Organocatalytic Asymmetric Conjugate Addition of Heteroaryl Moieties to α,β-Unsaturated Enones Using Boronates and 3,3′-Disubstituted Binaphthols

by

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AUTHOR'S DECLARATION

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

I understand that my thesis may be made electronically available to the public.

Abstract

Asymmetric conjugate addition is an important methodology for carbon-carbon bond formation in organic synthesis. While there is extensive literature on the asymmetric conjugate addition of a wide selection of donors to a variety of acceptors, there are relatively few reports on the asymmetric conjugate addition of heteroaryl groups. Almost all of these reports utilize catalytic amounts of both a rhodium compound and a chiral ligand, and usually employ organoboron reagents. Furthermore, these additions have been problematic due to protodeboronation. Other organocatalytic methods have offered low yields and moderate enantioselectivies.

The binaphthol / boronate catalyst system developed by the Chong group is effective in promoting asymmetric conjugate addition of 2-thienyl, 3-thienyl, 2-furyl, and 2-benzo[*b*]thienyl moieties to acyclic enones. The combination of 3,3'-disubstituted binaphthols with diethyl heteroarylboronates generated 1,4-adducts with good yields and high enantioselectivities (up to 100% yield and 99.9:0.1 er). This catalyst system complements known methods of conjugate addition of heteroaryl groups involving transition metal catalysts and cyclic enone acceptors and is the most effective organocatalytic system reported to date.

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To Evelyn, Melissa, Elicia and Esther

"The world is your laboratory. Experiment."
-Unknown

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List of Abbreviations

Å	angstrom
Acc	acceptor
acac	acetylacetonyl
Ar	aromatic group
Aux*	chiral auxiliary
BINAL-H	binaphthol-modified aluminum hydride
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	2,2'-dihydroxy-1,1'-binaphthol
Bu	butyl
n-BuLi	*n*-butyllithium
$C_2Br_2Cl_4$	1,2-dibromotetrachloroethane
chiraphos	(*R,R*)-2,3-bis(diphenylphosphino)butane
DFT	density functional theory
d	doublet
dd	doublet of doublets
ee	enantiomeric excess
eq	equivalent
er	enantiomeric ratio
Et	ethyl
EtOH	ethanol
et al.	et alia (and others)
h	hour
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
k	rate constant
L	ligand

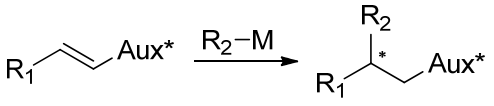
L*	chiral ligand
lit.	literature value
M	metal ion
Me	methyl
Me-DUPHOS	1,2-bis(2,5-dimethylphospholano)benzene
MeOH	methanol
mol	mole
MOM	methoxymethyl
MS	molecular sieves
MFSDA	methyl fluorosulfonyldifluoroacetate
Ph	phenyl
q	quartet
ROH	general alcohol
s	singlet
TADDOL	α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanol
THF	tetrahydrofuran
TMS	trimethylsilyl
TS	transition state
v/v	volume/volume

Chapter 1. Introduction

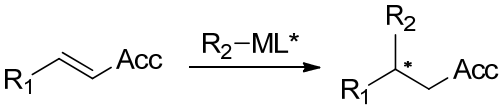
1.1 Conjugate addition

Conjugate addition, the addition of nucleophilic donors to activated double and triple bond acceptors, is an important method in organic synthesis.[1] In addition to the formation of a new carbon-carbon bond, the reaction may also give rise to a new stereogenic centre in the molecule. This class of reactions, also referred to as 1,4-additions or Michael additions, can be further classified as diastereoselective, enantioselective, or catalytic enantioselective additions (Figure 1.1).

Diastereoselective Conjugate Addition:



Enantioselective Conjugate Addition:



Catalytic Enantioselective Conjugate Addition:

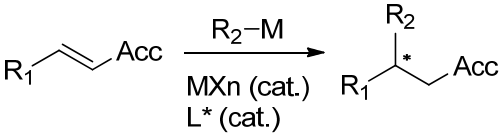


Figure 1.1 Classes of conjugate additions of a carbon nucleophile to Michael acceptors by organometallic reagents.[1] Aux* = chiral auxiliary, e.g. oxazolidinone, pseudoephedrine. Acc = acceptor, e.g. COR, COOR, NO_2. M = metal, e.g. Li, Mg, Cu, Zn, Rh, Pd. L*= chiral ligand, e.g. *(S)*-BINOL, *(S)*-BINAP, (*R*)-(*R*)-Me-DUPHOS.

Diastereoselective conjugate additions arise from addition to a chiral Michael acceptor, usually taking advantage of chiral auxiliaries such as Evans' oxazolidinones.[2] While the auxiliary

can be recycled, this approach requires extra steps in synthesis to initially incorporate the auxiliary and to cleave it afterwards. Enantioselective conjugate additions, such as the addition of lithium diorganocuprates to enones using terpene derivatives,[3] employ stoichiometric amounts of both the organometallic reagent and chiral ligand. In addition to the loss of expensive reagents in the course of the reaction, such reactions often exhibit high substrate specificity and thus have a narrow scope of acceptors.

Of increasing importance is the class of catalytic enantioselective conjugate additions, which use a transition metal as well as a chiral ligand in catalytic amounts. In these reactions, it is imperative that the uncatalyzed background reaction is negligible for high enantioselectivities.[1] Over the years, copper, rhodium and palladium complexes have been paired with organozinc, organolithium, organomagnesium, organoboron, organosilicon, organostannanes, and organobismuth compounds.[4-11]

1.2 Asymmetric induction

The chiral ligand is the sole entity in catalytic enantioselective conjugate additions that induces stereoselectivity in the product, so significant consideration is taken in the ligand design. Many chiral ligands contain C_2-symmetry, which can be defined as a molecule having an axis in which 180° rotation about this axis provides the same geometry as the starting geometry. This minimizes the number of possible diastereomeric transition states, allowing for greater stereochemical control as transition states leading to the unwanted product are disfavoured due to a higher energy barrier.[12-13] Using the enantioselective alkylation of cyclohexanone enamines as an example (as illustrated in Figure 1.2), enantioselectivities improved from 10-30% *ee* using

non-C_2-symmetrical proline esters to 80-90% *ee* with C_2-symmetrical *trans*-2,5-dimethylpyrrolidine.[14-18]

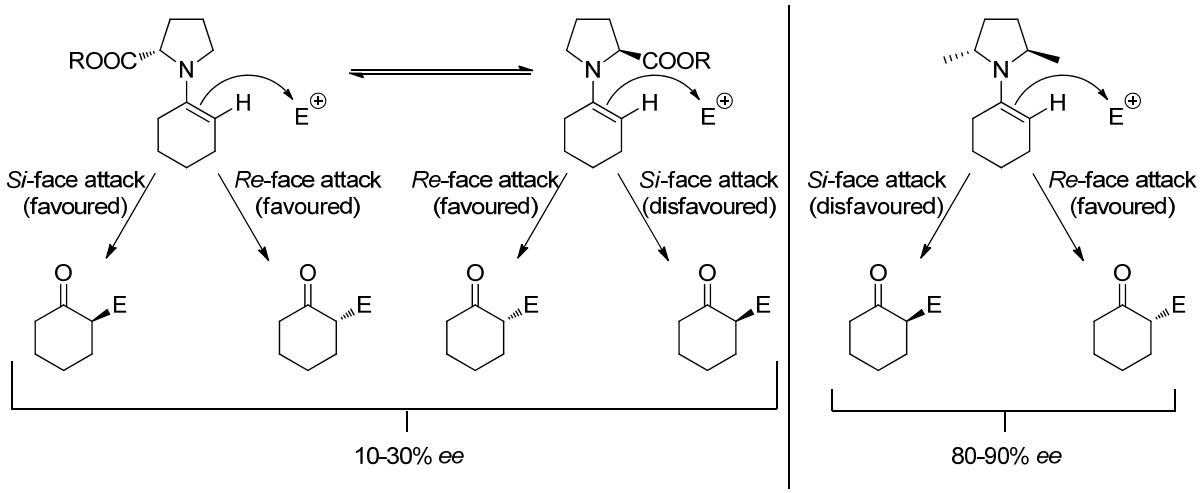


Figure 1.2 Selectivities arising from the enantioselective alkylation of cyclohexanone enamines with (a) proline esters and (b) *trans*-2,5-dimethylpyrrolidine.

A number of C_2-symmetric ligands have been developed over the years, including the aforementioned 2,5-dimethylpyrrolidine,[19] bis-sulfonamides,[20] tartrate esters,[21] α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOLs),[22] bis(diphenylphosphino)butane (Chiraphos),[23] 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP)[24] and 2,2'-dihydroxy-1,1'-binaphthol (BINOL) (Figure 1.3).[25]

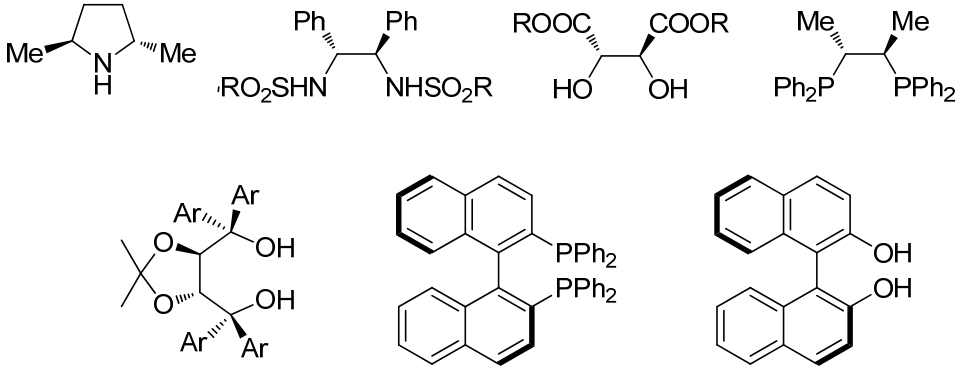


Figure 1.3 Selected C_2-symmetric ligands.

1.2.1 BINOL as a chiral mediator

2,2'-Dihydroxy-1,1'-binaphthol, or BINOL, has been used extensively in stereoselective C-C bond forming reactions including aldol reactions, allylations, alkynylations, Diels-Alder reactions, and Michael additions.[26-30] The parent BINOL ligand has been modified to enhance stereoselectivities, including substitutions at various locations to alter the electronic properties of the ligand as well as the steric environment around the metal centre. Some examples of modified BINOLs include H_8-BINOLs;[26] F_8-BINOLs;[27] 3,3'-,[28] 4,4'-, 6,6'-, and 7,7'-disubstituted BINOLs, and linked BINOLs[29] (Figure 1.4).

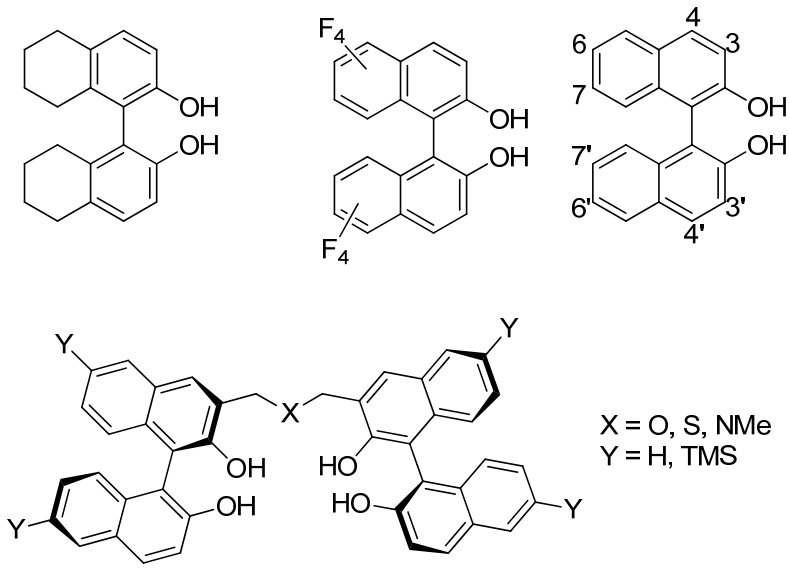


Figure 1.4 Modified BINOLs used in asymmetric synthesis.[26-29]

1.2.2 Boron in asymmetric synthesis

Boron was first used in asymmetric synthesis by Brown and Zweifel for the hydroboration of *cis*-2-butene with diisopinocampheylborane $(Ipc)_2BH$.[30] Since then, organoboron reagents have seen wide use due to their commercial availability, low toxicity,

compatibility with a number of functional groups, and stability to air and moisture, allowing for use of protic or aqueous solvents.[31,32] In addition, boron's effectiveness in asymmetric reactions can be attributed to its small size, allowing chiral ligands to exert greater influence on transition-state energetics compared to other organometallic reagents.[33] Organoboron reagents have regularly been coupled with rhodium catalysts to effect conjugate additions of aryl groups.[9,10]

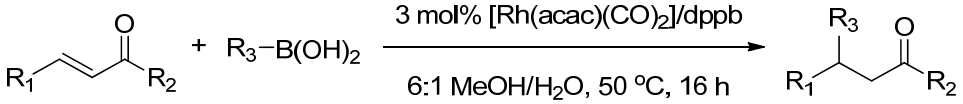
1.3 Heteroaryl groups

Heteroaryl groups, compounds containing at least one heteroatom within an aromatic ring, are prevalent in medicinal chemistry and natural products. An example is a quinoline ring in the alkaloid quinine, a compound isolated from the bark of the cinchona tree that has antimalarial, anti-inflammatory and analgesic properties.[34] Extensive research has gone into the introduction and formation of heteroaryl groups, including ring formations, hetero Diels-Alder reactions, and cross-coupling reactions. The stereoselective introduction of heteroaryl groups is therefore important in organic synthesis. This leads us to propose an investigation into the enantioselective conjugate addition of heteroaryl groups to enones using the binaphthol / boronate catalyst system developed by the Chong group.

Other methods of asymmetric conjugate addition of aryl groups are relevant to this thesis research. Starting with Miyaura's non-asymmetric rhodium-catalyzed reaction with organoboron reagents and Hayashi's revolutionary asymmetric version, to the use of other organometallic reagents, and finally to the use of *O*-monoacyltartaric acids as organocatalysts,literature on the conjugate addition of aryl and heteroaryl groups will be surveyed.

1.4 Conjugate Addition of Aryl Groups Using Organoboron Reagents

The first 1,4-addition of organoboron reagents to α,β-unsaturated enones was reported in 1997 by Miyaura (Scheme 1.1, Table 1.1).[35] The reaction was performed in the presence of a phosphine-rhodium catalyst system. The reaction proceeded in high yields (>90%) for acyclic systems (Table 1.1, entries 1-6), but only gave moderate yields (52%) for cyclic systems (Table 1.1, entry 7). However, several aspects of the reaction showed its promise for further development: firstly, the stability of organoboronic acids as discussed earlier; secondly, the background reaction in the absence of the rhodium catalyst is more negligible than those catalyzed by other organometallic reagents; thirdly, sp^2 carbons can be added to the β position, which was not possible with organocopper reagents; and lastly, the use of phosphine ligands, which have been studied extensively for other transition-metal catalyzed reactions.



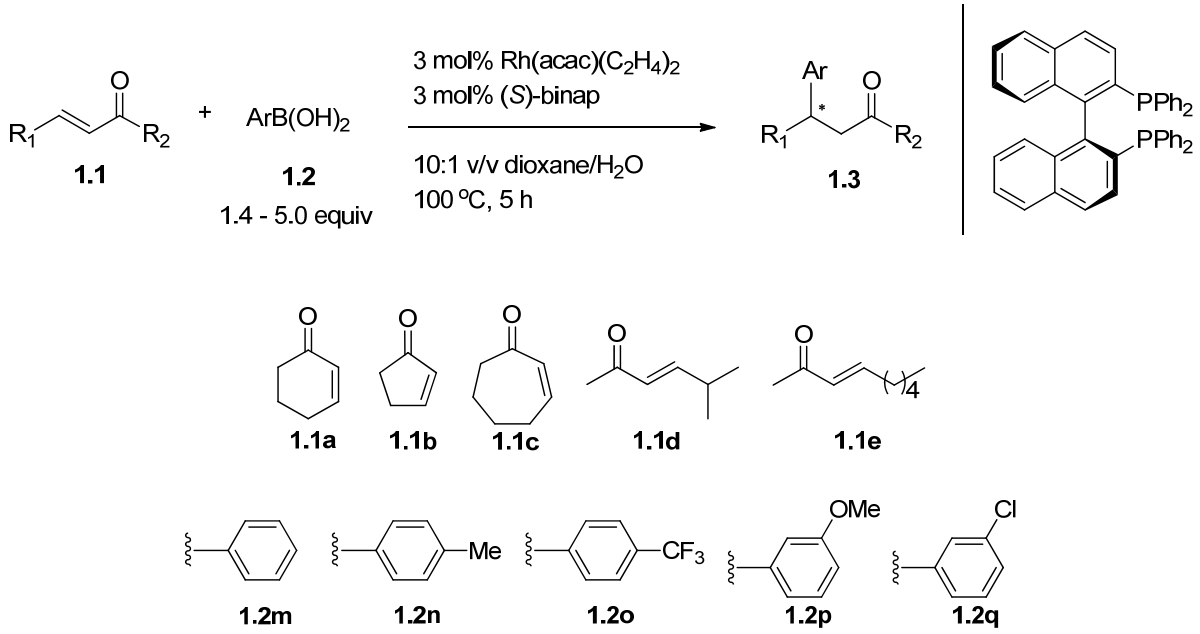
Scheme 1.1[35]

Table 1.1 Rhodium-catalyzed 1,4-addition of arylboronic acids[35]

entry	R^1	R^2	R^3	yield (%)
1	Me	Bu	Ph	99
2	Me	Ph	Ph	96
3	Ph	Me	Ph	99
4	Ph	Ph	Ph	86
5	H	Me	4-MeOPh	86
6	H	Me	2-MeOPh	84
7	2-cyclohexenone		Ph	56

1.5 Asymmetric Conjugate Addition of Aryl Groups Using Organoboron Reagents

Further investigation by Hayashi and Miyaura resulted in an asymmetric version of the reaction in the following year (Scheme 1.2, Table 1.2).[36] To effect asymmetric conjugate addition, the following adjustments were made: firstly, $Rh(acac)(C_2H_4)_2$ was used in place of $Rh(acac)(CO)_2$, as ethylene exhibits a weaker coordination to rhodium than carbon monoxide; the use of BINAP, a chiral bisphosphine ligand, in place of the dppb; high reaction temperature of 100 °C; and lastly the use of a dioxane/water solvent system. The reaction had a broad scope, involving both acyclic and cyclic acceptors as well as alkenyl and aryl donors and produced high enantioselectivities (91-99% ee). They also found that using up to a 5 mole excess of boronic acid compensated for the competing protodeboronation of boronic acid.



Scheme 1.2[36]

Table 1.2 Asymmetric 1,4-addition of boronic acids to enones catalyzed by *(S)*-BINAP and $Rh(acac)(CO)_2$.[36]

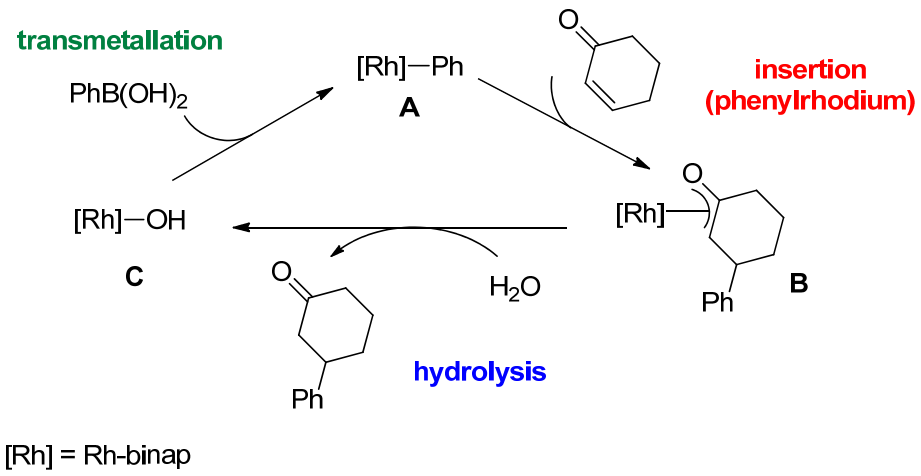
entry	enone	boronic acid	Yield (%)	% ee
1	**1.1a**	**1.2m**	>99	97
2	**1.1a**	**1.2n**	>99	97
3[a]	**1.1a**	**1.2o**	70	99
4	**1.1a**	**1.2p**	97	96
5	**1.1a**	**1.2q**	94	96
6	**1.1b**	**1.2m**	93	97
7	**1.1c**	**1.2m**	51	93
8	**1.1d**	**1.2m**	82	97
9	**1.1e**	**1.2m**	88	92

[a]In 10:1 *n*-propanol/H_2O

The scope of this reaction has been extended to include acceptors such as α,β-unsaturated esters and amides, alkenylphosphonates, and nitroalkenes; donors such as alkenylcatecholboronates, lithium trimethyl arylborates, and other organometallic reagents; and ligands such as amidomonophosphines, diphosphonites, substituted BINAP, and phosphine-ferrocene ligands.[10]

1.5.1 Catalytic Cycle[10]

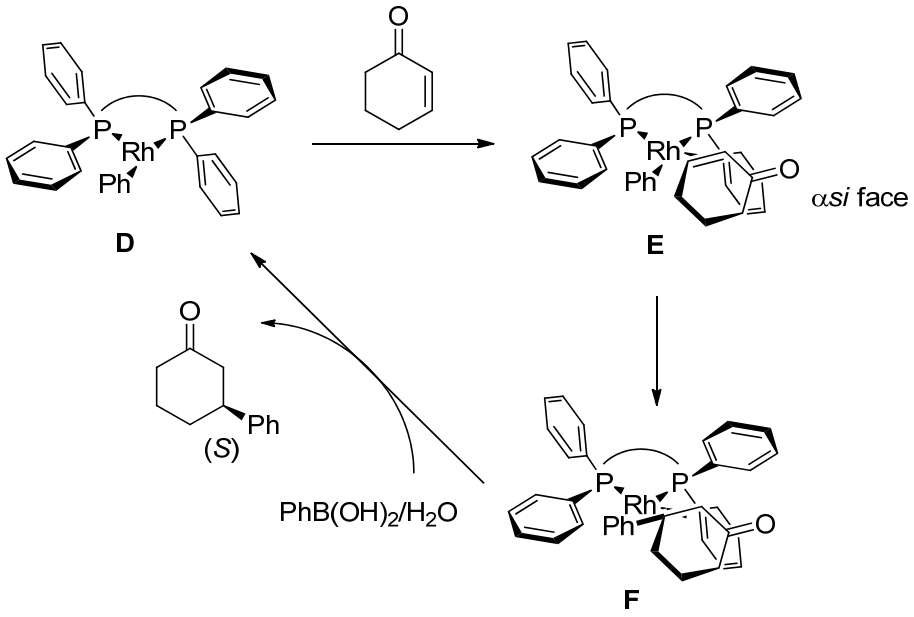
The catalytic cycle is exemplified in Scheme 1.3 with the phenylboration of 2-cyclohexenone, and involves three intermediate complexes: phenylrhodium **A**, η^3-oxa-π-allylrhodium **B**, and hydroxorhodium **C**. The cycle begins with transmetallation of the phenyl group from phenylboronic acid to the rhodium salt to generate **A**. The insertion of the conjugated double bond of 2-cyclohexenone to **A** then generates **B** upon isomerization. Addition of water produces the phenylated product and generates **C**. The cycle is completed when **A** is regenerated from transmetallation of the phenyl group to **C.** All species in the proposed catalytic cycle are supported by NMR spectroscopic studies.[10]



Scheme 1.3[10]

1.5.2 Rationalization of Configuration[10]

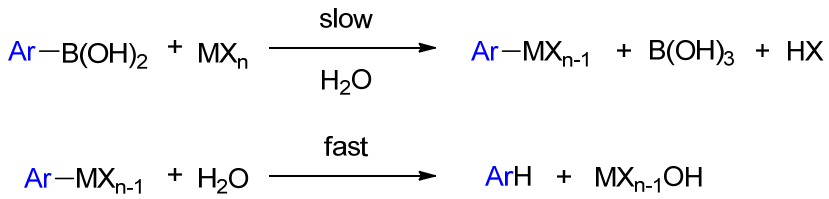
Previous knowledge of the coordinated BINAP structure[37] has allowed Hayashi and coworkers to suggest a model to determine the stereoselectivity of this catalytic reaction (Scheme 1.4). In their report, they theorize that the open α-*si* face of the carbon-carbon double bond coordinates to the *(S)*-Rh-BINAP complex **D** to form **E**, influenced by the steric hindrance of the upper part of the complex. A stereogenic centre of *S*-configuration is formed in **F** after migratory insertion of the phenyl group from the rhodium complex to the enone.



Scheme 1.4[10]

1.6 Rhodium-Catalyzed Asymmetric Conjugate Addition of Heteroaryl Groups

On the heels of Hayashi and Miyaura's findings, a number of reports have emerged regarding stereoselective introduction of electron-poor and electron-rich substituted phenyl rings to the β-position of Michael acceptors. These methods include the use of chiral rhodium,[10] palladium[38] and copper[39] catalysts, chiral diene ligands,[40] and other donor sources such as aryl titanates,[10] aryl trifluoroborates,[10] arylzinc chlorides,[41] arylsilicon,[10] and aryliridium[42] reagents. In comparison, reports of asymmetric 1,4-addition of heteroaryl groups have been much less common. This is due in part to the incompatibility of the heteroaryl donor with the given reaction conditions: the heteroatom coordinates strongly to the catalyst, facilitating protodeboronation and generating the protonated heteroarene as the major product instead of the desired 1,4-adduct (Scheme 1.5).[11,43] In order for 1,4-addition of heteroaromatics to be successful, different reaction conditions or more stable donor reagents would have to be used.

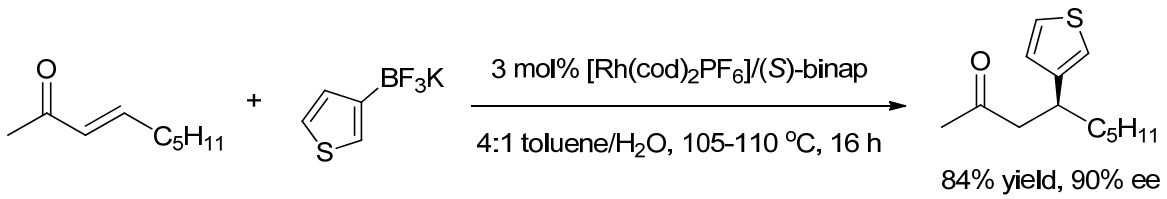


Scheme 1.5[11]

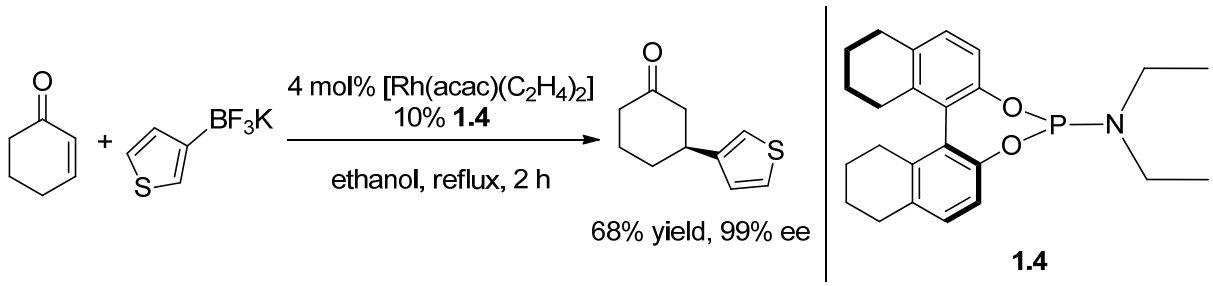
1.6.1 Potassium Organotrifluoroborates

The first investigations into more stable donor reagents employed the use of potassium organotrifluoroborates. These compounds are advantageous over other organoboron reagents as the pure product is easily prepared in high yields, does not require special storage conditions, and overcomes the problem of solvolysis.[44,45] In two separate reports, Genêt *et al.*[44] (Scheme 1.6)

as well as Feringa *et al.*[45] (Scheme 1.7) were able to stereoselectively add thiophene-3-trifluoroborate to acyclic and cyclic enones, respectively, under catalytic conditions. Both reactions had the benefit of low catalyst loadings and produced reasonable yields of 84% and 68%, respectively, and excellent enantioselectivities of 90% and 99% ee, respectively.



Scheme 1.6[44]

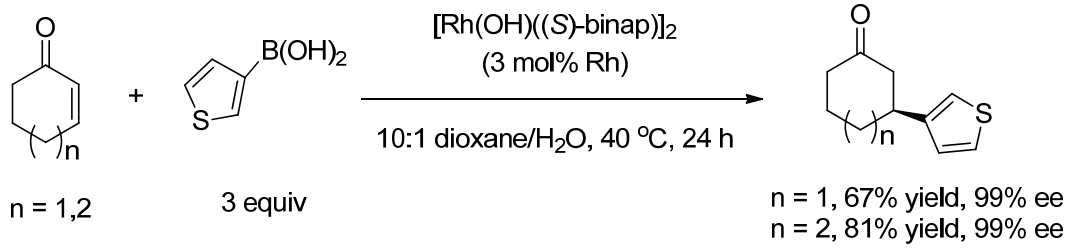


Scheme 1.7[45]

1.6.2 Boronic Acids with Hydroxorhodium Complex

Using a different rhodium complex, Hayashi and Yoshida were able to use boronic acids as a nucleophilic source.[46] They found that the hydroxo complex $[Rh(OH)(BINAP)]_2$ is more susceptible to transmetallation than the $Rh(acac)(C_2H_4)_2$ complex in the original asymmetric rhodium-catalyzed arylboration. As a result, the reaction proceeds at 35 °C as compared to 100 °C, suppressing protodeboronation and making this asymmetric addition possible. Using a rhodium-BINAP catalyst, they were able to add thiophene-3-boronic acid to a number

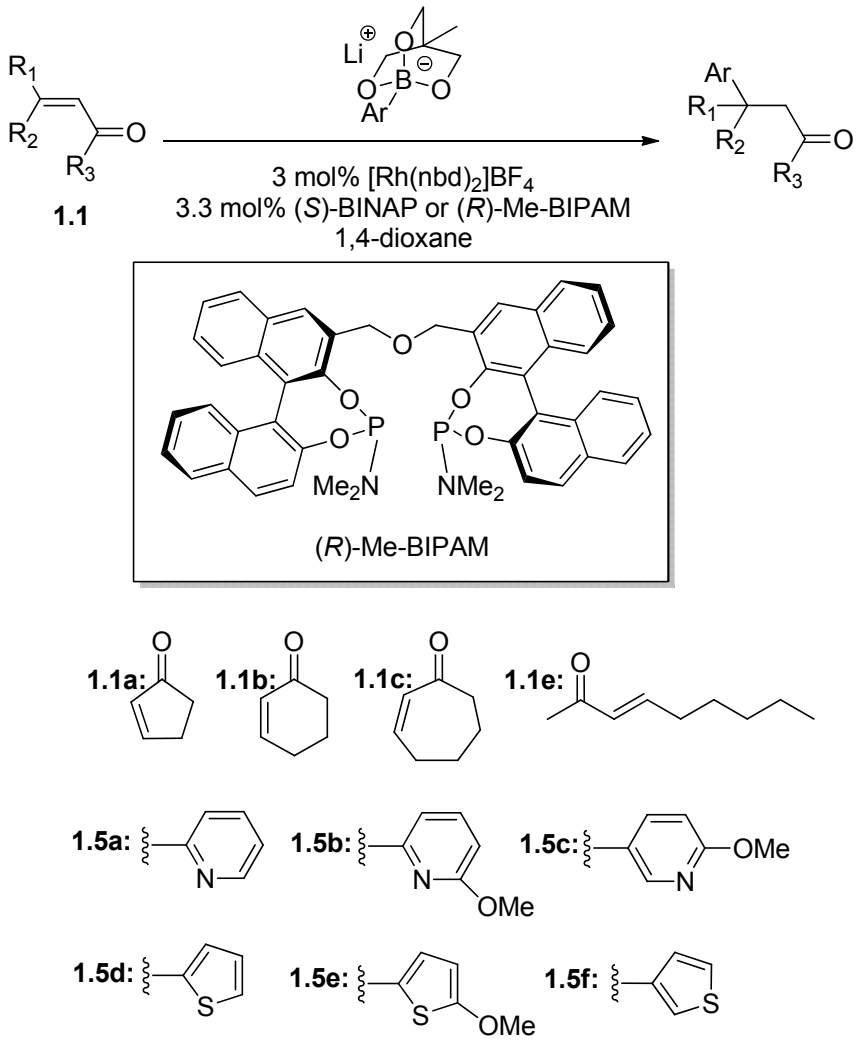
of cyclic and acyclic α,β-unsaturated carbonyl compounds in moderate yields and high enantioselectivites (67-82% yield and 94-99% ee) (Scheme 1.8).



Scheme 1.8[46]

1.6.3 Lithium Triolborates

Miyaura and coworkers[47] were able to add a number of pyridyl and thienyl groups and their methoxy derivatives to acyclic and cyclic enones using lithium triolborates in the presence of *(S)*-BINAP or *(S)*-Me-BIPAM in good yields (up to 96%) and excellent enantioselectivities (57-97% ee) (Scheme 1.9, Tables 1.3 and 1.4). Triolborates were found to be superior to the corresponding boronic acids or metal trifluoroborates due to the high nucleophilicity of the heteroaryl rings in these compounds as well as high solubility in organic solvents, eliminating the need of an aqueous solvent and preventing the protodeboronation of the organoboron compounds.



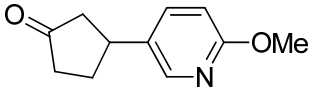
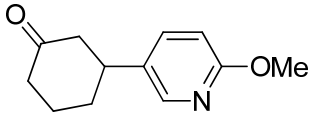
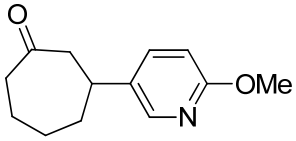
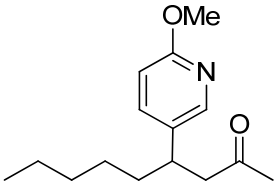
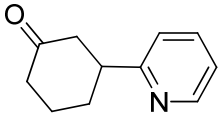
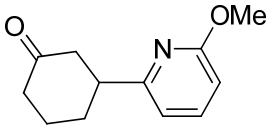
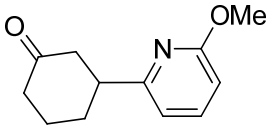
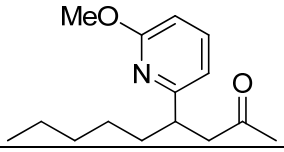
Scheme 1.9[47]

The 3-pyridyl derivatives and 3-thienyl were readily added to enones with excellent yields and selectivities (Table 1.3, entries 1-4 and Table 1.4, entries 1-3); use of *(S)*-Me-BIPAM in place of *(S)*-BINAP yielded excellent selectivities but lower yields with 2-pyridyl derivatives (Table 1.3, entries 5-8). However, the addition of unsubstituted 2-pyridyl and 2-thienyl were unsuccessful.

Two explanations were offered for the observed reactivity trends.[47] Firstly, the lower yields with 2-heteroaryl groups was attributed to a lower nucleophilicity at the 2-position.

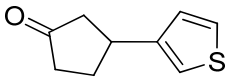
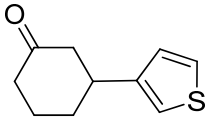
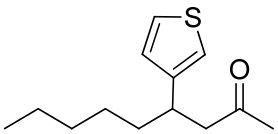
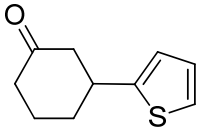
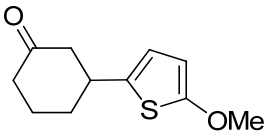
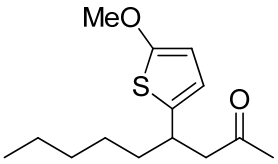
Secondly, it was noted that the methoxy group was required for two reasons: its position *ortho-* to the heteroatom blocks coordination of the heteroaryl ring to the catalyst, and its donation into the heteroaryl ring increases the rate of insertion of the enone into the rhodium-carbon bond.

Table 1.3 1,4-addition of substituted pyridylborates.[47]

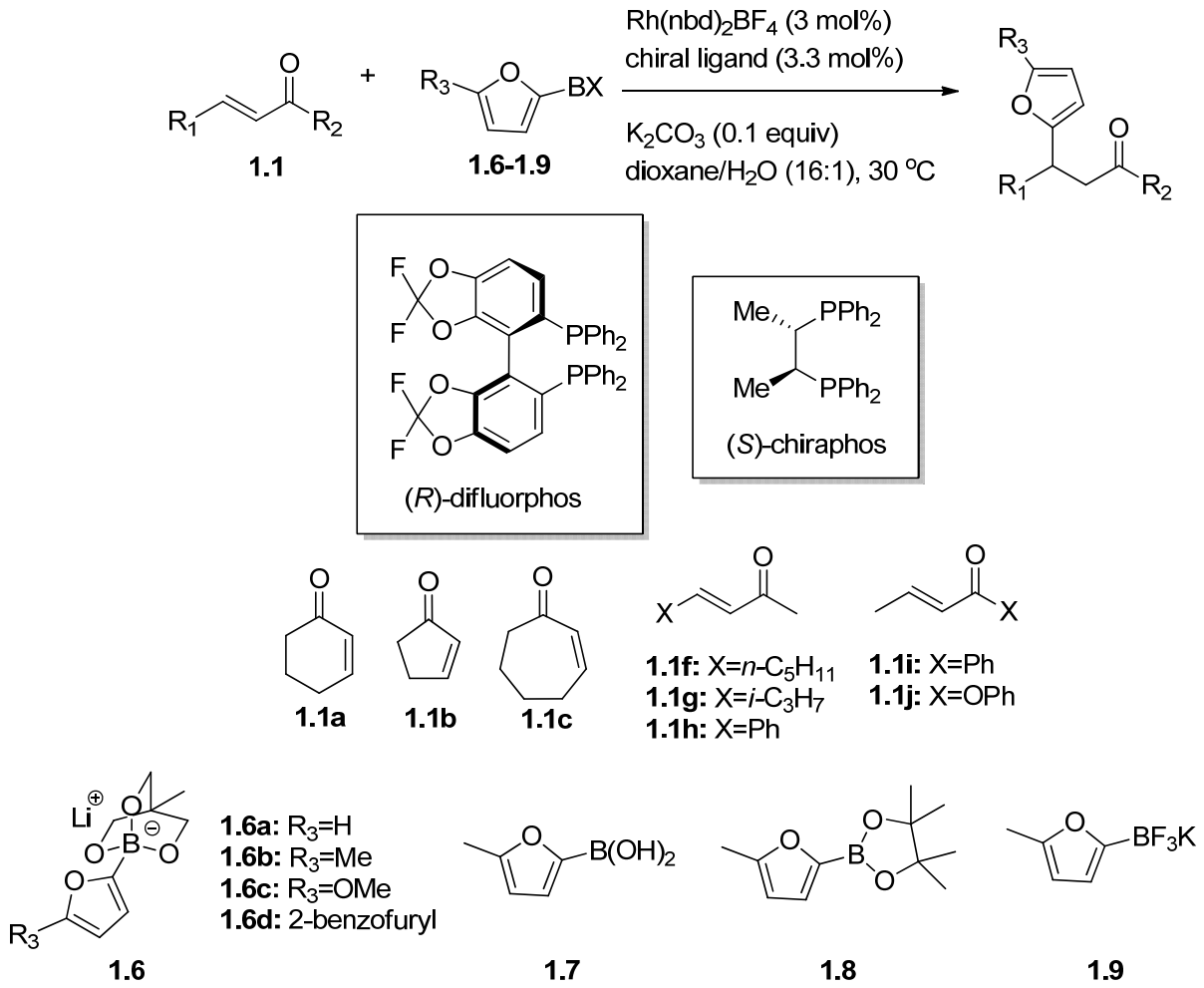
entry	enone	**1.5**	product	yield (%)	ee (%)
1	**1.1a**	**1.5c**		96	97
2	**1.1b**	**1.5c**		92	92
3	**1.1c**	**1.5c**		>90	93
4	**1.1d**	**1.5c**		97	91
5	**1.1b**	**1.5a**		0	-
6	**1.1b**	**1.5b**		56	55
7[a]	**1.1b**	**1.5b**		67	93
8[a]	**1.1d**	**1.5b**		63	81

[a](*R*)-Me-BIPAM was used in the presence of KOH

Table 1.4 1,4-addition of substituted thienylborates.[47]

entry	enone	**1.5**	product	yield (%)	ee (%)
1	**1.1a**	**1.5f**		90	88
2	**1.1b**	**1.5f**		90	90
3	**1.1d**	**1.5f**		93	84
4	**1.1b**	**1.5d**		trace	-
5	**1.1b**	**1.5e**		63	90
6	**1.1d**	**1.5e**		63	88

Miyaura expanded this work to include the introduction of 2-furyl groups, which are excellent masked synthetic equivalents to the hydroxycarbonyl group upon oxidation with ozone or $RuCl_3/NaIO_4$.[48] They found that the furylborates were more resistant to protonolysis than thienyl or pyridylborates. By adding a catalytic amount of a weak base, 10% K_2CO_3, they were able to lower the reaction temperature to 30 °C and improve enantioselectivities (Scheme 1.10, Table 1.5). Also, other chiral phosphate ligands were used to give rise to higher selectivities.



Scheme 1.10[48]

The best selectivity was found with a substituted furyl, 5-methylfurylborate (Table 1.5, entries 3-4, 10-13), whereas methoxyfuryl (Table 1.5, entry 5), benzofuryl (Table 1.5, entry 6) and unsubstituted furyl compounds gave lower selectivities (Table 1.5, entry 2). No arylation occurred with boronic acid, a pinacol ester derivative, and potassium trifluoroborate (Table 1.5, entries 7-9). Among cyclic enones, the best selectivities were also found with enone **1b** when *(R)*-difluorphos was used as the ligand (Table 1.5, entry 4), while other cyclic enones **1a** and **1c** yielded reasonable results (Table 1.5, entry 1 and entry 10, respectively). Aliphatic enones **1f** and **1g** generated excellent enantioselectivities and reasonable yields (Table 1.5, entry 11 and entry

12, respectively). Aromatic acyclic enones **1h-1j** generated lower selectivities (Table 1.5, entries 13-16), and in the case of enone **1h**, replacement of the chiral ligand with *(S,S)*-chiraphos generated a higher yield of 83% over 35% with *(S)*-binap with a slight decrease of selectivity from 96% ee to 91% ee (Table 1.5, entries 13-14).

Table 1.5[48] 1,4-addition of 2-furylborates[a]

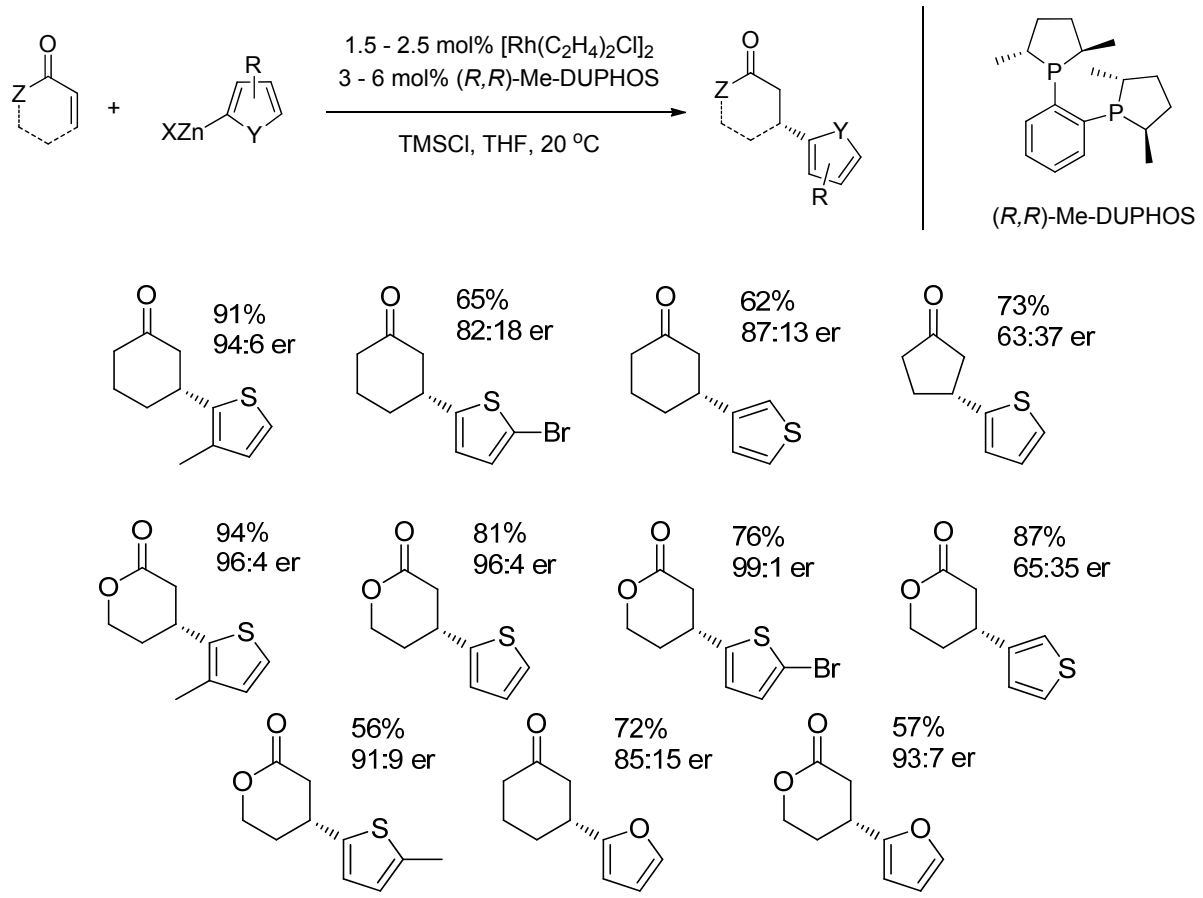
entry	enone	product	yield (%)[b]	% ee[c]
1	**1.1a**	**1.6b**	92	91
2	**1.1b**	**1.6a**	61	95
3	**1.1b**	**1.6b**	82	95
4[d]	**1.1b**	**1.6b**	78	98
5	**1.1b**	**1.6c**	52	94
6	**1.1b**	**1.6d**	43	93
7	**1.1b**	**1.7**	0	--
8	**1.1b**	**1.8**	trace	--
9	**1.1b**	**1.9**	0	--
10	**1.1c**	**1.6b**	65	95
11	**1.1f**	**1.6b**	90	99
12	**1.1g**	**1.6b**	79	99
13	**1.1h**	**1.6b**	35	96
14[e]	**1.1h**	**1.6b**	83	91
15	**1.1i**	**1.6b**	86	92
16	**1.1j**	**1.6b**	70	94

[a] Catalyzed by *(S)*-binap unless otherwise noted. [b] Isolated yields determined by chromatography. [c] Enantiomeric excess determined by chiral HPLC. [d] $[Rh(nbd)_2]BF_4$/*(R)*-difluorphos (5:5.5 mol%) was used at 50 °C. [e] $[Rh(nbd)_2]BF_4$/*(S,S)*-chiraphos (5:5.5 mol%) was used at 50 °C.

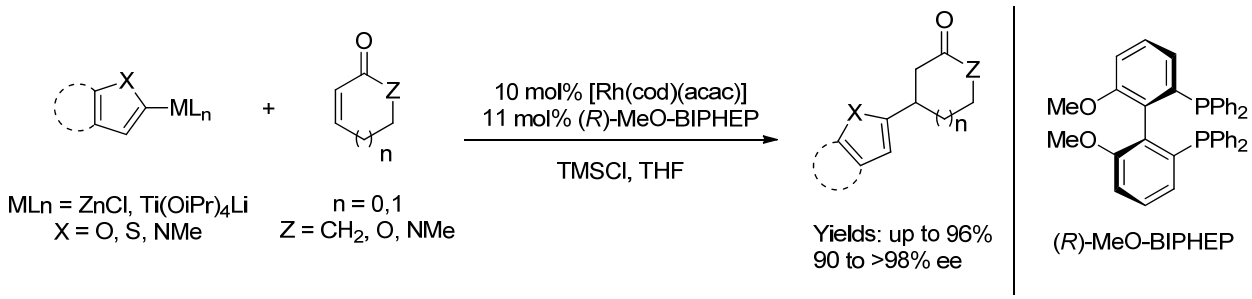
1.6.4 Organozinc Compounds

Of recent interest are organozinc compounds. Frost and coworkers[43,49] as well as Martin and coworkers[50] have independently reported the enantioselective addition of 2- and 3-heteroaryl groups to cyclic enones, lactones and lactams, with good results. While Frost *et al.* looked at simple thiophene and furan derivatives (Scheme 1.11), Martin *et al.* extended the range of donors to include fused ring groups such as benzofuran and benzothiophene (Scheme 1.12).

The use of organozinc compounds is advantageous as they are readily soluble in organic solvents, avoiding protodeboronation (which occurs with boronic acids in mixed organic/aqueous solutions); however, organozinc compounds will also react with proton sources in solution to generate the arene. In addition, the reaction schemes have several limitations.



Scheme 1.11[43]



Scheme 1.12[50]

Firstly, the use of organozinc compounds requires the addition of trimethylsilyl chloride (TMSCl) to form a more stable enolate intermediate, preventing side reactions such as the formation of oligomeric products. Secondly, while good results were typically seen with a lactone acceptor due to its lower reactivity, reactions with acceptors such as cyclopentenone were problematic. Further investigation showed that a significant background reaction was present with some donor-acceptor pairings, but it is not evident which pairings give rise to a higher background reaction and which do not. Finally, Frost's preliminary kinetic studies show a decreased reaction rate after one hour at room temperature, indicating possible catalyst decomposition to an inactive species and requiring additional amounts of the rhodium species and Me-DUPHOS ligand.

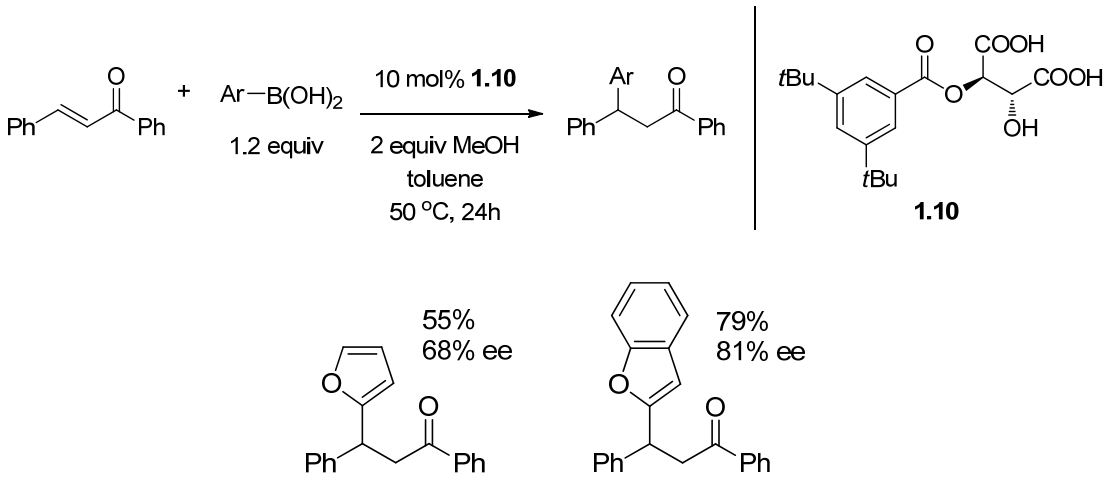
Organozinc compounds also exhibit opposite reactivity trends to the lithium triolborates: in Frost's investigation, 3-thienyl derivatives generated lower enantioselectivities compared to 2-thienyl derivatives. This was attributed to secondary interactions between the sulfur donor and either the zinc or rhodium complex that are necessary in influencing the transition state to evoke high selectivity.

1.6.5 Heteroaryl Titanates

In the same publication,[50] Martin and coworkers also looked at the use of heteroaryl titanates, favoured for their decreased susceptibility towards a racemic background reaction in cases where the corresponding organozinc compound was problematic. While the heteroaryl titanates generated high selectivities, many reactions were low yielding. Most promising were reactions involving furyl groups. However, although it was stated that the heteroaryl titanates and organozinc compounds were orthogonal methods, nothing was provided to substantiate this claim.

1.7 Organocatalytic Asymmetric Conjugate Addition of Heteroaryl Groups Using *O*-monoacyltartaric acids

There have been few reports on the use of organocatalysts to effect asymmetric conjugate addition. In 2010, Sugiura *et al.*[51] were able to use *O*-monoacyltartaric acids, particularly the 3,5-di(tert-butyl)-benzoyl derivative **1.10**, to catalyze the 1,4-addition of furyl- and benzofurylboronic acids to chalcone in acceptable yields and selectivities (Scheme 1.13).



Scheme 1.13

It was found that modifications to the parent tartaric acid to alter its electronic and steric effects were necessary to enhance the activity and selectivity of the catalyst. Furthermore, the use of toluene as the solvent as well as methanol as an additive were required to suppress the non-catalyzed background reaction to effect higher enantioselectivities.

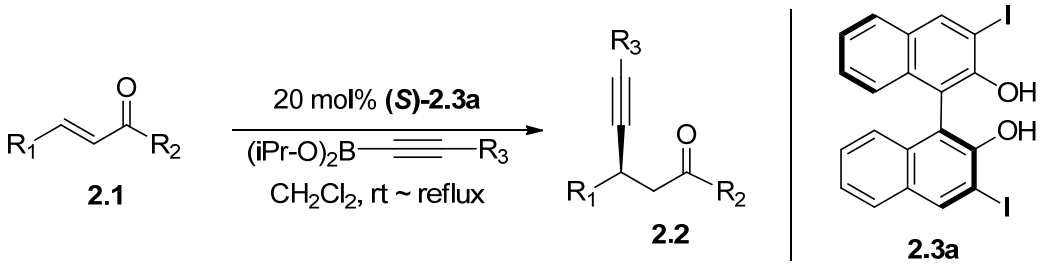
Although the enantioselectivities are moderate, Sugiura's work is of particular interest as it demonstrates the use of an organocatalytic system to effect conjugate addition of heteroaryl groups to enones. The next chapter will discuss the development and application of the organocatalytic binaphthol / boronate system that is the subject of this thesis.

Chapter 2. Previous Work with Alkynyl-, Alkenyl-, Allyl-, and Arylboronates

In previous work, the Chong group investigated the use of chiral binaphthol and 3,3'-disubstituted binaphthol compounds in place of chiral transition metal catalysts in asymmetric conjugate additions. Beginning with Wu's work with alkynylboration, the scope of the boronate/binaphthol system was extended to alkenyl-, allyl-, and arylboration of various α,β-unsaturated enones. This section will also cover similar research conducted by Schaus *et al.*

2.1 Alkynylboration

The report on the binaphthol / boronate catalyst system and its use in asymmetric alkynylboration[1] was vital in establishing many of the reaction conditions and compounds used with this system. Firstly, the reaction was identified as a ligand accelerated catalytic process with a negligible background reaction in the absence of the chiral binaphthol ligand. This process was a first for organoboron reagents. Further computational analysis by Pellegrinet and Goodman using the B3LYP/lacvp* level of theory supported the proposed catalytic cycle as the most favoured thermodynamic and kinetic pathway.[2] Secondly, it was found that substitution at the 3 and 3' positions yielded better enantioselectivities, particularly with electron withdrawing substituents such as chloro-, iodo- and trifluoromethyl. These substituents further increase boron's Lewis acidity and facilitate the reaction. Yields of up to 94% and 96% ee were reported with various acyclic enones (Scheme 2.1, Table 2.1).



2.1a: R_1 = Ph, R_2 = Ph; **2.1b**: R_1 = 1-naphthyl, R_2 = Ph
2.1c: R_1 = 2-furyl, R_2 = Ph; **2.1d**: R_1 = Ph, R_2 = Me

Scheme 2.1[1]

Table 2.1 Asymmetric alkynylboration of various enones using binaphthol catalyst **2.3a**[1]

entry	enone	R_3	time (h)	product	yield (%)	% ee
1	**2.1a**	*n*-C_6H_{13}	24	**2.2a**	94	86
2	**2.1b**	*n*-C_6H_{13}	12	**2.2b**	93	96
3	**2.1c**	*n*-C_6H_{13}	36	**2.2c**	78	88
4	**2.1d**	*n*-C_6H_{13}	48	**2.2d**	89	94
5	**2.1a**	Ph	24	**2.2e**	95	82
6	**2.1b**	Ph	24	**2.2f**	97	90
7	**2.1a**	CH_2OBn	24	**2.2g**	91	86
8	**2.1b**	CH_2OBn	24	**2.2h**	94	95

Stereochemistry was rationalized using a 6-membered chair transition state[1] (Figure 2.1), analogous to Brown's addition of alkynyl 9-BBN reagents to enones[3] and Noyori's asymmetric reduction of alkyl aryl ketones with BINAL-H.[4]

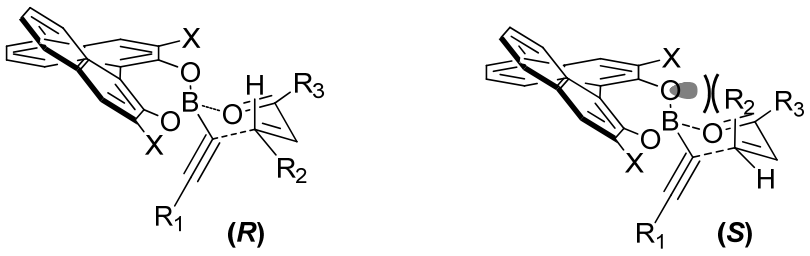


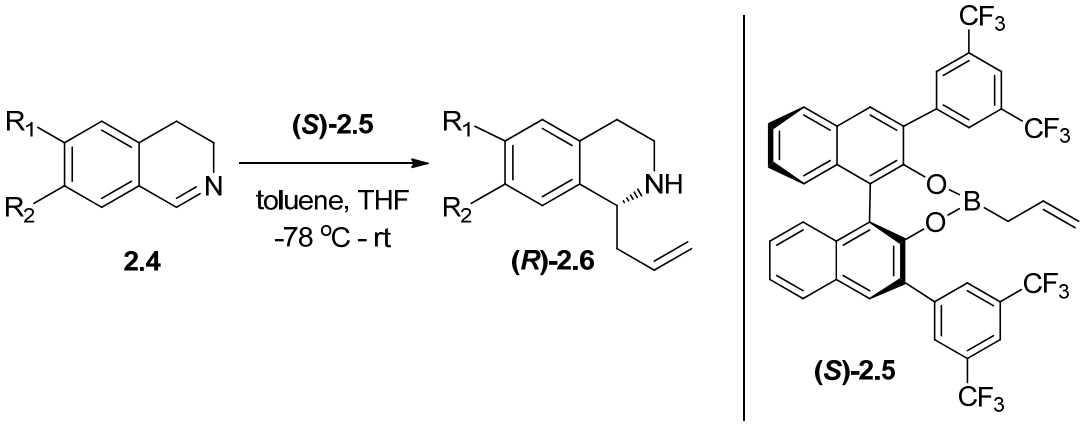
Figure 2.1 Favoured *(R)* and disfavoured *(S)* transition states of asymmetric alkynylboration with *(R)*-BINOL.[1]

It was found later that asymmetric alkynylboration, using stoichiometric amounts of binaphthol-modified alkynylboronates, could directly produce chiral propargylamines via conjugate addition to *N*-acylaldimines.[5] This method was applied to produce an antitubulin agent (–)-*N*-acetylcolchinol from 3-hydroxybenzaldehyde in four steps.

2.2 Allylboration

2.2.1 Stoichiometric Allylboration

Following the discovery of the alkynylboration chemistry, Wu and Chong reported on the stoichiometric allylboration of cyclic imines using 3,3'-disubstituted binaphthol ligands (Scheme 2.2).[6] The 3,3'-bis[3,5-$(CF_3)_2$-C_6H_3]-binaphthol ***(S)*-2.5** produced the best results, yielding 91% to >99% ee with a variety of cyclic imines (Table 2.2). The asymmetric allylboration was used to synthesize natural alkaloids (+)-crispine A, *R*-(–)-coniine·HCl, and *ent*-corynantheidol.[7]

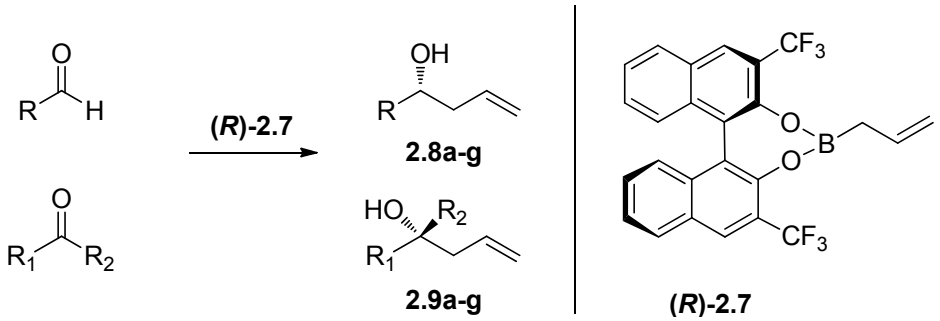


Scheme 2.2[6]

Table 2.2 Asymmetric allylboration of various cyclic imines with ***(S)*-2.5**[6]

entry	imine	R_1	R_2	product	yield (%)	% ee
1	**2.4a**	H	H	**2.6a**	92	95
2	**2.4b**	OMe	OMe	**2.6b**	78	98
3	**2.4c**	OCH_2O	OCH_2O	**2.6c**	86	98
4	**2.4d**	Cl	Cl	**2.6d**	88	95
5	**2.4e**	H	NO_2	**2.6e**	90	99

The work was later expanded to include the stoichiometric allylboration of ketones and aldehydes (Scheme 2.3), finding that the 3,3'-bis(trifluoromethyl)-binaphthol ***(R)*-2.7** provided the best results.[8] Lower selectivities were generated with aldehydes (Table 2.3) than ketones (Table 2.4). At the time, asymmetric allylboration of ketones was difficult: the only successful allylboration of acetophenone with Brown's α-pinene derived $Ipc_2BCH_2CH{=}CH_2$ generated product **2.9a** in 5% *ee*.



Scheme 2.3[8]

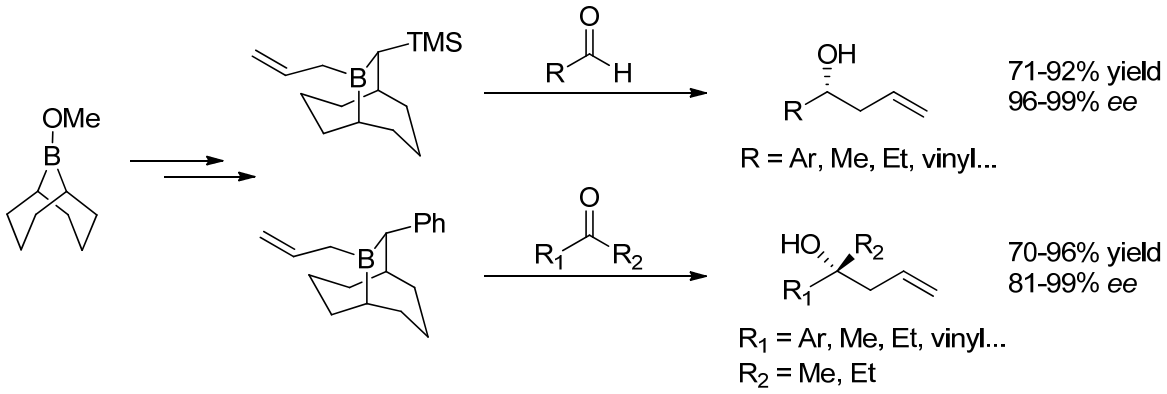
Table 2.3 Asymmetric allylboration of various aldehydes with ***(R)*-2.7**[8]

entry	R	product	yield (%)	er (*R*:*S*)
1	Ph	**2.8a**	90	98:2
2	4-$CH_3OC_6H_4$	**2.8b**	93	97:3
3	4-ClC_6H_4	**2.8c**	93	97:3
4	4-$O_2NC_6H_4$	**2.8d**	96	96:4
5	4-$CF_3C_6H_4$	**2.8e**	94	97:3
6	PhCH=CH	**2.8f**	98	88:12
7	*n*-C_6H_{11}	**2.8g**	90	88:12

Table 2.4 Asymmetric allylboration of various ketones with ***(R)*-2.7**[8]

entry	R_1	R_2	product	yield (%)	er (*R*:*S*)
1	Ph	CH_3	**2.9a**	88	96:4
2	Ph	CH_2Br	**2.9b**	87	97:3
3	4-$CH_3OC_6H_4$	CH_3	**2.9c**	95	99:1
4	4-ClC_6H_4	CH_3	**2.9d**	94	>99:1
5	PhCH=CH	CH_3	**2.9e**	91	88:12
6	*t*-Bu	CH_3	**2.9f**	75	95:5
7	$PhCH_2CH_2$	CH_3	**2.9g**	98	75:25

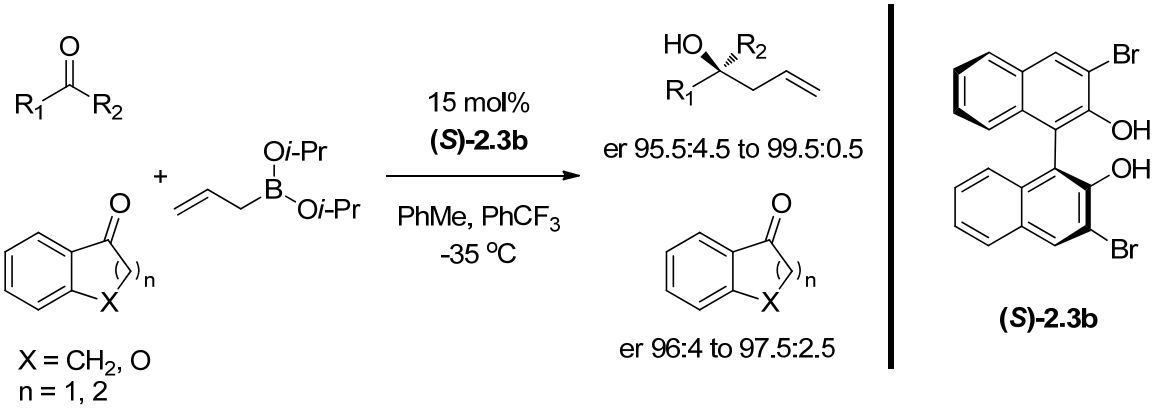
Since this report, Soderquist described the use of chiral borabicyclodecanes to effect the allylboration of aldehydes and ketones. In particular, the TMS derivative produced high enantioselectivies with aldehydes, while the phenyl derivative paired well with ketones (Scheme 2.4).[9,10]



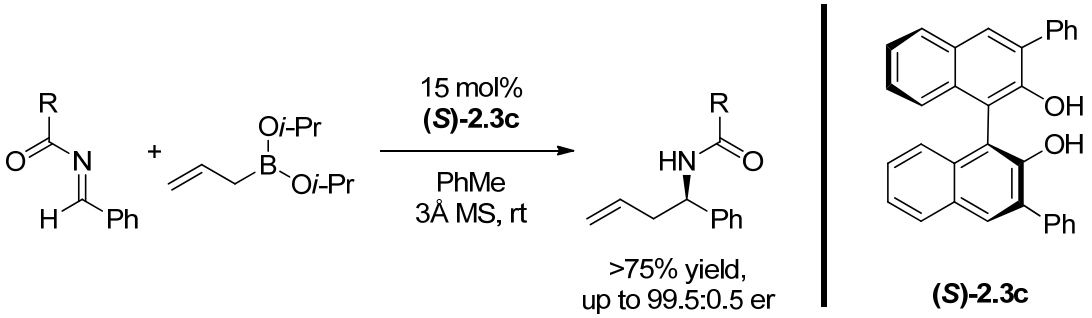
Scheme 2.4[9,10]

2.2.2 Catalytic Allylboration

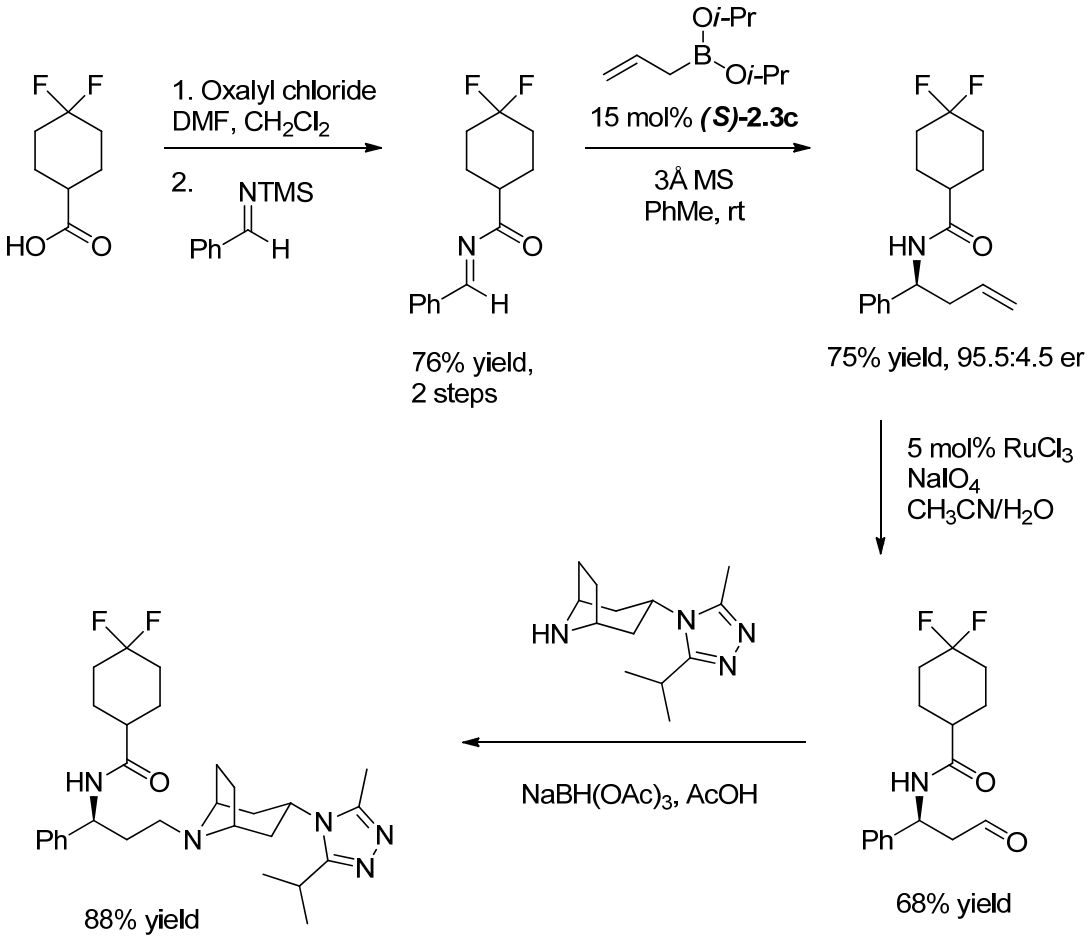
Schaus *et al.* expanded this work and developed catalytic versions of the allylboration of ketones[11,12] and acyl imines[13,14] using 3,3'-disubstituted binaphthols and isopropyl allylboronates. In the allylboration of ketones with 3,3'-dibromobinaphthol as represented in Scheme 2.5, both acyclic enones and cyclic enones were probed. With the allylboration of aryl imines, the 3,3'-diphenylbinaphthol was used (Scheme 2.6). The method was used to synthesize Maraviroc, an antiretroviral drug, from difluorocyclohexane carboximide imine (Scheme 2.7).[14]



Scheme 2.5[11,12]



Scheme 2.6[13,14]



Scheme 2.7[14]

The catalytic allylboration was possible with ketones but not aldehydes as the background reaction between aldehydes and achiral boronates could not be sufficiently suppressed. However, the background reaction with ketones was slow enough to allow for transesterification of the achiral boronate with the chiral binaphthol, generating higher enantioselectivities.

2.3 Alkenylboration

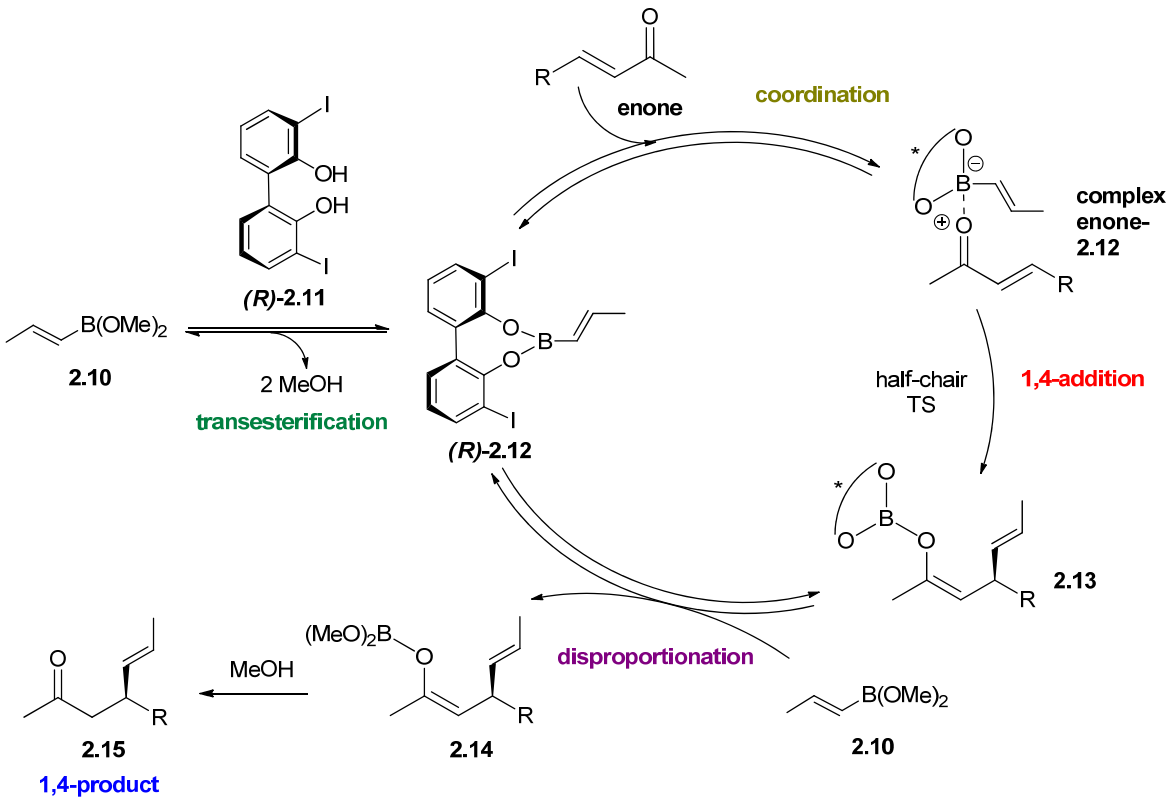
Further diversifying the scope of the binaphthol/boronate system is the catalytic alkenylboration of various acyclic enones.[15] The asymmetric alkenylboration yielded great results of up to 96% yield and >99.5:0.5 er and was similar to the alkynylboration reaction in many respects: optimal catalytic activity was found again with electron-withdrawing groups at the 3 and 3' positions. However, while poor results were observed with alkynylation of β-alkyl enones, alkenylboration works well with these substrates.

2.3.1 DFT Studies Providing Mechanistic Insight and Facial Selectivity

Pellegrinet and Goodman once again offered their insights to the mechanism of this reaction.[16] By conducting DFT calculations, at the B3LYP/631LAN level of theory, as well as FMO considerations, they proposed a catalytic cycle and provided an argument for facial selectivity.

2.3.1.1 Mechanistic Rationale and Catalytic Cycle

Using biphenol ***(R)*-2.11** to model 3,3'-diiodobinaphthol **2.3a**, Pellegrinet and Goodman proposed a catalytic cycle for the alkenylboration of enones (Scheme 2.7). The catalytic cycle involves the transesterification of the achiral alkenylboronate **2.10** with biphenol ***(R)*-2.11** followed by coordination of the biphenol-boronate ***(R)*-2.12** with the enone to form complex **enone-2.12**. 1,4-addition of the alkenyl group to the enone then proceeds through an *exo* sofa-like transition state to form **2.13**, and release of the biphenol moiety via disproportionation with **2.10** regenerates ***(R)*-2.12** and produces **2.14**. Further ligand exchange yields the product **2.15**.



Scheme 2.7[16]

It was found that transesterification with BINOL to form the BINOL-boronate as the active species was favoured over the achiral dimethyl boronate in several ways. Firstly, the transition state involving the BINOL-boronate has slightly shorter calculated bonds B-O1, C1′-C4, and C2′-C4 than the transition state involving the dimethyl boronate (Figure 2.2). This indicates that the bonds developing during 1,4-addition have stronger bonding interactions with the BINOL in place. In addition, there is a facial selectivity that arises, on the order of 4 kcal/mol in solution. Lastly, the free energy of activation with the BINOL-boronate complex was calculated to be more than 10 kcal/mol lower than the activation energy required for the dimethyl boronate. This indicates that the chiral BINOL-boronate species is likely to be the active species in solution to effect 1,4-addition.

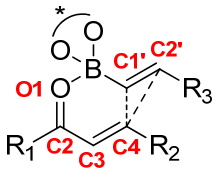


Figure 2.2 Developing bonds B-O1, C1′-C4, and C2′-C4.[16]

The calculated C-O-B-C1′ torsional angles in the BINOL-boronate species are 145°, rather than 0° or 180° in the dimethyl boronate, hindering the donation of the BINOL oxygen electrons into the boron atom. The oxygen lone pairs are delocalized into the aromatic BINOL system, which combined with the electron-withdrawing nature of the BINOL substituents, further enhances the Lewis acidity of boron.

After transesterification, the chiral BINOL-boronate coordinates to the enone, forming a tightly bound complex and lowering the activation free energy of the 1,4-addition. The conjugate addition proceeds with the B-O1 and C1′-C4 sigma bonds forming in a quasi-concerted fashion with the breaking of the B-C1′ bond and subsequent reorganization of π-electrons in the enone. With most of the entropy lost in this initial complex formation, the generation of the 1,4-product is favourable (-20 kcal/mol). This addition step is predicted to be irreversible due to the high energy barrier for the reverse reaction (33 kcal/mol). While the disproportionation of the 1,4-adduct with the dimethyl boronate was not studied in detail, the process is favourable (-9 kcal/mol) and is necessary to regenerate the BINOL catalyst.

The computed enantiomeric ratio arising from the reaction (er 98.4:1.6) is in excellent agreement with experimental values obtained (er 98.7:1.3), supporting their DFT model and choice of modeling method.

2.3.1.2 Facial Selectivity

While Wu and Chong proposed a 6-membered chair-like transition state, where selectivity arises from pseudoequatorial steric interactions, Pellegrinet and Goodman found that the key stereoselective step likely proceeds through an *exo* sofa-like transition state where the sp^2 hybridization of enone atoms are accommodated and atoms B, O1, C2, C3, and C4 are in the same plane (Figure 2.3).

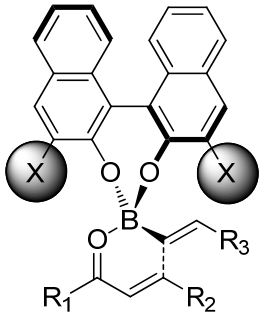
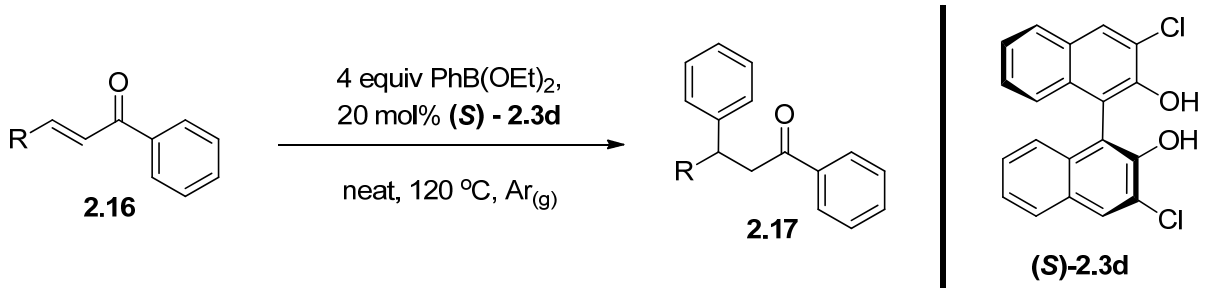


Figure 2.3 *Exo* sofa-like transition state for alkenylboration.[16]

Enantioselectivity in the reaction arises from destabilizing interactions on the unfavoured face: the iodo substituent on the chiral ligand has 3 close interactions with hydrogens on the alkenyl group as well as on the β-substituents on the enone, where the H-I distances are close to the sum of the van der Waals radii of hydrogen and iodine. This results in an effective shielding of the unfavoured face of the alkene by the substituent, leading to attachment on the other side of the enone. In the favoured face, steric interactions are avoided as the substituent is almost perpendicular to the plane of the enone. With *(R)*-BINOL, the front face of the alkene is shielded, disfavouring attack to the back β-*si* face of the enone.

2.4 Arylboration

The work by Turner showed that catalytic arylboration of α,β-unsaturated enones was possible. [17] Using 3,3'-dichlorobinaphthol **2.3d**, Turner was able to add phenyl in an enantioselective fashion to a number of enones with good yields (67-88%) and selectivities (up to 99:1 er) (Scheme 2.8, Table 2.5). It is interesting to note the phenylboration of (*E*)-3-(furan-2-yl)-1-phenylprop-2-en-1-one (Table 2.5, entry 11), which was low yielding but generated excellent enantioselectivity.



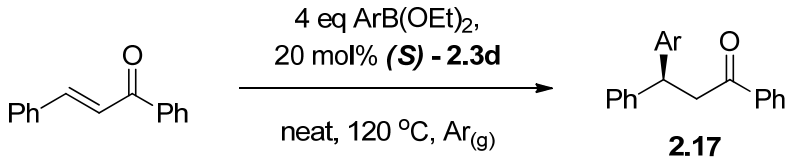
Scheme 2.8[17]

Table 2.5 Phenylboration of various enones with 20 mol% ***(S)*-2.3d**[17]

entry	R	product	time (h)	yield (%)[a]	er[b]
1	1-naphthyl	**2.17a**	32	86	2:98
2	4-MePh	**2.17b**	72	90	9:91
3	4-MeOPh	**2.17c**	48	66	6:94
4	4-ClPh	**2.17d**	48	74	10:90
5	4-BrPh	**2.17e**	96	66	11:89
6	2-MePh	**2.17f**	48	75	1:99
7	Me	**2.17g**	24	66	7:93
8[c]	*i*-Pr	**2.17h**	72	72	12:88
9[d]	*n*-Bu	**2.17i**	72	40	9:91
10	*n*-pentyl	**2.17j**	24	54	9:91
11[c]	furan-2-yl	**2.17k**	72	28	98:2

[a] Isolated yields after column chromatography, 100% conversion unless otherwise stated. [b] Enantiomeric ratio determined by HPLC analysis, reported in order of elution. [c] 83% conversion. [d] 95% conversion.

A study was also carried out on the arylboration of chalcone with phenyl moieties having electron-donating and electron-withdrawing substituents (Scheme 2.9, Table 2.6). While all the reported enantioselectivities were excellent (89:11 to 99.5:0.5 er), aryl groups with electron-withdrawing substituents generally required longer reaction times with incomplete conversion and poor yields.



Scheme 2.9[17]

Table 2.6 Arylboration of chalcone with 20 mol% ***(S)*-2.3d**[17]

entry	Ar	product	time (h)	yield (%)[a]	er[b]
1	4-MeOPh	**2.18a**	29	88	89:11
2	4-MePh	**2.18b**	20.5	84	93:7
3[c]	4-ClPh	**2.18c**	46	67	91:9
4	2-MePh	**2.18d**	48.5	70	95:5
5	3-MePh	**2.18e**	48.5	73	99.5:0.5
6[d]	4-CF_3Ph	**2.18f**	73	21	91:9

[a] Isolated yields after column chromatography, 100% conversion unless otherwise stated. [b] Enantiomeric ratio determined by HPLC analysis, reported in order of elution. [c] 75% conversion. [d] 25% conversion.

Previous investigations with alkynyl-, alkenyl-, allyl- and arylboration have demonstrated that the BINOL/boronate system is successful in effecting asymmetric conversions to a variety of compounds. With the knowledge gained regarding boronate synthesis, catalyst design, and the catalytic cycle, it is of interest to expand upon the scope of this catalyst system to include the 1,4-addition of heteroaryl moieties.

Chapter 3. Asymmetric Heteroarylboration of α,β-Unsaturated Carbonyl Compounds

Building upon the successful asymmetric conjugate addition of phenyl groups to α,β-unsaturated enones via arylboration,[1] we are interested in extending the scope of the organocatalytic binaphthol / boronate system to include 1,4-addition of heteroaromatic groups. While a fair amount of literature addresses the topic of symmetric conjugate addition of phenyl rings to enones, as covered in Chapter 1, the analogous reaction of heteroaromatics is still relatively uncommon. Currently, all the existing related reactions employ the use of metal catalysts or reagents, and *O*-monoacyltartaric acids are the only organocatalysts used to date with moderate results. If the binaphthol / boronate system is successful in effecting heteroarylboration to α,β-unsaturated enones, it will introduce an effective way to add a heteroaromatic group β to the carbonyl without the use of transition metals.

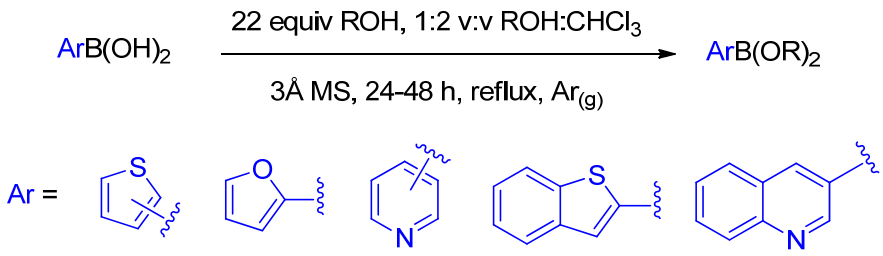
For this investigation, heteroarylboronates containing three kinds of heteroaryl groups were used: five-membered thien-2-ylboronate, thien-3-ylboronate, and furan-2-ylboronate; six-membered pyrid-3-ylboronate and pyrid-4-ylboronate; and fused systems benzo[*b*]thien-2-ylboronate and quinoline-3-boronate.

The investigation into heteroarylboration was divided into three parts. Firstly, the diethyl heteroarylboronate and chiral binaphthol starting materials were synthesized. The investigation then focused on the general reactivity of the 2-thienyl moiety. The catalyst of choice was determined through screening of various binaphthols, followed by establishing optimal reaction conditions. The reactivity of the 2-thienyl group was then compared to the reactivity of the phenyl group used in Turner's arylborations in a competitive arylboration experiment. In the third part of the investigation, the heteroarylboration of various enones was executed with a variety of heteroarylboronates with chosen 3,3'-dichlorobinaphthol ***(S)*-3.1a** to

probe the scope and selectivity of the reaction. This chapter concludes with a discussion of the findings and a proposed catalytic cycle and mechanistic rationale.

3.1 Preparation of Diethyl Heteroarylboronates

The boronates used as part of the binaphthol / boronate catalyst system are required to exhibit appropriate stability to the reaction conditions used in the asymmetric transformations. The appropriate boronate should readily undergo transesterification with BINOL, a key step in the catalytic cycle as discussed in Section 2.3.1.1, yet not be liable to hydrolysis to form the corresponding boronic acid. Using boronates that are too stable and do not transesterify with ease may lead to decreased reactivity or a slower reaction time. On the other hand, using boronates that are unstable to reaction conditions may lead to an incomplete reaction. As the use of diethyl phenylboronates were found to be effective in phenylborations,[1] diethyl heteroarylboronates were synthesized for use in the heteroarylborations. The same procedure was employed to synthesize the heteroarylboronates (Scheme 3.1).

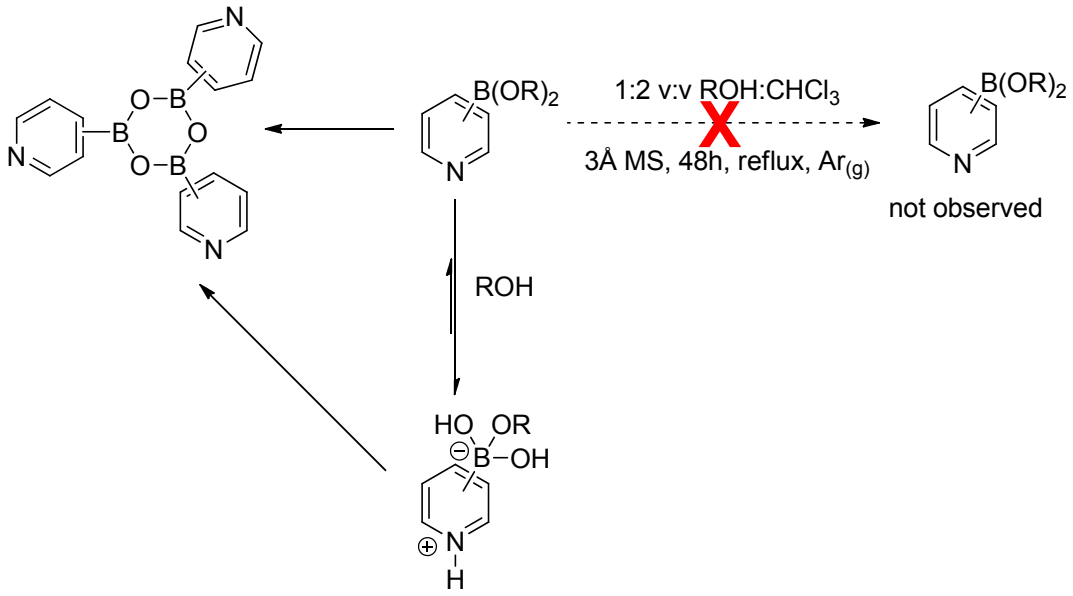


Scheme 3.1

Commercially available boronic acids were purchased from Matrix Scientific. Esterification of these boronic acids involved the reflux of the boronic acid with a large excess of ethanol in solution with chloroform, in the presence of molecular sieves and under anhydrous

conditions. As the esterification is an equilibrium process, the use of molecular sieves, the azeotropic nature of the ethanol/chloroform solution, and an argon environment served to irreversibly remove water from the reaction to favour the esterified product.[2]

While the syntheses of thienyl and furyl boronates[1] were successful, the syntheses of dialkyl 3-pyridyl and 4-pyridyl boronates were unsuccessful, producing instead the corresponding boroxine. One possible explanation may be due to the fact that the pyridine boronic acid is in zwitterionic form. The presence of pyridine may not allow for the esterification to proceed and the dehydration to the boroxine occurs instead (Scheme 3.2). To remove the basic pyridine nitrogen from the reaction, attempts were made to oxidize the pyridyl boronic acids to *N*-oxides. However, these endeavours were also unsuccessful.



Scheme 3.2

3.2 Preparation of Chiral Binaphthol Catalysts

Control and optimization of enantioselectivity of the arylboration can be enhanced by changing the stereoelectronic properties of the binaphthol ligand. This can be achieved by

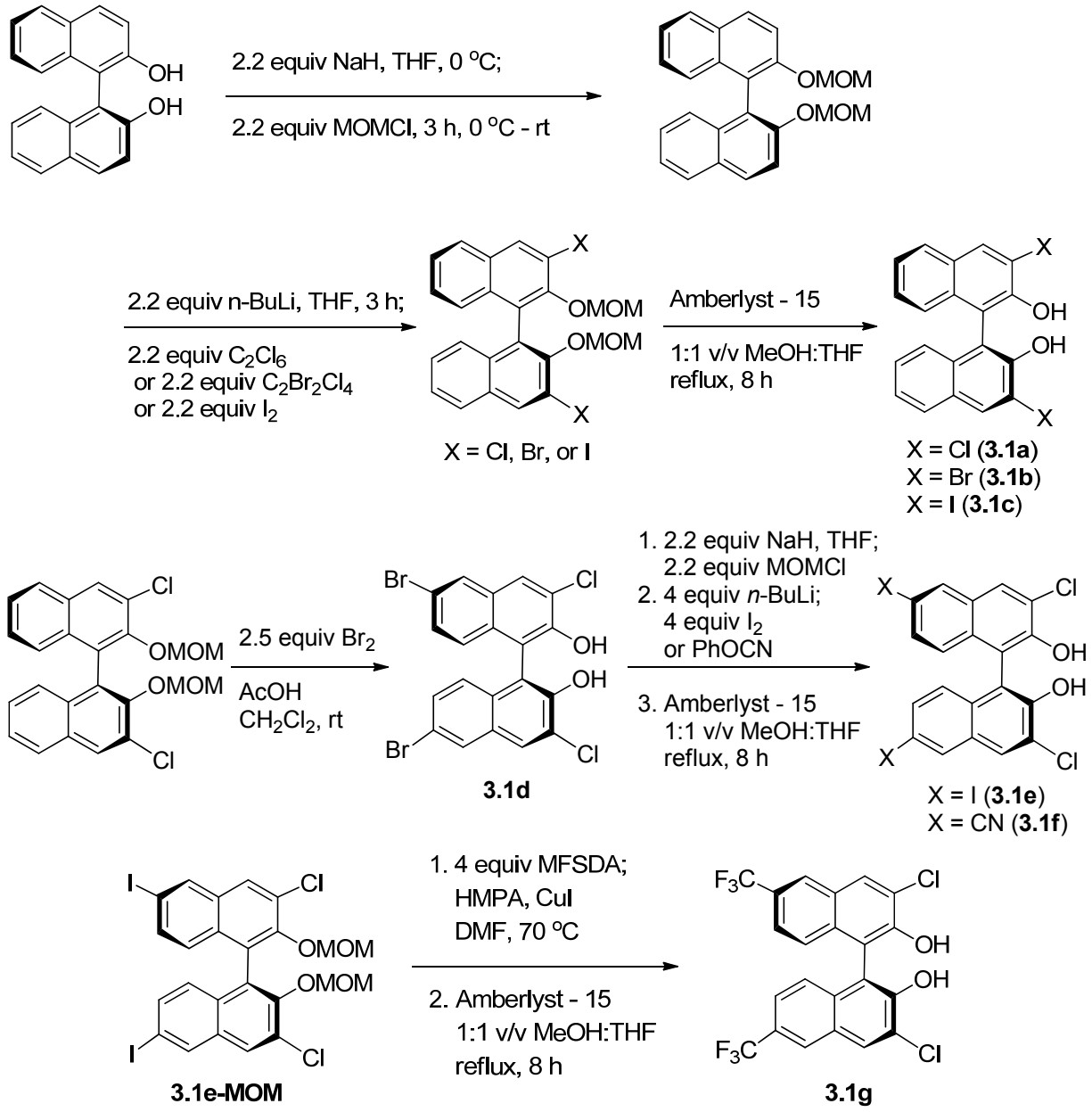
adding electronegative substituents to the binaphthol ligand in the 3 and 3' positions as well as the 6 and 6' positions. Based on past work, 3,3'-dichlorobinaphthol generates the best yield and selectivities for phenylboration.[3] This is based on the fact that electronegative substituents at the 3 and 3' positions draw electron density towards themselves via an inductive effect. By decreasing the amount of electron donation of the binaphthol oxygen atoms to boron, the Lewis acidity of the boron increases and further enhances the resulting arylboration.

However, the reaction time with the 3,3'-dichlorobinaphthol is typically long; with phenylboration, the reaction time was 3 days. The work of fellow colleague Dr. Patel with the binaphthol ligand has shown that additional substitution at the 6 and 6' positions increases the reaction rate without sacrificing yields or selectivity.[4] Favoured substitutions are with electronegative groups that can best stabilize an adjacent developing partial negative charge, such as cyano and trifluoromethyl. Iodo and bromo groups exhibit only moderate increase in catalyst activity.

(S)-BINOL is available commercially. Preparation of the ligands (Scheme 3.3) begins with protection of the diol with chloromethyl methyl ether (MOMCl). Treatment with *n*-butyllithium then metallates the 3 and 3' positions to generate the dilithiated intermediate. Subsequent addition of an electrophile substitutes at the 3 and 3' positions. Finally, removal of the MOM group yields the 3,3'-disubstituted binaphthol catalyst (**3.1a, 3.1b, 3.1c**).

To further substitute at the 6 and 6' positions, the MOM-protected 3,3'-dichlorobinaphthol undergoes electrophilic aromatic substitution with bromine to generate the 6,6'-dibromo-3,3'-dichlorobinaphthol compound (**3.1d**). Reprotection of the diol with MOMCl, followed by metallation with *n*-BuLi and treatment with iodine or phenyl cyanate generates the tetrasubstituted ligand after deprotection (**3.1e, 3.1f**). To generate the bis(trifluoromethyl) ligand, the protected 6,6'-diiodo-3,3'-dichlorobinaphthol ligand **3.1e-MOM**

undergoes a copper-assisted trifluoromethylation with methyl fluorosulfonyldifluoroacetate (MFSDA). Finally, removal of the MOM group yields the tetrasubstituted binaphthol catalyst (**3.1g**).



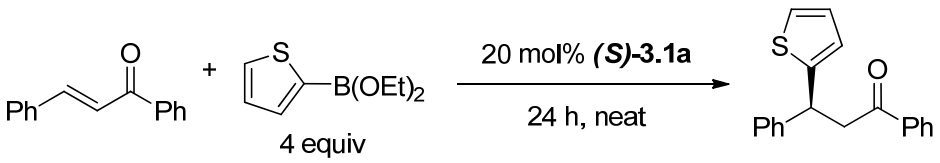
Scheme 3.3

After synthesizing the heteroarylboronate reagents and binaphthol catalysts, the investigation then focused on establishing the heteroarylboration reaction with thien-2-ylboronate.

3.3 Initial Investigation into Heteroarylboration

3.3.1 Reactivity of Thien-2-ylboronate

The previous research into phenylboration (Section 2.4) indicated the use of high reaction temperatures for long periods of time were necessary to facilitate the arylboration process (Scheme 3.4). However, temperatures in excess of 120 °C could promote the background racemic reaction as well as lead to decomposition of the arylboronate. Hence, after the successful 1,4-addition of thien-2-ylboronate to chalcone at 120 °C in 6 h, the reaction temperature was dropped to 70-80 °C. To our delight, the thien-2-ylboronate also added at this lower temperature in 91% yield and 96:4 er (Table 3.1, entry 2). Further monitoring and enantiomeric purity analysis, to be discussed in Section 3.3.5, yielded the optimal reaction conditions of 70 °C for 24 h.



Scheme 3.4

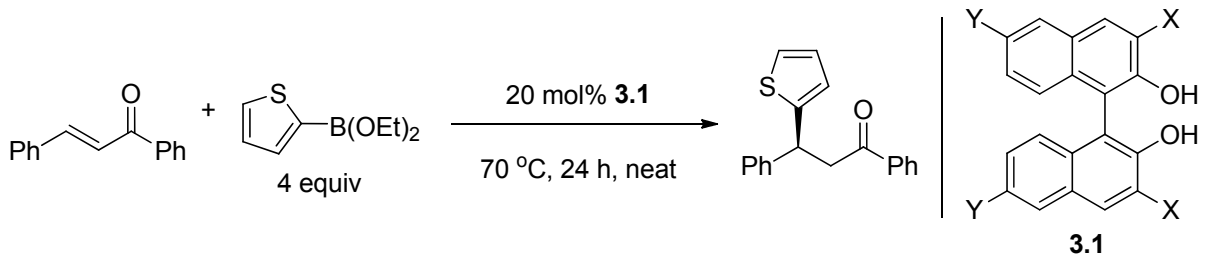
Table 3.1 Thien-2-ylboration of chalcone with ***(S)*-3.1a**

entry	Reaction Temperature (°C)	time (h)	yield (%)[a]	er
1	120	24	80	85:15
2	70	24	91	96:4

[a] Isolated yields after column chromatography.

3.3.2 Screening of Binaphthols

After establishing an optimal reaction temperature, a number of substituted binaphthols were screened to determine the catalyst that could best effect the asymmetric heteroarylboration (Scheme 3.5). As mentioned previously, it is proposed that more electron-withdrawing substituents on the binaphthol at the 3 and 3' positions as well as the 6 and 6' positions would increase the reactivity of the binaphthol/boronate system. This is possible by drawing electron density away from the boron atom and increasing its Lewis acidity. By increasing the reactivity of the binaphthol ligand, it is possible to lower reaction temperatures and thus enhance the enantioselectivity of the reaction. However, the results shown in Table 3.2 are inconsistent with this proposal. Firstly, the reaction with BINOL ***(S)*-3.1e** and 3,3',6,6'-tetrasustituted BINOL ***(S)*-3.1g** yielded unpromising enantioselectivies of 85:15 er. Secondly, it is not clear why no trend was observed correlating the electronic nature of the ligand and the selectivity of the reaction, as 3,3'-dichlorobinaphthol ***(S)*-3.1a** and 3,3'-diiodobinaphthol ***(S)*-3.1c** both afforded higher selectivities than 3,3'-dibromobinaphthol ***(R)*-3.1b** (Table 3.2, entries 1-3).



Scheme 3.5

Table 3.2 Thien-2-ylboration of chalcone with **3.1a-c, 3.1g-h**

entry	BINOL	Substituent		yield (%)[a]	er of 2-thienyl adduct[b] *(S)*:*(R)*
		X	Y		
1	***(S)*-3.1a**	Cl	H	91	96:4
2	***(R)*-3.1b**	Br	H	88	83:17
3	***(S)*-3.1c**	I	H	83	99:1
4	***(R)*-3.1h**	CF_3	H	88	97:3
5	***(S)*-3.1i**	CN	H	91	85:15
6	***(S)*-3.1g**[c]	Cl	CF_3	82	85:15

[a] Isolated yields after column chromatography. [b] Enantiomeric ratio determined by HPLC analysis, reported in order of elution. [c] Enantiomeric purity of ligand was later found to be 85:15.

Further analysis into the enantiomeric purity of 3,3′,6,6′-tetrasubstituted binaphthol ***(S)*-3.1g** (Table 3.2, entry 6) using HPLC indicated that the final deprotection of these binaphthols leads to racemization during their synthesis. In fact, the enantiomeric purity of the adduct using binaphthol ***(S)*-3.1g** was comparable to the enantiomeric purity of the binaphthol used suggesting that this ligand, if attainable in high enantiomeric purity, would give very high selectivities. Unfortunately, various deprotection methods endeavored by Dr. Patel were unsuccessful in suppressing this racemization.[4] As a result, BINOLs ***(S)*-3.1a** and ***(S)*-3.1c** were chosen for further investigation. However, even though BINOL ***(S)*-3.1c** afforded the best selectivity, BINOL ***(S)*-3.1a** allowed for better separation of the product from the BINOL ligand and thus higher isolated yields were obtained, and so was used as the primary BINOL of choice.

3.3.3 Optimization of Reaction Conditions

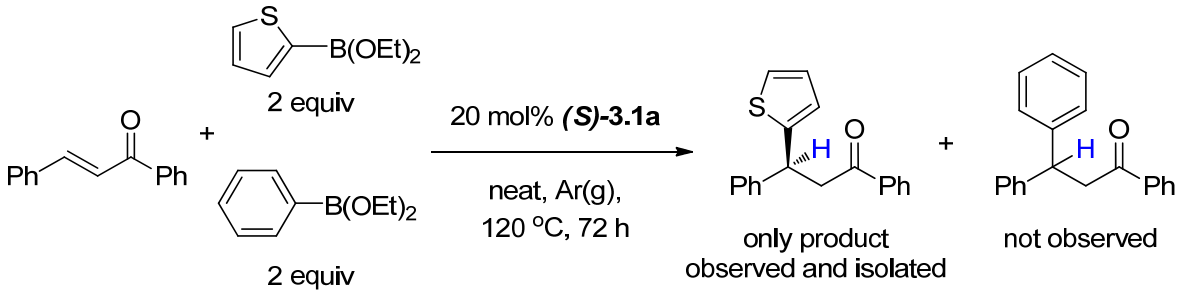
With the reaction temperature and time established and a catalyst chosen, the focus then shifted to decreasing the amount of heteroarylboronate used in the reaction. The phenylboration investigation indicated that an excess of five equivalents of the boronate was necessary to account for any possible decomposition of the boronate at the reaction temperature of 120 °C. However, with a lower reaction temperature of 70 °C and a more reactive heteroaryl species, it is possible that the amount of boronate could be decreased to minimize waste.

As the reaction is run neat in boronate, it was found that a certain volume was necessary to ensure the reaction went to completion. For a reaction involving 100 mg (0.39-0.49 mmol) of enone, it was found that the overall volume of the neat heteroarylboronate needed to be at least 300 μL for efficient conversion of the α,β-unsaturated enone to the heteroaryl adduct. This corresponds to 3.0 to 4.0 equivalents of heteroarylboronate depending on the reagent used.

3.3.4 Competitive Arylboration

As noted in the previous sections, the ease of thien-2-ylboration at lower temperatures indicated that the addition of the 2-thienyl moiety was faster compared to the 1,4-addition of the phenyl group. A competition experiment was thus devised in which equal amounts of the phenylboronate and the thien-2-ylboronate were added simultaneously to the reaction mixture (Scheme 3.6). The reaction was monitored via NMR spectroscopy at various time intervals: the signal corresponding to the methine proton at the newly formed sp^3 β-carbon appears between δ 5.2-5.0 ppm for the 2-thienyl adduct and between δ 4.9-4.7 ppm for the phenyl adduct. Initially, only the methine peak corresponding to the 2-thienyl adduct was noted in the NMR spectra. After 72 hours, the methine peak corresponding to the phenyl adduct was not noticeable, while

the peak corresponding to the 2-thienyl product was clearly evident (Figure 3.1). Finally, only the 2-thienyl adduct was isolated from the final reaction mixture.



Scheme 3.6

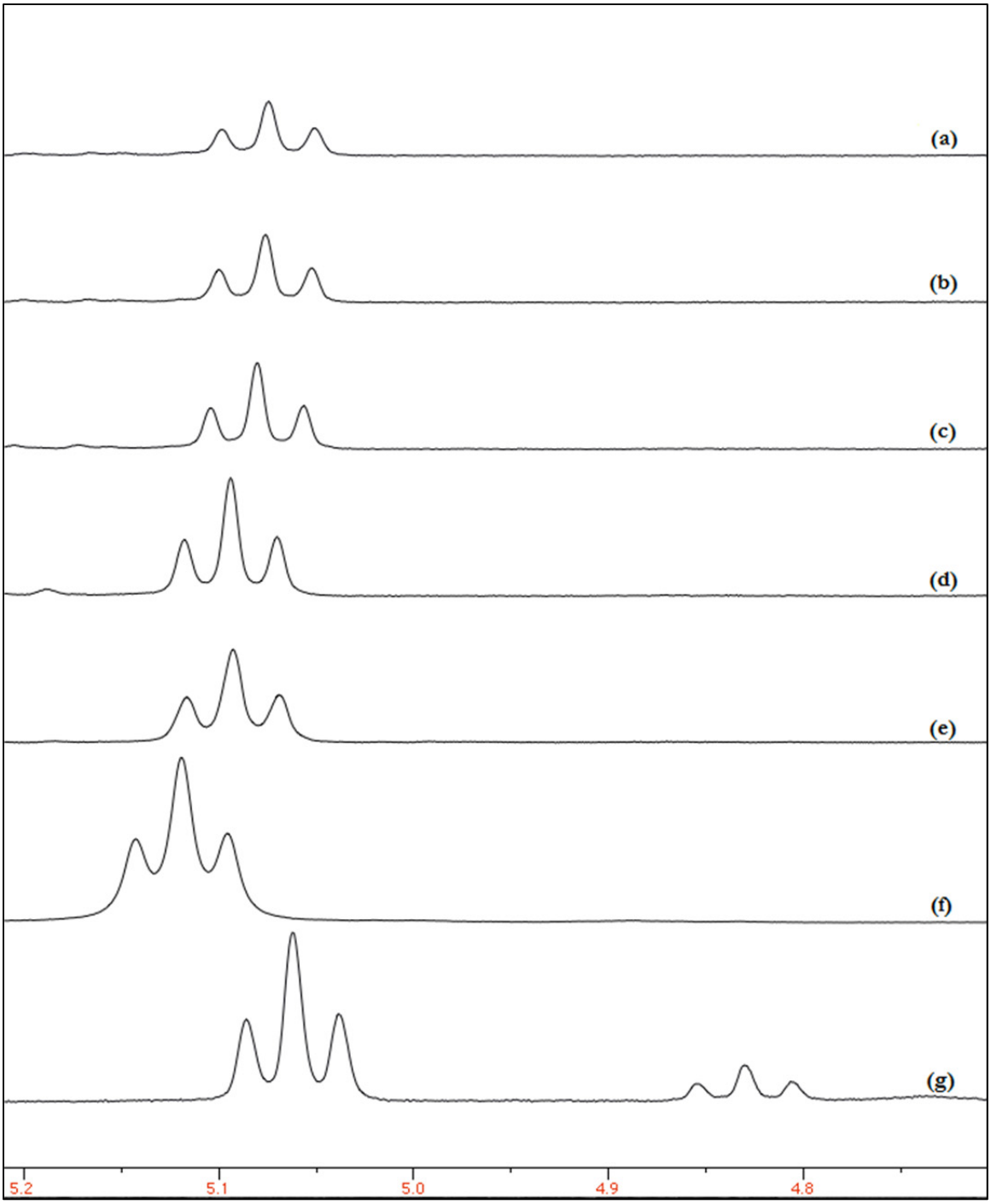
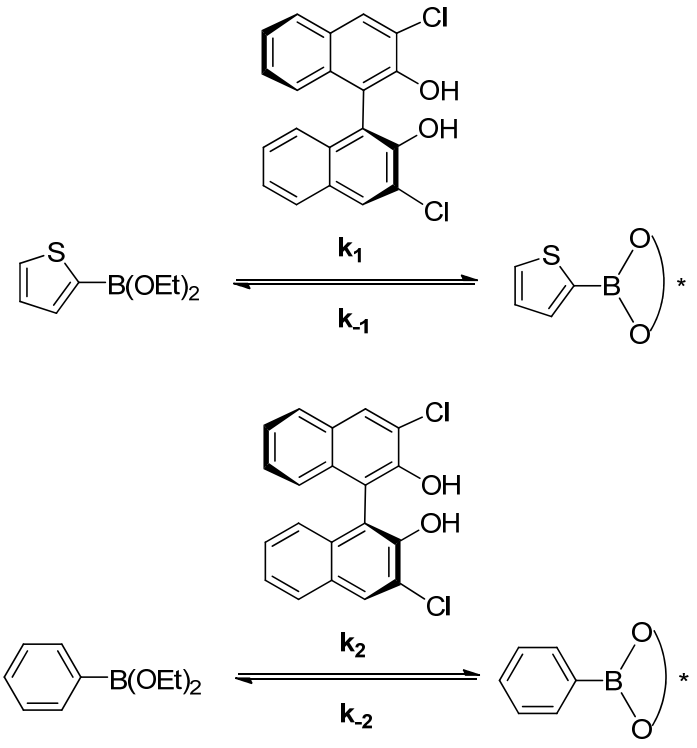


Figure 3.1 ^{1}H NMR spectra of methine peak region in competitive arylboration, corrected to $CDCl_3$ (δ 7.24). Spectra are shown on an absolute scale, corresponding to the following times: (a) 1 h, (b) 2.5 h, (c) 5 h, (d) 7.5 h, (e) 23 h, (f) 72 h, (g) 5 h spiked with equal amounts of 2-thienyl adduct and phenyl adduct.

The reaction was run at 120 °C for 72 h, the conditions in which phenylboration had an equal chance to proceed. This was to allow for the formation of the final phenyl adduct from any intermediates in the reaction. Further discussion of the catalytic cycle is covered in Section 3.5.1.

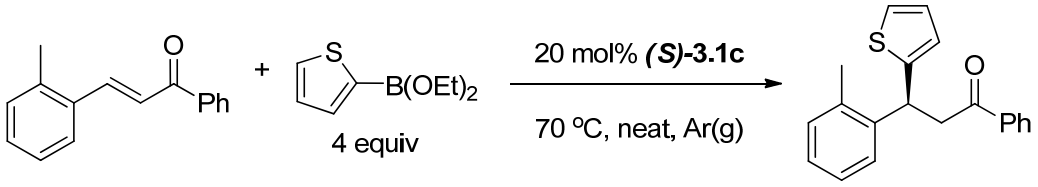
In addition to the isolation of a single 2-thienyl product based on NMR spectroscopy, there are two other important implications of this experiment. Firstly, it is not evident whether the rates of transesterification of the boronate with BINOL is comparable between the 2-thienyl moiety and the phenyl moiety (Scheme 3.7, k_1 and k_2). If the ligand exchange is significantly faster with the thien-2-ylboronate than the phenylboronate ($k_1 >> k_2$), then the reaction does not truly measure the rate of addition of the 2-thienyl group relative to the phenyl group. However, it is expected that the ligand exchange rates are comparable between the two arylboronates. Secondly, the reaction proceeded to completion with only two equivalents of the thien-2-ylboronate. Based on the results outlined in Section 3.1.2, a minimum volume of 300 μL was necessary for the reaction to go to completion. In small-scale reactions, this meant it was not possible to determine whether the use of less than three equivalents of boronate could still effectively bring the heteroarylboration to completion. The use of two equivalents of the thien-2-ylboronate meant that it is indeed possible to use less of the heteroarylboronate to effectively produce the 1,4-adduct. In large-scale reactions, the minimum volume required should not be an issue. It should then be possible to use ~1 equivalent of boronate in the reaction.



Scheme 3.7

3.3.5 Changing Enantiomeric Purity

Another reaction involving thien-2-ylboronate and *o*-tolyl chalcone was devised in which aliquots were taken at different times (Scheme 3.8). Upon working up these aliquots, it was noted that the enantiomeric ratios changed as the reaction proceeded (Table 3.3). It appears that the enantiomeric purity increased over time, from 92.5:7.5 er in the aliquot taken at 4 h to 99.2:0.8 er in the aliquot taken at 30 h.



Scheme 3.8

Table 3.3 Changing enantiomeric purity over time

entry	time elapsed (h)	er[a]
1	4	92.5:7.5
2	8	96.7:3.3
3	12	95.0:5.0
4	24	98.5:1.5
5	30	99.2:0.8

[a] 0.2 mL aliquots were taken at each time point.

The changing enantiomeric purity suggests that there is some mechanism of reversibility in the reaction. However, according to the catalytic cycle outlined by Goodman and Pellegrinet,[5] to be discussed in Section 3.5.1, the reaction mechanism as we understand it indicates that reversibility is not possible for the step involving 1,4-addition.

Another possible explanation of the changing enantiomeric purity over time relates to the changing enantiomeric purity in different fractions. During the purification of the same reaction, it was noted that the enantiomeric ratio changed depending on the fraction obtained from the column (Table 3.4). This is unusual but not unprecedented: Kagan *et al* noted similar findings in the purification of sulfoxides.[6] With sulfoxides, the difference in enantiomeric ratios between fractions was much greater, ranging from 33% *ee* to 95% *ee*. The change was attributed to the formation of a chiral column from achiral silica by the sulfoxide group of the compound.

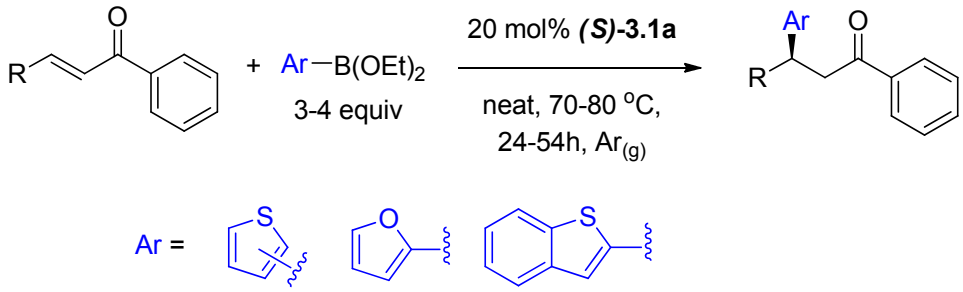
Table 3.4 Changing enantiopurity with fraction

entry	fractions	er
1	1-2	92.5:7.5
2	3-4	95.0:5.0
3	5-8	97.0:3.0

In obtaining earlier fractions for analysis due to the presence of an impurity at a similar R_f value in later fractions, the reaction may appear to have a mechanism of reversibility allowing for a change in enantiomeric purity as the reaction proceeds with time. However, these findings were not investigated further. To prevent any unknown factors contributing to differences in enantiomeric purity in the reactions, subsequent reactions were run to 24-30 h and all fractions were combined for HPLC analysis.

3.4 Results

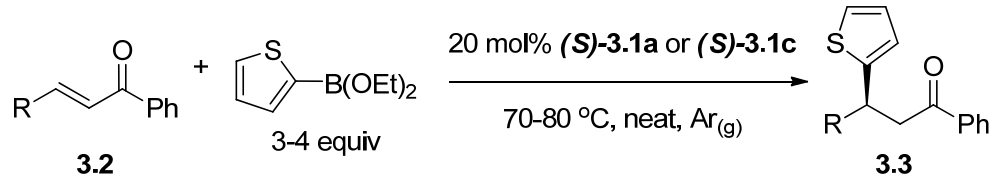
The results of thien-2-ylboration, thien-3-ylboration, furan-2-ylboration, and benzo[*b*]thien-2-ylboration according to the reaction shown in Scheme 3.9 are presented.



Scheme 3.9

3.4.1 Thien-2-ylboration

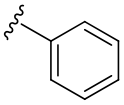
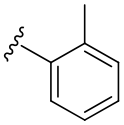
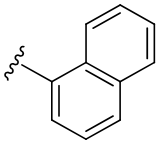
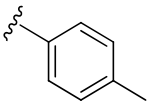
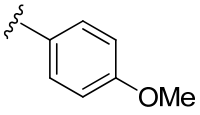
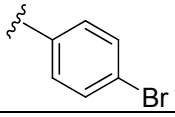
The results of thien-2-ylboration (Scheme 3.10) are provided in Table 3.5. The thien-2-yl group added successfully in 1,4-fashion to various substituted chalcones with high yields and enantioselectivities. It was noted that enones substituted at the *ortho* position generated higher selectivities than those at the *para* position. This will be discussed further in Section 3.5.2.



Scheme 3.10

Reactions were repeated with BINOL ***(S)*-3.1c** as the catalyst and generated higher selectivities overall, indicating that the 3,3′-diiodobinaphthol is a more effective catalyst compared to 3,3′-dichlorobinaphthol ***(S)*-3.1a.**

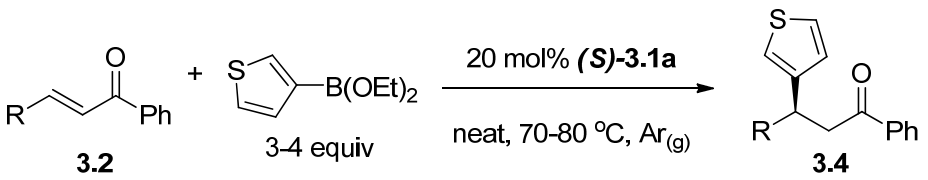
Table 3.5 Thien-2-ylboration of various enones with ***(S)*-3.1a**

Entry	R		product	Time (h)	er [a] (% yield)[b] ***(S)*-3.1a**	***(S)*-3.1c**
1		**3.2a**	**3.3a**	24	95.6:4.4 (91)	99.0:1.0 (83)
2		**3.2b**	**3.3b**	24	98.5:1.5 (82)	99.0:1.0 (87)
3		**3.2c**	**3.3c**	24	99.0:1.0 (97)	99.0:1.0 (85)
4		**3.2d**	**3.3d**	30	89:11 (96)	93:7(91)
5		**3.2e**	**3.3e**	48	8.5:91.5 (86)	8.0:92.0 (84)
6		**3.2f**	**3.3f**	45	93.5:6.5[c] (91)	96.0:4.0[c] (95)

[a] Enantiomeric ratio determined by HPLC analysis, reported in order of elution. Analysis performed with 4.6 x 250 mm ChiralCel OD-H, 254 nm detection unless otherwise noted. [b] Isolated yields after column chromatography. [c] HPLC analysis performed with 4.6 x 250 mm ChiralCel AD-H.

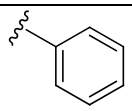
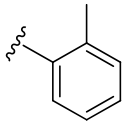
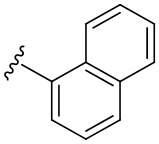
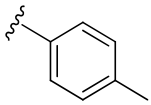
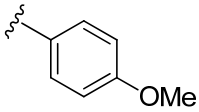
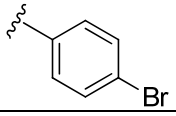
3.4.2 Thien-3-ylboration

The results of thien-3-ylboration using BINOL ***(S)*-3.1a** (Scheme 3.11) are provided in Table 3.6. The thien-3-yl group added successfully in 1,4-fashion to various substituted chalcones with high yields and enantioselectivities. Similar to the results from thien-2-ylboration, enones with substitutions at the *ortho* position generally yielded higher enantioselectivities than those substituted at the *para* position. Overall, selectivities are lower for thien-3-ylboration than thien-2-yl boration. This could be attributed to the heteroatom in the 3-position in the ring. The effect of the heteroaryl group on selectivity will be discussed in Section 3.5.3.



Scheme 3.11

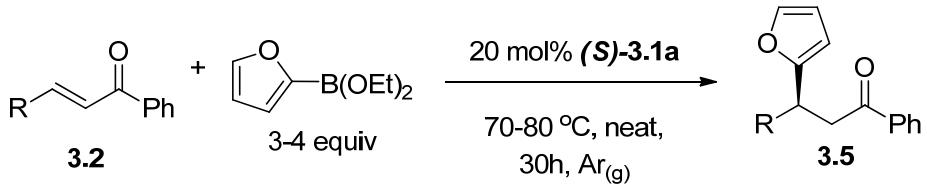
Table 3.6 Thien-3-ylboration of various enones with ***(S)*-3.1a**

Entry	R		Product	Time (h)	Yield (%)[a]	er[b]
1		**3.2a**	**3.4a**	30	93	91.9:8.1
2		**3.2b**	**3.4b**	30	92	97.8:2.2
3		**3.2c**	**3.4c**	54	98	98.2:1.8
4		**3.2d**	**3.4d**	54	99.7	85.0:15.0
5		**3.2e**	**3.4e**	30	96	11:89
6		**3.2f**	**3.4f**	30	99	93.0:7.0

[a] Isolated yields after column chromatography. [b] Enantiomeric ratio determined by HPLC analysis, reported in order of elution. Analysis performed with 4.6 x 250 mm ChiralCel OD-H, 254 nm detection unless otherwise noted.

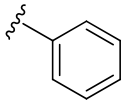
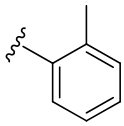
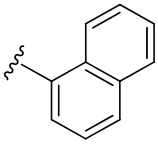
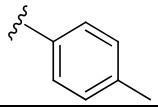
3.4.3 Furan-2-ylboration

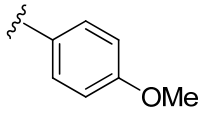
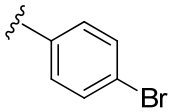
The results of furan-2-ylboration (Scheme 3.12) are provided in Table 3.7. The 2-furyl group added successfully in 1,4-fashion to various substituted chalcones with good yields and enantioselectivities. In line with results reported previously, *ortho*-substituted enones generated higher enantioselectivities than *para*-substituted enones. Overall, selectivities are lowest among all the heteroarylboronates. The selectivities with different heteroaryl groups will be discussed in Section 3.5.3.



Scheme 3.12

Table 3.7 Furan-2-ylboration of various enones with ***(S)*-3.1a**

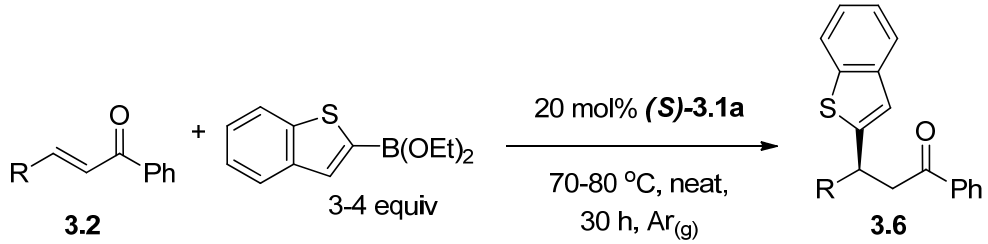
Entry	R		Product	Yield (%)[a]	er[b]
1		**3.2a**	**3.5a**	92	89.0:11.0
2		**3.2b**	**3.5b**	85	94.4:5.6
3		**3.2c**	**3.5c**	93	99.9:0.1
4		**3.2d**	**3.5d**	73	82:18

Entry	R	Product	Yield (%)[a]	er[b]
5		**3.2e** **3.5e**	76	15.6:84.4
6		**3.2f** **3.5f**	78	14.0:86.0

[a] Isolated yields after column chromatography. [b] Enantiomeric ratio determined by HPLC analysis, reported in order of elution. Analysis performed with 4.6 x 250 mm ChiralCel OD-H, 254 nm detection unless otherwise noted.

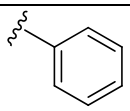
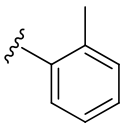
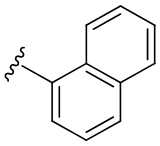
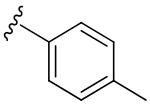
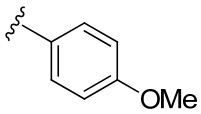
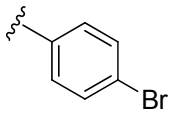
3.4.4 Benzo[*b*]thien-2-ylboration

The results of benzo[*b*]thien-2-ylboration (Scheme 3.13) are provided in Table 3.8. The benzo[*b*]thien-2-yl group added successfully in 1,4-fashion to various substituted chalcones with excellent yields and enantioselectivities. Again, *ortho*-substituted enones generated higher enantioselectivities than *para*-substituted enones. The selectivities are also reversed due to the order of elution from the column but are reported here with the major enantiomer first. Overall, the selectivities obtained for benzo[*b*]thien-2-ylboration are very close to the selectivities obtained for thien-3-ylboration.



Scheme 3.13

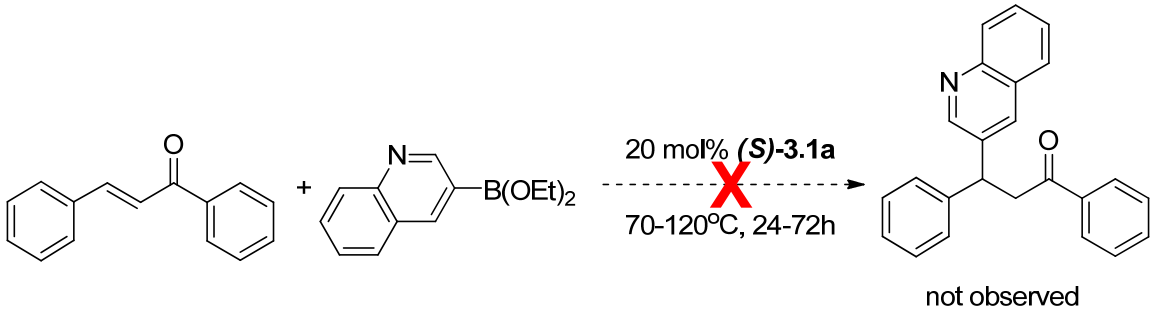
Table 3.8 Benzo[*b*]thien-2-ylboration of various enones with ***(S)*-3.1a**

Entry	R		Compound	Yield (%)[a]	er[b]
1		**3.2a**	**3.6a**	99	8.0:92.0
2		**3.2b**	**3.6b**	95	2.5:97.5
3		**3.2c**	**3.6c**	100	3.0:97.0
4		**3.2d**	**3.6d**	100	16.0:84.0
5		**3.2e**	**3.6e**	95	9.0:91.0
6		**3.2f**	**3.6f**	99	10.0:90.0

[a] Isolated yields after column chromatography. [b] Enantiomeric ratio determined by HPLC analysis, reported in order of elution. Analysis performed with 4.6 x 250 mm ChiralCel OD-H, 254 nm detection unless otherwise noted.

3.4.5 *N*-Heteroarylboronates

As mentioned previously in Section 3.1, the syntheses of the 3-pyridyl and 4-pyridyl boronates were unsuccessful for use as reagents. The diethyl quinoline-3-boronate was generated successfully as per literature procedures and exhibited better stability to reaction conditions. The synthesis and stability of the quinoline-3-boronate, shown in Scheme 3.14, can be attributed to a less basic nitrogen atom in the quinoline group. The pK_a of quinoline is 4.61 compared to 5.23 for pyridine. Another possible explanation is that substitution *ortho* to the nitrogen atom prevents coordination of the nitrogen lone pairs to the boron atom. However, after prolonged hours and at higher reaction temperatures, the quinolone-3-boronate failed to react and generate the corresponding quinoline adduct (Scheme 3.15).



Scheme 3.14

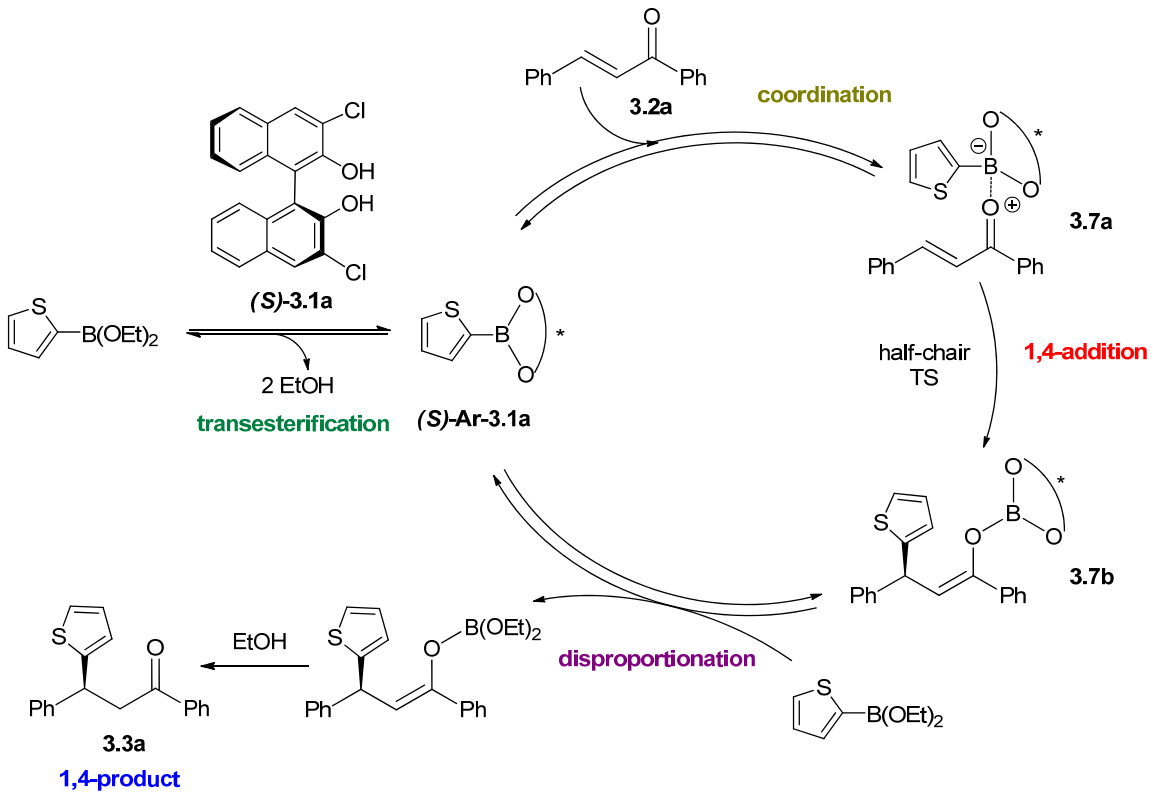
3.5 Discussion

3.5.1 Catalytic Cycle

The catalytic cycle is expected to be similar to the revised alkenylboration cycle proposed by Pellegrinet and Goodman[5] and is as follows: the diethyl arylboronate undergoes transesterification with BINOL ligand ***(S)*-3.1a** to generate the chiral arylboronate intermediate ***(S)*-Ar-3.1a** *in situ*. This Lewis acidic intermediate then coordinates strongly to the enone **3.2a** substrate, bringing the heteroaryl group into the vicinity of the enone and facilitating the enantioselective 1,4-addition of **3.7a** to **3.7b** through a half-chair transition state. Disproportionation with the achiral diethyl arylboronate releases the chiral ligand and completes the catalytic cycle. The resulting arylated adduct reacts with ethanol to give the 1,4-product **3.3a**. This cycle is represented in Scheme 3.15.

The proposed catalytic cycle predicts that the 1,4-addition occurs irreversibly, as the energy barrier to the reverse reaction is high. In alkenylborations, this energy barrier was calculated to be 33 kcal/mol. Therefore, this catalytic cycle would not explain the changing enantiomeric purity over the course of the reaction as mentioned previously in Section 3.3.5. If the results outlined in Section 3.3.5 are factual, further insights into the mechanism are necessary to proposed to account for those results.

This catalytic cycle differs slightly to the one proposed previously by the Chong group for alkynylboration, alkenylboration, and phenylboration as it adds the initial coordination step. While there are differences between a heteroaryl moiety and an alkenyl moiety, it is expected that the arguments used for alkenylboration should also be valid for heteroarylboration.



Scheme 3.15

3.5.2 Explaining Enantioselectivity

To rationalize the enantioselectivity that arises from the catalyzed reaction, the proposed transition state was examined. Inspiration is drawn from Pellegrinet and Goodman's investigation into alkenylboration as discussed in Section 2.3.1.[5]

It is proposed that the reaction proceeds through a six-membered half-chair transition state involving one boron, one oxygen, four carbons and two double bonds (Figure 3.2, shown in red). A closer look into the favoured and disfavoured transition states involving the β-*si* and β-*re* faces respectively provides a clearer picture of the enantioselectivity that arises from the reaction (Figure 3.3). The 5-membered heteroaryl group fits into the space between the chiral boronate and the enone. In the favoured transition state ***Si*-3.3b-TS**, steric interactions

between the BINOL chloro substituent and the *β*-aryl group are minimized, while the disfavoured transition state ***Re*-3.3b-TS** has a number of interactions between the *β*-aryl group and the BINOL chloro substituent. The disfavoured steric interactions are more pronounced with enones containing *ortho*-substitutents.

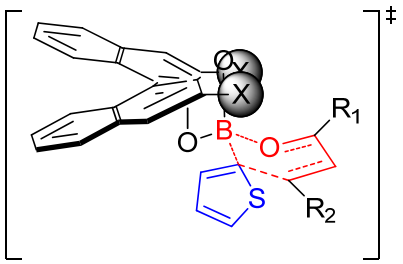


Figure 3.2 Sofa-like transition state for heteroarylboration.

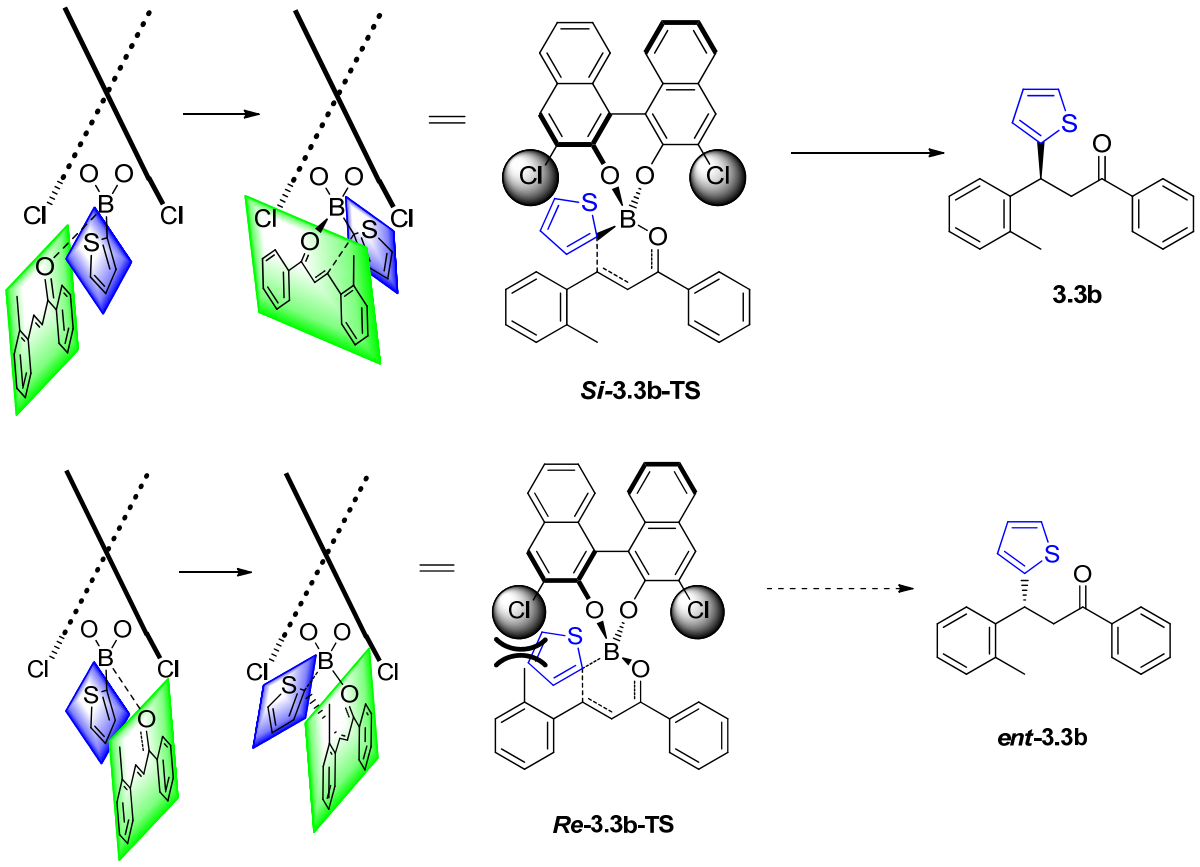


Figure 3.3 Initial coordination and favoured (a) and disfavoured (b) transition states leading to the major product **3.3b** and minor product *ent*-**3.3b**.

3.5.3 Effect of Heteroaryl Group on Reactivity and Selectivity

The addition of a 5-membered heteroaryl group was found to occur more readily than a larger 6-membered phenyl group, a finding that is supported by NMR spectroscopy (Section 3.3.3). This is attributed to the smaller size of the heteroaryl group, thus decreasing the steric interactions between itself, BINOL, and the enone in the transition state.

It appears the asymmetric heteroarylboration itself is highly selective, as the increased selectivity is not just due to decreased temperature. Upon lowering the reaction temperature from 120 °C with an enantiomeric purity of 85.0:15.0, the enantiomeric ratio at 70 °C is expected to be 86.8:12.2 based on the Gibbs free energy relationship between enantiomeric ratio and temperature. However, the enantiomeric purity of 95.6:4.4 of the product at 70 °C is much higher than expected. A possible explanation for increased reactivity involves the partial charges in the transition state: Figure 3.4 shows that the transfer of a moiety from the binaphthol / boronate complex to the enone is facilitated when the moiety transferred stabilizes the developing negative charge. It is hypothesized that a heteroaryl group stabilizes the transition state better than a phenyl group due to the presence of a heteroatom. This increased stabilization would lead to an increase in reaction rates.

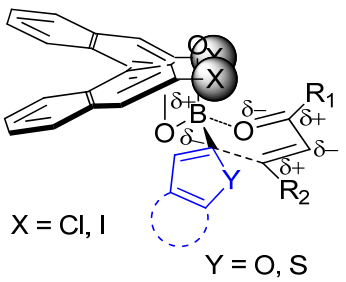


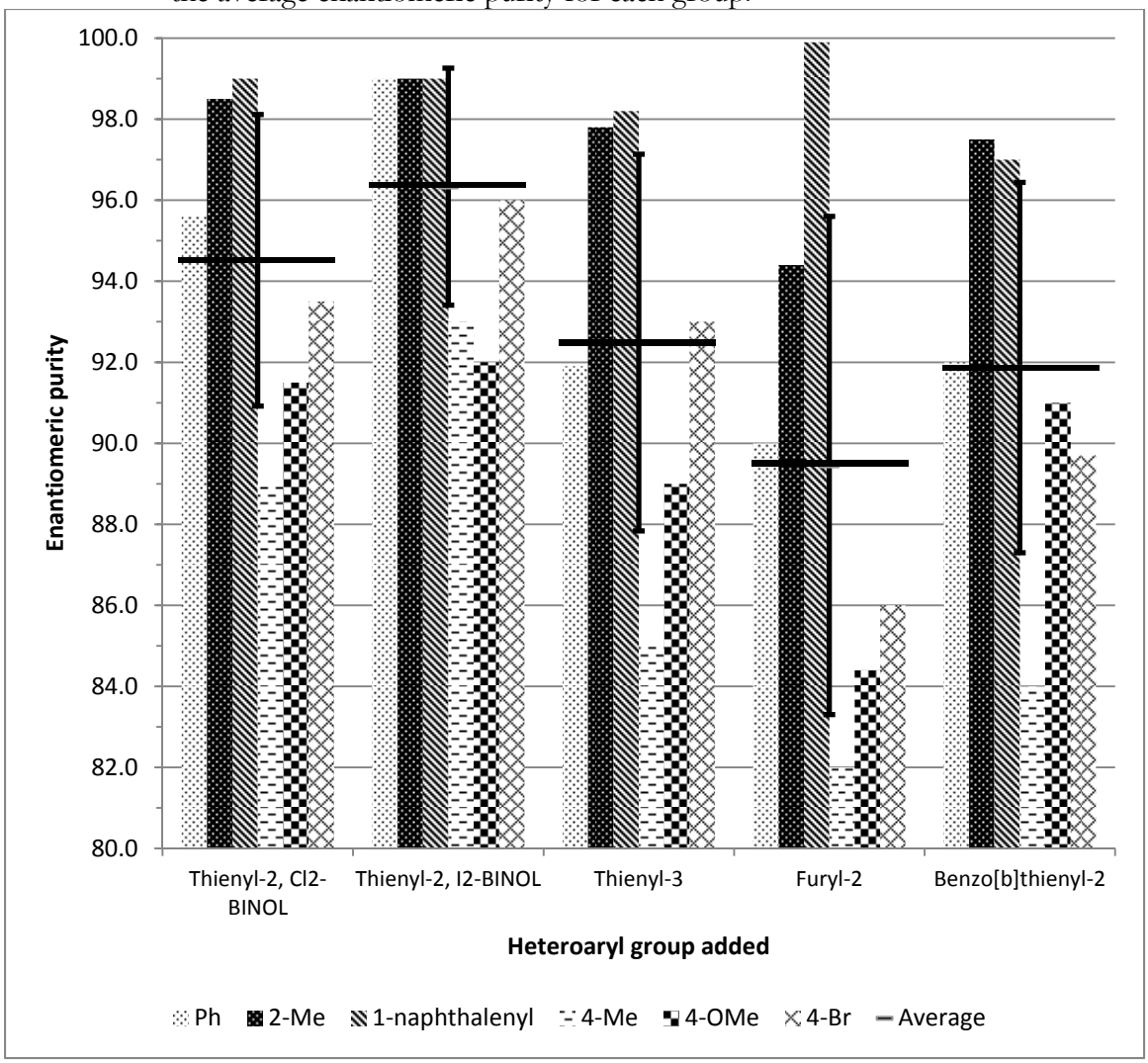
Figure 3.4 Developing partial charges in the transition state.

Chart 3.1 compares the enantiomeric purities of the 1,4-adducts from the various heteroarylboration reactions. It is evident that the thien-2-ylboronate paired with BINOL **3.1c** generates the best enantioselectivities, followed closely by the thien2-ylboronate paired with BINOL **3.1a**. The thien-3-ylboronate and the benzo[*b*]thien-2-ylboronate appear to exhibit similar selectivities. Finally, the furan-2-ylboronate exhibits the lowest selectivities of all of the heteroarylboronates.

The argument proposed with the developing partial charges in the transition state may suggest that the presence of a heteroatom at the 2-position is favoured than at the 3-position. While that may account for the slight differences between selectivities for the 2-thienyl group versus the 3-thienyl group, it does not explain the differences in selectivities between the 2-furyl group and the 2-thienyl group. In the latter comparison, the 2-furyl group would be expected to generate higher enantioselectivies. The slightly lower selectivies for the 2-benzo[*b*]thienyl group can be attributed to the steric bulk around the thienyl ring.

However, if the bars denoting the standard deviation of the obtained selectivities are taken into account, it can be seen that the selectivity differences between the groups are minor. Furthermore, results like the furan-2-ylboration of *(E)*-3-(naphthalen-1-yl)-1-phenylprop-2-en-1-one, which generated an enantiomeric ratio of 99.9:0.1, indicate that there are no obvious trends between selectivity and the heteroaryl group added.

Chart 3.1 Selectivities obtained from heteroarylboration, grouped according to the heteroaryl group added. Bars representing the standard deviation are shown for the average enantiomeric purity for each group.



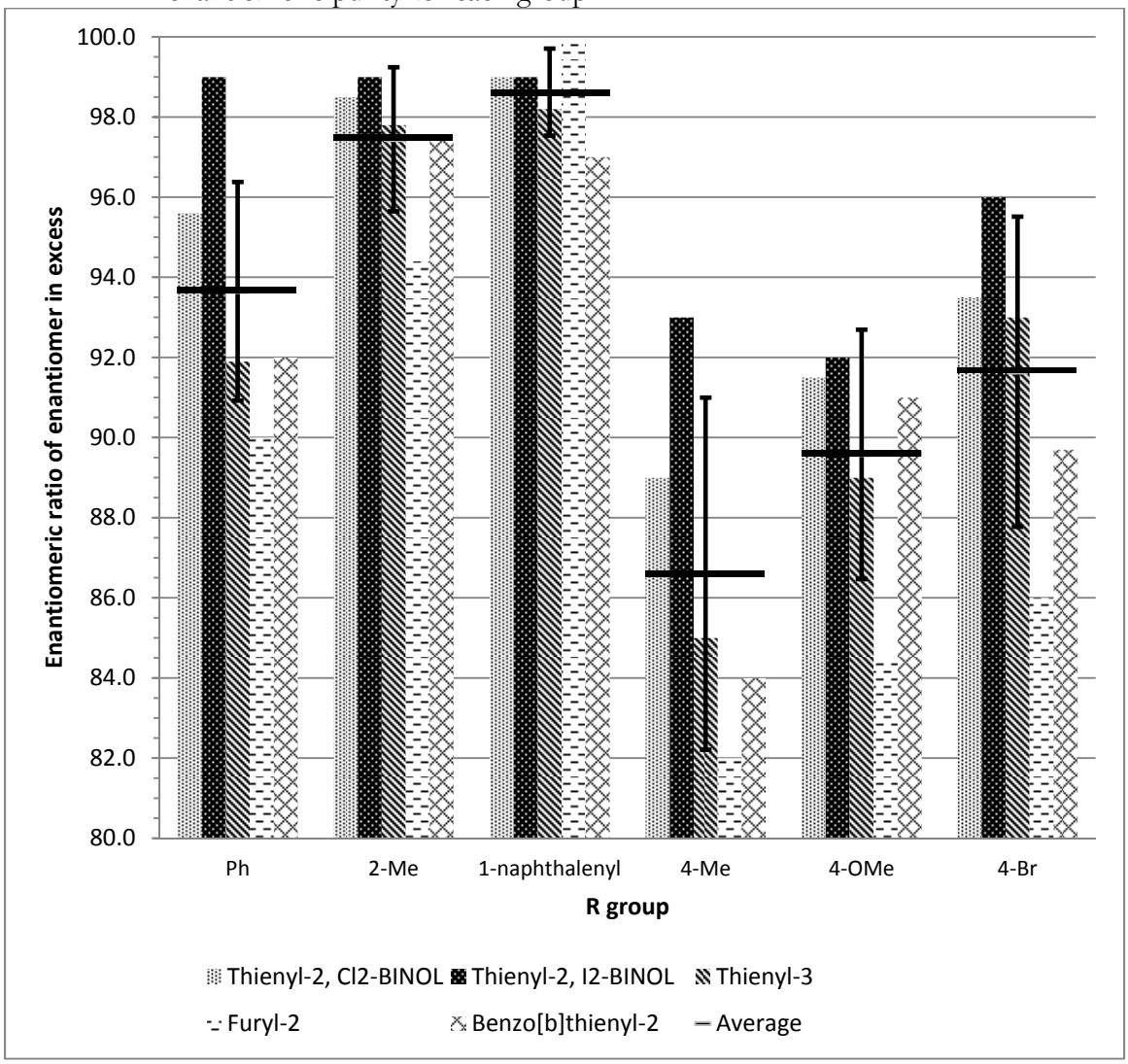
3.5.4 Effect of α,β-Unsaturated Carbonyl Compounds on Reactivity and Selectivity

Comparison of the enantioselectivities of the various heteroaryl adducts in Chart 3.2 shows generally higher enantioselectivities for *ortho*-substituted enones and lower enantioselectivites overall for *para*-substituted enones, indicating that there is a greater dependence on the substrate rather than the heteroaryl moiety. Among the *para*-substituted enones, the *p*-tolyl chalcone shows remarkably low selectivity.

It is hypothesized that the steric interactions arising from the disfavoured β-*re* transition state in *ortho*-substituted enones results in higher enantioselectivities. As discussed in Section 3.5.2, the *ortho* substituent on the enone would come into close proximity of the ligand substituent at the 3' position in the disfavoured β-*re* transition state, leading to a higher propensity of the reaction to proceed through the favoured β-*si* transition state.

It is not clear why *para*-substituted enones exhibit lower selectivities.

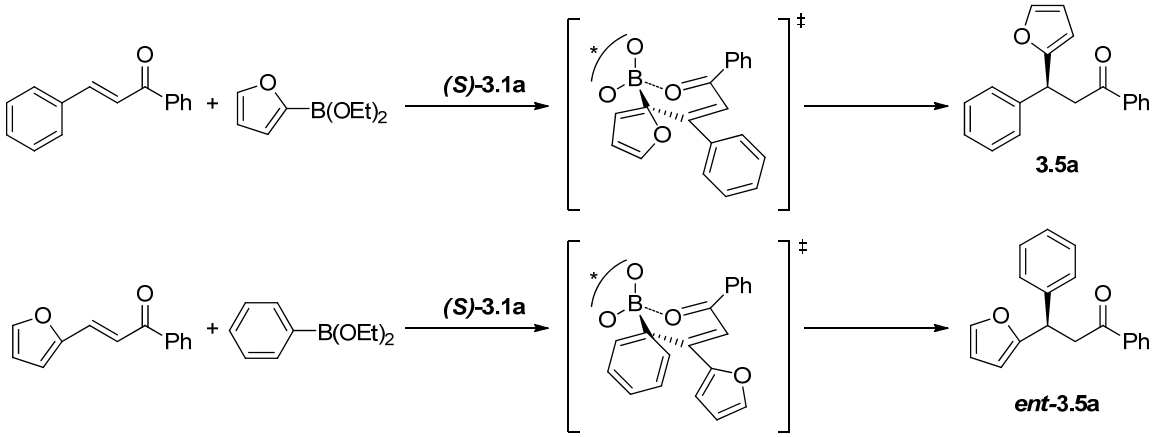
Chart 3.2 Selectivities obtained from heteroarylboration, grouped according to the R group on the enone. Bars representing the standard deviation are shown for the average enantiomeric purity for each group.



3.5.5 Determination of Enantioselectivity

The enantioselectivity of the reactions were determined by chiral HPLC analysis of adducts obtained from reactions catalyzed by racemic and *(S)*-BINOL compounds. The racemic product allows for determination of the retention time for both *(R)* and *(S)* products. Enantiomeric purity is determined with HPLC analysis (4.6 x 250 mm Chiralcel OD-H or 4.6 x 250 mm Chiralpak AD-H, 254 nm) with an eluting solvent of isopropanol:hexanes (up to 2% isopropanol).

The optical rotation of *(S)*-1,3-diphenyl-3-(furan-2-yl)propan-1-one **3.5a** was compared to literature values[1] to verify the absolute configuration of the compound. The specific rotation obtained was $[\alpha]^{25}{}_{D}$ +31.9 (94:6 er, *c* 1 , $CHCl_3$), which was opposite of the literature value $[\alpha]^{25}{}_{D}$ –36.7 (99:1 er, *c* 1 , $CHCl_3$) for the *(R)* enantiomer and indicated that the *(S)* enantiomer was formed. In addition, the major *(S)* product from the furan-2-ylboration of chalcone was found to elute first on HPLC (4.6 x 250 mm ChiralCel OD-H), while the major *(R)* product from the phenylboration of *(E)*-3-(furan-2-yl)-1-phenylprop-2-en-1-one was the second product eluted. Scheme 3.16 depicts the selectivity arising from furan-2-ylboration and phenylboration: although the aryl group adds on the same β-*Si* face of the enone, the opposite enantiomer arises.



Scheme 3.16

3.6 Conclusion

The additions of heteroaryl groups to various α,β-unsaturated enones were effective, proceeding with good yields greater than 70% and with good to excellent selectivities up to 99.9:0.1 er. Of the heteroaryl groups investigated, all of the five-membered heteroarylboronates added with ease, while the six-membered *N*-heteroarylboronates involving the 3-pyridyl and 4-pyridyl moieties could not be synthesized. Among the fused ring systems, the benzo[*b*]thien-2-ylboration proceeded effortlessly, while the quinoline-3-boration did not proceed at elevated temperatures and extended periods of time. The selectivity of the heteroarylborations were found to be dependent more on the substitution of the enone than the identity of the heteroatom, which could be explained with the proposed transition states giving rise to the favoured and disfavoured products.

The completion of this investigation expands the scope of the binaphthol / boronate catalytic system and simultaneously adds an effective complementary method of conjugate addition to those involving transition metal catalysts. In particular, the system provides a method for metal-free addition of heteroaryl groups to the β-position of acyclic enones, in contrast to the number of transition metal-catalyzed methods involving mainly cyclic enones. The binaphthol / boronate catalyst system is also found to be more effective than Sugiura's *O*-monoacyltartaric acids for the addition of the 2-furyl group to chalcone as presented in Section 1.7, with a 60% improvement over the yield and a 10% improvement over the enantioselectivity.

3.7 Experimental

3.7.1 General Experimental

All reactions were performed using flame-dried glassware under an argon atmosphere. THF and diethyl ether were freshly distilled from Na/benzophenone. Arylboronates and chiral 3,3′-disubstituted binaphthols were synthesized using procedures previously reported by Wu and Chong.[7] *(S)*-1,1'-Bi-2-naphthol was purchased from Wilmington Pharmatech Company, Newark, DE (>99% purity). IR spectra were recorded as thin films between NaCl plates using dichloroethane as solvent for both liquids and solids. ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ and are referenced to $CHCl_3$ (δ 7.24). ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ and are referenced to $CDCl_3$ (δ 77.0). ^{13}C NMR spectra for diethyl heteroarylboronates do not show the carbon bearing the boron atom due to fast quadrupolar relaxation. ^{11}B NMR spectra were recorded at 96 MHz in $CDCl_3$ and are referenced to external standard $BF_3{\cdot}OEt_2$ in $CDCl_3$ (δ 0.0). Optical rotations were recorded on a Rudolph Autopol III digital polarimeter in cells with 10 cm path length. Enantiomeric purity was determined by HPLC analysis (4.6 x 250 mm ChiralCel OD-H or ChiralPak AD-H, 254 nm detection). Heteroarylboronic acids for synthesis of arylboronates were purchased from Matrix Scientific, Columbia, SC (>95% purity).

3.7.2 General Procedure for the Preparation of Diethyl Heteroarylboronates

In a round-bottomed flask equipped with a stir bar, a soxhlet extractor containing 3Å molecular sieves, a condenser and a gas inlet, 1 equivalent of arylboronic acid was refluxed with 22 equivalents ethanol in solution with chloroform (1:2 v/v ethanol:chloroform) under argon atmosphere for 48 h unless otherwise noted. After removing the solvent *in vacuo,* the diethyl arylboronate was stored under argon and used without further purification.

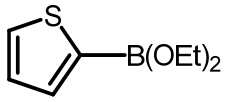
3.7.2.1 Large Scale Synthesis of Diethyl Thien-2-ylboronate

In a 500 mL round-bottomed flask equipped with a stir bar, a soxhlet extractor containing 3Å molecular sieves, a condenser and a gas inlet, thien-2-yl boronic acid (10.0 g, 0.1 mol, 1 equiv) was refluxed in 140 mL of ethanol (31 equiv) and 280 mL of chloroform under argon atmosphere for 48 h. The solvent was removed *in vacuo* (20 torr, then 0.1 torr) to yield 12.4 g of a brown oil (86% yield). The diethyl thien-2-ylboronate was stored under argon and used without further purification.

3.7.2.2 Small Scale Synthesis of Diethyl Furan-2-ylboronate

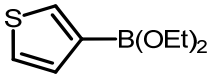
In a 250 mL round-bottomed flask equipped with a stir bar, a soxhlet extractor containing 3Å molecular sieves, a condenser and a gas inlet, furan-2-yl boronic acid (3.0 g, 26.6 mmol, 1 equiv) was refluxed in 50 mL of ethanol (32 equiv) and 100 mL of chloroform under argon atmosphere for 48 h. The solvent was removed *in vacuo* (20 torr, then 0.1 torr) to yield 3.4 g of a brown oil (76% yield). The diethyl furan-2-ylboronate was stored under argon and used without further purification.

3.7.2.2.1 Diethyl thien-2-ylboronate



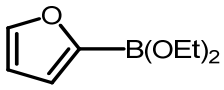
Diethyl thien-2-ylboronate was synthesized according to the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (t, J = 7.2 Hz, 6H), 4.20 (q, J = 7.0 Hz, 4H), 7.15 (d, J = 4.4 Hz, 1H), 7.21 (t, J = 4.5 Hz, 1H), 7.63 (d, J = 3.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.0, 131.2, 128.0, 60.3, 17.5. ^{11}B NMR (96 MHz, $CDCl_3$): δ 25.7.

3.7.2.2.2 Diethyl thien-3-ylboronate



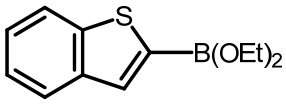
Diethyl thien-3-ylboronate was synthesized according to the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, J = 6.9 Hz, 6H), 4.06 (q, J = 6.9 Hz, 4H), 7.3 (m, 1H), 7.72 (d, J = 3.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.1, 132.1, 125.0, 60.2, 17.6. ^{11}B NMR (96 MHz, $CDCl_3$): δ 26.8.

3.7.2.2.3 Diethyl furan-2-ylboronate



Diethyl furyl-2-ylboronate was synthesized according to the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, J = 7.0 Hz, 6H), 4.15 (q, J = 6.6 Hz, 4H), 6.38 (q, J = 1.8 Hz, 1H), 6.96 (d, J = 3.4 Hz, 1H), 7.59 (d, J = 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.2, 122.5, 109.9, 59.9, 17.2. ^{11}B NMR (96 MHz, $CDCl_3$): δ 23.7.

3.7.2.2.4 Diethyl benzo[*b*]thien-2-ylboronate

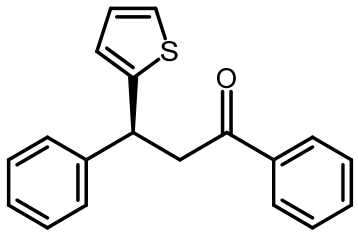


Diethyl benzo[*b*]thien-2-ylboronate was synthesized according to the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (t, J = 7.2 Hz, 6H), 4.26 (q, 2.7Hz, 4H), 7.44-7.38 (m, 2H), 7.97-7.87 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.0, 140.5, 132.8, 125.0, 124.1, 124.0, 122.2, 60.3, 17.5. ^{11}B NMR (96 MHz, $CDCl_3$): δ 26.0.

3.7.3 General Procedure for the Heteroarylboration of α,β-Unsaturated Enones

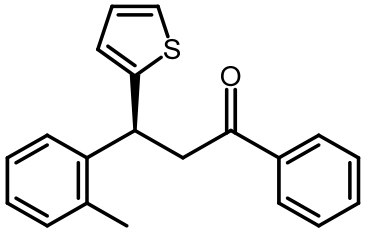
To a 2-neck 3 mL round-bottomed flask equipped with a magnetic vane, a condenser and septum, were added sequentially the enone (0.50 mmol) and BINOL (0.10 mmol). After purging for 10 minutes under argon, diethyl arylboronate (4.0 mmol) was added via syringe. The solution was stirred at 70-80 °C for 30 h. The solution was then purified by flash column chromatography (40-63 μm silica gel 60, hexanes:ether 24:1 unless otherwise noted).

3.7.3.1 *(S)*-1,3-Diphenyl-3-(thien-2-yl)propan-1-one (**3.3a**)[8]



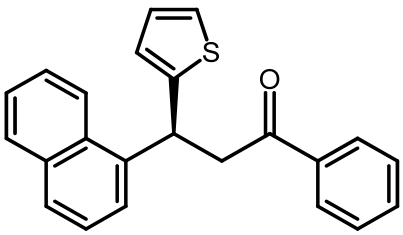
This compound is a white solid, prepared from (*E*)-chalcone, diethyl thien-2-ylboronate, and *(S)*-3,3'-dichloro-2,2'-dihydroxy-1,1'-binaphthol (91% yield) or *(S)*-3,3'-diiodo-2,2'-dihydroxy-1,1'-binaphthol (83% yield) according to the general procedure with 24 h at 70-80 °C. m.p. 75-77 °C (lit. m.p. 76-77 °C); $[\alpha]^{25}_{D}$ +9.0 (99.0:1.0 er, *c* 1 , $CHCl_3$); IR (NaCl, film): 2955, 1685, 1076, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.73 (dd, J = 7.1 Hz, 17.2 Hz, 1H), 3.74 (dd, J = 7.2 Hz, 17.2 Hz, 1H), 5.10 (dd, J = 7.1, 7.2 Hz, 1H), 6.86 (m, 1H), 6.91 (dd, J=3.5 Hz, 4.9 Hz, 1H), 7.14 (dd, J = 1.0 Hz, 5.1 Hz, 1H), 7.40 (m, 8H), 7.95 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.3, 148.3, 143.8, 136.8, 133.1, 128.6, 128.6, 128.0, 127.6, 126.8, 126.6, 124.2, 123.8, 46.1, 41.6; MS m/z (relative intensity): 292 (M^+, 13), 187 (M^+-PhCO, 17), 173 (M^+-$PhCOCH_2$, 100), 105 ($PhCO^+$, 68), 77 (Ph^+, 84). The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 99.2/0.8, flow rate = 0.8 mL/min), t_R = 25.4 min *(R)*, t_R = 29.0 min *(S)*.

3.7.3.2 *(S)*-1-Phenyl-3-(thien-2-yl)-3-(*o*-tolyl)propan-1-one (**3.3b**)



This compound is a yellow oil, prepared from (*E*)-1-phenyl-3-(*o*-tolyl)prop-2-en-1-one, diethyl thien-2-ylboronate, and *(S)*-3,3'-dichloro-2,2'-dihydroxy-1,1'-binaphthol (82% yield) or *(S)*-3,3'-diiodo-2,2'-dihydroxy-1,1'-binaphthol (87% yield) according to the general procedure with 24 h at 70-80 °C. $[\alpha]^{25}_{D}$ –17.1 (98.5:1.5 er, *c* 1 , $CHCl_3$); IR (NaCl, film): 2954, 1685, 1075, 766 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.72 (dd, *J* = 7.0 Hz, 17.3 Hz, 1H), 3.80 (dd, *J* = 7.2 Hz, 17.3 Hz, 1H), 5.27 (dd, *J* = 7.1, 7.1 Hz, 1H), 6.74 (m, 1H), 6.85 (dd, *J* = 3.6, 5.1 Hz, 1H), 7.08 (dd, *J*=1.1 Hz, 5.1 Hz, 1H), 7.15 (m, 3H), 7.28 (m, 1H), 7.43 (m, 2H), 7.54 (m, 1H), 7.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.5, 148.2, 141.8, 136.9, 136.0, 133.1, 130.7, 128.6, 128.0, 126.7, 126.5, 126.2, 124.3, 123.7, 45.9, 37.1, 19.7; MS *m/z* (relative intensity): 306 (M^+, 15), 187 (M^+-$PhCOCH_2$, 100), 105 ($PhCO^+$, 77), 77 (Ph^+, 73). The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 99.2/0.8, flow rate = 1 mL/min), t_R = 18.3 min *(S)*, t_R = 23.2 min *(R)*.

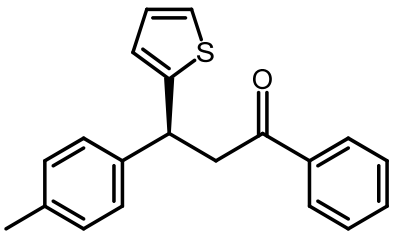
3.7.3.3 *(S)*-3-(Naphthalen-1-yl)-1-phenyl-3-(thien-2-yl)propan-1-one (**3.3c**)[8]



This compound is a white solid, prepared from *(E)*-3-(naphthalen-1-yl)-1-phenylprop-2-en-1-one, diethyl thien-2-ylboronate, and *(S)*-3,3'-dichloro-2,2'-dihydroxy-1,1'-binaphthol (97% yield)

or *(S)*-3,3'-diiodo-2,2'-dihydroxy-1,1'-binaphthol (85% yield) according to the general procedure, with 24 h at 70-80 °C at 70-80 °C. m.p. 144-146 °C (lit. m.p. 152-153 °C); $[\alpha]^{25}_{D}$ –2.6 (99.0:1.0 er, *c* 1 , $CHCl_3$); IR (NaCl, film): 2955, 1687, 1076, 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.83 (dd, *J* = 5.6 Hz, 17.4Hz, 1H), 3.99 (dd, *J* = 8.3 Hz, 17.3 Hz, 1H), 5.93 (dd, *J* = 5.7, 8.3 Hz, 1H), 6.45 (m, 2H), 7.09 (dd, *J*=1.4 Hz, 4.9 Hz, 1H), 7.48 (m, 7H), 7.74 (dd, J = 2.2 Hz, 7.2 Hz, 1H), 7.84 (m, 1H), 7.95 (m, 2H), 8.21 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.4, 148.0, 139.8, 136.9, 134.1, 133.2, 131.2, 128.9, 128.6, 128.1, 127.7, 126.7, 126.4, 125.7, 125.4, 124.8, 124.4, 123.8, 123.4, 46.1, 36.7; MS *m/z* (relative intensity): 342 (M^+, 16), 237 (M^+-PhCO, 10), 223 (M^+-$PhCOCH_2$, 100), 105 ($PhCO^+$, 53), 77 (Ph^+, 52). The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 99.2/0.8, flow rate = 0.8 mL/min), t_R = 49.8 min *(S)*, t_R = 60.1 min *(R)*.

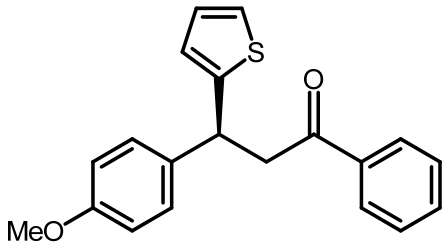
3.7.3.4 *(S)*-1-Phenyl-3-(thien-2-yl)-3-(*p*-tolyl)propan-1-one (**3.3d**)



This compound is a white solid, prepared from (*E*)-1-phenyl-3-(*p*-tolyl)prop-2-en-1-one, diethyl thien-2-ylboronate, and *(S)*-3,3'-dichloro-2,2'-dihydroxy-1,1'-binaphthol (96% yield) or *(S)*-3,3'-diiodo-2,2'-dihydroxy-1,1'-binaphthol (91% yield) according to the general procedure for 30 h at 70-80 °C. m.p. 87-88 °C; $[\alpha]^{25}_{D}$ +1.6 (93.0:7.0 er, *c* 1 , $CHCl_3$); IR (NaCl, film): 2955, 1686, 1075, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H), 3.72 (dd, *J* = 7.2 Hz, 17.1 Hz, 1H), 3.83 (dd, *J* = 7.1 Hz, 17.1 Hz, 1H), 5.07 (dd, *J* = 7.1, 7.2 Hz, 1H), 6.86 (m, 1H), 6.91 (dd, *J*=3.5 Hz, 5.0 Hz, 1H), 7.13 (m, 3H), 7.26 (m, 2H), 7.45 (m, 2H), 7.56 (m, 1H), 7.96 (m, 2H); ^{13}C

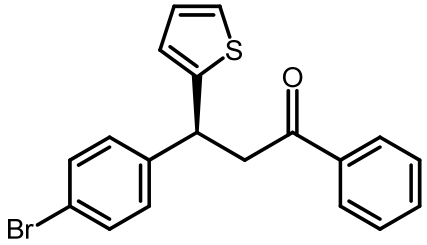
NMR (75 MHz, $CDCl_3$): δ 197.4, 148.7, 140.8, 136.9, 136.3, 133.1, 129.2, 128.6, 128.0, 127.5, 126.6, 124.1, 123.7, 46.2, 41.2, 21.0; MS *m/z* (relative intensity): 342 (M^+, 16), 237 (M^+-PhCO, 10), 223 (M^+-$PhCOCH_2$, 100), 105 ($PhCO^+$, 53), 77 (Ph^+, 52). The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 98/2, flow rate = 0.7 mL/min), t_R = 15.0 min *(S)*, t_R = 17.2 min *(R)*.

3.7.3.5 *(S)*-3-(4-Methoxyphenyl)-1-phenyl-3-(thien-2-yl)propan-1-one (**3.3e**)



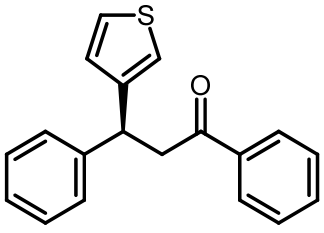
This compound is a white solid, prepared from (*E*)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one, diethyl thien-2-ylboronate, and *(S)*-3,3'-dichloro-2,2'-dihydroxy-1,1'-binaphthol (86% yield) or *(S)*-3,3'-diiodo-2,2'-dihydroxy-1,1'-binaphthol (84% yield) according to the general procedure for 48 h at 70-80 °C. m.p. 86-87 °C; $[\alpha]^{25}_D$ +4.2 (91.5:8.5 er, *c* 1 , $CHCl_3$); IR (NaCl, film): 2955, 1686, 1076, 767 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.71 (dd, *J* = 7.4 Hz, 17.0 Hz, 1H), 3.79 (s, 3H), 3.80 (dd, *J* = 7.0 Hz, 17.0 Hz, 1H), 5.04 (dd, *J* = 7.2, 7.2 Hz, 1H), 6.86 (m, 3H), 6.91 (dd, *J*=3.5 Hz, 5.0 Hz, 1H), 7.14 (dd, J = 0.8 Hz, 5.1 Hz, 1H), 7.27 (m, 2H), 7.47 (m, 2H), 7.57 (m, 1H), 7.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.5, 158.3, 148.9, 136.9, 135.9, 133.1, 128.6, 128.5, 128.0, 126.6, 124.0, 123.7, 113.9, 55.1, 46.3, 40.8; MS *m/z* (relative intensity): 322 (M^+, 4), 217 (M^+-PhCO, 1), 203 (M^+-$PhCOCH_2$, 100), 105 ($PhCO^+$, 26), 77 (Ph^+, 43). The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 99.2/0.8, flow rate = 1.0 mL/min), t_R = 28.3 min *(R)*, t_R = 32.2 min *(S)*.

3.7.3.6 *(S)*-3-(4-Bromophenyl)-1-phenyl-3-(thien-2-yl)propan-1-one (**3.3f**)



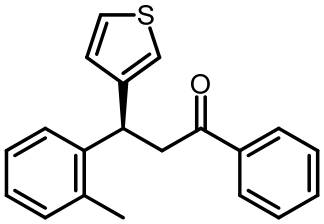
This compound is a white solid, prepared from (*E*)-3-(4-bromophenyl)-1-phenylprop-2-en-1-one, diethyl thien-2-ylboronate, and *(S)*-3,3'-dichloro-2,2'-dihydroxy-1,1'-binaphthol (91% yield) or *(S)*-3,3'-diiodo-2,2'-dihydroxy-1,1'-binaphthol (94% yield) according to the general procedure at 70-80 °C for 45 h. m.p. 79-81 °C; $[\alpha]^{25}_{D}$ –1.4 (93.5:6.5 er, *c* 1 , $CHCl_3$); IR (NaCl, film): 2955, 1687, 1073, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.67 (dd, *J* = 7.6 Hz, 17.2 Hz, 1H), 3.77 (dd, *J* = 6.8 Hz, 17.3 Hz, 1H), 5.01 (dd, *J* = 7.1, 7.2 Hz, 1H), 6.81 (m, 1H), 6.88 (dd, *J*=3.6 Hz, 5.1 Hz, 1H), 7.13 (dd, J = 1.1 Hz, 5.1 Hz, 1H), 7.19 (m, 2H), 7.42 (m, 4H), 7.55 (m, 1H), 7.91 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.0, 147.6, 142.7, 136.7, 133.2, 131.6, 129.4, 128.6, 128.0, 126.7, 124.3, 124.0, 120.6, 45.9, 40.9; MS *m/z* (relative intensity): 372 (M^+, 3), 253 (M^+-$PhCOCH_2$, 36), 251 (M^+-$PhCOCH_2$, 36), 105 ($PhCO^+$, 100), 77 (Ph^+, 81). The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 99.8/0.2, flow rate = 0.7 mL/min), t_R = 32.5 min *(S)*, t_R = 41.5 min *(R)*.

3.7.3.7 *(S)*-1,3-Diphenyl-3-(thien-3-yl)propan-1-one (**3.4a**)



This compound is a white solid, prepared in 93% yield from (*E*)-chalcone, diethyl thien-3-ylboronate, and *(S)*-3,3'-dichloro-2,2'-dihydroxy-1,1'-binaphthol according to the general procedure at 70-80 °C for 30 h. m.p. 71-73 °C; $[\alpha]^{25}_{D}$ +26.4 (93.7:6.3 er, *c* 1 , $CHCl_3$); IR (NaCl, film): 2955, 1684, 1079, 769 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.63 (dd, *J* = 7.1 Hz, 17.0 Hz, 1H), 3.77 (dd, *J* = 7.2 Hz, 17.0 Hz, 1H), 4.86 (dd, *J* = 7.2, 7.2 Hz, 1H), 6.91 (dd, *J* = 1.3 Hz, 5.0 Hz, 1H), 6.95 (m, 1H), 7.18 (m, 2H), 7.25 (m, 4H), 7.43 (m, 2H), 7.53 (m, 1H), 7.90 (m, 1H), 7.92 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.9, 144.9, 143.8, 136.9, 133.0, 128.5, 128.5, 127.9, 127.7, 127.6, 126.4, 125.6, 120.3, 45.2, 41.7; MS *m/z* (relative intensity): 292 (M^+, 3), 187 (M^+-PhCO, 30), 173 (M^+-$PhCOCH_2$, 18), 105 ($PhCO^+$, 84) 77 (Ph^+, 100). The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 98/2, flow rate = 0.8 mL/min), t_R = 16.8 min *(S)*, t_R = 20.2 min *(R)*.

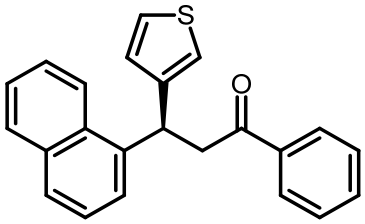
3.7.3.8 *(S)*-1-Phenyl-3-(thien-3-yl)-3-(*o*-tolyl)propan-1-one (**3.4b**)



This compound is a yellow oil, prepared in 92% yield from (*E*)-1-phenyl-3-(*o*-tolyl)prop-2-en-1-one, diethyl thien-3-ylboronate, and *(S)*-3,3'-dichloro-2,2'-dihydroxy-1,1'-binaphthol according to the general procedure at 70-80 °C for 30 h. $[\alpha]^{25}_{D}$ –25.5 (97.8:2.2 er, *c* 1 , $CHCl_3$); IR (NaCl, film): 2955, 1686, 1081, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.66 (dd, *J* = 6.9 Hz, 17.2 Hz, 1H), 3.76 (dd, *J* = 7.4 Hz, 17.1 Hz, 1H), 5.12 (dd, *J* = 7.1, 7.1 Hz, 1H), 6.90 (m, 2H), 7.19 (m, 5H), 7.45 (m, 2H), 7.56 (m, 1H), 7.95 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.0, 144.7, 141.9, 137.0, 136.0, 133.0, 130.7, 128.6, 128.0, 127.7, 126.4, 126.4, 126.1, 125.6,

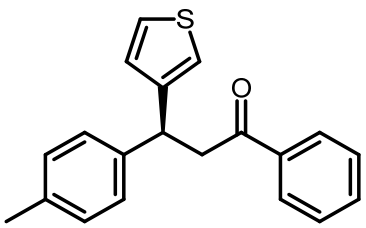
120.7, 44.9, 37.4, 19.7; MS *m/z* (relative intensity): 306 (M^+, 2), 201 (M^+-PhCO, 17), 187 (M^+-$PhCOCH_2$, 11), 105 ($PhCO^+$, 86), 77 (Ph^+, 100). The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 98/2, flow rate = 0.7 mL/min), t_R = 16.1 min *(S)*, t_R = 20.1 min *(R)*.

3.7.3.9 *(S)*-3-(Naphthalen-1-yl)-1-phenyl-3-(thien-3-yl)propan-1-one (**3.4c**)



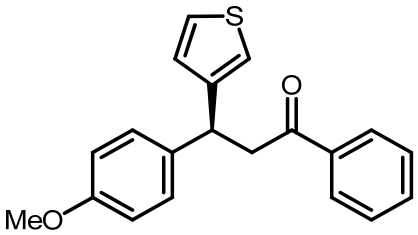
This compound is a white solid, prepared in 98% yield from *(E)*-3-(naphthalen-1-yl)-1-phenylprop-2-en-1-one, diethyl thien-3-ylboronate, and *(S)*-3,3'-dichloro-2,2'-dihydroxy-1,1'-binaphthol according to the general procedure at 70-80 °C for 54 h. m.p. 146-148 °C; $[\alpha]^{25}_D$ +33.4 (98.2:0.8 er, *c* 1 , $CHCl_3$); IR (NaCl, film): 2955, 1686, 1081, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.66 (dd, *J* = 5.4 Hz, 17.3 Hz, 1H), 3.93 (dd, *J* = 8.5 Hz, 17.3 Hz, 1H), 5.75 (dd, *J* = 5.5, 8.3 Hz, 1H), 6.95 (m, 2H), 7.19 (dd, *J* = 3.0, 4.9 Hz, 1H), 7.40 (m, 7H), 7.74 (d, *J* = 8.0, 1H), 7.85 (m, 1H), 7.95 (m, 2H), 8.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.9, 144.6, 139.9, 136.9, 134.0, 133.1, 131.3, 128.8, 128.6, 128.0, 127.9, 127.3, 126.2, 125.6, 125.5, 125.3, 124.5, 123.5, 120.8, 45.0, 37.0; MS *m/z* (relative intensity): 342 (M^+, 13), 237 (M^+-PhCO, 17), 223 (M^+-$PhCOCH_2$, 100), 105 ($PhCO^+$, 68), 77 (Ph^+, 84). The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 98/2, flow rate = 0.7 mL/min), t_R = 32.8 min *(S)*, t_R = 39.2 min *(R)*.

3.7.3.10 *(S)*-1-Phenyl-3-(thien-3-yl)-3-(*p*-tolyl)propan-1-one (**3.4d**)



This compound is a white solid, prepared in 99.7% yield from (*E*)-1-phenyl-3-(*p*-tolyl)prop-2-en-1-one, diethyl thien-3-ylboronate, and *(S)*-3,3'-dichloro-2,2'-dihydroxy-1,1'-binaphthol according to the general procedure at 70-80 °C for 54 h.. m.p. 88-90 °C; $[\alpha]^{25}_{D}$ +33.1 (85.0:15.0 er, *c* 1 , $CHCl_3$); IR (NaCl, film): 2955, 1686, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H), 3.66 (dd, *J* = 7.2 Hz, 17.0 Hz, 1H), 3.76 (dd, *J* = 7.2 Hz, 16.9 Hz, 1H), 4.88 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.00-6.95 (m, 2H), 7.24-7.11 (m, 5H), 7.48-7.43 (m, 2H), 7.58-7.53 (m, 1H), 7.97-7.95 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.0, 145.2, 140.9, 137.0, 136.0, 133.0, 129.2, 128.6, 128.0, 127.7, 127.6, 125.7, 120.3, 45.3, 41.4, 21.0. MS *m/z* (relative intensity): 306 (M^+, 2), 201 (M^+-PhCO, 15), 187 (M^+-$PhCOCH_2$, 25), 105 ($PhCO^+$, 79), 77 (Ph^+, 99). The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 98/2, flow rate = 0.7 mL/min), t_R = 15.0 min *(S)*, t_R = 17.2 min *(R)*.

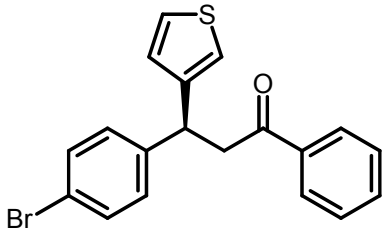
3.7.3.11 *(S)*-3-(4-Methoxyphenyl)-1-phenyl-3-(thien-3-yl)propan-1-one (**3.4e**)



This compound is a white solid, prepared in 96% yield from (*E*)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one, diethyl thien-3-ylboronate, and *(S)*-3,3'-dichloro-2,2'-dihydroxy-1,1'-binaphthol according to the general procedure. m.p. 95-97 °C; $[\alpha]^{25}_{D}$ +15.8 (89.0:11.0 er, *c* 1 ,

$CHCl_3$); IR (NaCl, film): 2955, 1686, 1080, 761 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.62 (dd, J = 7.4 Hz, 16.9 Hz, 1H), 3.71 (dd, J = 7.1 Hz, 16.9 Hz, 1H), 3.75 (s, 3H) 4.83 (dd, J = 7.2, 7.2 Hz, 1H), 6.85-6.81 (m, 2H), 6.92 (dd, J = 1.2 Hz, 5.0 Hz, 1H), 6.96-6.95 (m, 1H), 7.22-7.16 (m, 3H), 7.45-7.40 (m, 2H), 7.56-7.51 (m, 1H), 7.94-7.91 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.0, 158.1, 145.4, 137.0, 136.0, 133.0, 128.7, 128.5, 128.0, 127.7, 125.6, 120.2, 113.9, 55.1, 45.3, 41.0; MS m/z (relative intensity): 322 (M^+, 1), 217 (M^+-PhCO, 3), 203 (M^+-$PhCOCH_2$, 49), 105 ($PhCO^+$, 58), 77 (Ph^+, 100). The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 98/2, flow rate = 0.5 mL/min), t_R = 38.2 min *(S)*, t_R = 39.7 min *(R)*.

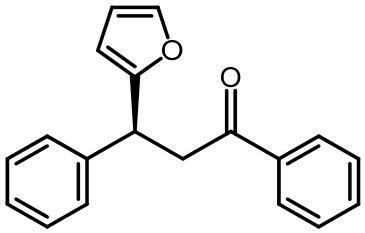
3.7.2.12 *(S)*-3-(4-Bromophenyl)-1-phenyl-3-(thien-3-yl)propan-1-one (**3.4f**)



This compound is a white solid, prepared in 99% yield (*E*)-3-(4-bromophenyl)-1-phenylprop-2-en-1-one, diethyl thien-3-ylboronate, and *(S)*-3,3'-dichloro-2,2'-dihydroxy-1,1'-binaphthol according to the general procedure at 70-80 °C for 30 h. m.p. 82-83 °C; $[\alpha]^{25}_D$ +16.5 (93.0:7.0 er, c 1 , $CHCl_3$); IR (NaCl, film): 2955, 1686, 1072, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.62 (dd, J = 7.6 Hz, 17.1 Hz, 1H), 3.72 (dd, J = 7.1 Hz, 17.1 Hz, 1H), 4.84 (dd, J = 7.2, 7.2 Hz, 1H), 6.89 (dd, J = 1.3, 5.0 Hz, 1H), 6.97-6.96 (m, 1H), 7.16-7.12 (m, 2H), 7.23 (dd, J = 2.9 Hz, 5.0 Hz, 1H), 7.46-7.37 (m, 4H), 7.57-7.52 (m, 1H), 7.94-7.91 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.5, 144.3, 142.9, 136.8, 133.2, 131.6, 129.6, 128.6, 128.0, 127.5, 126.0, 120.5, 120.3, 44.9, 41.2; MS m/z (relative intensity): 372 (M^+, 13), 267 (M^+-PhCO, 17), 265 (M^+-PhCO), 105 ($PhCO^+$,

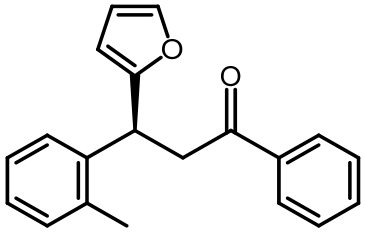
100), 77 (Ph^+, 84). The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 98/2, flow rate = 0.5 mL/min), t_R = 38.2 min *(S)*, t_R = 39.7 min *(R)*.

3.7.2.13 *(S)*-1,3-Diphenyl-3-(furan-2-yl)propan-1-one (**3.5a**)[1]



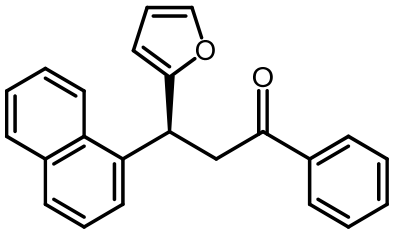
This compound was prepared from (*E*)-chalcone, diethyl furan-2-ylboronate, and *(S)*-3,3'-dichloro-2,2'-dihydroxy-1,1'-binaphthol (92% yield) or *(S)*-3,3'-diiodo-2,2'-dihydroxy-1,1'-binaphthol (91% yield) as a white solid after silica gel chromatography using hexanes:ether, 25:1. m.p. 70-72 °C (lit. m.p. 63-65 °C); $[\alpha]^{25}_D$ +31.9 (94:6 er, *c* 1 , $CHCl_3$) [lit.[1] (*R* enantiomer): $[\alpha]^{25}_D$ –36.7 (99:1 er, *c* 1 , $CHCl_3$)]; IR (NaCl, film): 2955, 1686, 1077, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.55 (dd, *J* = 7.0 Hz, 17.1 Hz, 1H), 3.81 (dd, *J* = 7.3 Hz, 17.2 Hz, 1H), 4.83 (dd, *J* = 7.2, 7.2 Hz, 1H), 6.03 (m, 1H), 6.25 (dd, *J*=1.9 Hz, 3.2 Hz, 1H), 7.38 (m, 9H), 7.93 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.4, 156.6, 141.9, 141.4, 136.8, 133.0, 128.5, 128.0, 127.7, 126.8, 110.1, 105.7, 43.5, 40.2; MS *m/z* (relative intensity): 276 (M^+, 10), 171 (M^+-PhCO, 11), 157 (M^+-$PhCOCH_2$, 100), 105 ($PhCO^+$, 86), 77 (Ph^+, 55). The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column analysis (ChiralCel OD-hexanes/*i*-PrOH = 99.2/0.8, flow rate = 0.8 mL/min), t_R = 27.0 min *(S)*, t_R = 29.1 min *(R)*.

3.7.2.14 *(S)*-1-Phenyl-3-(furan-2-yl)-3-(*o*-tolyl)propan-1-one (**3.5b**)



This compound is a yellow oil, prepared in 85% yield from (*E*)-1-phenyl-3-(*o*-tolyl)prop-2-en-1-one, diethyl furan-2-ylboronate, and *(S)*-3,3'-dichloro-2,2'-dihydroxy-1,1'-binaphthol according to the general procedure at 70-80 °C for 30 h. $[\alpha]^{25}_{D}$ +28.9 (94.4:5.6 er, *c* 1 , $CHCl_3$); IR (NaCl, film): 2956, 1686, 1074, 768 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.47 (s, 3H), 3.55 (dd, *J* = 6.7 Hz, 17.3 Hz, 1H), 3.85 (dd, *J* = 7.5 Hz, 17.3 Hz, 1H), 5.11 (dd, *J* = 7.1 Hz, 7.1 Hz, 1H), 6.97 (m, 1H), 6.26 (dd, *J* = 1.9, 3.1 Hz, 1H), 7.19 (m, 4H), 7.30 (m, 1H), 7.45 (m, 2H), 7.54 (m, 1H), 7.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.5, 156.7, 141.4, 140.0, 136.8, 135.9, 133.1, 130.6, 128.5, 128.0, 126.8, 126.7, 126.2, 110.1, 105.8, 42.9, 35.9, 19.6. MS *m/z* (relative intensity): 290 (M^+, 9), 185 (M^+-PhCO, 7), 171 (M^+-$PhCOCH_2$, 100), 105 ($PhCO^+$, 97), 77 (Ph^+, 75). The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 99.2/0.8, flow rate = 0.8 mL/min), t_R = 21.9 min *(S)*, t_R = 29.7 min *(R)*.

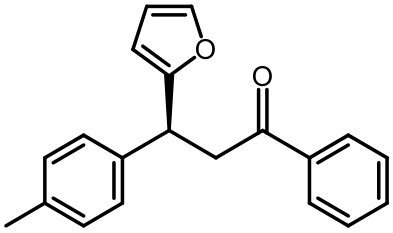
3.7.2.15 *(S)*-3-(Naphthalen-1-yl)-1-phenyl-3-(furan-2-yl)propan-1-one (**3.5c**)



This compound is a white solid, prepared in 93% yield from *(E)*-3-(naphthalen-1-yl)-1-phenylprop-2-en-1-one, diethyl furan-2-ylboronate, and *(S)*-3,3'-dichloro-2,2'-dihydroxy-1,1'-binaphthol according to the general procedure at 70-80 °C for 30 h. m.p. 132-133 °C; $[\alpha]^{25}_{D}$

+35.6 (99.9:0.1 er, *c* 1 , $CHCl_3$); IR (NaCl, film): 2955, 1686, 1075, 769 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.59 (dd, *J* = 5.1 Hz, 17.5 Hz, 1H), 4.03 (dd, *J* = 8.8 Hz, 17.5 Hz, 1H), 5.73 (dd, *J* = 5.1 Hz, 8.8 Hz, 1H), 6.05 (m, 1H), 6.27 (dd, *J* = 1.9, 3.2 Hz, 1H), 7.43 (m, 8H), 7.74 (m, 1H), 7.86 (m, 1H), 7.95 (m, 2H), 8.21 (d, *J* = 8.32 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.4, 156.3, 141.4, 138.1, 136.7, 134.0, 133.1, 131.0, 128.9, 128.5, 128.0, 127.5, 126.3, 125.6, 125.3, 124.8, 123.1, 110.2, 106.4, 43.2, 35.6; MS *m/z* (relative intensity): 326 (M^+, 10), 221 (M^+-PhCO, 6), 207 (M^+-$PhCOCH_2$, 100), 105 ($PhCO^+$, 81), 77 (Ph^+, 60). The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 99.2/0.8, flow rate = 1.0 mL/min), t_R = 27.0 min *(S)*, t_R = 36.1 min *(R)*.

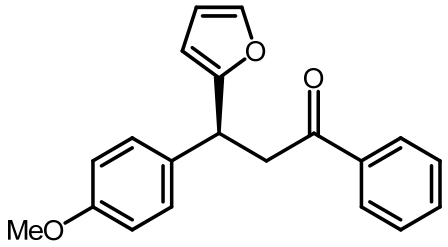
3.7.2.16 *(S)*-1-Phenyl-3-(furan-2-yl)-3-(*p*-tolyl)propan-1-one (**3.5d**)



This compound is obtained as a yellow oil, prepared in 73% yield from (*E*)-1-phenyl-3-(*p*-tolyl)prop-2-en-1-one, diethyl thien-2-ylboronate, and *(S)*-3,3'-dichloro-2,2'-dihydroxy-1,1'-binaphthol according to the general procedure. $[\alpha]^{25}_D$ +32.3 (82.0:8.0 er, *c* 1 , $CHCl_3$); IR (NaCl, film): 2955, 1686, 768 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 3H), 3.55 (dd, *J* = 7.2 Hz, 17.1 Hz, 1H), 3.82 (dd, *J* = 7.3 Hz, 17.1 Hz, 1H), 4.83 (dd, *J* = 7.2 Hz, 7.2 Hz, 1H), 6.05 (d, *J* = 3.2 Hz, 1H), 6.27 (dd, *J* = 2.0, 2.8 Hz, 1H), 7.17 (dd, *J* = 8.0 Hz, 30.3 Hz, 4H), 7.30 (m, 1H), 7.44 (m, 2H), 7.55 (m, 1H), 7.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.5, 156.9, 141.4, 138.9, 136.9, 136.3, 133.0, 129.2, 128.5, 128.0, 127.6, 110.1, 105.6, 43.6, 39.8, 21.0; MS *m/z* (relative intensity): 290 (M^+, 1), 185 (M^+-PhCO, 3), 171 (M^+-$PhCOCH_2$, 83), 105 ($PhCO^+$, 100),

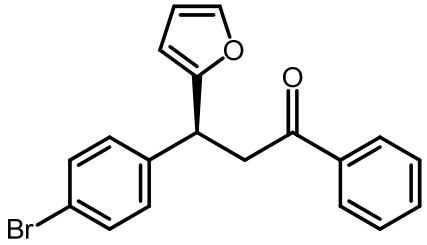
77 (Ph^+, 95). The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 99.2/0.8, flow rate = 1.0 mL/min), t_R = 21.0 min *(S)*, t_R = 24 min *(R)*.

3.7.2.17 *(S)*-3-(4-Methoxyphenyl)-1-phenyl-3-(furan-2-yl)propan-1-one (**3.5e**)



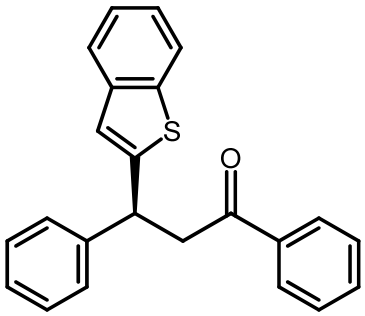
This compound is obtained as a yellow oil, prepared in 76% yield from (*E*)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one, diethyl furan-2-ylboronate, and *(S)*-3,3'-dichloro-2,2'-dihydroxy-1,1'-binaphthol according to the general procedure. $[\alpha]^{25}_{D}$ +16.1 (84.4:5.6 er, *c* 1 , $CHCl_3$); IR (NaCl, film): 2956, 1684, 1076, 766 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.53 (dd, *J* = 7.4 Hz, 17.1 Hz, 1H), 3.75 (s, 3H), 3.79 (dd, *J* = 7.0 Hz, 17.2 Hz, 1H), 4.80 (dd, *J* = 7.2 Hz, 7.2 Hz, 1H), 6.02 (d, *J* = 3.1 Hz, 1H), 6.26 (dd, *J* = 1.8, 2.9 Hz, 1H), 6.84 (m, 2H), 7.24 (m, 2H), 7.30 (m, 1H), 7.43 (m, 2H), 7.52 (m, 1H), 7.94 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.5, 158.3, 157.1, 141.4, 136.9, 134.0, 133.0, 128.8, 128.5, 128.0, 113.9, 110.1, 105.5, 55.1, 43.7, 39.5; MS *m/z* (relative intensity): 306 (M^+, 1), 201 (M^+-PhCO, 1), 187 (M^+-$PhCOCH_2$, 100), 105 ($PhCO^+$, 72), 77 (Ph^+, 94). The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 99.2/0.8, flow rate = 1.0 mL/min), t_R = 25.7min *(R)*, t_R = 28.9 min *(S)*.

3.7.2.18 *(S)*-3-(4-Bromophenyl)-1-phenyl-3-(furan-2-yl)propan-1-one (**3.5f**)



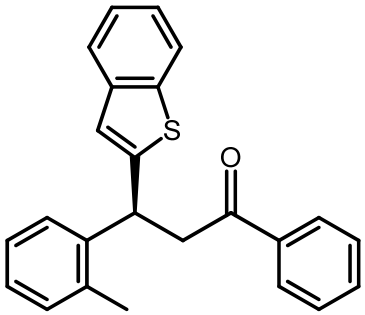
This compound is obtained as a yellow oil, prepared in 78% yield from (*E*)-3-(4-bromophenyl)-1-phenylprop-2-en-1-one, furan-2-ylboronate, and *(S)*-3,3'-dichloro-2,2'-dihydroxy-1,1'-binaphthol according to the general procedure. $[\alpha]^{25}_{D}$ +15.0 (86.0:14.0 er, *c* 1 , $CHCl_3$); IR (NaCl, film): 2955, 1687, 1074, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.80 (dd, *J* = 7.6 Hz, 17.3 Hz, 1H), 3.78 (dd, *J* = 6.7 Hz, 17.3 Hz, 1H), 4.80 (dd, *J* = 7.1 Hz, 7.1 Hz, 1H), 6.03 (m, 1H), 6.27 (dd, *J* = 1.9, 3.1 Hz, 1H), 7.19 (m, 2H), 7.30 (m, 1H), 7.42 (m, 4H), 7.54 (m, 1H), 7.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.0, 156.0, 141.6, 140.9, 136.6, 133.2, 131.6, 129.6, 128.6, 128.0, 120.6, 110.2, 105.9, 43.2, 39.6; MS *m/z* (relative intensity): 354 (M^+, 1), 237 (M^+-$PhCOCH_2$, 7), 235 (M^+-$PhCOCH_2$, 7), 105 ($PhCO^+$, 100), 77 (Ph^+, 74). The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 98.0/2.0, flow rate = 0.75 mL/min), t_R = 19.9 min *(S)*, t_R = 20.6 min *(R)*.

3.7.2.19 3-(Benzo[*b*]thien-2-yl)-1,3-diphenylpropan-1-one (**3.6a**)



This compound is a white solid, prepared from (*E*)-chalcone, diethyl benzo[*b*]thien-2-ylboronate, and *(S)*-3,3'-dichloro-2,2'-dihydroxy-1,1'-binaphthol (99% yield) or *(S)*-3,3'-diiodo-2,2'-dihydroxy-1,1'-binaphthol (94% yield) according to the general procedure. m.p. 97-98 °C; $[\alpha]^{25}_{D}$ +30.8 (93.0:7.0 er, *c* 1 , $CHCl_3$); IR (NaCl, film): 2956, 1686, 1076, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.77 (dd, *J* = 7.0 Hz, 17.3 Hz, 1H), 3.91 (dd, *J* = 7.3 Hz, 17.3 Hz, 1H), 5.15 (dd, *J* = 7.0, 7.1 Hz, 1H), 7.08 (s, 1H), 7.34 (m, 11H), 7.64 (m, 1H), 7.71 (d, *J* = 7.61 Hz, 1H), 7.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.1, 149.1, 143.0, 139.7, 139.3, 136.8, 133.2, 128.6, 128.6, 128.0, 127.7, 127.0, 124.1, 123.7, 123.1, 122.0, 120.7, 45.5, 42.1; MS *m/z* (relative intensity): 342 (M^+, 12), 237 (M^+-PhCO, 55), 223 (M^+-$PhCOCH_2$, 55), 103 ($PhCO^+$, 100), 77 (Ph^+, 76). The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 99.2/0.8, flow rate = 1.0 mL/min), t_R = 34.6 min *(R)*, t_R = 49.7 min *(S)*.

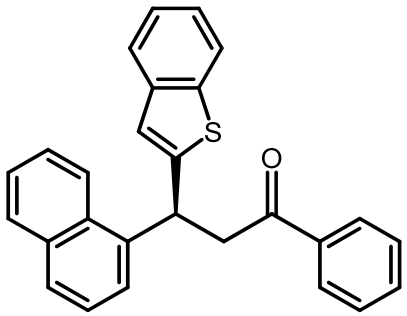
3.7.2.20 *(S)*-3-(Benzo[*b*]thien-2-yl)-1-phenyl-3-(*o*-tolyl)propan-1-one (**3.6b**)



This compound is a yellow oil, prepared in 95% yield from (*E*)-1-phenyl-3-(*o*-tolyl)prop-2-en-1-one, diethyl benzo[*b*]thien-2-ylboronate, and *(S)*-3,3'-dichloro-2,2'-dihydroxy-1,1'-binaphthol according to the general procedure. $[\alpha]^{25}_{D}$ –10.0 (97.5:2.5 er, *c* 1 , $CHCl_3$); IR (NaCl, film): 2955, 1686, 1075, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.55 (s, 3H), 3.86 (dd, *J* = 6.9 Hz, 17.5 Hz, 1H), 3.96 (dd, *J* = 7.2 Hz, 17.5 Hz, 1H), 5.46 (dd, *J* = 7.0 Hz, 7.0 Hz, 1H), 7.07 (s, 1H), 7.61-7.26 (m, 9H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 8.05-8.02 (m, 2H); ^{13}C NMR (75

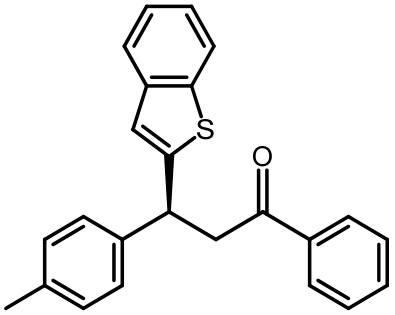
MHz, $CDCl_3$): δ 197.3, 149.2, 141.2, 139.8, 139.4, 136.9, 136.3, 133.3, 130.9, 128.7, 128.1, 127.0, 126.5, 126.4, 124.2, 123.8, 123.1, 122.1, 121.0, 45.4, 37.8, 19.8; MS *m*/*z* (relative intensity): 356 (M^+, 1), 251 (M^+-PhCO, 6), 237 (M^+-$PhCOCH_2$, 6), 105 ($PhCO^+$, 68), 77 (Ph^+, 76). The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 98/2, flow rate = 1 mL/min), t_R = 18.1 min *(R)*, t_R = 23.4 min *(S)*.

3.5.2.21 *(S)*-3-(Benzo[*b*]thien-2-yl)-3-(naphthalen-1-yl)-1-phenylpropan-1-one (**3.6c**)



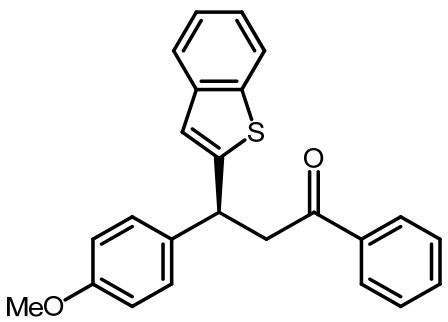
This compound is a white solid, prepared in 100% yield from *(E)*-3-(naphthalen-1-yl)-1-phenylprop-2-en-1-one, diethyl benzo[*b*]thien-2-ylboronate, and *(S)*-3,3'-dichloro-2,2'-dihydroxy-1,1'-binaphthol according to the general procedure. m.p. 148-149 °C; $[\alpha]^{25}_D$ +53.8 (97.0:3.0 er, *c* 1 , $CHCl_3$); IR (NaCl, film): 2955, 1686, 1073, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.88 (dd, *J* = 5.6 Hz, 17.6 Hz, 1H), 4.10 (dd, *J* = 8.2, 17.6 Hz, 1H), 7.02 (dd, *J* = 6.0, 7.6 Hz, 1H), 7.08 (s, 1H), 7.28-7.21 (m, 2H), 8.00-7.42 (m, 14H), 8.27 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.1, 148.9, 139.7, 139.3, 138.9, 136.7, 134.1, 133.3, 131.2, 128.9, 128.6, 128.1, 127.8, 126.4, 125.7, 125.3, 124.5, 124.1, 123.7, 123.4, 123.1, 122.0, 121.3, 45.5, 37.3; MS *m*/*z* (relative intensity): 342 (M^+, 13), 237 (M^+-PhCO, 17), 223 (M^+-$PhCOCH_2$, 100), 105 ($PhCO^+$, 68), 77 (Ph^+, 84). The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 98/2, flow rate = 0.8 mL/min), t_R = 40.7 min *(R)*, t_R = 61.4 min *(S)*.

3.7.2.22 3-(Benzo[*b*]thien-2-yl)-1-phenyl-3-(*p*-tolyl)propan-1-one (**3.6d**)



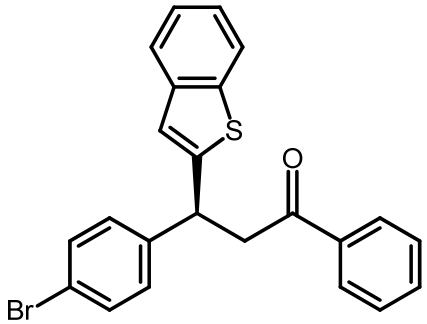
This compound is a white solid, prepared in 100% yield from (*E*)-1-phenyl-3-(*p*-tolyl)prop-2-en-1-one, diethyl benzo[*b*]thien-2-ylboronate, and *(S)*-3,3'-dichloro-2,2'-dihydroxy-1,1'-binaphthol according to the general procedure. m.p. 105-106 °C; $[\alpha]^{25}_{D}$ +16.1 (84.0:16.0 er, *c* 1 , $CHCl_3$); IR (NaCl, film): 2955, 1685, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.37 (s, 3H), 3.80 (dd, *J* = 7.1 Hz, 17.4 Hz, 1H), 3.94 (dd, *J* = 7.2 Hz, 17.3 Hz, 1H), 5.17 (dd, *J* = 7.1, 7.1 Hz, 1H), 7.12 (s, 1H), 7.26 (m, 6H), 7.47 (m, 2H), 7.58 (m, 1H), 7.68 (m, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 8.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.2, 149.5, 140.1, 139.8, 139.4, 136.8, 136.6, 133.2, 129.4, 128.6, 128.1, 127.7, 124.1, 123.8, 123.1, 122.1, 120.6, 45.6, 41.8, 21.1; MS *m*/*z* (relative intensity): 356 (M^+, 1), 251 (M^+-PhCO, 6), 237 (M^+-$PhCOCH_2$, 13), 105 ($PhCO^+$, 38), 77 (Ph^+, 70). The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 98/2, flow rate = 1.0 mL/min), t_R = 24.2 min *(R)*, t_R = 37.6 min *(S)*.

3.7.2.23 3-(Benzo[*b*]thien-2-yl)-3-(4-methoxyphenyl)-1-phenylpropan-1-one (**3.6e**)



This compound is a white solid, prepared in 95% yield from (*E*)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one, diethyl benzo[*b*]thien-2-ylboronate, and *(S)*-3,3'-dichloro-2,2'-dihydroxy-1,1'-binaphthol according to the general procedure. m.p. 107-108 °C; $[\alpha]^{25}_{D}$ +32.2 (91.0:9.0 er, *c* 1 , $CHCl_3$); IR (NaCl, film): 2955, 1686, 1066, 768 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.77 (dd, *J* = 7.2 Hz, 17.2 Hz, 1H), 3.78 (s, 3H), 3.90 (dd, *J* = 7.1 Hz, 17.2 Hz, 1H), 5.13 (dd, *J* = 7.1, 7.1 Hz, 1H), 6.91-6.88 (m, 2H), 7.10 (s, 1H), 7.35-7.23 (m, 4H), 7.48-7.43 (m, 2H), 7.59-7.54 (m, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 8.01-7.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.2, 158.5, 149.8, 139.8, 139.4, 136.8, 135.2, 133.2, 128.8, 128.6, 128.1, 124.2, 123.8, 123.1, 122.1, 120.5, 114.1, 55.2, 45.7, 41.5; MS *m/z* (relative intensity): 372 (M^+, 1), 253 (M^+-$PhCOCH_2$, 16), 105 ($PhCO^+$, 35), 77 (Ph^+, 78). The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 98/2, flow rate = 1.0 mL/min), t_R = 28.0 min *(S)*, t_R = 52.8 min *(R)*.

3.7.2.24 *(S)*-3-(Benzo[*b*]thien-2-yl)-3-(4-bromophenyl)-1-phenylpropan-1-one (**3.6f**)



This compound is a white solid, prepared in 99% yield from (*E*)-3-(4-bromophenyl)-1-phenylprop-2-en-1-one, diethyl benzo[*b*]thien-2-ylboronate, and *(S)*-3,3'-dichloro-2,2'-dihydroxy-1,1'-binaphthol according to the general procedure. m.p. 105-107 °C; $[\alpha]^{25}_{D}$ +22.3 (89.7:10.3 er, *c* 1 , $CHCl_3$); IR (NaCl, film): 2955, 1687, 1073, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.74 (dd, *J* = 6.8 Hz, 16.4 Hz, 1H), 3.87 (dd, *J* = 6.3 Hz, 17.3 Hz, 1H), 5.10 (dd, 1H), 7.73-7.06 (m, 14H),

7.96 (d, J = 6.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.7, 148.3, 142.0, 139.6, 139.3, 136.6, 133.3, 131.7, 129.5, 128.7, 128.0, 124.3, 123.9, 123.2, 122.1, 120.9, 45.3, 41.6; MS m/z (relative intensity): 372 (M^+, 13), 267 (M^+-PhCO, 17), 265 (M^+-PhCO), 105 ($PhCO^+$, 100), 77 (Ph^+, 84). The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 98/2, flow rate = 0.8 mL/min), t_R = 29.0 min *(S)*, t_R = 45.7 min *(R)*.

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Chapter 1 References

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