2, flow rate = 0.5 mL/min) t_R = 18.40 min (*R*), t_R = 20.39 min (*S*).

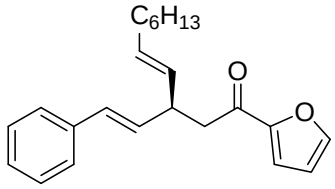
2.7.6.7 (*R*,*E*)-1-(Furan-2-yl)-3-(naphthalen-1-yl)undec-4-en-1-one (2.71f)



$[\alpha]_{589}^{25}$ -12.1 (97.9:2.1 er, c = 0.75, THF); yield: 29%. Yellow viscous oil; IR (neat): 1677 (C=O), 1568, 1468, 1084, 1018, 971, 778 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.23 (1 H, d, *J* = 8.3 Hz), 7.83 (1 H, d, *J* = 7.8 Hz), 7.71 (1 H, t, *J* = 4.7 Hz), 7.55-7.40 (5 H, m), 7.15 (1 H, d, *J* = 3.5 Hz), 6.49 (1 H, m), 5.72 (1 H, dd, *J* = 15.4, 6.8 Hz), 5.49 (1 H, dt, *J* = 15.3, 6.6 Hz), 4.90 (1 H, m), 3.45 (1 H, dd, *J* = 15.9, 9.3 Hz), 3.23 (1 H, dd, *J* = 15.9, 5.0 Hz), 1.98-1.91 (2 H, m), 1.34-1.18

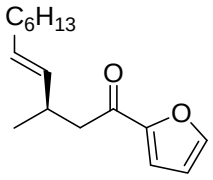
(8 H, m), 0.83 (3 H, t, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$): δ 187.7, 153.0, 146.1, 139.9, 133.9, 131.8, 131.3, 131.2, 128.7, 127.0, 125.9, 125.4, 125.3, 124.0, 123.5, 116.9, 112.1, 44.2, 38.6, 32.4, 31.5, 29.1, 28.6, 22.5, 14.0; MS (EI) *m/z* (relative intensity): 381 (2), 167 (M^+-$C_{12}H_{17}O_2$, 53); HRMS *m/z* Calcd: for $C_{25}H_{28}O_2$ (M^+): 360.2089. Found: 360.2096; the enantiomeric purity was determined by HPLC analysis: (ChiralCel OD, hexane/*i*-PrOH = 98/2, flow rate = 0.5 mL/min) t_R = 27.00 min (*R*), t_R = 32.28 min (*S*).

2.7.6.8 (*R*,*E*)-1-(Furan-2-yl)-3-((*E*)-styryl)undec-4-en-1-one (2.71g)



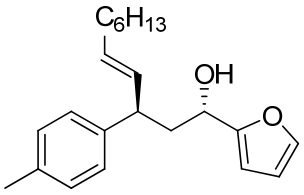
$[\alpha]_{589}^{25}$ -6.7 (97.5:2.5 er, c = 1.03, THF); yield: 37%. Yellow viscous oil; IR (neat): 1677 (C=O), 1568, 1468, 1261, 1085, 1019, 968, 801 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.55 (1 H, s), 7.32-7.15 (6 H, m), 6.51 (1 H, m), 6.39 (1 H, d, J = 15.9 Hz), 6.17 (1 H, dd, J = 15.9, 7.2 Hz), 5.55-5.39 (2 H, m), 5.58 (1 H, m), 3.14-2.87 (2 H, m), 2.00-1.93 (2 H, m), 1.33-1.13 (8 H, m), 0.85 (3 H, t, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 187.9, 153.1, 146.3, 137.4, 132.1, 131.8, 130.7, 129.8, 128.4, 127.1, 126.2, 117.1, 112.2, 43.8, 41.7, 32.5, 31.7, 29.3, 28.8, 22.6, 14.1; MS (EI) *m/z* (relative intensity): 331 (2), 95 (M^+-$C_{18}H_{25}$, 22); HRMS *m/z* Calcd: for $C_{23}H_{28}O_2$ (M^+): 336.2089. Found: 335.2094; the enantiomeric purity was determined by HPLC analysis: (ChiralCel OD, hexane/*i*-PrOH = 98/2, flow rate = 0.5 mL/min) t_R = 21.85 min (*R*), t_R = 25.89 min (*S*).

2.7.6.9 (*R*,*E*)-1-(Furan-2-yl)-3-methylundec-4-en-1-one (2.71h)



$[\alpha]_{589}^{25}$ -1.9 (96.8:3.2 er, c = 1.20, THF); yield: 89%. Colourless oil; IR (neat): 1680 (C=O), 1569, 1469, 1087, 1008, 969, 760 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.53 (1 H, s), 7.12 (1 H, d, *J* = 3.4 Hz), 6.48 (1 H, m), 5.43-5.28 (2 H, m), 2.83-2.62 (3 H, m), 1.90-1.86 (2 H, m), 1.30-1.10 (8 H, m), 1.02 (3 H, d, *J* = 6.3 Hz), 0.83 (3 H, t, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$): δ 188.8, 153.2, 146.2, 134.2, 129.5, 116.9, 112.1, 45.7, 33.2, 32.4, 31.7, 29.4, 28.7, 22.6, 20.5, 14.0; MS (EI) *m/z* (relative intensity): 269 (2), 95 (M^+-$C_{11}H_{21}$, 91); HRMS *m/z* Calcd: for $C_{16}H_{24}O_2$ (M^+): 248.1776. Found: 248.1768; the enantiomeric purity was determined by HPLC analysis: (ChiralCel OD, hexane/*i*-PrOH = 99.5/0.5, flow rate = 0.5 mL/min) t_R = 18.73 min (*S*), t_R = 22.28 min (*R*).

2.7.7 Synthesis of (1*S*,3*R*,*E*)-1-(Furan-2-yl)-3-p-tolylundec-4-en-1-ol (2.83)



This compound was prepared via modification of existing oxazaborolidine catalyzed (CBS) reduction perform on ketone in the literature.[98,129]

To a solution of ketone **2.71b** (1 equiv, 0.16 g, 0.49 mmol) in dry THF (20 mL) and cooled down to -30 °C, $BH_3.SMe_2$ (2 equiv, 1.00 mL, 0.98 mmol, 10 M in SMe_2) was added while stirring under argon atmosphere. This was followed by the subsequent addition of (R)-Me

CBS reagent **2.76** (0.2 equiv, 0.10 mL, 0.10 mmol, 1 M in toluene) at -30°C. The reaction was monitored by TLC. After 1 h of stirring, the reaction was quenched with MeOH (0.50 mL). The reaction mixture was concentrated and the crude was purified by silica column chromatography (Hex/Et_2O: 10:1) to furnish the desired alcohol in 88% yield. Colourless oil; IR (neat): 3379 (O–H), 2925, 1513, 1458, 1010, 970, 735 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.37 (furylH, 1 H, s), 7.13-7.03 (ArH, 4 H, m), 6.32 (furylH, 1 H, m), 6.21 (furylH, 1 H, m), 5.58-5.47 (C<u>H</u>=C<u>H</u>, 2 H, m), 4.66 (HOC<u>H</u>$_2$, 1 H, t, *J* = 6.8 Hz), 3.40 (CH=CHC<u>H</u>$_2$, 1.H, m), 2.32 (ArC<u>H</u>$_3$, 3 H, s), 2.19 (HOCHC<u>H</u>$_2$, 2 H, t, *J* = 7.2 Hz), 2.01 (CH=CHC<u>H</u>$_2$, 2 H, m), 1.90 (O<u>H</u>, 1 H, br s), 1.35-1.17 (C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$, 8 H, m), 0.88 (CH_2C<u>H</u>$_3$, 3 H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 156.7, 142.0, 141.7, 135.7, 132.8, 131.3, 129.2, 127.2, 110.1, 106.0, 65.8, 44.6, 41.6, 32.6, 31.7, 29.4, 28.8, 22.6, 21.0, 14.1; MS (EI) *m/z* (relative intensity): 331 (4), 326 (M^+, 29), 308 (M^+-H_2O, 34), 223 (M^+-C_8H_7, 93); HRMS *m/z* Calcd: for $C_{16}H_{24}O_2$ (M^+): 326.2246. Found: 326.2252; the enantiomeric purity was determined by HPLC analysis: (ChiralCel OD, hexane/*i*-PrOH = 99/1, flow rate = 0.5 mL/min) t_R = 16.26 min (*S*), t_R = 18.61 min (*R*); 99:1 er.

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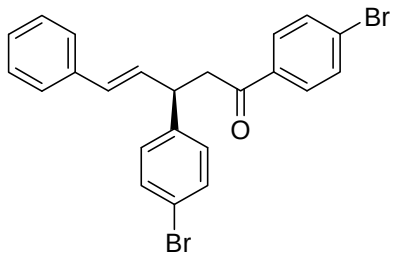
Appendix

X-Ray Crystallographic Data for

(*R*,*E*)-1,3-Bis(4-bromophenyl)-5-phenylpent-4-en-1-one (compound **2.73**)



2.73

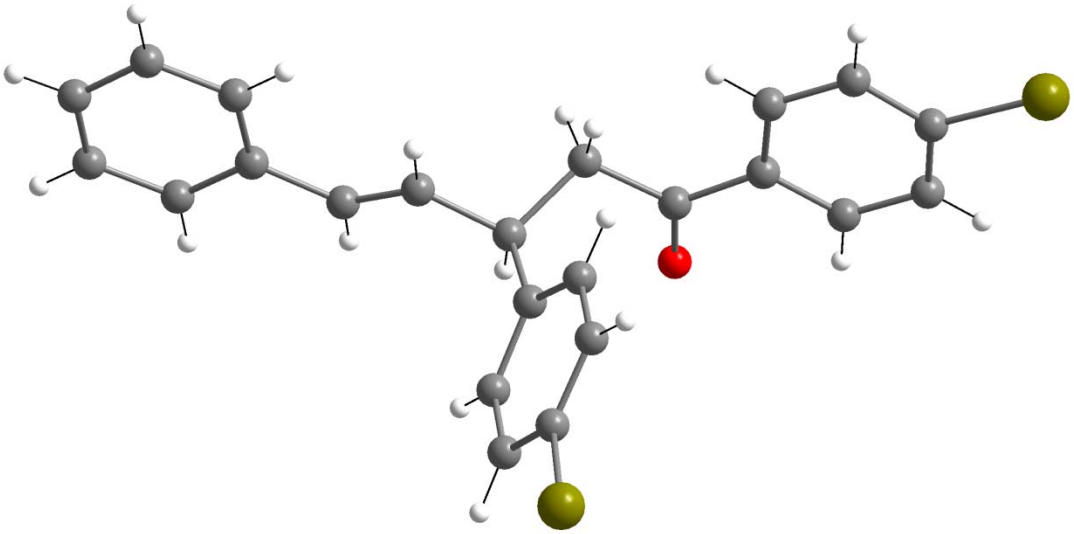


Table 1 Crystal Data and Structure Refinement for Compound **2.73**

Empirical formula	$C_{23}H_{18}Br_2O$
Formula weight	470.19 g/mol
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, $P2_1$
Unit cell dimensions	a = 8.0749(13) Å, b = 5.9244(10) Å, c = 20.580(3) Å, β = 99.916(3) º
Volume	969.8(3) $Å^3$
Z, Calculated density	2, 1.610 g/cm^3
Absorption coefficient	4.188 mm^{-1}
F(000)	468
Crystal size	0.50 x 0.23 x 0.10 mm
Theta range for data collection	3.01 to 30.00 deg.
Limiting indices	-11<=h<=11, -8<=k<=8, -28<=l<=28
Reflections collected / unique	14692 / 5530 [$R_{(int)}$ = 0.0222]
Completeness to theta = 30.00	99.3 %
Max. and min. transmission	0.7305 and 0.1575
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5530 / 1 / 235
Goodness-of-fit on F^2	1.060
Final R indices [I>2σ(I)]	R1 = 0.0257, wR2 = 0.0665
R indices (all data)	R1 = 0.0288, wR2 = 0.0675
Absolute structure parameter	0.014(7)
Largest diff. peak and hole	0.716 and -0.963 $e^-.Å^{-3}$

Table 2 Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters ($Å^2$ x 10^3) for Compound **2.73**

	x	y	z	U (eq)
Br (1)	-1926 (1)	1672 (1)	1180 (1)	43 (1)
Br (2)	-10525 (1)	2213 (1)	-2711 (1)	52 (1)
O (1)	-3858 (3)	-5695 (3)	-1375 (1)	48 (1)
C (1)	-3159 (3)	-3883 (4)	-1384 (1)	30 (1)
C (2)	-2664 (2)	-3058 (4)	-2023 (1)	30 (1)
C (3)	-4074 (2)	-3485 (4)	-2618 (1)	26 (1)
C (4)	-3475 (2)	-2894 (4)	-3255 (1)	28 (1)
C (5)	-3489 (3)	-4327 (4)	-3752 (1)	29 (1)
C (6)	-2975 (2)	-3810 (4)	-4391 (1)	29 (1)
C (7)	-3348 (3)	-5421 (5)	-4897 (1)	40 (1)
C (8)	-2918 (4)	-4997 (6)	-5515 (1)	52 (1)
C (9)	-2126 (3)	-3025 (6)	-5631 (1)	50 (1)
C (10)	-1728 (3)	-1440 (5)	-5135 (1)	46 (1)
C (11)	-2172 (3)	-1839 (4)	-4519 (1)	38 (1)
C (12)	-2764 (2)	-2516 (3)	-770 (1)	27 (1)
C (13)	-1950 (3)	-427 (4)	-737 (1)	30 (1)
C (14)	-1659 (3)	808 (4)	-155 (1)	32 (1)
C (15)	-2215 (3)	-63 (4)	395 (1)	30 (1)
C (16)	-3009 (3)	-2125 (4)	380 (1)	35 (1)
C (17)	-3281 (2)	-3353 (4)	-198 (1)	32 (1)
C (18)	-5649 (2)	-2123 (4)	-2584 (1)	23 (1)
C (19)	-7197 (2)	-2941 (4)	-2900 (1)	27 (1)
C (20)	-8657 (3)	-1723 (4)	-2925 (1)	30 (1)
C (21)	-8565 (3)	389 (4)	-2630 (1)	29 (1)
C (22)	-7057 (3)	1261 (4)	-2300 (1)	29 (1)
C (23)	-5617 (3)	-20 (4)	-2281 (1)	28 (1)

Table 3 Hydrogen Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters ($Å^2$ x 10^3) for Compound **2.73.**

	x	Y	z	U (eq)
H (2A)	-1629	-3846	-2094	36
H (2B)	-2417	-1421	-1987	36
H (3A)	-4371	-5125	-2629	32
H (4A)	-3065	-1410	-3302	33
H (5A)	-3863	-5820	-3691	35
H (7A)	-3890	-6792	-4819	48
H (8A)	-3176	-6082	-5857	62
H (9A)	-1850	-2747	-6054	60
H (10A)	-1156	-91	-5212	55
H (11A)	-1919	-736	-4182	46
H (13A)	-1590	159	-1119	36
H (14A)	-1092	2218	-133	39
H (16A)	-3366	-2695	764	42
H (17A)	-3824	-3779	-210	38
H (19A)	-7246	-4383	-3104	32
H (20A)	-9704	-2315	-3139	37
H (22A)	-7016	2697	-2092	35
H (23A)	-4577	553	-2054	34

Table 4 Bond lengths [Å] and angles [º] for **2.73.**

Bond Length (Å)		Bond Angle (°)	
Br (1)-C (15)	1.896 (2)	O (1)-C (1)-C (12)	120.05 (19)
Br (2)-C (21)	1.900 (2)	O (1)-C (1)-C (2)	119.28 (19)
O (1)-C (1)	1.215 (3)	C (12)-C (1)-C (2)	120.66 (18)
C (1)-C (12)	1.488 (3)	C (1)-C (2)-C (3)	111.52 (17)
C (1)-C (2)	1.520 (3)	C (4)-C (3)-C (18)	108.23 (15)
C (2)-C (3)	1.543 (2)	C (4)-C (3)-C (2)	110.33 (16)
C (3)-C (4)	1.514 (2)	C (18)-C (3)-C (2)	112.65 (15)
C(3)-C (18)	1.518 (3)	C (5)-C (4)-C (3)	123.9 (2)
C (4)-C (5)	1.328 (3)	C (4)-C (5)-C (6)	125.9 (2)
C (5)-C (6)	1.478 (3)	C (11)-C (6)-C (7)	118.63 (19)
C (6)-C (11)	1.383 (3)	C (11)-C (6)-C (5)	123.89 (18)
C (6)-C (7)	1.406 (3)	C (7)-C (6)-C (5)	117.5 (2)
C (7)-C (8)	1.399 (4)	C (8)-C (7)-C (6)	119.8 (3)
C (8)-C (9)	1.372 (5)	C (9)-C (8)-C (7)	120.5 (2)
C (9)-C (10)	1.384 (4)	C (8)-C (9)-C (10)	120.3 (2)
C (10)-C (11)	1.394 (3)	C (9)-C (10)-C (11)	119.4 (3)
C (12)-C (13)	1.398 (3)	C (6)-C (11)-C (10)	121.3 (2)
C (12)-C (17)	1.405 (3)	C (13)-C (12)-C (17)	118.52 (18)
C (13)-C (14)	1.389 (3)	C (13)-C (12)-C (1)	123.58 (18)
C (14)-C (15)	1.385 (3)	C (17)-C (12)-C (1)	117.88 (19)
C (15)-C (16)	1.377 (3)	C (14)-C (13)-C (12)	121.07 (19)
C (16)-C (17)	1.379 (3)	C (15)-C (14)-C (13)	118.5 (2)
C (18)-C (23)	1.392 (3)	C (16)-C (15)-C (14)	121.81 (19)
C (18)-C (19)	1.393 (3)	C (16)-C (15)-Br (1)	119.20 (15)
C (19)-C (20)	1.376 (3)	C (14)-C (15)-Br (1)	118.97 (17)
C (20)-C (21)	1.387 (3)	C (15)-C (16)-C (17)	119.44 (19)
C (21)-C (22)	1.388 (3)	C (16)-C (17)-C (12)	120.6 (2)
C (22)-C (23)	1.383 (3)	C (23)-C (18)-C (19)	117.82 (19
		C (23)-C (18)-C (3)	123.08 (18)
		C (19)-C (18)-C (3)	119.00 (18)
		C (20)-C (19)-C (18)	121.94 (19)
		C (19)-C (20)-C (21)	118.42 (19)
		C (20)-C (21)-C (22)	121.77 (19)
		C (20)-C (21)-Br (2)	119.57 (15)
		C (22)-C (21)-Br (2)	118.60 (16)
		C (23)-C (22)-C (21)	118.17 (19)
		C (22)-C (23)-C (18)	121.84 (19)