Design and Synthesis of 3,3'-Disubstituted-binaphthyl Alkynyl Boron Reagents for Asymmetric Conjugate Addition of Alkynyl Groups to Enones and 1,2-Addition to Aldehydes

by

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Abstract

The preparation of a variety of 3,3'-disubstituted-2,2'-dihydroxy-1,1'-binaphthyls is described and their utility in the preparation of lithium binaphthylisopropylalkynylborates is demonstrated. The use of the resulting boronates in asymmetric conjugate addition and 1,2-addition is described.

A number of 3,3'-diaryl-2,2'-bis(methoxymethoxy)-1,1'-binaphthyls were prepared by Suzuki cross-coupling methodology in excellent yields from 3,3'-dibromo-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl. Preparation of the dibromide by the DoM method, followed by trapping with $BrCl_2CCCl_2Br$, is successful and practical. 3,3'-Dicyanated binaphthyl can be prepared by trapping the dilithiated intermediate in the DoM process by phenyl cyanate. 3,3'-Bis(trifluoromethyl) binaphthyl was effectively prepared by the reaction between methyl fluorosulphonyldifluoroacetate and 3,3'-diiodo-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl.

Attempts to obtain *B*-methoxybinaphtholborane by a few related literature methods were unsuccessful. Trials on the preparation of binaphtholborane also failed.

Lithium binaphthylisopropylalkynylborate was prepared successfully using a simple procedure that required only one step from binaphthol and lithium alkynyltriisopropylborate. The procedure can be used as a general method to synthesize lithium (3,3'-disubstituted-binaphthyl)-isopropyl-alkynyl-boronate. Decomposing the boronates by $BF_3{\cdot}OEt_2$ or HCl produced the corresponding alkynylbinaphthylboronates. However, the borates are unstable after isolation from the reaction solution. It was possible to employ the boronates *in situ* in the asymmetric syntheses such as conjugate addition to enones and 1,2-addition to aldehydes.

Asymmetric conjugate addition of alkynyl groups to prochiral enones with chiral boronates was performed. A variety of alkynyl binaphthyl boronates with different groups on 3,3'-positions of the binaphthyl moiety were utilized in the conjugate addition. All enantiomeric excesses of products from the addition with the chiral boron reagents were significantly increased by changing ligands from (*R*)-2,2'-binaphthyl to (*R*)-3,3'-diaryl-2,2'-binaphthyl groups. The boronates having iodo and trifluoro groups on 3,3'-positions of binaphthyl moiety provided enantioselectivities comparable to those observed with the 3,3'-diarylbinaphthyl boronates.

The enantioselectivity of the conjugate addition was found to be dependent on the size and electronegativity of the 3,3'-substituents, as well as on the connectivity between the binaphthyl and the substituents. Electron withdrawing groups on 3,3'-positions of binaphthyl moiety increased the rate of the conjugate addition. Both steric and electronic differences of the substituents attached to β carbon of enones were found to be significant in determining the steric outcome of the conjugate addition reaction.

The asymmetric alkynylation of hydrocinnamaldehyde and isobutyraldehyde was performed successfully using several boronates. However, the 1,2-adduct yields were low and enantioselectivities were poor. Nevertheless, these initial results provide the basis for further improvement of the reaction.

HPLC with a Chiracel OD column was found to be an efficient analytical tool in the determination of enantiomeric excesses of the 1,4-adducts and 1,2-adducts.

Acknowledgements

I would like to take this opportunity to express my deepest thanks to Professor Michael Chong for his guidance, patience, and support during my studies. He is always available for helpful discussion, and an extraordinary supervisor whom I have ever met.

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I would like to thank everyone, the present and former, in the Chong Group for their help, support and companionship. I will remember these enjoyable days in the Group always.

Finally, my special thanks are due to my wife Jin for her love, patience, encouragement, and support.

For my wife Jin, my parents and my daughter Shirley.

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List of Abbreviations and Tradenames

Ac	acetyl
acac	acetonylacetonate
anal.	analysis
approx.	approximate
aq	aqueous
Ar	aromatic or aryl
ATBN	aluminum tris[3-phenyl-2-(1,1'-binaphthoxide)]
ATBN-F	aluminum tris[3-(4-fluorophenyl)-2-(1,1'-binaphthoxide)]
9-BBN	9-borabicyclo[3.3.1]nonane
BINAL-H	2,2'-(1,1'-binaphthoxy)aluminum hydride
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	2,2'-dihydroxy-1,1'-binaphthyl
BLA	Bronsted acid assisted chiral Lewis acid
Bn	benzyl
Boc	*t*-butoxycarbonyl
bp	boiling point
br	broad
BTF	benzotrifluoride
Bu	butyl
c	cyclo
c	concentration (g per 100 mL)

Calcd	calculated
cat	catalytic
d	doublet
DAIB	3-exo-(dimethylamino)isoborneol
de	diastereomeric excess
DiBAH	diisobutylaluminum hydride
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane
DMAP	4-*N*,*N*-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DoM	directed ortho metallation
E^+	electrophile
EDG	electron donating group
ee	enantiomeric excess
EI	electron impact
eq or equiv	equivalent(s)
Et	ethyl
ether	diethyl ether
EWG	electron withdrawing group
FT-IR	Fourier transform infrared spectroscopy
GC	gas chromatography

GC-MS	gas chromatography and mass spectrometry
HMPA	hexamethylphosphoric triamide
HPLC	high performance (or pressure) liquid chromatography
Hz	Hertz
i	iso
IR	infrared
J	spin coupling constant
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
lit	literature
m	multiplet
M	metal [e.g. $B(OR)_2$, ZnX, SnR_3 or MgX]
M	molar
max	maximum
*m*CPBA	*m*-chloroperbenzoic acid
Me	methyl
m/e	mass/charge
min	minute(s)
mL	millilitre
mmol	millimole
mol	mole
MOM	methoxymethyl
mp	melting point

MS	mass spectrometry
MVK	methyl vinyl ketone
n	normal
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
Nu	nucleophile
o	*ortho*
oct	octet
PDC	pyridinium dichromate
pet ether	petroleum ether (60-80 °C fraction)
Ph	phenyl
ppm	parts per million
Pr	propyl
PTSA	*p*-toluenesulfonic acid
q	quartet
quant	quantitative
quint	quintet
R	alkyl group
R_f	retention factor
R_t	retention time
rt	room temperature
s	singlet

s	secondary
SEM	2-trimethylsilylethoxymethyl
sept	septet
S_N2	substitution nucleophilic bimolecular
t	triplet
t	tertiary
TBDMS or TBS	*t*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	trimethylsilyl
Tol	tolyl
TPDDOL	α,α,α',α'-tetraphenyl-1,3-dioxolan-4,5-dimethanol
triflate	trifluoromethanesulfonate
Un	unsaturated group
UV	ultraviolet spectroscopy
wt	weight
xs	excess

CHAPTER 1. INTRODUCTION

1.1. Purpose and Scope of the Thesis

Cuprates are the most common reagents for Michael-type reactions.[1,2] Numerous asymmetric conjugate additions using cuprate reagents have been reported in the literature.[1,2a-d,f] However, asymmetric alkynyl 1,4-addition has not been seen in the literature because alkynyl groups can not be transferred using cuprates due to the tight back bonding between the d electrons of copper and π^* orbitals of acetylenic groups.[2f] Thus, asymmetric alkynyl 1,4-addition still remains a challenge for organic chemists. This thesis will describe a successful rational approach which has permitted the design and preparation of a new class of boron reagents that can be used to transfer alkynyl groups to enones in a stereoselective way. The synthesis of some useful binaphthyl ligands, preparation of boron reagents from these ligands, and discussion of 1,4-addition using these reagents to achieve high stereoselectivities will be presented. The ability of these reagents to effect 1,2-additions to aldehydes will also be discussed.

1.2. Binaphthyl Reagents Used in Asymmetric Synthesis

1.2.1. C_2 Symmetry

As pointed out by Kagan and Dang in 1972,[3] when a C_2 ligand is bound to a metal center, the reagent feels the same chiral situation, independent of its approach to the substrate. In other words, the presence of a C_2 symmetry axis within the chiral auxiliary can serve the very important function of dramatically reducing the number of possible competing, diastereomeric transition states. For example the enantioselective alkylation of cyclohexanone through chiral enamines has been carried out by Yamada *et al.*[4,5] using various proline esters. The use of proline esters yielded alkylation products of low enantiomeric excess in the range of 10 to 30%. The use of (+)-*trans*-2,5-dimethylpyrrolidine by Whitesell and Felman gave much higher ee's (80-90%).[6] Whitesell and Felman[7] pointed out that enamine formed from the reaction of cyclohexanone and (*S*)-methyl proline yields a compound which can exist in two distinct conformations (A & B) (Figure 1.1). Thus there are four possible transition states for alkylation. Only one is greatly disfavored and so the overall facial differentiation is small. However, the introduction of a C_2 symmetric amine such as (+)-*trans*-2,5-dimethylpyrrolidine as a chiral auxiliary in this reaction allows the formation of the enamine in which there is only one conformation (Figure 1.2) and only two possible transition states, one of which is favored. Alkylation proceeds mainly *via* one pathway, ensuring high stereoselectivity.

Figure 1.1. Alkylation of chiral enamines formed from (S)-methyl proline and cyclohexanone.

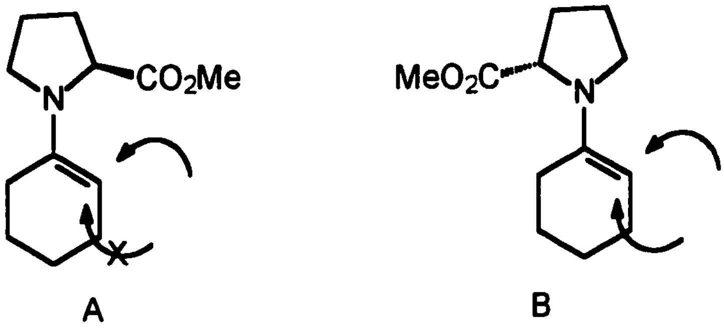
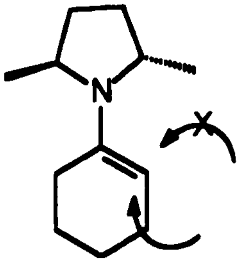


Figure 1.2. Alkylation of chiral enamines formed from (+)-trans-2,5-dimethylpyrrolidine and cyclohexanone.



The above examples point out that C_2 symmetric chiral auxiliaries can be of great help in obtaining optically active compounds with high enantioselectivity. In fact, a large collection of molecules with C_2 symmetry have been developed and many such molecules have been used as chiral auxiliaries.[8] A very useful group of such chiral auxiliaries is the binaphthyl family. They have shown excellent discrimination and are useful synthetically in directing various chemical reactions.

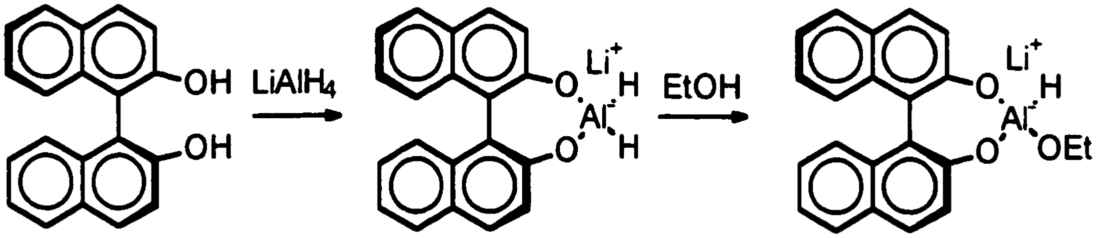
1.2.2. Some Advantages of Binaphthyl Groups

The binaphthyl moiety is very useful in that it is axially chiral, exceedingly stable and has shown a strong directing ability in a variety of reactions. At least four advantages of binaphthyl ligands are: (1) A variety of chemical transformations and reactions can be performed on the ligand without loss of stereochemical integrity. (2) Binaphthyls containing a variety of heteroatoms at the 2 and 2' positions can be synthesized. This allows tailoring of the electronic properties by choosing the appropriate substituent. (3) Binaphthyls have shown themselves to be optically stable under extreme reaction conditions. Dixon *et al.* observed that the specific rotation of 2,2'-dimethyl-1,1'-binaphthyl remained unchanged after 40 h in 1-methylnaphthalene solution at 240 °C.[9] The compound has a calculated energy barrier to configurational inversion of 34.9 kcal/mol.[10] (4) It is possible to introduce substitutions at the 3 and 3' positions of binaphthyls so that the stereo induction can be enhanced significantly.[11,12]

1.2.3. Some Typical Examples of Stereoselective Reactions Using Binaphthyl Reagents

The first successful use of binaphthyl reagent might be the use of BINAL-H (**1.1**), introduced by Noyori *et al.* in 1979.[13] The reaction of optically pure 2,2'-dihydroxy-1,1'-binaphthyl (**1.2**) with $LiAlH_4$ in a ratio of 1:1 (Scheme 1.1) provides an adduct (**1.3**); the successive reaction with an achiral alcohol gives rise to the reducing species in solution, BINAL-H. When the reagent is used in the enantioselective reduction of alkyl aryl ketones, the corresponding secondary alcohols are obtained in ee's up to 100%. The proposed mechanism for the reduction suggests that not only steric interactions are responsible for the stereoselectivity but also electronic effects play an important role.[14] Specifically, the transition state (B) possessing axial-Un and equatorial-R groups is destabilized by the substantial n-π type electronic repulsion between the axially oriented binaphthoxyl oxygen and the unsaturated moiety (Figure 1.3). The reaction proceeds predominantly *via* the transition state (A).

Scheme 1.1

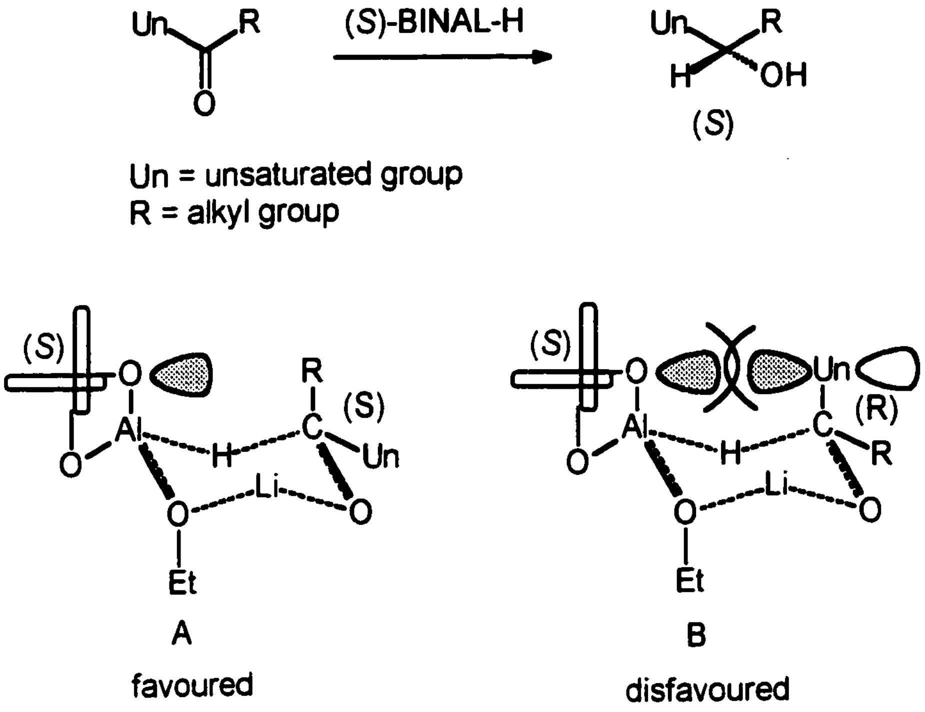


1.2

1.3

(*S*)-BINAL-H
1.1

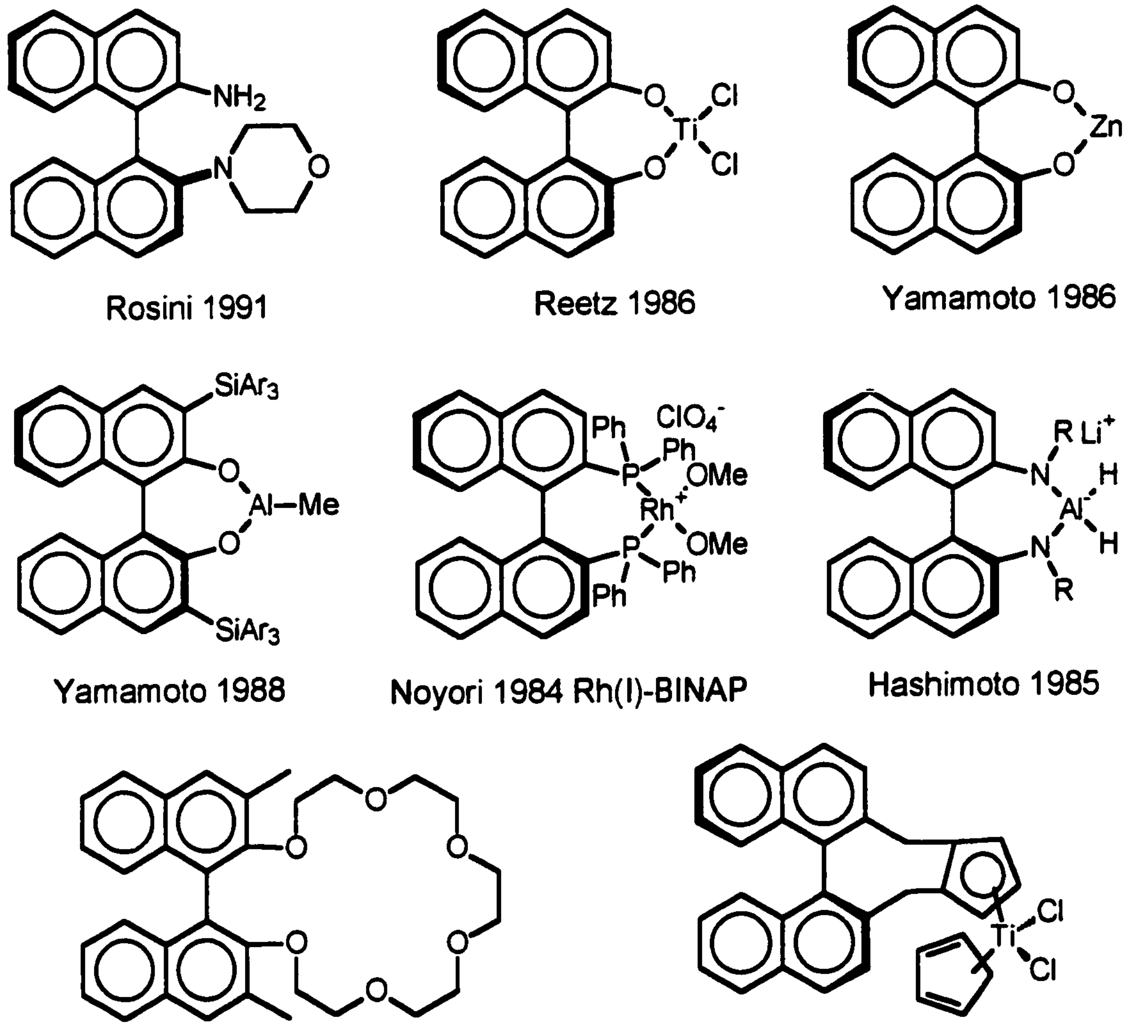
Figure 1.3. Proposed mechanism of reduction of alkyl and aryl ketones by BINAL-H.



The utility and importance of binaphthyl reagents as chiral auxiliaries in enantioselective reactions have been reviewed by Rosini *et al.*[15] The review provides a description on a variety of 2,2'-disubstituted-1,1'-binaphthyls following a classification on the basis of the nature of the substituents on the 2 and 2' positions. Various binaphthyl based reagents[12,16a-g] are shown in Figure 1.4.

Since the review, more novel binaphthyl based reagents have been reported in the literature. Some of them are summarized below.

Figure 1.4. Some binaphthyl based reagents listed by author and date of first use.



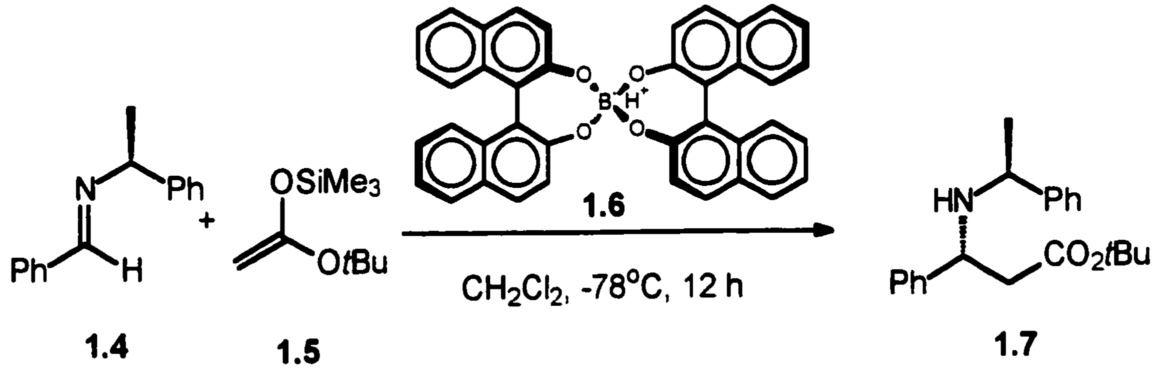
Rosini 1991 Reetz 1986 Yamamoto 1986

Yamamoto 1988 Noyori 1984 Rh(I)-BINAP Hashimoto 1985

Cram 1978 Halterman 1989

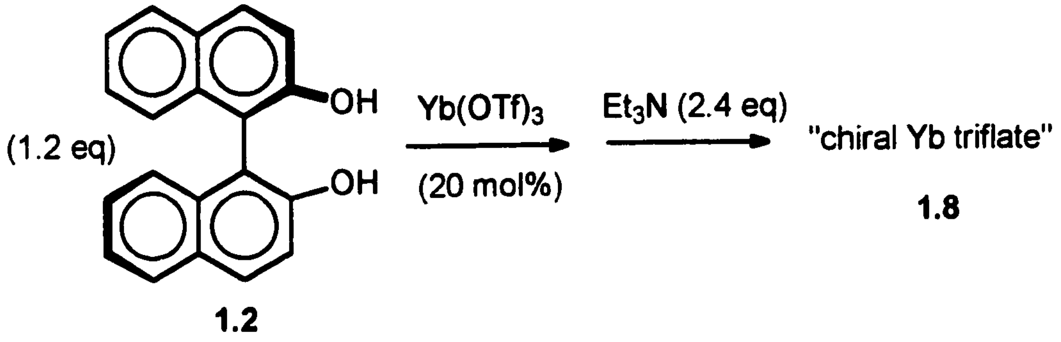
A new type of chiral promoter for double asymmetric induction of aza Diels-Alder and aldol-type reactions of imines is prepared from trialkyl borates and optically pure binaphthol.[17] The aldol-type reactions of a number of *N*-benzhydrylimines derived from aromatic aldehydes with the ketene silyl acetal derived from *tert*-butyl acetate mediated by the Bronsted acid assisted chiral Lewis acid (BLA) afford *β*-amino acid esters with high enantioselectivity. Reaction of (*S*)-**1.4** with trimethylsilyl ketene acetal **1.5** derived from *tert*-butyl acetate in the presence of (*R*)-**1.6** (1 equiv) at -78 °C for 12 h provided the corresponding aldol-type adduct **1.7** in 63% yield with 94% de (Scheme 1.2).

Scheme 1.2

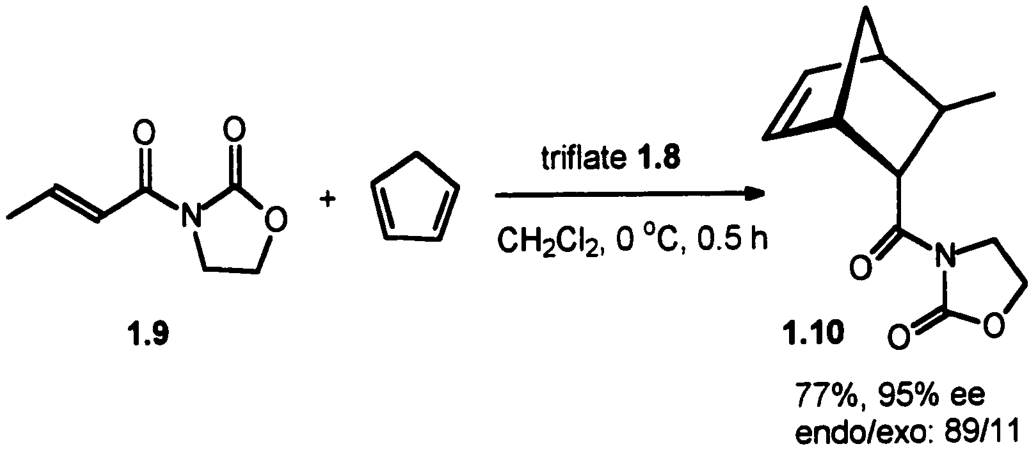


Chiral binaphthyl lanthanide triflates **1.8** were developed by Kobayashi *et al.* (Scheme 1.3).[18] In the presence of a catalytic amount of the triflate **1.8**, acyl-1,3-oxazolidin-2-one **1.9** reacted with cyclopentadiene to afford the Diels-Alder adduct **1.10** in high yield and with high enantiomeric excess (Scheme 1.4).

Scheme 1.3

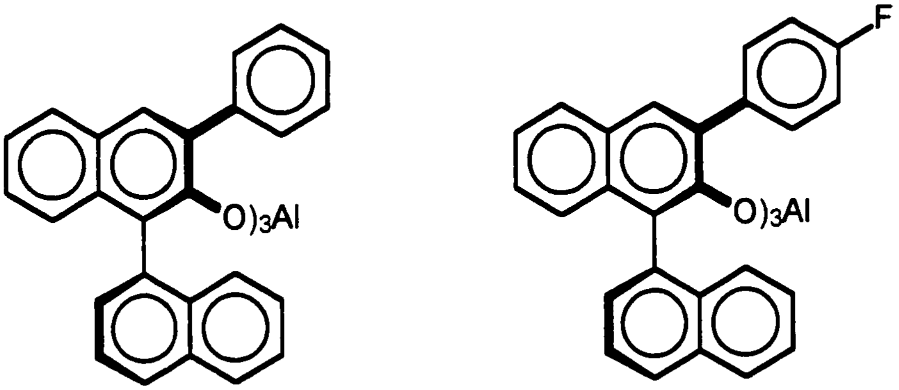


Scheme 1.4



An interesting report from Yamamoto *et al.*[19] describes the molecular design of binaphthyl Lewis acid reagents for an asymmetric Claisen rearrangement. (*R*)-aluminum tris[3-phenyl-2-(1,1'-binaphthoxide)] [(*R*)-ATBN] (**1.11**) and (*R*)-aluminum tris[3-(4-fluorophenyl)-2-(1,1'-binaphthoxide)] [(*R*)-ATBN-F] (**1.12**) were prepared from special designed binaphthyl moieties (Figure 1.5) and subsequently reacted with allyl vinyl ether (R = cyclohexyl) (**1.13**) at -78 °C for 25 h to furnish rearrangement product **1.14** in 78% yield and with 61% ee for (*R*)-ATBN, and in 85% yield, with 86% ee for (*R*)-ATBN-F (Scheme 1.5).

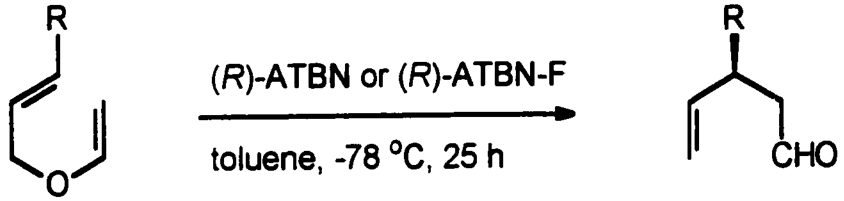
Figure 1.5. Structures of (R)-ATBN and (R)-ATBN-F.



(*R*)-ATBN **1.11**

(*R*)-ATBN-F **1.12**

Scheme 1.5



R = cyclohexyl

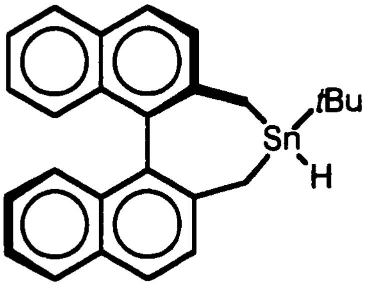
1.13

1.14

(*R*)-ATBN: 78% yield, 61% ee
(*R*)-ATBN-F: 85% yield, 86% ee

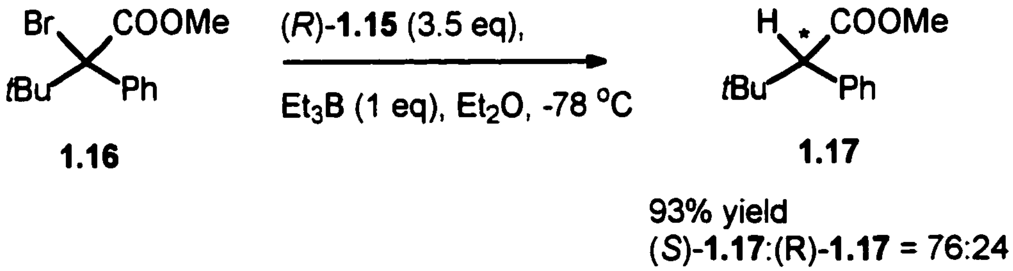
Enantioselective radical reactions continue to be a challenging concept. Recently, Metzger *et al.* reported an enantioselective hydrogen transfer from a chiral binaphthyl tin hydride **1.15** (Figure 1.6) to a prochiral carbon-centered radical.[20] The reaction of the bromoester **1.16** with **1.15** at -78 °C led to the reduction product in 93% yield and in a ratio of (*S*)-**1.17**:(*R*)-**1.17** = 76:24 (52% ee) (Scheme 1.6).

Figure 1.6. Structure of chiral binaphthyl tin hydride.



1.15

Scheme 1.6

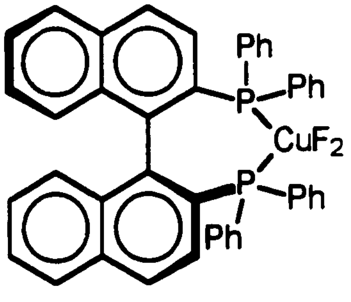


93% yield
(*S*)-**1.17**:(R)-**1.17** = 76:24

Carreira *et al.* reported a modified BINAP Lewis acid catalyst **1.18** (Figure 1.7) which initiated enantioselective dienolate additions to aldehydes.[21] When a solution of enol silane **1.19** is successively treated with 5 mol % of (*S*)-BINAP-CuF_2

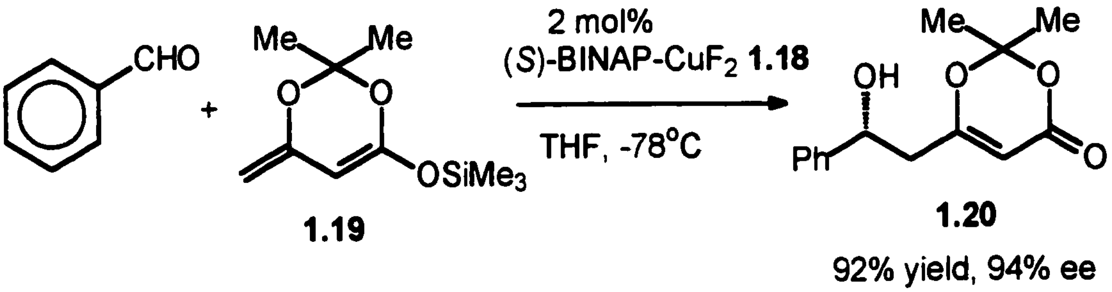
(**1.18**) at -78 °C and benzaldehyde, the adduct **1.20** was isolated in 92% yield and with 94% ee (Scheme 1.7).

Figure 1.7. Structure of (S)-BINAP-CuF$_2$.



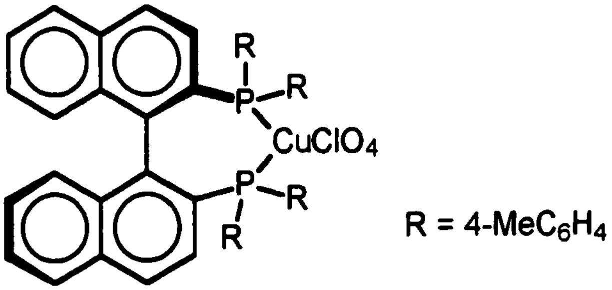
1.18

Scheme 1.7



A similar modified BINAP Lewis acid catalyst **1.21** (Figure 1.8) was reported by Lectka *et al.*[22] The catalyst has been successfully used in catalytic, enantioselective alkylation of chelating α-amino ester with enolsilane nucleophiles. Slow addition of 1.1 equiv of enol silane **1.23** over the course of 24 h into a solution of the α-imino ester **1.22** containing 5 mol % (*R*)-Tol-BINAP-$CuClO_4 \cdot (CH_3CN)_2$ (**1.21**) at 0 °C gave the protected amino acid **1.24** in 91% yield and with 98% ee (Scheme 1.8).[22a] As proposed in the mechanism, the imine N and carbonyl O can form a stable five-membered chelate ring with the chiral Lewis acid catalyst **1.21**, providing additional rigidity to an activated complex **1.25** and nucleophilic attack to the complex affords the high product selectivity (Figure 1.9).[22a]

Figure 1.8. Structure of (R)-Tol-BINAP-$CuClO_4 \cdot (CH_3CN)_2$.



1.21

Scheme 1.8

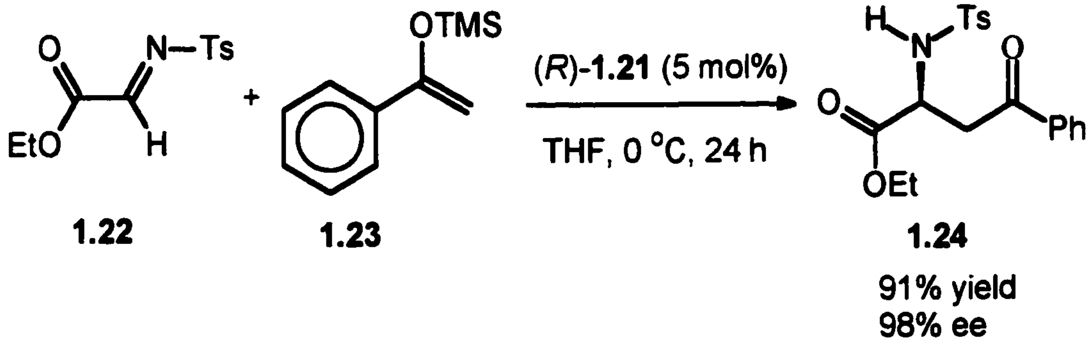
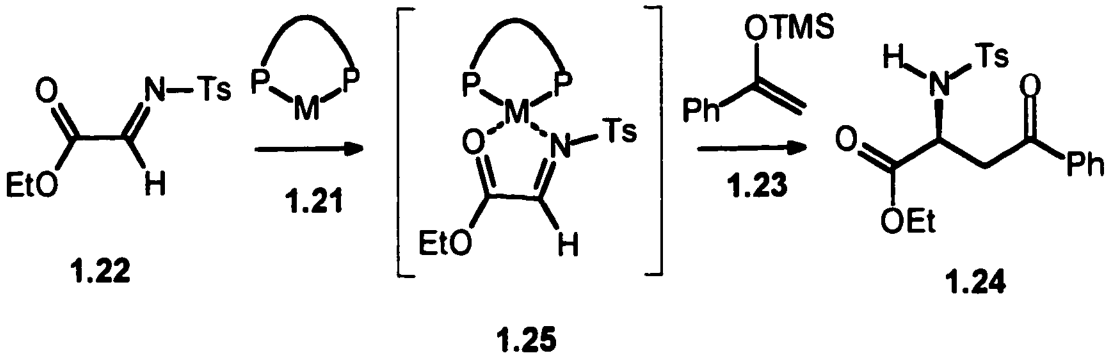
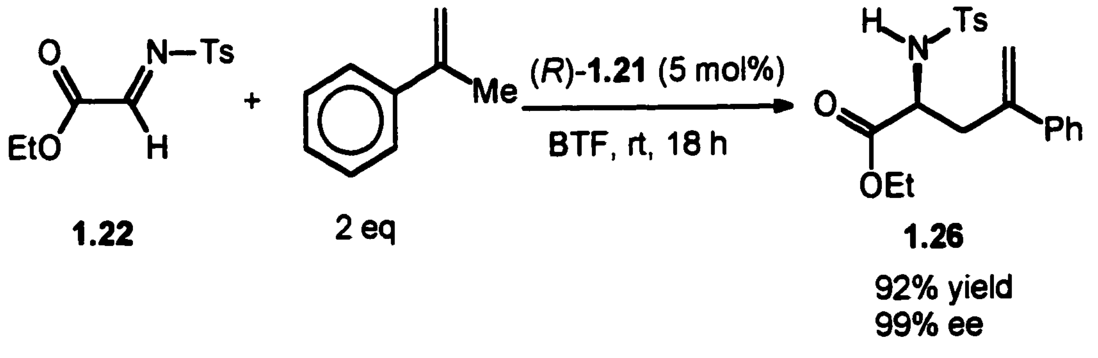


Figure 1.9. Chelate coordination of amide and imine nitrogen.



A more recent paper describes the efficient, catalytic, enantioselective imino ene reaction of α-amino ester **1.22** with alkenes catalyzed by the Lewis acid complex **1.21**.[23] Reaction of 1 equiv of **1.22** and 2 equiv of α-methylstyrene catalyzed by 5 mol % (*R*)-Tol-BINAP-CuClO$_4$•(CH$_3$CN)$_2$ [**1.21**•(CH$_3$CN)$_2$] in benzotrifluoride (BTF) at rt for 18 h affords an *α*-amino acid derivative **1.26** in 92% yield and 99% ee (Scheme 1.9).

Scheme 1.9



1.3. Chiral Boron Reagents in Asymmetric Synthesis

1.3.1. General Consideration of Chiral Boron Reagents

The small size of the boron atom (atomic radius: 82 pm), which is only slightly larger than carbon (atomic radius: 77 pm), results in strong steric interactions between adjacent groups leading to highly diastereoselective reactions.[24] Boron derived reagents have proven to be very useful in directed asymmetric synthesis. In fact, the first non-enzymatic asymmetric synthesis with high enantioselectivity was a hydroboration.[25] Since then, there have been five major classes of chirally directed synthetic processes reported for organoboranes:[26] (1) hydroboration of olefins;[27] (2) allyl- and crotyl-borane reactions with aldehydes;[28] (3) homologation of boronic esters;[29] (4) reduction of carbonyl compounds with boranes[30] or borohydrides,[31] and (5) boron enolate condensations.[32] The strong ligand binding and history of high stereoselective induction suggest that boron-based chiral reagents may provide efficient asymmetric tools for other reactions in which researchers are still trying to pursue high stereoselectivities. Most commonly, asymmetric induction has been proposed to result from interactions of the chiral ligand in 6-membered transition states.[28]

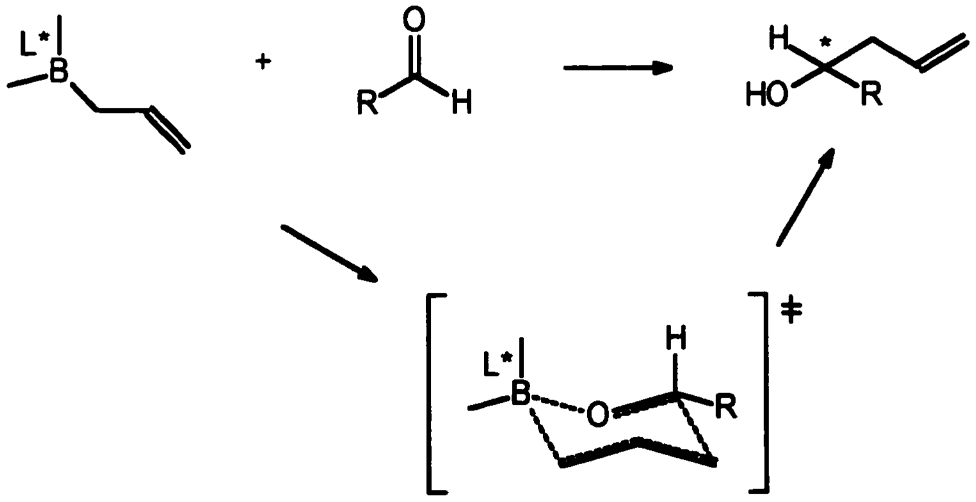
There is no need to discuss all the chirally directed synthetic processes for organoboranes in detail here, since their chemistry is well established. However, because the mechanistic similarity of asymmetric allylborations to that of achiral conjugate addition reactions using boron reagents (it will be discussed later in Chapter IV) provided a common ground for investigation into asymmetric conjugate reactions, asymmetric allylboration reactions will be discussed in some detail.

1.3.2. Chiral Boron Reagents for the Allylboration Reactions

1.3.2.1. Mechanism

Asymmetric allylboration reactions apparently proceed *via* the initial complexation of the carbonyl oxygen with boron, followed by transfer of the allyl group from boron to the carbonyl carbon, involving a six-membered transition state **1.27** (Figure 1.10).

Figure 1.10. Mechanism of Asymmetric Allylborations.

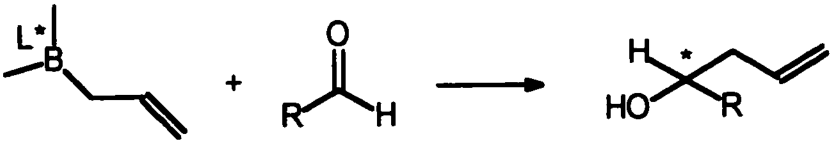


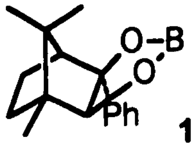
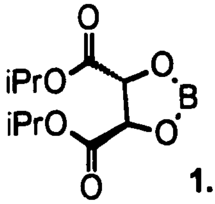
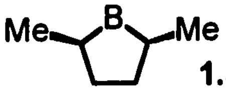
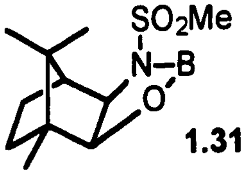
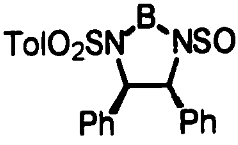
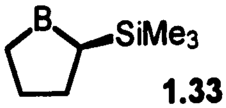
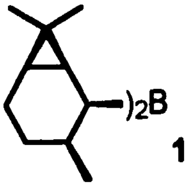
1.27

1.3.2.2. Some Asymmetric Allylborations of Aldehydes

A number of research groups have demonstrated that the stereochemical outcome of this reaction process can be effectively manipulated through the use of a variety of chiral nontransferable ligands. Table 1.1 summarizes some typical examples of asymmetric allylboron reagents **1.28-1.34** that have been reported by Hoffmann,[33] Roush,[34] Masamune,[35,36] Reetz,[37] Corey,[38] and Brown.[39] All chiral boron reagents provide high enantioselectivities in good to excellent yields. However, it must be pointed out that while reagents **1.31**, **1.32**, and **1.33** also afford comparatively high enantioselectivities, each of these reagents requires the preparation of the chiral auxiliaries in several steps and some even require resolution.[36,38]

Table 1.1. Chiral Reagents for Allylboration Reactions of Aldehydes.



boron ligand moiety	author	year	R	yield	ee	ref.
 **1.28**	Hoffmann	1981	nPr	72%	93%	33
 **1.29**	Roush	1985	nC_7H_{15}	86%	79%	34
 **1.30**	Masamune	1986	nPr	93%	86%	35
 **1.31**	Reetz	1988	nPr	96%	78%	37
 **1.32**	Corey	1989	nC_5H_{11}	95%	>90%	38
 **1.33**	Masamune	1989	Et	96%	80%	36
 **1.34**	Brown	1990	nPr	94%	73%	39

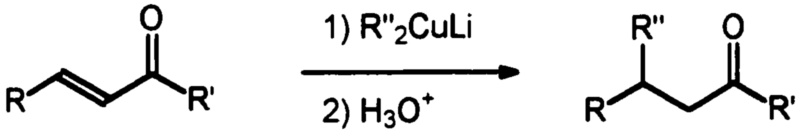
1.4. Conjugate Additions

1.4.1. Achiral Conjugate Additions

1.4.1.1. Cuprates

The Michael reaction has been generally defined as a C-C homologation reaction involving conjugate, nucleophilic additions to *α,β*-unsaturated carbonyl systems. The conjugate addition of cuprates to enones represents a powerful method for selective C-C bond formation (Scheme 1.10).[1,2]

Scheme 1.10

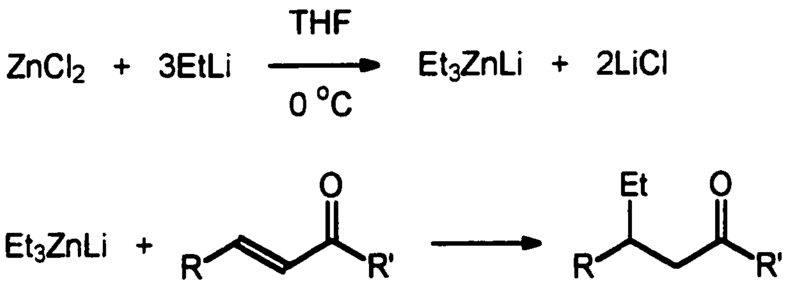


Cuprates cannot transfer alkynyl groups in the conjugate reactions;[40] therefore alkynyl groups are used as residual ligands (or so called dummy ligands).[2f] These ligands tend to be bound more tightly to copper relative to other *sp*^{3}- and *sp*^{2}-hybridized carbon atoms. This is likely due to strong back bonding between *d* electrons of copper and π^* orbitals of the acetylenic group.[2f]

1.4.1.2. Zincates

A parallel development on conjugate addition by organozinc reagents has also been reported. Initiated by the discovery of Isobe and co-workers,[41] the facile conjugate addition of lithium triorganozincates has also been demonstrated. (Scheme 1.11).

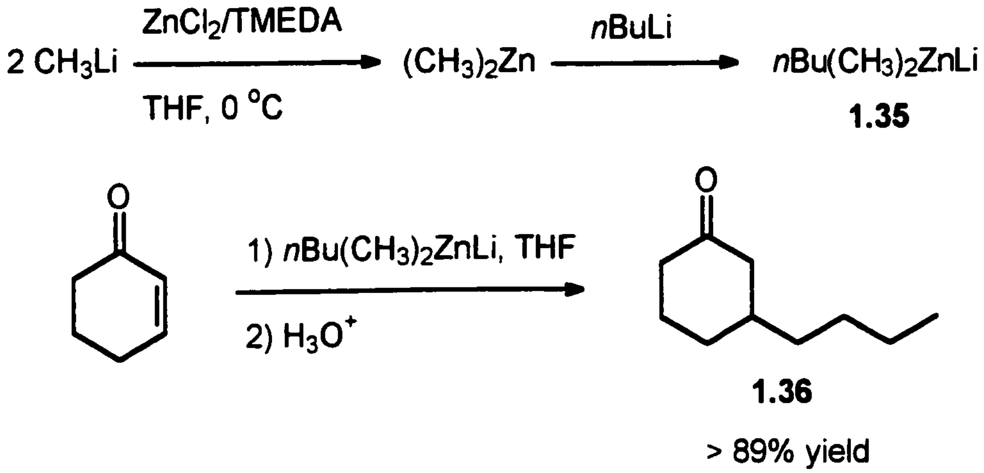
Scheme 1.11



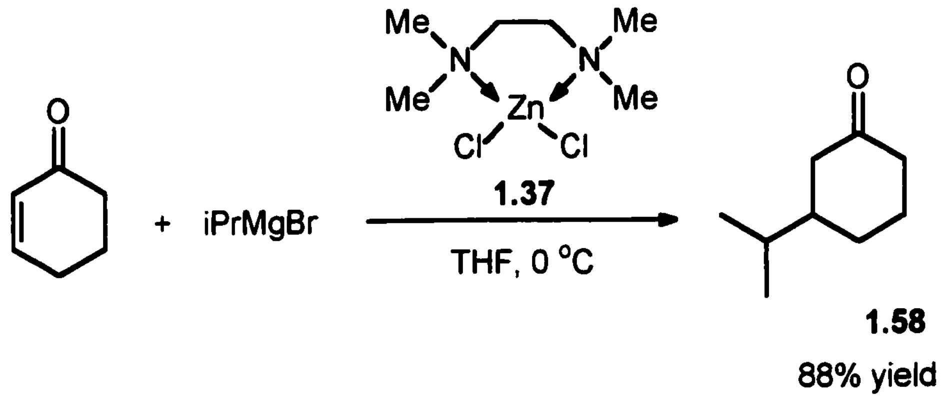
Subsequent studies resulted in selective alkyl group transfer from mixed lithium trialkylzincates **1.35**.[42] The addition of *n*-butyl to 2-cyclohexenone gives 1,4-addition product **1.36** in excellent yield (Scheme 1.12).

Feringa and co-workers[43] reported 1,4-additions of Grignard reagents mediated by *N,N,N',N'*-tetramethylethylenediamine zinc dichloride (**1.37**) (Scheme 1.13).

Scheme 1.12



Scheme 1.13

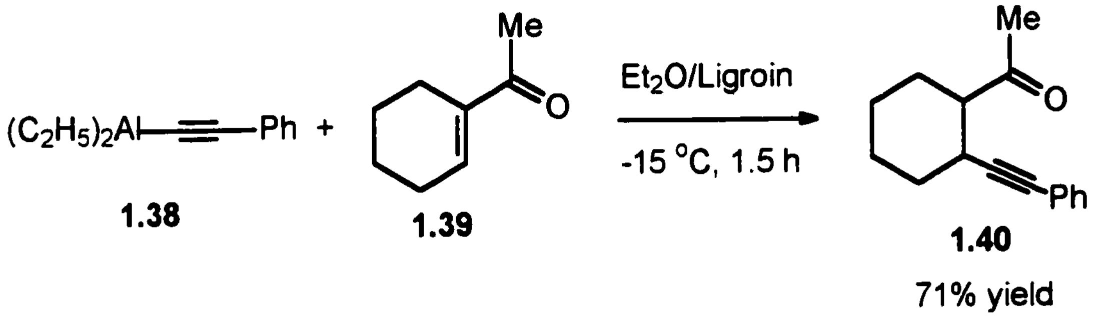


1.4.1.3. 1,4-Addition of Alkynyl Groups to Enones

1.4.1.3.1. Alkynylalanes

Hooz has achieved the conjugate addition of alkynylalanes to α,β-unsaturated ketones.[44] An example of this chemistry is pictured in Scheme 1.14.

Scheme 1.14

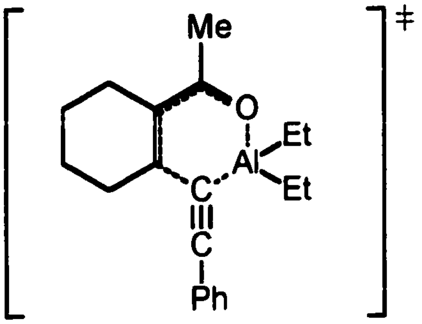


The alkynylalane **1.38** reacts with 1-acetylcyclohexene **1.39** in Et_2O/ligroin (1:10) at -15 °C for 1.5 h to afford the adduct **1.40** in 71% yield.

The mechanism of this reaction involves the intramolecular delivery of an alkynyl group through a six-membered transition state depicted in Figure 1.11.[44a]

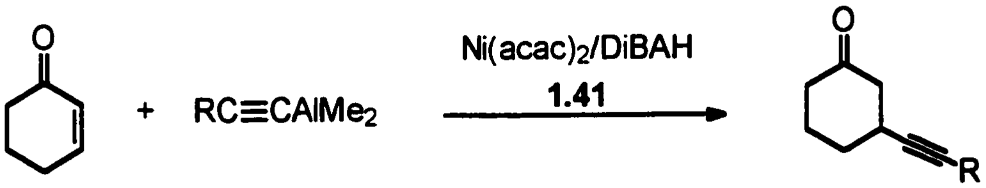
However, this reaction is complicated by the concurrent formation of large amounts of the 1,2-addition product in most cases. Acetylenic alanes conjugately add only to those enones capable of achieving an *s-cis* conformation. Moreover, the reaction was observed to be highly sensitive to solvent effects, requiring frequent changes in individual reactions.

Figure 1.11. Proposed transition state of 1,4-addition of alkynylalane to 1-acetylcyclohexene.



Conjugate addition of terminal alkynyl groups to cycloenones has also been successfully achieved using diethylalknylalanes and nickel complex **1.41** as a catalyst by Schwartz and co-workers (Scheme 1.15).[45] The nickel complex **1.41** catalyzes conjugate addition to both *s-cis* and *s-trans* enones.

Scheme 1.15

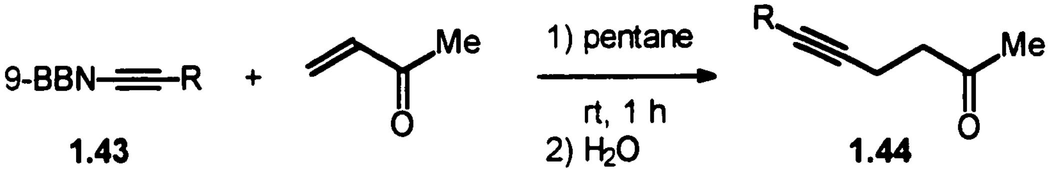


R = *t*Bu **1.42a** 72% yield
R = *n*Bu **1.42b** 71% yield
R = SiMe$_3$ **1.42c** 80% yield

1.4.1.3.2. Alkynylboranes

In 1976, Brown reported that alkynylboranes would undergo conjugate addition of alkynyl groups to enones with good yields.[46] *B*-1-Alkynyl-9-BBN **1.43** undergoes a smooth 1,4-addition in pentane at rt onto methyl vinyl ketone (MVK). Hydrolysis of the initially formed enol borinate intermediates provide the corresponding 4-alkynyl-2-butanones **1.44** in high yields (Scheme 1.16).

Scheme 1.16



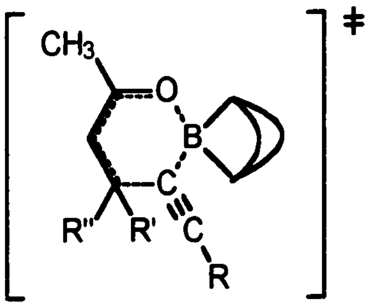
R	Yield
iBu	100%
*n*Bu	96%
Ph	80%
c-hexyl	97%

The reaction proceeds through a cyclic transition state (Figure 1.12), giving the enol borinate intermediate, which is hydrolyzed to the desired product.[46]

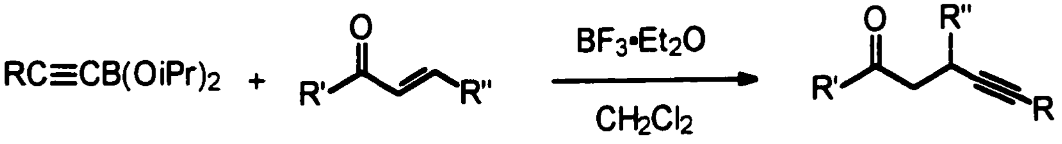
Suzuki and co-workers reported that in the presence of $BF_3 \cdot OEt_2$, (1-alkynyl)-diisopropoxyboranes reacted with enones to give 1,4-addition products in good yields

(Scheme 1.17).[47] The cyclic enones (*s-trans* conformers) give no 1,4-addition products.

Figure 1.12. Transition State of Conjugate Addition of B-1-alkynyl-9-BBN to Enones.



Scheme 1.17



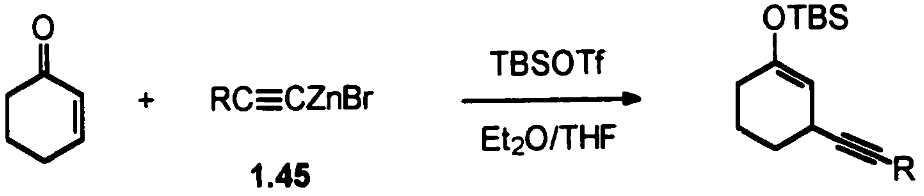
R	R'	R''	reaction condition	yield/%
*n*Bu	Ph	Ph	40 °C/8 h	85
*n*Bu	Me	Ph	rt/48 h	60
*n*Bu	Hex	Me	0 °C/120 h	70
Ph	Ph	Ph	40 °C/3 h	81
Ph	Hex	Me	0 °C/ 88 h	84

1.4.1.3.3. Use of Silyl Promoters

(a) Alkynylzinc Reagents and Lithium Trimethylalkynylaluminates

Kim and co-worker reported that the conjugate addition of alkynyl groups to enones could be achieved by alkynylzinc reagents **1.45** using *t*-butyldimethylsilyl triflate (TBSOTf) as a promoter (Scheme 1.18).[48]

Scheme 1.18



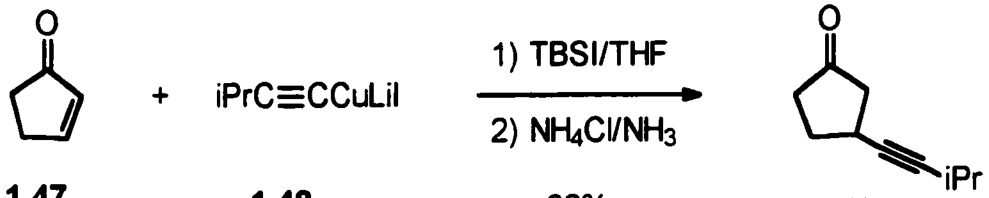
R = Ph	**1.46a** 96% yield
R = *n*Bu	**1.46b** 79% yield
R = $SiMe_3$	**1.46c** 70% yield

Under the same reaction condition, lithium trimethylalkynylaluminates were also used to make β-alkynyl ketones.[49]

(b) Alkynylcuprates

With promotion by trimethylsilyl iodide (TMSI), addition of pentynyl copper-LiI (**1.48**) to 2-cyclopentenone (**1.47**) was successful and afforded 1,4-product **1.49** in 68% yield (Scheme 1.19),[50] although alkynylcuprates generally do not add to the β position of enones.[40]

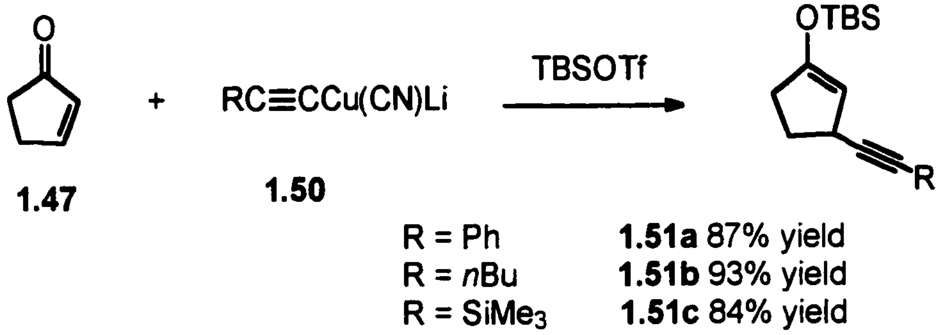
Scheme 1.19



1.47 **1.48** 68% **1.49**

The addition can also be carried out by alkynylcuprates (**1.50**) promoted by TBSOTf, with much better yields (Scheme 1.20).[51]

Scheme 1.20



1.4.2. Asymmetric Conjugate Additions of Organometallics to Prochiral Enones

1.4.2.1. General

Since conjugate addition creates a chiral carbon at the β-position of pro-chiral enones, the utility of Michael addition reactions for C-C bond formation has stimulated a significant amount of work to achieve a general method for asymmetric conjugate addition to enones. Several comprehensive reviews in the area which focus on the asymmetric conjugate addition have appeared.[52] In this thesis, it is not necessary to explore each example of asymmetric conjugate addition in detail; however, some impressive examples and the latest developments in the area are discussed.

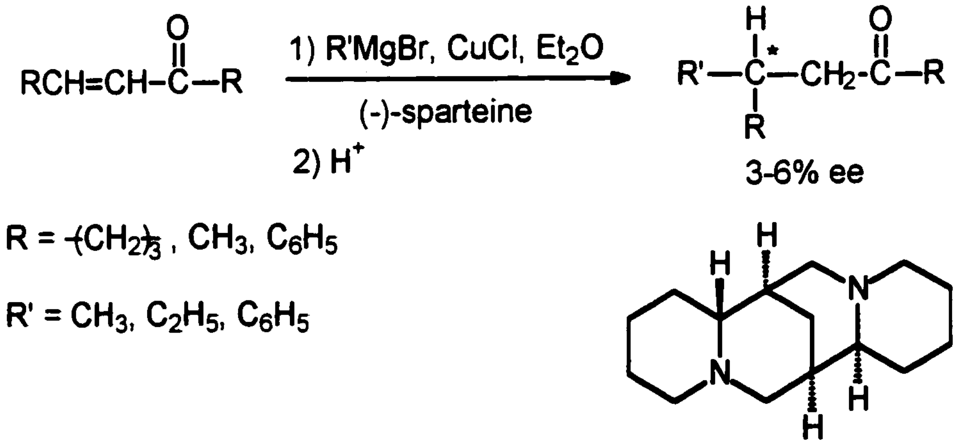
1.4.2.2. Using cuprates

To achieve high enantioselectivities, the main stream of research has concentrated on the control of the stereocenter using chirally modified organocuprate reagents.

1.4.2.2.1. Magnesium cuprates

In 1972, Kretchmer reported the first asymmetric induction in conjugate addition to enones *via* organomagnesium cuprate reagents with (-)-sparteine **1.52** (Scheme 1.21).[53]

Scheme 1.21

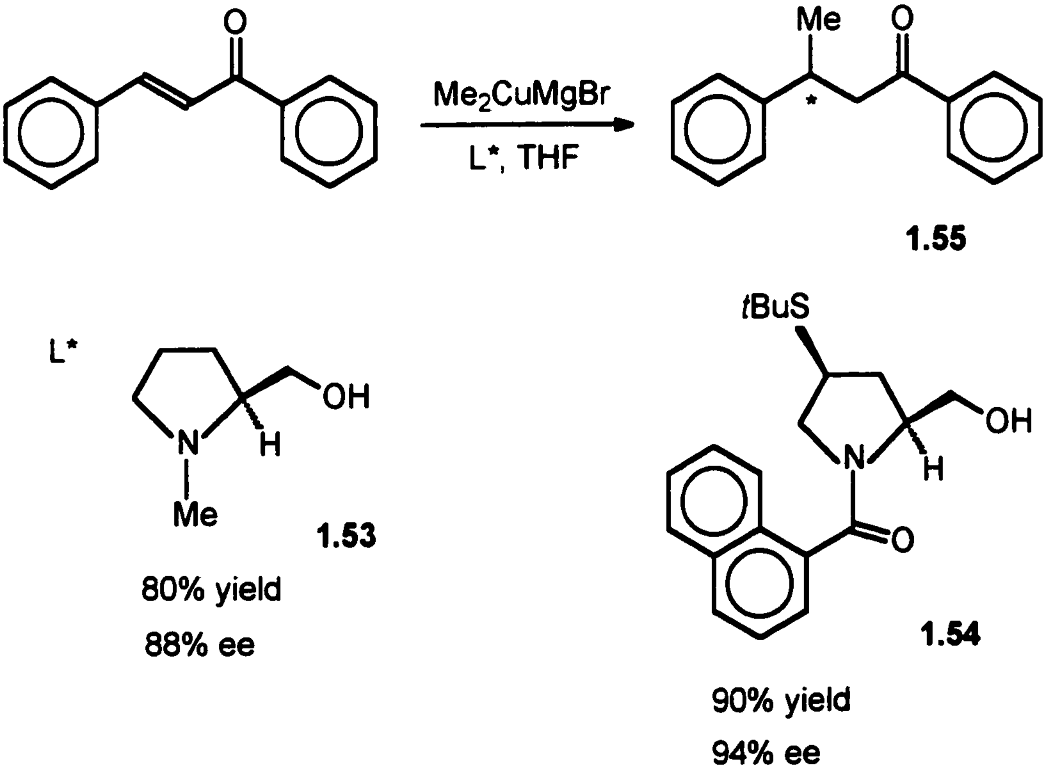


(-)-sparteine **1.52**

Since then, numerous approaches to achieve asymmetric conjugate addition have been reported. Impressive results were obtained by several groups on cuprates with chiral non transferable ligands.

Leyendecker and co-workers reported the addition of $Me_2CuMgBr$ to chalcone using *N*-substituted (*S*)-prolinol (**1.53**) as bidentate chiral ligands and 4(*S*)-(*tert*-butylthio)-(*S*)-prolinol (**1.54**) as tridentate chiral ligand with ee's as high as 94% (Scheme 1.22).[54]

Scheme 1.22



1.55

1.53

80% yield
88% ee

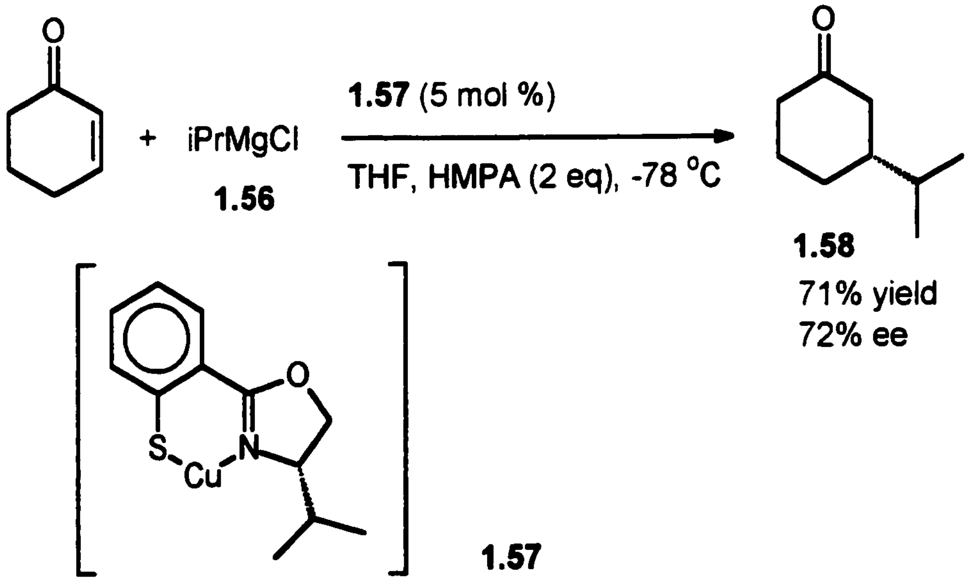
1.54

90% yield
94% ee

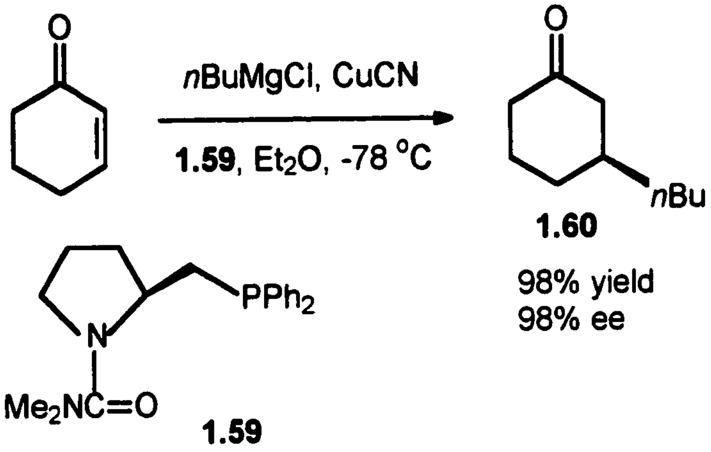
Pfaltz *et al.* reported that chiral mercaptoaryl-oxazolines as ligands could be used in asymmetric Cu-catalyzed 1,4-addition of Grignard reagents to enones.[55] The best results were obtained when the Grignard reagent **1.56** was slowly added at -78 °C to a THF solution containing the catalyst **1.57**, 2-cyclohexenone, and 2 equiv of HMPA (Scheme 1.23).

Tomioka *et al.* reported that an asymmetric conjugate addition of organomagnesium cuprates controlled by a stoichiometric amount of chiral phosphine **1.59** to 2-cyclohexenone afforded 1,4-adduct **1.60** with up to 98% ee (Scheme 1.24).[56]

Scheme 1.23



Scheme 1.24



1.4.2.2.2. Lithium cuprates

Corey and co-workers[57] reported the enantioselective addition of chiral cuprate reagents to 2-cycloalkenones using (+)- and (-)-ephedrine derived chiral ligands to afford product with high enantioselectivities up to 95% ee. Thus, using ethyllithium, the reagent **1.62** derived from **1.61** reacted with 2-cyclohexenone in THF at -78 °C to produce (*R*)-(+)-3-ethylcyclohexanone (**1.63**) in 66% yield and with >95% ee (Scheme 1.25).

Scheme 1.25

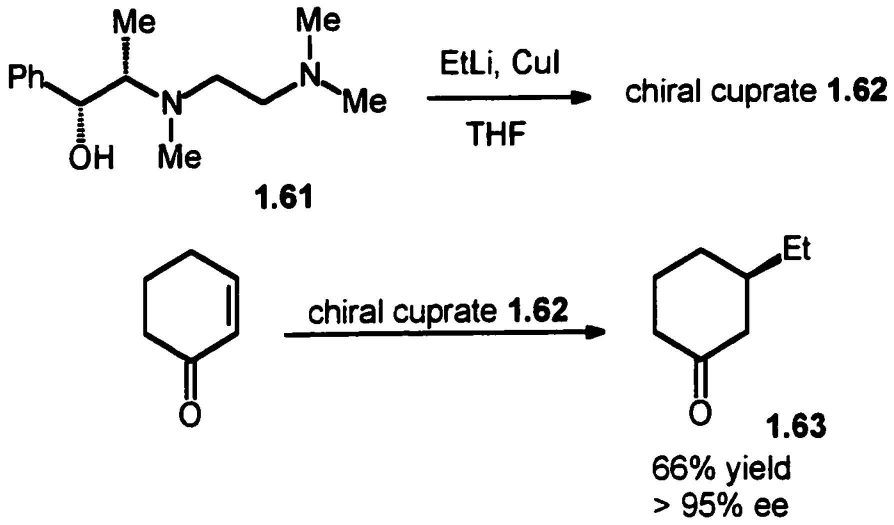
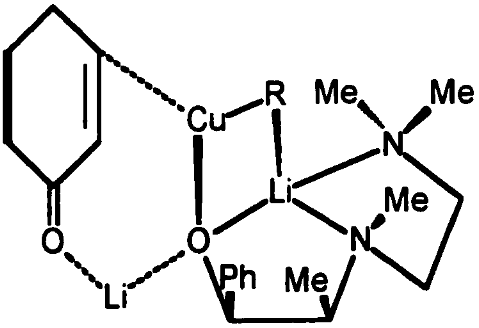


Figure 1.13. Mechanistic model of conjugate addition of (-)-ephedrine derived cuprate to 2-cyclohexenone.

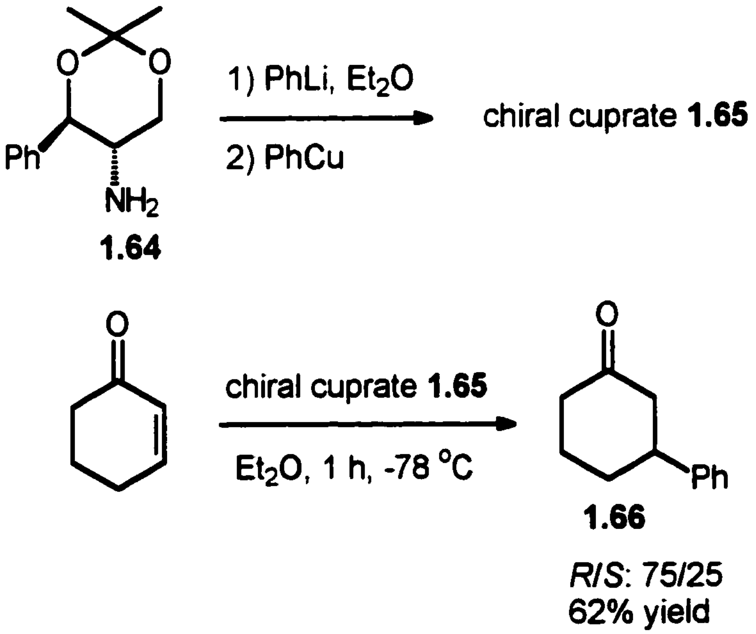


To understand the results, a mechanistic model was depicted (Figure 1.13).[57] In this model, lithium is chelated by the conjugate base of **1.61** as a tridentate ligand

and associated with an alkylcopper fragment. Selective interaction with the *re* face of C(3) in 2-cyclohexenone is proposed to occur such that nucleophilic copper forms a d,π^* - complex as the carbonyl oxygen coordinates with a second lithium ion which is held in place by the alkoxy group from **1.61**.

In 1986, Bertz *et al.*[58] reported an asymmetric conjugate addition of a phenyl group to 2-cyclohexenone using cuprate reagents by varying the chiral ligand cation, solvent, salt addition, and temperature to afford 1,4-adduct with 0-66% ee. One of the best cases (from a total of 49 variations) giving a product **1.66** in 62% yield with 50% ee, is depicted in Scheme 1.26.

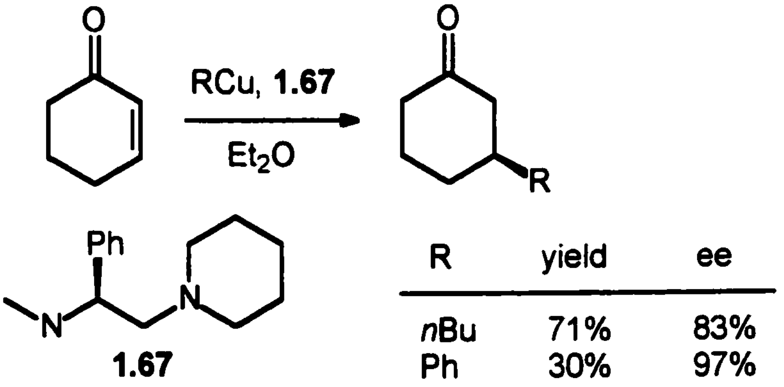
Scheme 1.26



A series of chiral secondary amines have been screened as non-transferable ligands for the promotion of enantioselectivity in conjugate addition to 2-cyclohexenone by Rossiter and co-workers.[59] The best results were obtained when these reactions were run in DMSO or ether. Ligand **1.67** gives the best results with enantiomeric excesses as high as 97% when the transferable ligand is phenyl (Scheme 1.27).

A new chiral amidophosphine ligand **1.68** was applied by Tomioka in an enantioselective conjugate addition of lithium dimethylcuprate to chalcone providing the corresponding 1,4-adduct **1.69** in 84% ee (Scheme 1.28).[60]

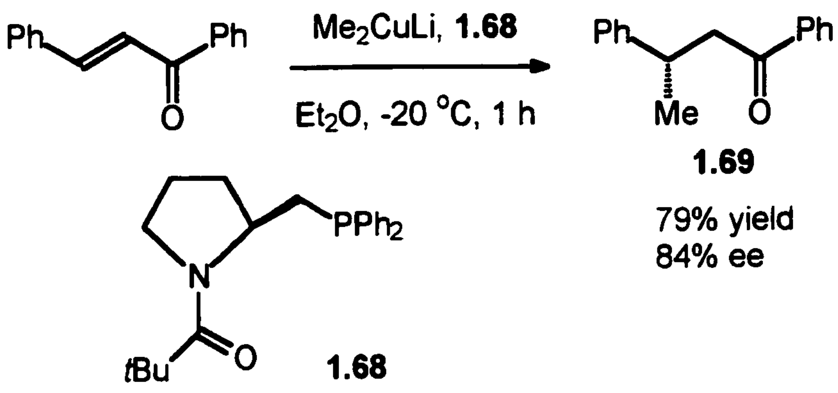
Scheme 1.27



1.67

R	yield	ee
*n*Bu	71%	83%
Ph	30%	97%

Scheme 1.28



1.69

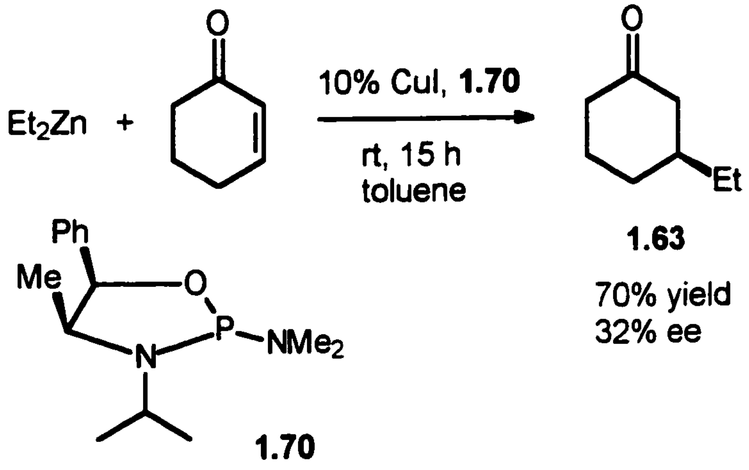
79% yield
84% ee

1.68

1.4.2.2.3. Zinc cuprates

In 1993, Alexakis *et al.* reported an asymmetric conjugate addition in which diethylzinc was added to 2-cyclohexenone with 10% copper iodide and a catalytic amount of a chiral phosphorus ligand **1.70** (Scheme 1.29).[61]

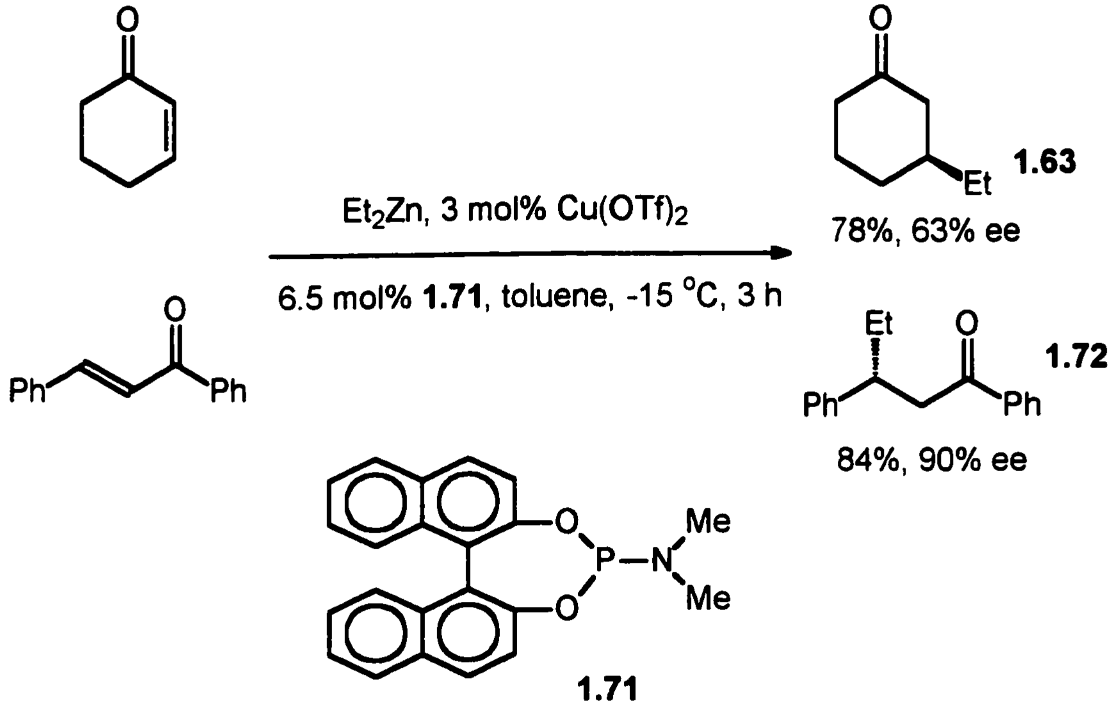
Scheme 1.29



In 1996, Feringa *et al.* reported that chiral copper catalysts are capable of facilitating conjugate addition of readily available dialkylzinc reagents to cyclic and acyclic enones in high yields and with ee values up to 90%.[62] Two examples of these conjugate additions are demonstrated in Scheme 1.30.

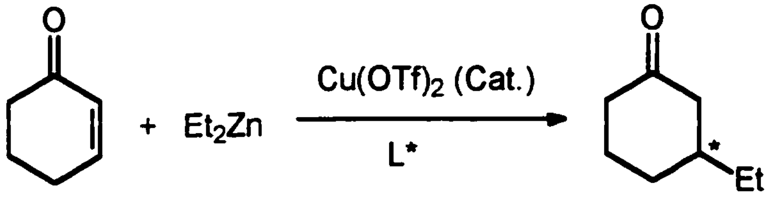
There are at least four more recent papers which report the asymmetric conjugate addition of diethylzinc cuprates to 2-cyclohexenone. (Table 1.2).[63] One report by Alexakis and co-workers employs thirteen commercial available phosphine ligands such as (+)-DIOP, (*S*)-Norphos, (*S*)-BINAP, *etc* to afford the 1,4-adduct with up to 44% ee.[63a]

Scheme 1.30

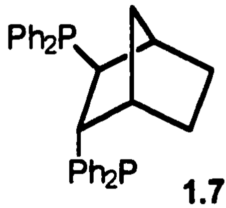
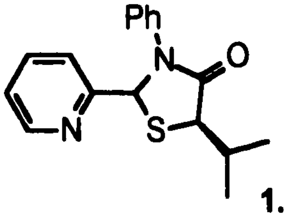
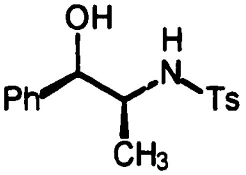
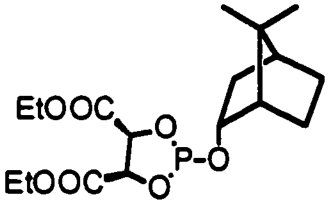


Feringa and co-workers reported the development of several new ligands derived from chiral α-mercapto which gave 39-62% ee's for diethylzinc cuprate additions to 2-cyclohexenone.[63b] Sewald and co-workers reported from 6-31% enantiomeric excess for the conjugate addition of diethylzinc to cyclohexenone in the presence of catalytic amounts of homochiral sulfonamides and copper (I) salt.[63c] Most recently, Alexakis and co-workers reported the asymmetric conjugate addition of diethylzinc to 2-cyclohexenone with copper (II) triflate and chiral phosphite (**1.76**) to afford 1,4-addition product with up to 65% ee.[63d]

Table 1.2. Variation of the chiral ligand in the asymmetric conjugate addition of diethylzinc to 2-cyclohexenone.



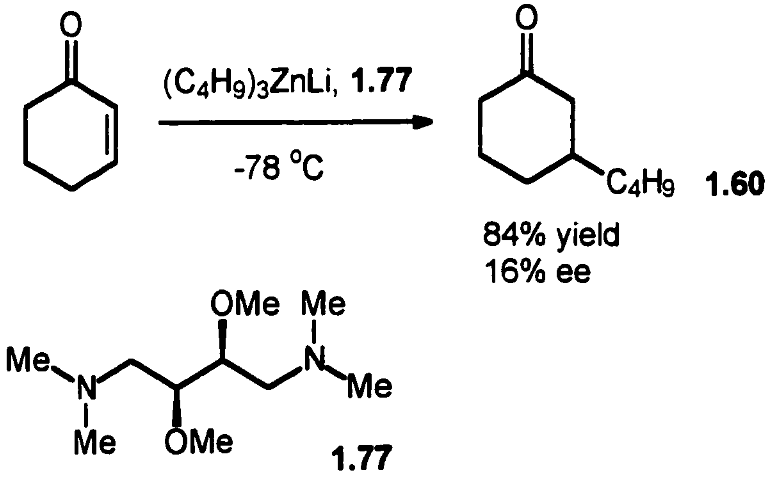
1.63

L*	author	yield (%)	ee (%)	*R*/*S*
 **1.73**	Alexakis	81	44	*S*
 **1.74**	Feringa	>70	62	*R*
 **1.75**	Sewald	26	31	*R*
 **1.76**	Alexakis	77	65	*S*

1.4.2.3. Using Zincates

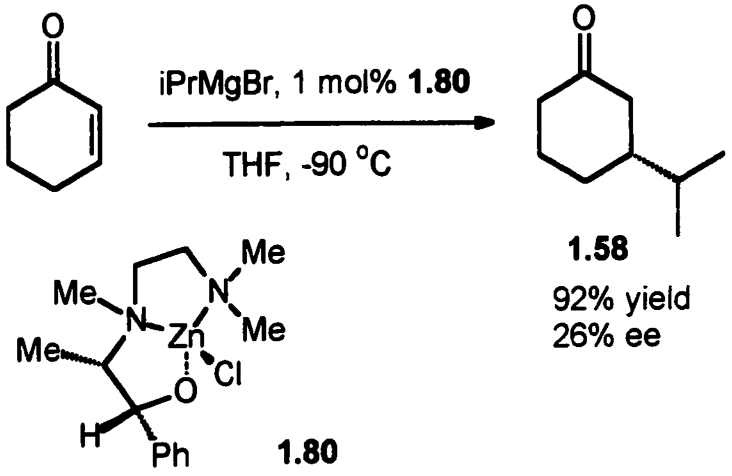
Langer and Seebach[64] reported the enantioselective addition of lithium trialkylzincates to 2-cyclohexenone using (*S,S*)-1,4-bis(methylamino)-2,3-dimethoxybutane **1.77** as a chiral ligand to afford the 1,4-adduct with 16% ee (Scheme 1.31).

Scheme 1.31



Feringa *et al.* reported the first results of the enantioselective 1,4-additions of Grignard reagents catalyzed by chiral zinc (II) complexes.[65] The best results were obtained when the 1,4-addition of iPrMgBr to 2-cyclohexenone using catalytic amounts of chiral zinc complex **1.80** (Scheme 1.32).

Scheme 1.32

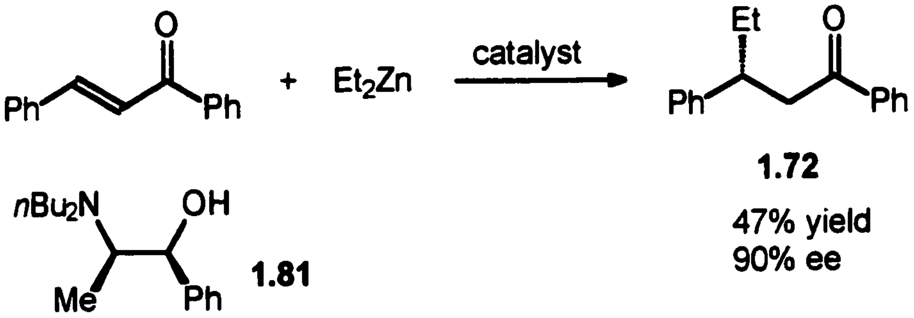


1.58
92% yield
26% ee

1.80

Soai *et al.* reported asymmetric synthesis of optically active β-substituted ketones by highly enantioselective catalytic conjugate addition of dialkylzinc reagents to acyclic enones using a catalyst system of Nickel (II)-chiral ligand **1.81** plus an achiral ligand in acetonitrile/toluene (Scheme 1.33).[66]

Scheme 1.33



1.72
47% yield
90% ee

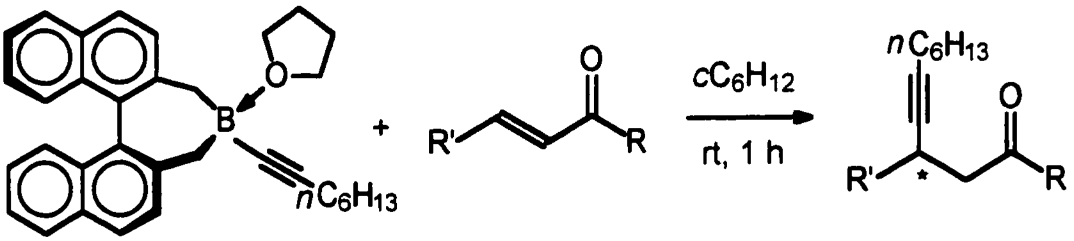
1.81

Catalyst = Ni (II) + chiral ligand **1.81** + 2,2'-bipyridyl in MeCN/toluene

1.4.2.4. Using chiral organoborane

The first and only asymmetric conjugate addition of a 1-alkynyl group to a variety of acyclic enones using binaphthyl modified boron reagents was reported by MacDonald.[67] The alkynylbinaphthylborane reagent **1.82** proved to be an effective reagent for the conjugate transfer of a 1-octynyl group to enones, with yields of 1,4-addition products generally greater than 88% and consistently low enantioselectivities (12-40% ee) (Scheme 1.34).

Scheme 1.34



1.82

R'	R	yield (%)	ee (%)
CH_3	C_6H_5	96	37
C_6H_5	CH_3	94	14
C_6H_5	C_6H_5	93	22

1.5. Asymmetric 1,2-Additions to Aldehydes

1.5.1. Organozinc

Organometallics such as alkyllithiums with chiral complexing reagents,[68] organotitaniums[69] have been applied in enantioselective 1,2-addition; however most have achieved very limited success. In contrast, considerable progress has been made with the enantioselective addition of dialkyl- and alkenylzinc compounds to aldehydes using chiral amino alcohols as ligands.[70]

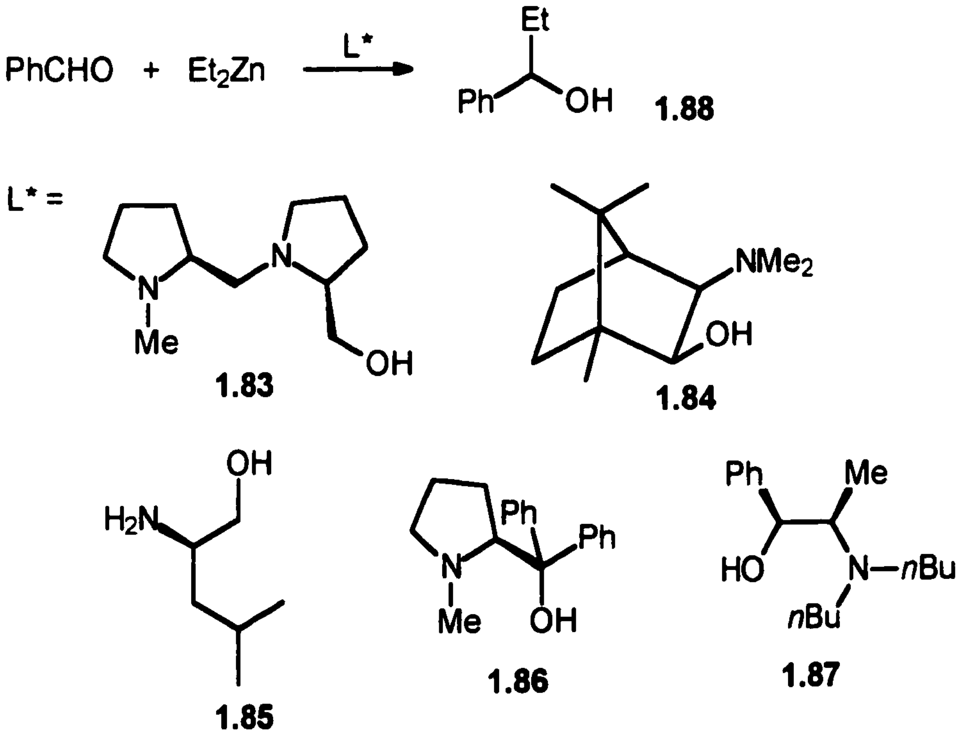
Dialkylzinc complexes once were considered to be unreactive towards addition to aldehydes because the reaction was extremely slow (*e.g.*, reduction). The problems were solved by the discovery in the late 1970's that the proline derivative **1.83** catalyzed the addition of diethylzinc to benzaldehyde (Figure 1.14).[71]

Noyori *et al.* found that using (-)-3-exo-(dimethylamino)isoborneol (DAIB) (**1.84**) as the ligand afforded (*S*)-1-phenyl-1-propanol (**1.88**) in 98% yield with 99% ee.[72] Oguni *et al.* reported that the addition of Et_2Zn to benzaldehyde provided the secondary alcohol with moderate enantioselectivity (49% ee) in the presence of (*S*)-leucinol (**1.85**).[73]

Several other kinds of ligands have been developed and used in the 1,2-addition (*e.g.*, piperazines, 1,2-diols, etc), but *β*-amino alcohols have been used most frequently, especially those derived from isoborneol, proline and norephedrine. Figure 1.14 shows a representative of each of these kinds of ligands (**1.83-1.87**).

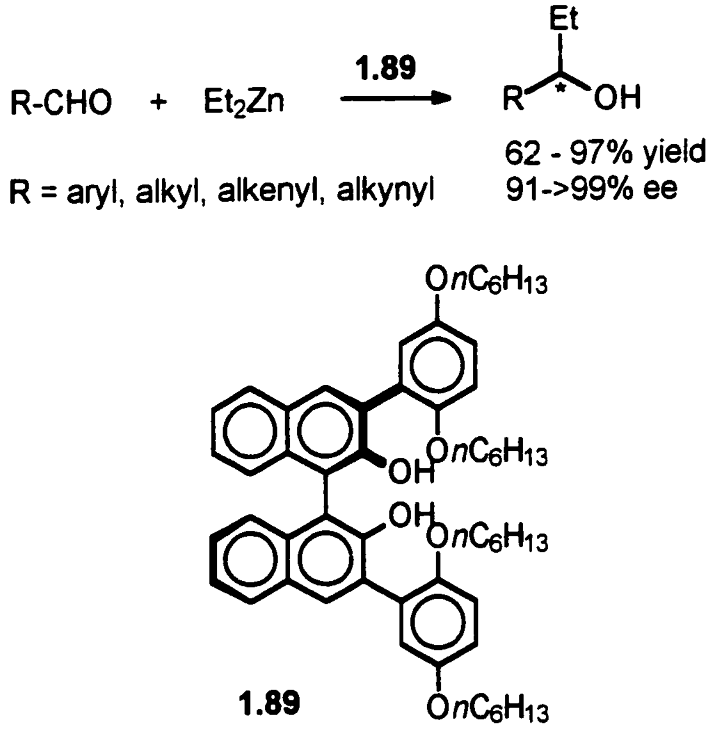
Reactions with these ligands are generally quite good and usually provide 1,2-addition product in high yields (>80%) and with high enantioselectivities (80->99% ee).

Figure 1.14. Enantioselective 1,2-addition of diethylzinc to benzaldehyde.



Most recently, Pu *et al.* reported that a modified 3,3'-disubstituted binaphthol **1.89** as catalyst for the enantioselective addition of diethylzinc to aldehydes afforded products in excellent yields (62-97%) and with great enantioselectivities (up to >99% ee) (Scheme 1.35).[74] Both aromatic and aliphatic aldehydes have been treated with the reagent and provided excellent results. Regioselectivity of the reaction is excellent: α,β-unsaturated aldehydes exclusively undergo 1,2-addition at the aldehyde carbonyl.

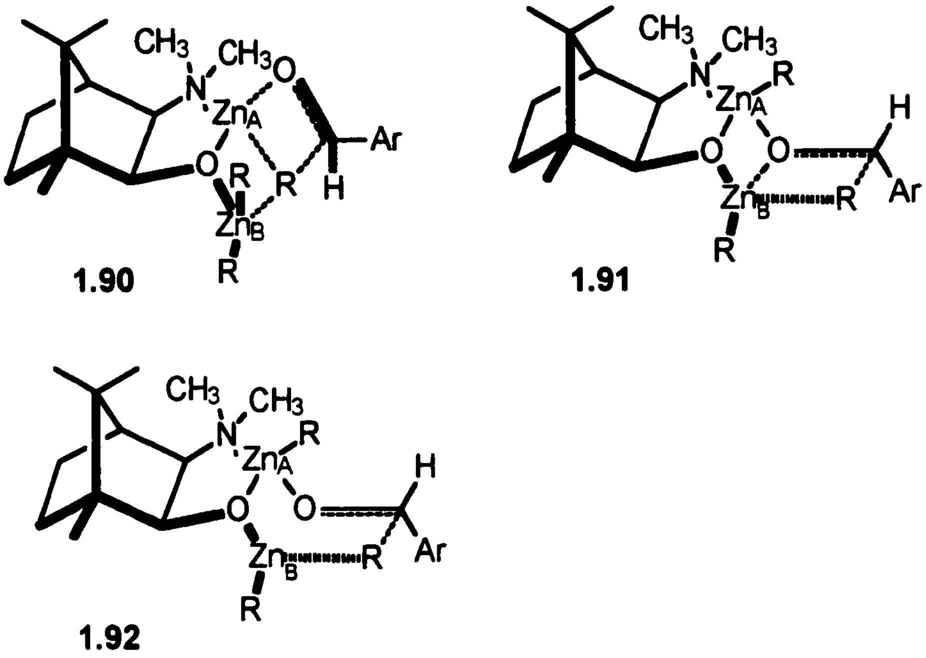
Scheme 1.35



The mechanism of the reaction of diethylzinc catalyzed by ligands is not known. However, some transition states (**1.90**, **1.91**, **1.92**) for the reaction using ligand **1.84** have been proposed by Noyori and co-workers. (Figure 1.15).[70b]

It is currently believed that the catalyst and the organozinc form a dimeric complex as a catalyst precursor. All three assemblies are in full accord with experimental findings.

Figure 1.15. Proposed transition states for 1,2-addition of diethylzinc to aldehydes catalyzed by ligand 1.84.



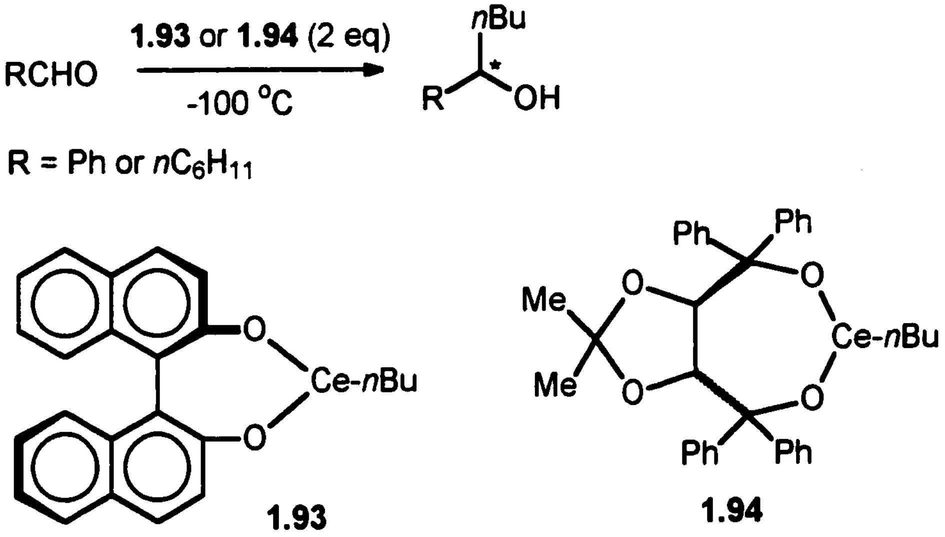
1.90 **1.91** **1.92**

1.5.2. Cerium Reagents

Greeves *et al.* reported the use of homochiral binaphthol-modified organocerium reagent **1.93** and α,α,α',α'-tetraphenyl-1,3-dioxolan-4,5-dimethanol (TPDDOL) organocerium reagent **1.94** in the enantioselective addition of alkyl groups to aldehydes (Figure 1.16).[75]

The highest enantiomeric excess (70% ee) was obtained when cyclohexanecarboxaldehyde was reacted with the reagent **1.94**.

Figure 1.16. Use of organocerium reagents in the enantioselective addition.



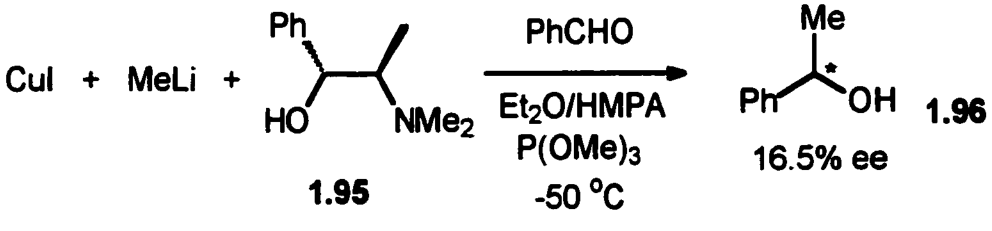
1.93

1.94

1.5.3. Organocuprates

Crabbe and co-workers reported the first enantioselective organocuprate 1,2-addition to benzaldehyde with an enantiomeric excess of 16.5% (Scheme 1.36).[76]

Scheme 1.36

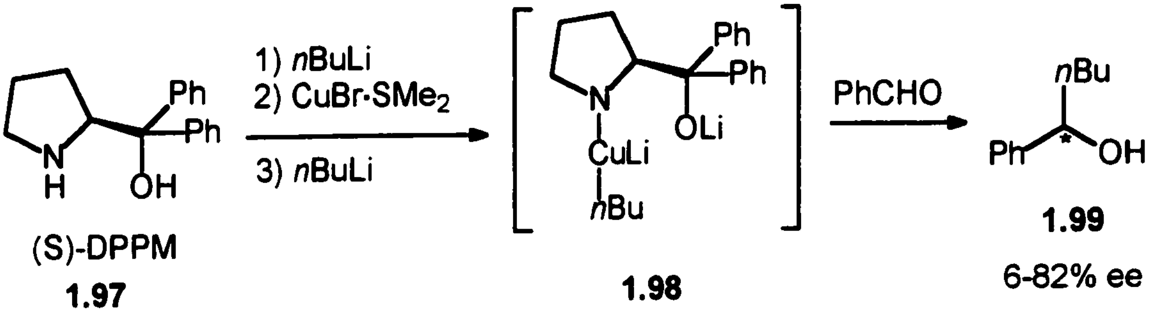


1.95

1.96

Kennedy tested the effectiveness of chiral pyrrolidines in enantioselective cuprate 1,2-addition to benzaldehyde.[77] When (*S*)-DPPM **1.97** was used, the 1,2-addition of benzaldehyde afforded product **1.99** in 3-22% yields and with 6-82% ee *via* an intermediate **1.98** (Scheme 1.37).

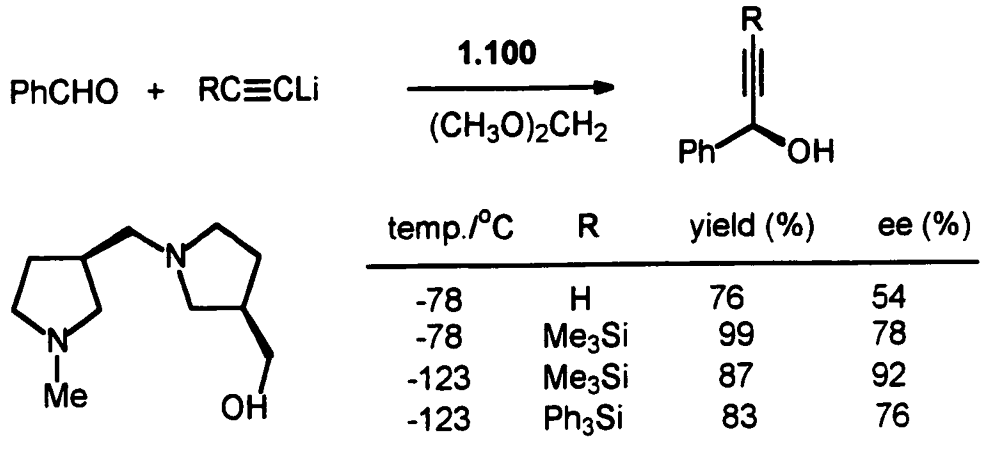
Scheme 1.37



1.5.4. Enantioselective Alkynylation of Aldehydes

In 1979, Mukaiyama and co-workers reported an efficient method for the synthesis of the optically active alkynyl alcohols.[78] This indicates the start of the enantioselective alkynylation of aldehydes. The method employed the pyrrolidine derived ligand **1.100** (Figure 1.14) to induce the stereoselective addition of lithium trialkylsilylacetylide onto benzaldehyde (Scheme 1.38). It is noted that enantioselectivity of the addition depended predominantly on the trialkylsilyl group of the acetylene.

Scheme 1.38



temp./°C	R	yield (%)	ee (%)
-78	H	76	54
-78	Me_3Si	99	78
-123	Me_3Si	87	92
-123	Ph_3Si	83	76

1.100

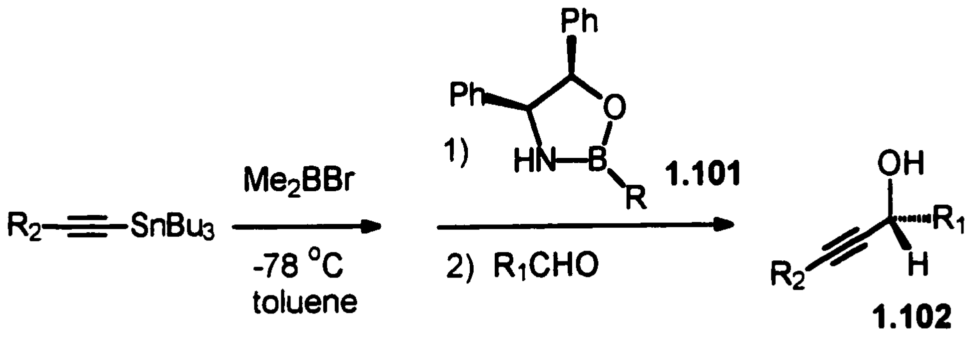
Reaction temperature and groups on the silicon also had a big influence on the enantioselectivities.

Soai and co-workers reported that the use of trialkynylzinc reagents instead of alkynyllithium reagents in the addition onto aldehydes, catalyzed by (*S*)-(+)-(1-methylpyrrolidin-2-yl)diphenylmethanol [(*S*)-MPDPM] (**1.86**) afforded the products in excellent yields (up to 100%) with good enantiomeric excesses (up to 78% ee).[79]

A highly enantioselective alkynylation of aldehydes promoted by chiral oxazaborolidines has been reported by Corey and Cimprich.[80] The procedure involves addition of a solution of bromodimethylborane in methylcyclohexane (1 equiv) to a solution of the alkynylstannane (1,3-1.5 equiv) in toluene at -78 °C. A solution of the oxazaborolidine **1.101** (0.25-1.0 equiv in toluene) is added after 30 min, and after an additional 15 min, the aldehyde is added. The reactions are generally complete after 8-24 h at -78 °C.

Table 1.3 summarizes some representative results. All reactions give excellent enantioselectivities (>85% ee), and good to excellent yields which make the reaction practical and attractive.

Table 1.3. Enantioselective alkynylation of aldehydes.



R_1	R_2	**1.101** R (equiv)	yield of **1.102** (%)	ee (%)
$c\text{C}_6\text{H}_{11}$	Ph	Bu (1.0)	96	90
$c\text{C}_6\text{H}_{11}$	$n\text{C}_5\text{H}_{11}$	Bu (1.0)	82	95
Ph	Ph	Bu (1.0)	78	96
Ph	$n\text{C}_5\text{H}_{11}$	Bu (1.0)	28	94
tBu	Ph	Bu (1.0)	71	97
$c\text{C}_6\text{H}_{11}$	Ph	Ph (0.25)	80	85
$n\text{C}_5\text{H}_{11}$	Ph	Ph (0.25)	77	93

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CHAPTER 2. SYNTHESIS OF 3,3'-DISUBSTITUTED BINAPHTHYLS

2.1. Introduction

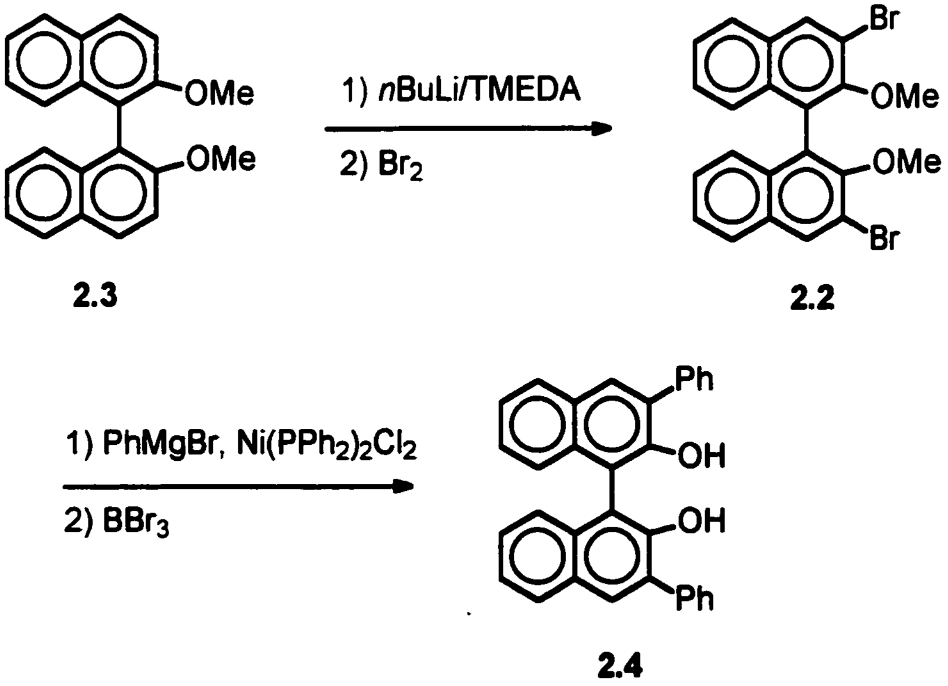
2.1.1. Synthesis of 3,3'-Disubstituted Binaphthyls

A variety of binaphthyl reagents have been reported and used as chiral auxiliaries in enantioselective reactions (see Section 1.2 of this thesis for some examples). Many binaphthyl ligands and chiral auxiliaries are commercially available. Among them, 2,2'-dihydroxy-1,1'-binaphthyl (**2.1**) is the most readily available, and by far the most inexpensive because of its ease of synthesis and resolution into its constituent enantiomers.[1,2] Many of the related commercially available, optical pure, 2,2'-disubstituted binaphthyls are derived from optically pure **2.1**. There are quite a number of successful examples in the literature in which the 3,3'-disubstituted BINOL's have been prepared and used as chiral ligands and auxiliaries.[3] These molecules are available *via* a number of synthetic routes, the most common being directed *ortho*-metallation of suitably *O*-protected BINOL, and oxidative coupling of 3-substituted 2-naphthols.

2.1.1.1. Directed *Ortho* Metallation (DoM) and Suzuki Cross Coupling Methods

The DoM approach has shown the greatest synthetic utility due to the wide range of functionality that can be introduced. The first example of this was reported by Cram and coworkers in 1978 in the synthesis of 3,3'-dibromo substituted system **2.2** (Scheme 2.1).[3a] The methyl protected binaphthyl **2.3** was treated with *n*BuLi in TMEDA, then quenched with Br_2 to give 3,3'-dibromo binaphthyl **2.2**. The molecule **2.2** was substituted with PhMgBr catalyzed by $Ni(PPh_2)_2Cl_2$, followed by demethylation with BBr_3 to give 3,3'-diphenyl-2,2'-dihydroxy-1,1'-binaphthyl (**2.4**).

Scheme 2.1

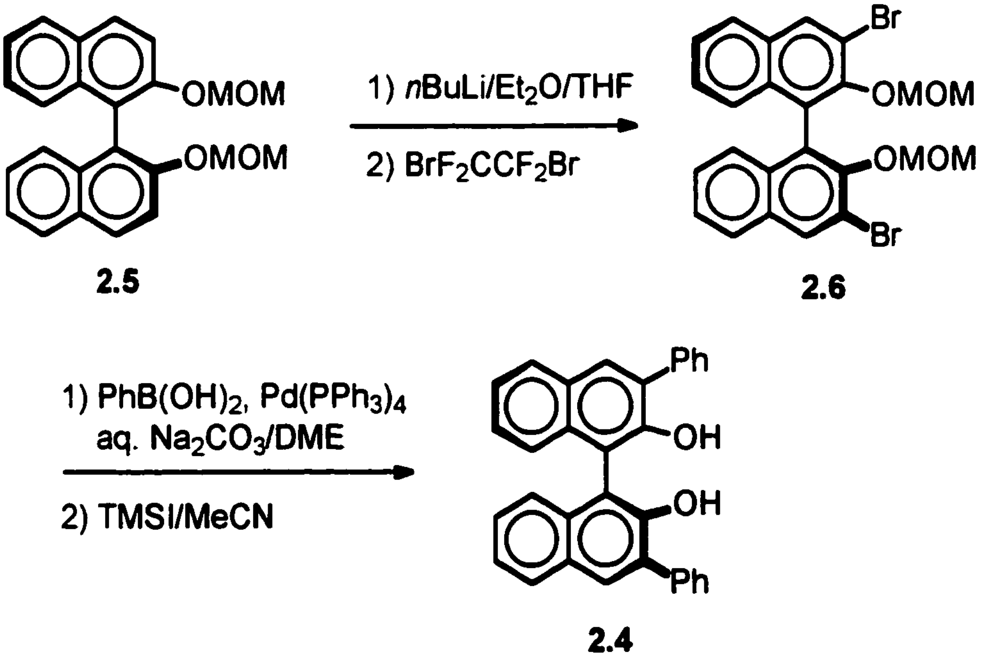


2.3 **2.2** **2.4**

Following the DoM/deprotection sequence developed by Cram, a variety of 3,3'-disubstituted binaphthols have been synthesized.[3b,4] The use of MOM, SEM, and *N,N*-diethylcarbamoyloxy directed metallation groups has also been reported.[5a-d]

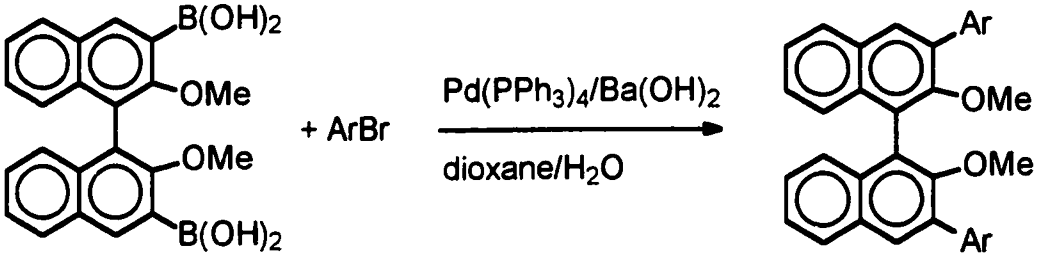
Snieckus and coworkers reported the MOM group-based directed *ortho* metallation route to 3,3'-disubstituted binaphthols.[5a,b] A number of different 3,3'-diaryl binaphthyls were prepared using 3,3'-disubstituted MOM BINOL's. Thus metallation/bromination of **2.5** led to 3,3'-dibromo product **2.6** in good yields, and the dibromo compound **2.6** was treated with phenylboronic acid under Suzuki cross coupling conditions[5c] to furnish **2.7** which, without isolation, was converted into the BINOL **2.4** in 87% yield (Scheme 2.2).

Scheme 2.2



Recently, the Suzuki cross coupling of 3,3'-diboronic acid of BINOL **2.8** with aryl bromides was reported.[6] The reaction was reported to proceed in high yields for the cross coupling of phenyl and 2-naphthyl bromides (Scheme 2.3).

Scheme 2.3



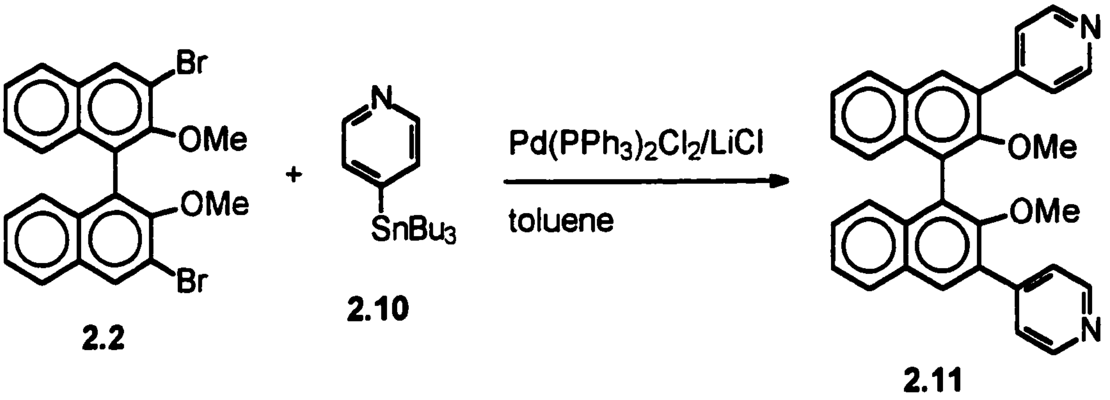
2.8 **2.9**

Ar	yield/%
Ph	73
2-Naph	70

2.1.1.2. Stille Cross Coupling Method

The Stille cross coupling has also been used in the synthesis of 3,3'-disubstituted BINOL. Reaction of dibromide **2.2** with 4-pyridyltributyltin **2.10** under Pd catalysis afforded the 3,3'-disubstituted BINOL **2.11** in 98% yield (Scheme 2.4).[4b] Addition of LiCl to the reaction seems important. Reaction without LiCl gave only a moderate yield of product **2.11**.

Scheme 2.4

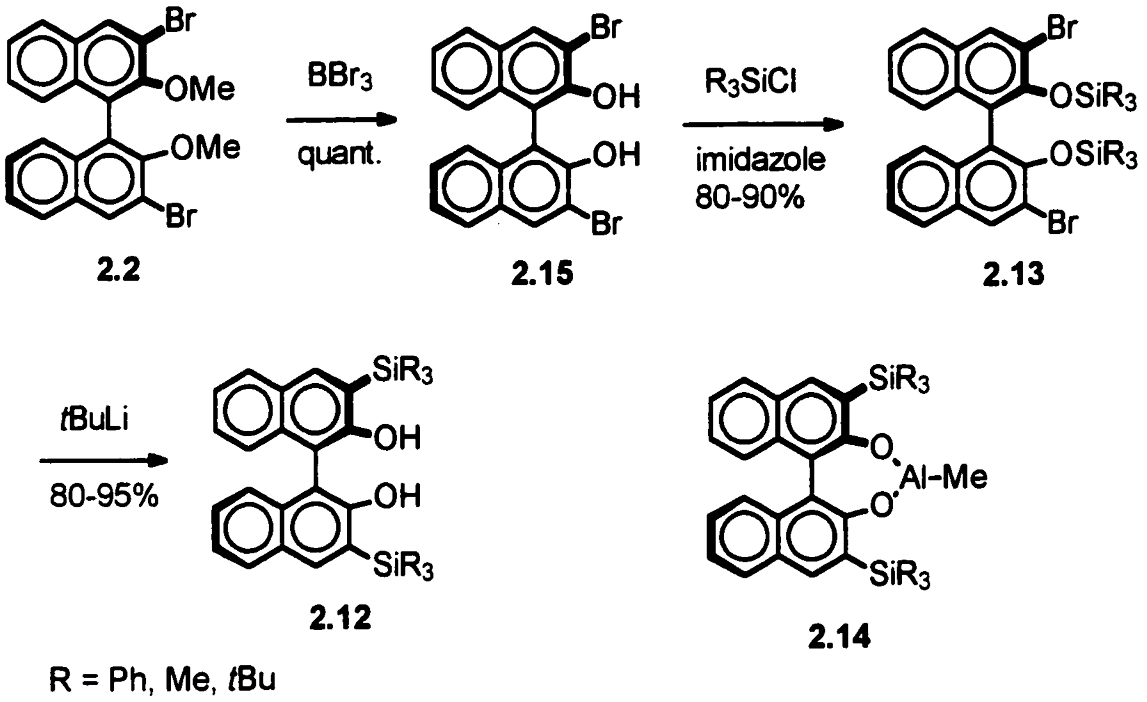


2.2 + **2.10** → **2.11**

2.1.1.3. Intramolecular 1,3-Rearrangement of Bis(trialkylsilyl Ether) of 3,3'-Dibromo BINOL

Yamamoto and co-workers reported an effective method for preparation of sterically hindered binaphthol derivatives **2.12** *via* an intramolecular 1,3-rearrangement of bis(trialkylsilyl ethers) of 3,3'-dibromo-BINOL (**2.13**) with *t*BuLi (Scheme 2.5).[4f] Modified organoaluminum catalysts of **2.14** have been used quite effectively for asymmetric hetero-Diels-Alder reactions[3c,d] and Claisen rearrangements.[3e]

Scheme 2.5



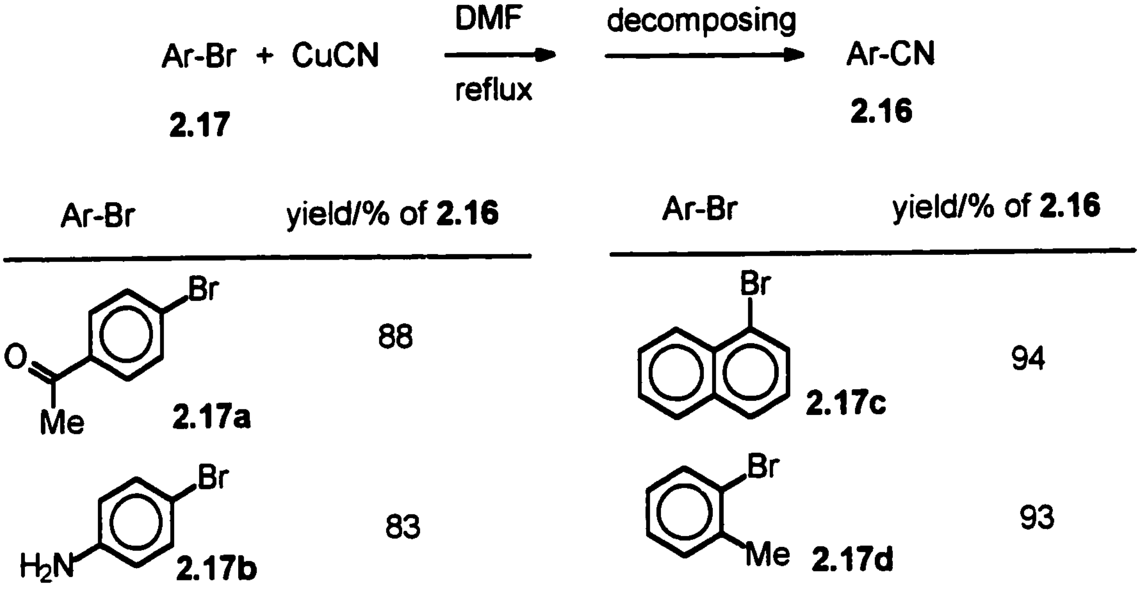
2.2 **2.15** **2.13** **2.12** **2.14**

2.1.2. Introducing the Cyano Group on Aromatic Rings and Unsaturated Compounds

2.1.2.1. Preparing Nitriles from Aryl Halides and Cuprous Cyanide

A commonly used procedure for the preparation of aryl nitriles **2.16** is the reaction of aryl bromides **2.17** and activated aryl chlorides (at high temperature, >190 °C) with cuprous cyanide in DMF under reflux condition to give excellent yield of the cyano product (Scheme 2.6).[7]

Scheme 2.6



The reaction forms a copper complex **2.18** first, which then decomposes (Scheme 2.7). The decomposing procedure is important for ensuring recovery of the products. Friedman and Shechter also improved the preparation by developing more effective procedures for decomposing the complex **2.18**.[7] Three reagents were found to be excellent for destroying the reaction complex. These reagents are aqueous ferric chloride, aqueous ethylenediamine, and aqueous sodium cyanide.

Scheme 2.7

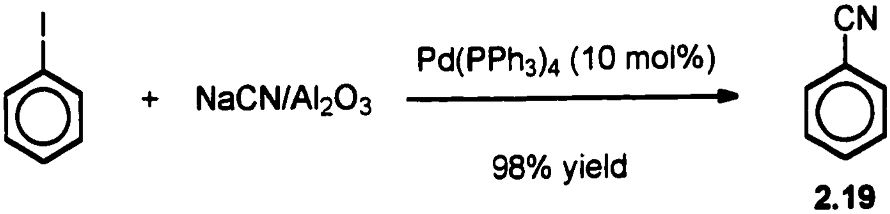
$$2\,\text{Ar-X} + \text{CuCN} \longrightarrow \underset{\textbf{2.18}}{[\text{Ar-CN}]_2\text{CuX}} + \text{CuX}$$

$$\underset{\textbf{2.18}}{[\text{Ar-CN}]_2\text{CuX}} \longrightarrow 2\,\text{Ar-CN} + \text{CuX}$$

2.1.2.2. Alumina Assisted Aryl Cyanation

Regen and Dalton reported an improved procedure for aryl cyanation using $Pd(PPh_3)_4$ based on the use of neutral alumina either as a support for NaCN or as a co-catalyst.[8] Reaction of $NaCN/Al_2O_3$ with iodobenzene in toluene in the presence of 10% $Pd(PPh_3)_4$ at 80 °C for 2 h afforded a quantitative conversion to the nitrile **2.19** (Scheme 2.8). Impregnated NaCN on alumina was used. The pre-treatment of NaCN was done by mixing NaCN with Al_2O_3 in water, evaporating off the water and drying the mixture at 110 °C for 4 h *in vacuo*.[9]

Scheme 2.8

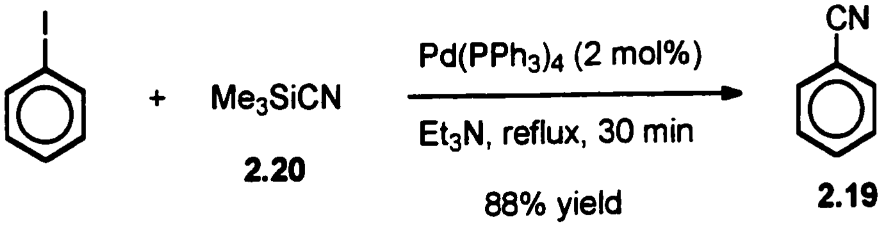


2.19

2.1.2.3. Cyanation of Aryl Halides by Trimethylsilyl Cyanide

Chatani and Hanafusa reported a synthetic method for aryl cyanides based on a palladium-catalyzed reaction of aryl halides with trimethylsilyl cyanide (**2.20**).[10] For example, iodobenzene, **2.20**, and $Pd(PPh_3)_4$ in Et_3N were allowed to react under reflux for 30 min to give benzonitrile (**2.19**) in 88% yield (Scheme 2.9).

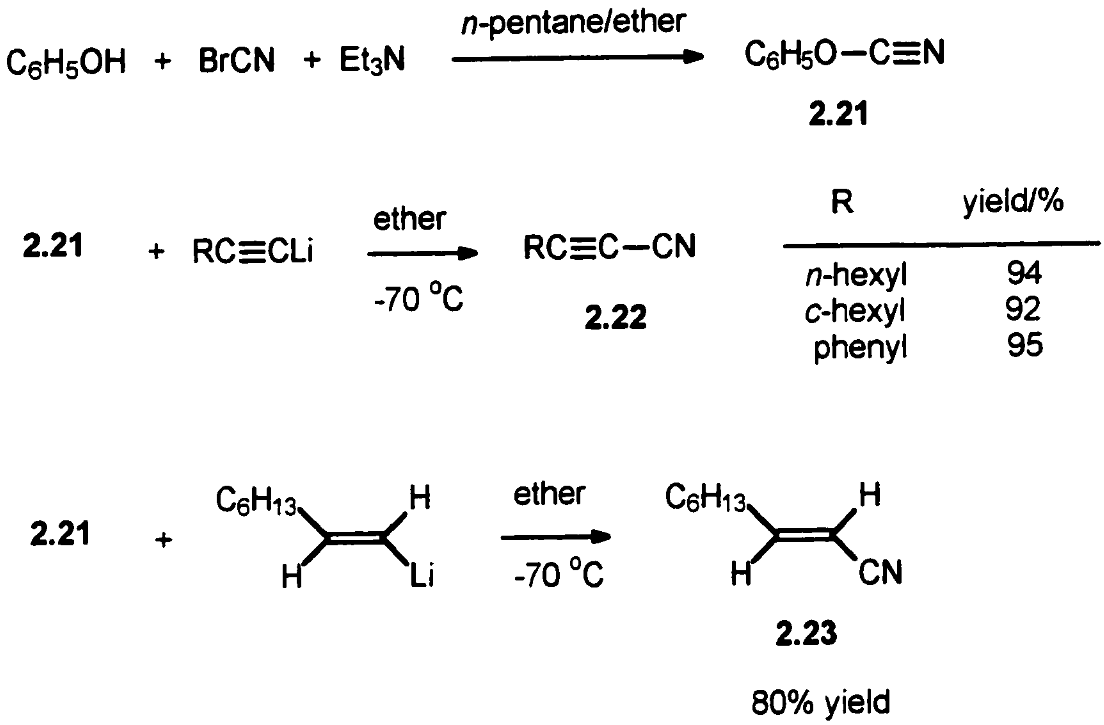
Scheme 2.9



2.1.2.4. Preparation of α,β-Unsaturated Nitriles

Zweifel and Murray reported an improved procedure for the preparation of phenyl cyanate (**2.21**) and its utilization for the synthesis of α,β-unsaturated nitriles.[11] The preparation of **2.21** was accomplished by treatment of a mixture of phenol and cyanogen bromide in *n*-pentane/ether at 0 °C for 1 h (Scheme 2.10). In turn **2.21** could be used as the electrophile for trapping lithium acetylenides and 1-lithio-1-alkenes to afford 2-alkynenitriles **2.22** and 2-alkenenitriles **2.23**, respectively, all in good to excellent yields (Scheme 2.10).

Scheme 2.10



R	yield/%
n-hexyl	94
c-hexyl	92
phenyl	95

2.1.3. Trifluoromethylations of Aromatic Rings

Trifluoromethylated compounds have found a large number of industrial uses from dyes[12,13] and polymers[14], to pharmaceuticals and agrochemicals[15,16]. A number of reviews have been published regarding their preparations.[16,17] It would be interesting to determine if 3,3'-bis(trifluoromethyl)binaphthol could be prepared and used as a chiral auxiliary in the asymmetric synthesis.

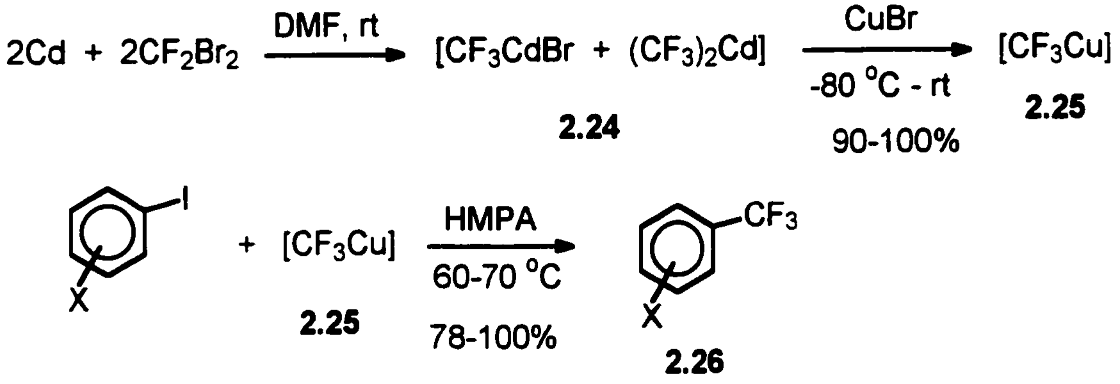
2.1.3.1. Physical Properties of the Trifluoromethyl Group

The Van der Waals radius of 2.7 Å for a trifluoromethyl group compares to 2.0 Å for a methyl group and 3.5 Å for a trichloromethyl group, whilst its Van der Waals volume (hemisphere) of 42.5 $Å^3$ compares to that of 16.8 $Å^3$ for the methyl group.[18] The trifluoromethyl group has an electronegativity (3.5) similar to that of oxygen (3.5)[19] and a larger hydrophobic parameter (1.07)[20]. Moreover, the strong C-F bond in trifluoromethylated compounds confers extra stability upon a molecule.[15] Overall the trifluoromethyl group imparts a variety of physical properties upon a molecule unlike any other substituent.

2.1.3.2. Preparation of Trifluoromethylated Aromatic Compounds *via* (Trifluoromethyl)copper

Burton and co-workers developed a procedure for the preparation of (trifluoromethyl)copper, a reagent which could be used to react with aryl iodides to afford trifluoromethylated aromatic compounds in excellent yields (Scheme 2.11).[21] CF_2Br_2 was treated with cadmium in DMF to give a mixture **2.24**; addition of CuBr to the mixture at -80 °C, then slowly warming up to rt, afforded (trifluoromethyl)copper (**2.25**) solution. Reaction between aryl iodides and **2.25** furnished the trifluoromethylated aromatic compounds **2.26** in 78-100 % yields.

Scheme 2.11

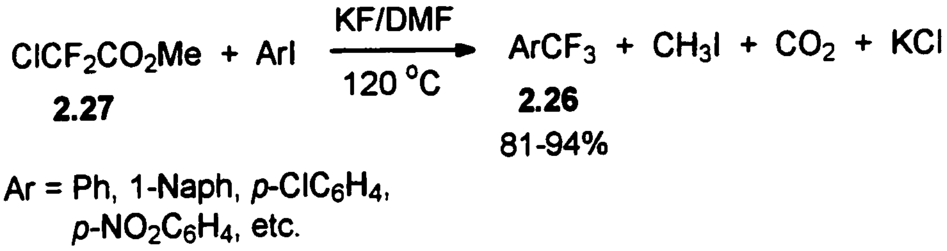


X = H, NO_2, CH_3, OCH_3, Br, Cl

2.1.3.3. Preparation of Trifluoromethylated Compounds *via* Methyl Chlorodifluoroacetate (2.27)

That treatment of methyl chlorodifluoroacetate (**2.27**) with organic halides in the presence of KF and CuI in DMF gave the corresponding trifluoromethylated derivatives (**2.26**) in moderate to high yields has been reported by Chen and co-workers (Scheme 2.12).[22] High temperature (normally at 120 °C) was required for this method; otherwise, no reaction was detected.[22,23]

Scheme 2.12



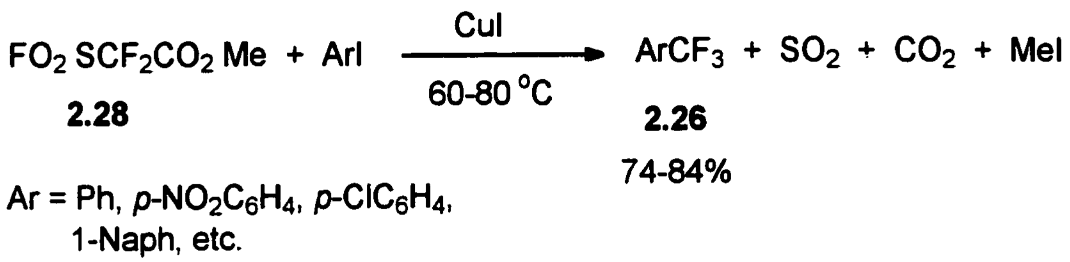
$$\underset{\textbf{2.27}}{ClCF_2CO_2Me} + ArI \xrightarrow[120\ ^{\circ}C]{KF/DMF} \underset{\substack{\textbf{2.26}\\ 81\text{-}94\%}}{ArCF_3} + CH_3I + CO_2 + KCl$$

Ar = Ph, 1-Naph, *p*-ClC_6H_4,
p-$NO_2C_6H_4$, etc.

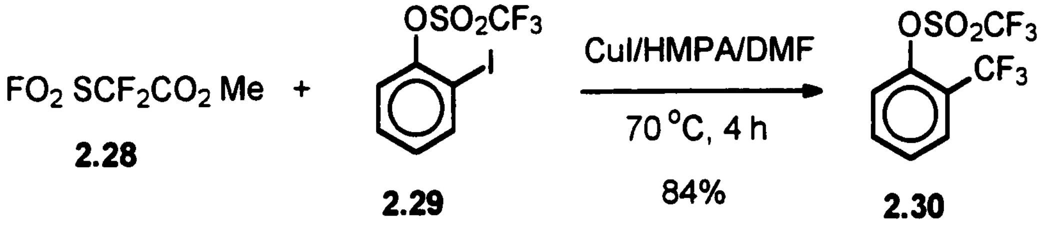
2.1.3.4. Preparation of Trifluoromethylated Compounds *via* Methyl Fluorosulphonyldifluoroacetate (2.28)

Chen and co-workers also reported that methyl fluorosulphonyldifluoroacetate (**2.28**), in the presence of CuI could be used as the source of the trifluoromethyl group which replaced the halogen in aryl iodides (Scheme 2.13).[24] Recently, in accordance with the hypothesis that the reactive species, trifluoromethylcopper **2.25** might exist and could be stabilized by addition of HMPA[21b], Qing and co-workers[23] found that addition of HMPA to a solution of **2.28**, CuI and relatively unreactive iodide **2.29** in DMF, followed by stirring of the resultant mixture for 4 h at 70 °C provided product **2.30** in 84% yield (Scheme 2.14).

Scheme 2.13



Scheme 2.14



2.2. Proposal

A number of examples have shown that substituents on the 3,3'-positions of BINOL can enhance stereoselectivities for certain types of reactions (See section 1.2).[3b-e] However, these substituents are quite limited to groups such as methyl, phenyl, trialkylsilyl. Synthesis of more 3,3'-disubstituted BINOL's with variation of the substituents is still needed. To achieve good enantioselectivities in asymmetric 1,4- and 1,2-addition (it will be discussed in Chapter 4 and 5, respectively), a series of

3,3'-disubstituted BINOL's were designed and synthesized. One might understand more of the reaction mechanisms with consideration of the physical properties of these substituents such as size, electronegativity and by analyzing results from experiments.

Modification of the DoM and Suzuki cross-coupling procedure for the synthesis of 3,3'-diaryl BINOL's[5a,b] was proposed to afford a series of BINOL's with more different 3,3'-disubstituents. The BINOL derivatives with the trifluoromethyl and the cyano group were targeted for synthesis because both have high electronegativities and were previously unknown.

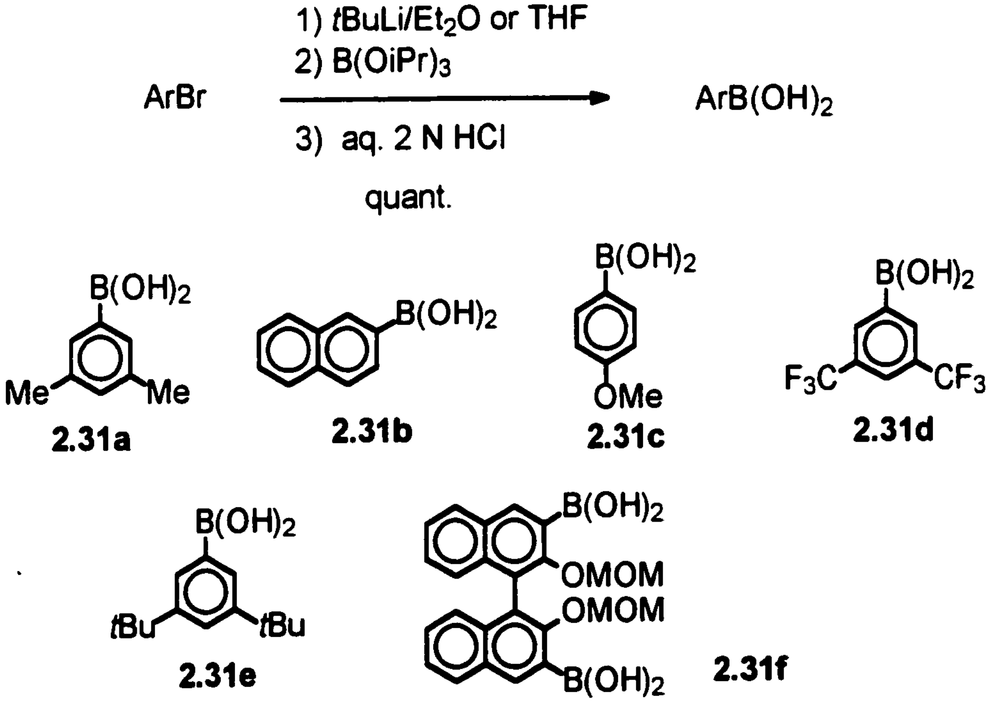
2.3. Results and Discussion

2.3.1. Preparation of Arylboronic Acids

The requisite arylboronic acids that were not commercially available were prepared *via* lithium-bromine exchange (Scheme 2.15). Addition of $B(OiPr)_3$ to the lithiated intermediates in ether or THF from the lithium-bromine exchange method afforded $Li^+[ArB(OiPr)_3]^-$, followed by hydrolysis under acidic condition to provide arylboronic acids **2.31a-2.31e**. Since solubility tests showed that all arylboronic acids formed here were soluble in ether, in the work-up step, the ether layer was separated and the aqueous layer was extracted with ether twice. All organic solutions were combined, dried over Na_2SO_4, and concentrated to give fluffy solids in quantitative yields. These arylboronic acids were pure enough to be used in the following Suzuki cross-coupling without further purification.

3,3'-Dilithio-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl (**2.32**) required for the preparation of **2.31f** was prepared by DoM methodology that will be discussed in section 2.3.3.1. After the preparation of the lithiated intermediate, synthesis followed that described for other arylboronic acids.

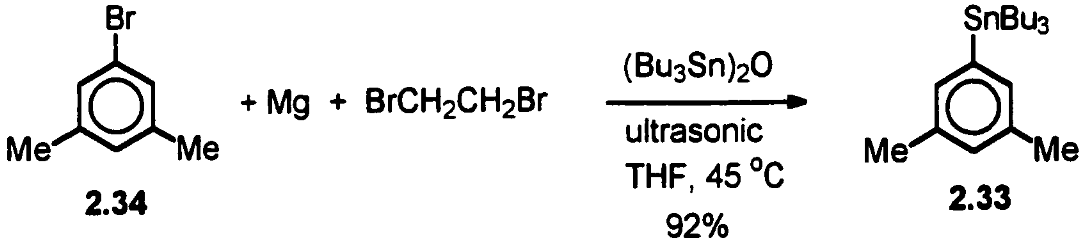
Scheme 2.15



2.3.2. Preparation of 3,5-Dimethylphenyltributylstannane (2.33)

Lee and Dai reported that arylstannanes were prepared by an ultrasound-promoted reaction of aryl bromides, magnesium powder, 1,2-dibromoethane, and bis(tributyltin) oxide in excellent yields.[25] Following this procedure, 3,5-dimethylphenyltributylstannane (**2.33**) was readily prepared from 3,5-dimethylbromobenzene (**2.34**) in 92% yield (Scheme 2.16). A commercial ultrasonic cleaning bath (39 kHz) was used to provide the ultrasound. Addition of $BrCH_2CH_2Br$ to the reaction was essential to initiate the formation of the Grignard reagent under the ultrasonic conditions. The purification was carried out *via* flash column chromatography using hexane alone as eluent without any difficulty.

Scheme 2.16



2.34

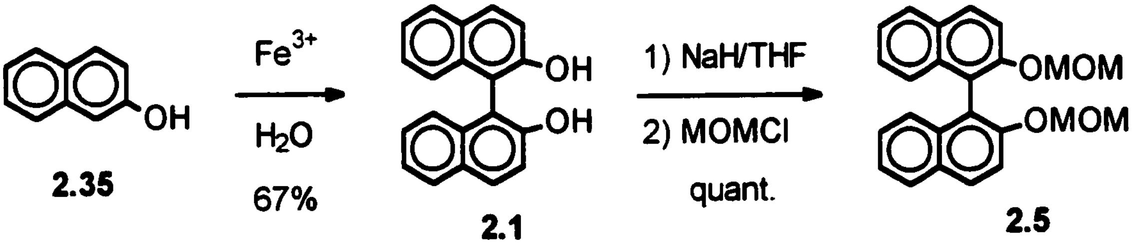
2.33

2.3.3. Preparation of 3,3'-Disubstituted BINOL's

2.3.3.1. Preparation of 3,3'-Dihalo-2,2'-Bis(methoxymethoxy)-1,1'-Binaphthyl and 3,3'-Dimethyl-2,2'-Bis(methoxymethoxy)-1,1'-Binaphthyl

Three steps were required for the preparation of 3,3'-dihalo-2,2'-bis(methoxymethoxy)-1,1'-binaphthyls **2.6** and **2.36** from 2-naphthol (**2.35**). The first, (±)-BINOL (**2.1**) was synthesized following a procedure from the literature.[1a,b] The oxidative coupling of **2.35** suspended in aqueous Fe^{3+} solution gave (±)-BINOL (±)-(**2.1**) in 67% yield (Scheme 2.17). The second, (±)-BINOL was converted into the bis(methoxymethoxy) ether **2.5** by treatment of BINOL with NaH in THF, then MOMCl.

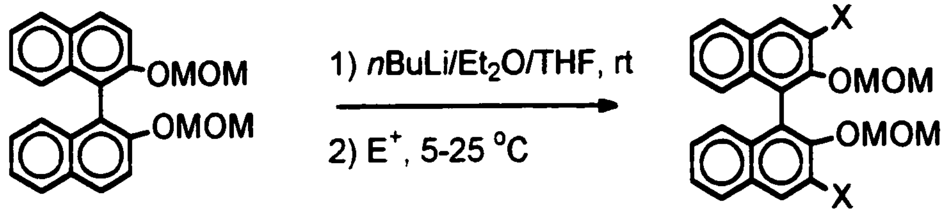
Scheme 2.17



The third step involved the introduction of 3,3'-dibromo substitution onto **2.5**, to give **2.6**. This was achieved *via* DoM methodology developed by Snieckus and co-workers (Scheme 2.18).[5a,b] However, due to high prices and environmental issues, the electrophile, BrF_2CCF_2Br which is a low boiling (47°C) liquid, was replaced by $BrCl_2CCCl_2Br$. This solid can be easily prepared from reaction of tetrachloroethene and bromine. The major drawback of using $BrCl_2CCCl_2Br$ in the reaction was that the 3,3'-dibromo product was contaminated with an amount (maximum possible 50%) of 3,3'-bromochloro by-product. The 3,3'-bromochloro contamination was indicated by MS and ^1H NMR spectroscopy. After a few trials, it was found that when $BrCl_2CCCl_2Br$ was used to trap 3,3'-dilithio-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl (**2.32**), the reaction temperature had to be controlled between 5 °C and 25 °C to ensure that minimum (less than 5% from ^1H NMR spectroscopy) chlorinated products formed in the reaction.

Use of iodine and methyl iodide as electrophiles gave the 3,3'-diiodo compound **2.36** in 88% yield and the 3,3'-dimethyl compound **2.37** in 96% yield, respectively (Scheme 2.18). Similar to the preparation of **2.6**, the trapping temperature had to be controlled between 5 °C and 25 °C to ensure the high yield. Best results were obtained where iodine and methyl iodide were added into the reaction in one portion, quickly.

Scheme 2.18

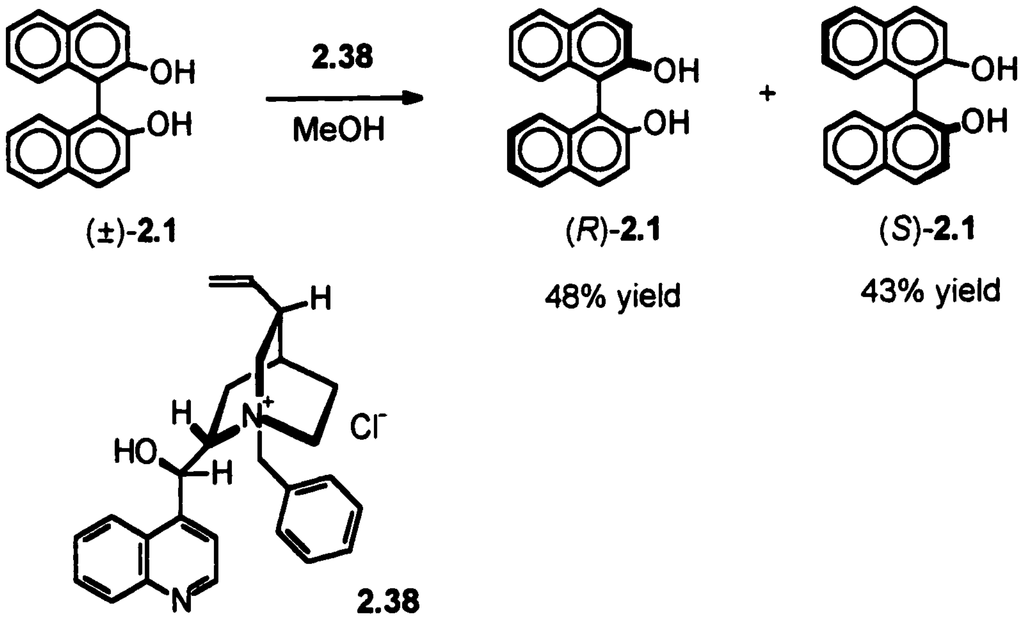


2.5

$E^+ = BrCl_2CCCl_2Br$	**2.6** X = Br (85% yield)
$E^+ = I_2$	**2.36** X = I (88% yield)
$E^+ = MeI$	**2.37** X = Me (96% yield)

To prepare (*R*)-**2.6**, (*R*)-**2.36** and (*R*)-**2.37**, (*R*)-**2.1** was used in the first step. (*R*)-**2.1** was obtained by resolution of (±)-BINOL (**2.1**) according to the literature.[2b] Following the procedure, using the chiral resolving agent, (8*S*,9*R*)-(-)-*N*-benzylcinchonidinium chloride **2.38**, enantiomerically pure (*R*)-**2.1** and (*S*)-**2.1** were obtained in 48% and 43% yields, respectively, without much difficulty (Scheme 2.19).

Scheme 2.19

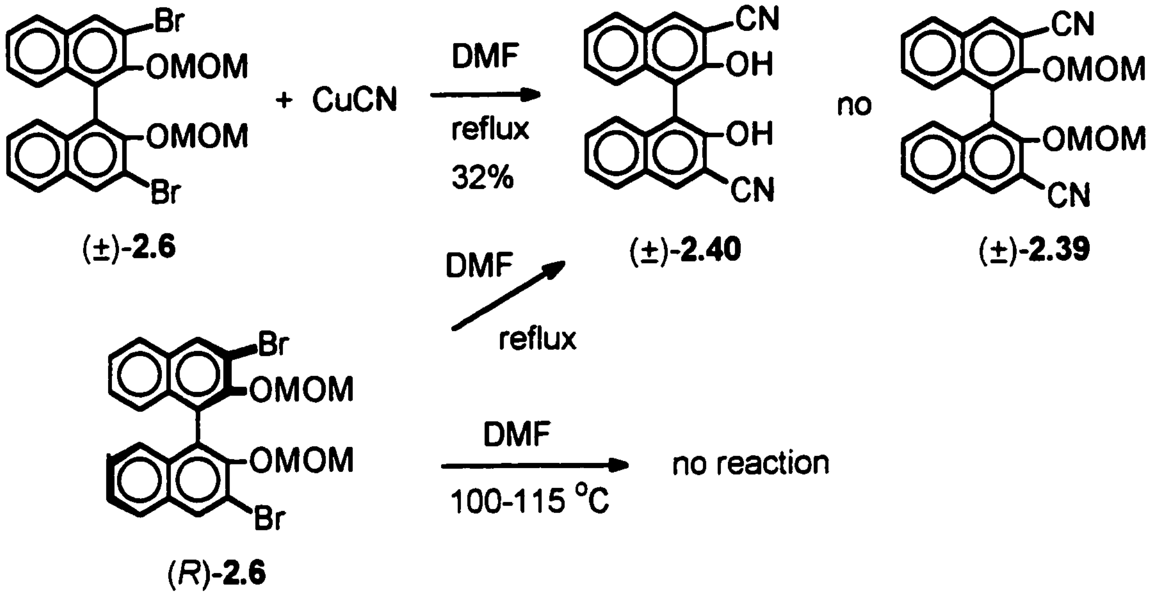


2.3.3.2. Preparation of 3,3'-Dicyano-2,2'-Bis(methoxymethoxy)-1,1'-Binaphthyl (2.39)

2.3.3.2.1. Reaction of Bromide 2.6 and CuCN

In accordance with a procedure for preparing aryl cyanides from aryl bromides,[7] reaction of **2.6** with CuCN in DMF under reflux did take place and afforded a 32% yield of 3,3'-dicyano-2,2'-dihydroxy-1,1'-binaphthyl (**2.40**) instead of **2.39** (Scheme 2.20). However, purification of the product proved to be very difficult due to the abnormal solubility and crystallization of **2.40** and impurities in the reaction mixture. By solubility tests, it was found that the crude mixture dissolved mostly in THF, moderately in CH_3CN and EtOAc, and did not or barely dissolved in CH_2Cl_2, $CHCl_3$, MeOH or hexanes. After many attempts, a successful purification procedure which required column chromatography three times and recrystallization from THF/CH_3CN/CH_2Cl_2 solvent system was employed to afford pure **2.40**. The high reaction temperature (153 °C) might be the main factor for the MOM ether being cleaved off. Besides the cleavage, the high temperature caused the reaction to form racemic product **2.40** when (*R*)-**2.6** was the starting material, despite the claim that the binaphthyl compounds could stand high temperature without racemization.[26] Thus, the procedure was not suitable for preparation of enantiomerically pure 3,3'-dicyano-2,2'-dihydroxy-1,1'-binaphthyl. Attempts to effect the reaction at low temperature (100-115 °C) to avoid racemization were unsuccessful: no products were detected by TLC after 24 h.

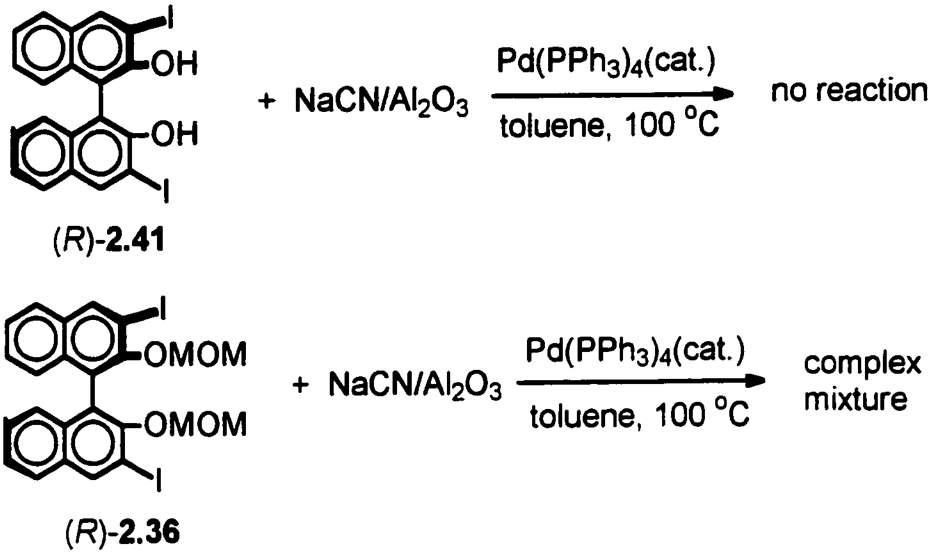
Scheme 2.20



2.3.3.2.2. Reaction of Iodide and NaCN/Al_2O_3 Catalyzed by $Pd(PPh_3)_4$

Following a procedure in the literature,[9] impregnated NaCN/Al_2O_3 was prepared quite readily. The reaction of **2.41** and NaCN/Al_2O_3 in toluene catalyzed by $Pd(PPh_3)_4$ at 100 °C provided no product (Scheme 2.21). Under the same reaction conditions, **2.36** did react with NaCN/Al_2O_3, but the reaction gave a complicated mixture which was difficult to purify. It was recognized that this method was not an effective way to provide the target molecule due to the complex reaction nature.

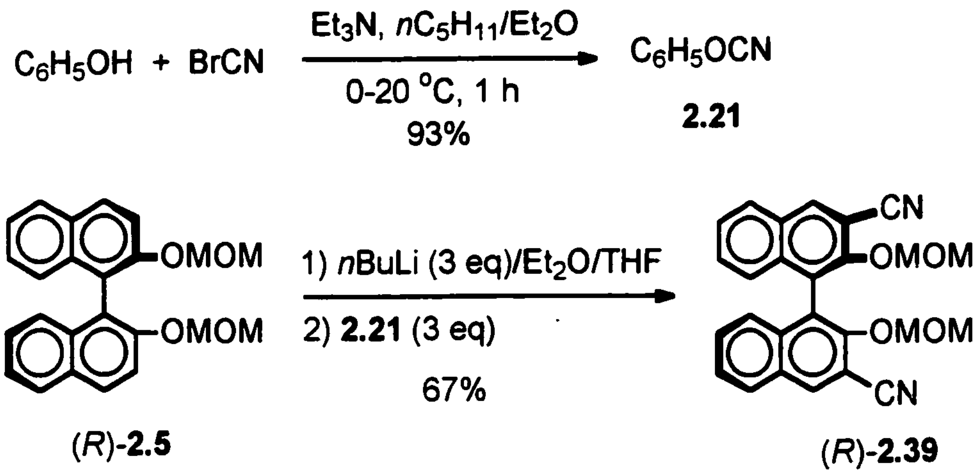
Scheme 2.21



2.3.3.2.3. Reaction of 3,3'-Dilithio Binaphthyl with Phenyl Cyanate (2.21)

After unsuccessful attempts, our attention was turned to the method for preparation of α,β-unsaturated nitriles developed by Zweifel and co-workers.[11] Because of the similarity of lithium acetylenides, vinyllithium compounds, and aryllithiums one might prepare **2.39** by the reaction of a 3,3'-dilithio 2,2-bis(methoxymethoxy)-binaphthyl and phenyl cyanate (**2.21**). 3,3'-Dilithio-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl (**2.32**) could be easily obtained by DoM methodology which has been described previously. **2.21** was prepared by reacting phenol with cyanogen bromide in pentane/ether in excellent yield (93%) (Scheme 2.22). Therefore, **2.32** prepared by treating (*R*)-**2.5** with *n*BuLi at rt was quenched with **2.21** at 5-25 °C to afford (*R*)-**2.39** in 67% yield without optimization.

Scheme 2.22

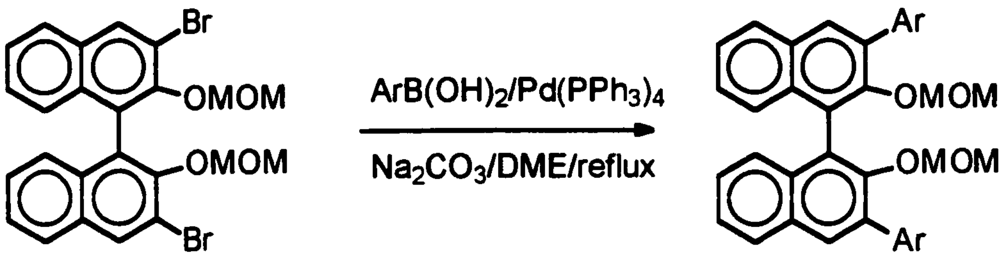


2.3.3.3. Preparation of 3,3'-Diaryl-2,2'-Bis(methoxymethoxy)-1,1'-Binaphthyls

2.3.3.3.1. *Via* Suzuki Cross-Coupling Method

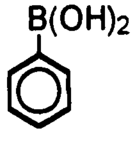
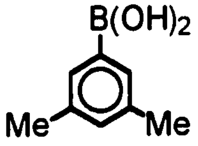
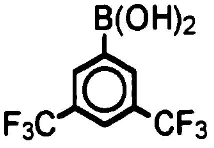
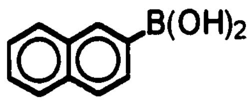
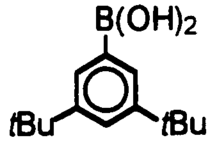
The Suzuki cross-coupling reaction of 3,3'-dibromo-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl **2.6** was carried out in DME using aqueous Na_2CO_3 under a nitrogen or argon atmosphere. The cross-coupling reactions provided 3,3'-diaryl-2,2'-bis(methoxymethoxy)-1,1'-binaphthyls **2.7** and **2.43-2.47** in excellent yields with a variety of arylboronic acids (Scheme 2.23). In all cases, the desired 3,3'-diaryl product was readily purified by flash column chromatography. Large excesses of arylboronic acids were used to suppress the formation of the 3-monosubstituted products and to ensure that the reaction proceeded to completion.

Scheme 2.23



(±) - or (*R*)-**2.6**

2.7, **2.43-2.47**

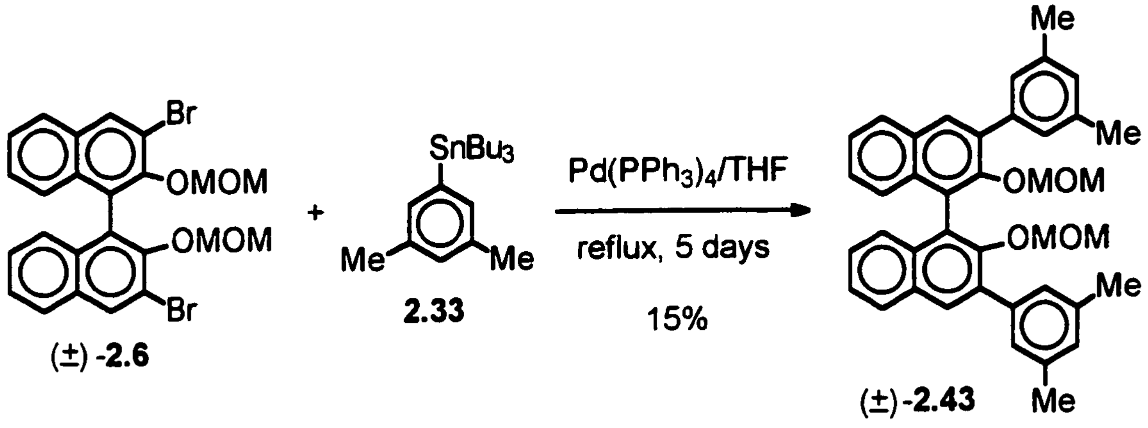
$ArB(OH)_2$	product/yield	$ArB(OH)_2$	product/yield
 **2.42**	(±) - or (*R*)-**2.7** 85%	 **2.31c**	(±) - or (*R*)-**2.45** 92%
 **2.31a**	(±) - or (*R*)-**2.43** 93%	 **2.31d**	(*R*)-**2.46** 85%
 **2.31b**	(±) - or (*R*)-**2.44** 85%	 **2.31e**	(*R*)-**2.47** 99%

When (±)-**2.31f** was used to react with 3,5-dimethylphenyl bromide **2.34** under the same conditions, TLC of the reaction mixture showed that a complicated mixture developed. The desired product (±)-**2.43** was detected as a minor component in the mixture. The reason for this might be that the binaphthyl nucleophile was not strong enough or was too bulky to react with the palladium inserted aryl bromide intermediate during the catalytic cycle.[5e] Changing the catalyst precursor from $Pd(PPh_3)_4$ to $Pd(PPh_3)_2Cl_2$ did not improve the reaction.

2.3.3.3.2. *Via* Stille Cross-Coupling Method

Stille cross-coupling between (±)-**2.6** and **2.33** in THF catalyzed by $Pd(PPh_3)_4$ under reflux conditions was very slow and provided a low yield after five days (Scheme 2.24). Changing the catalyst to $Pd(PPh_3)_2Cl_2$/CuI did not improve the reaction. However, Fujita and co-workers reported a successful Stille cross-coupling between dibromide **2.2** with 4-pyridine tributyltin **2.10** catalyzed by $Pd(PPh_3)_2Cl_2$ and LiCl (Scheme 2.4).[4b] The reaction in the absence of LiCl largely reduced the yield of product. Although it was not clear what role LiCl played in the reactions, the presence of LiCl in the reaction was important for obtaining the excellent yield (98%). It might be worthwhile to try their catalyst system in our attempts in the future.

Scheme 2.24



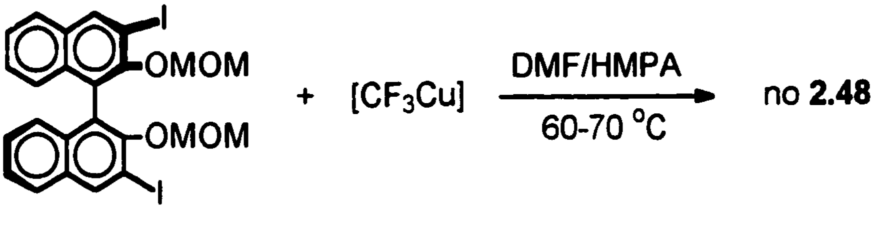
2.3.3.4. Preparation of (*R*)-3,3'-Bis(trifluoromethyl)-2,2'-Bis(methoxymethoxy)-1,1'-Binaphthyl (2.48)

2.3.3.4.1. *Via* Burton's Method

Attempts to obtain **2.48** using Burton's method[21] were unsuccessful. Following the literature procedure, [CF_3Cu] was prepared *in situ* and then allowed to react with **2.36**. This provided no desired target molecule **2.48**, but a complicated mixture resulted instead (Scheme 2.25).

Scheme 2.25

$$2Cd + 2CF_2Br_2 \xrightarrow{\text{DMF, rt}} [CF_3CdBr + (CF_3)_2Cd] \xrightarrow[-78\ ^{\circ}C\ -\ rt]{\text{CuBr/HMPA}} [CF_3Cu]$$

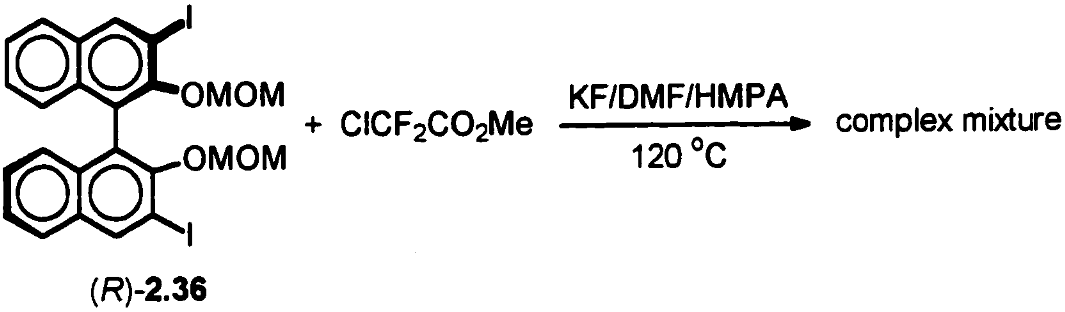


(*R*)-**2.36**

2.3.3.4.2. Using Methyl Chlorodifluoroacetate

The reaction of **2.36**, methyl chlorodifluoroacetate (**2.27**) and KF in DMF/HMPA at 120 °C also gave a complicated mixture in which very little product **2.48** formed (Scheme 2.26). Purification was not performed. The problem of forming a mixture might be due to the high temperature. However, if the reaction temperature was below 120 °C, no reaction was observed, and the starting material and reagent were recovered unchanged. The recovery of the reagent revealed that a reaction temperature higher than 120 °C was required to effect the desired reaction.[27]

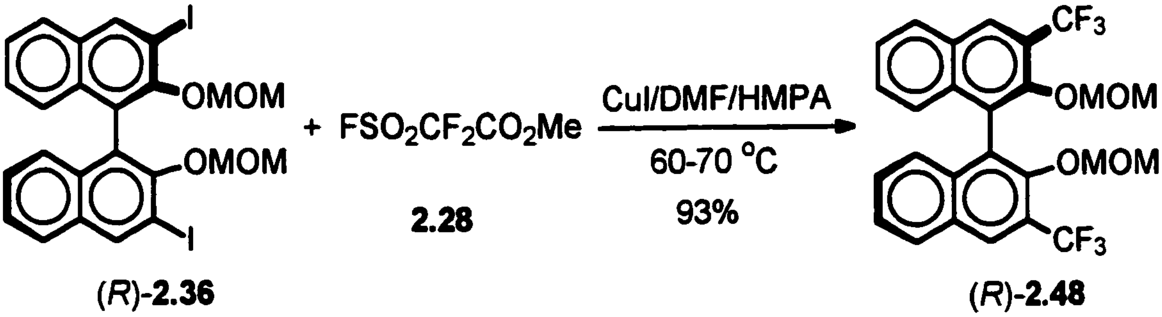
Scheme 2.26



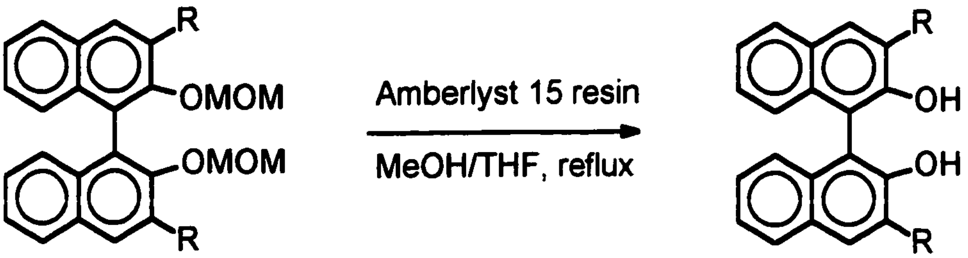
2.3.3.4.3. Using Methyl Fluorosulphonyldifluoroacetate

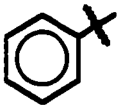
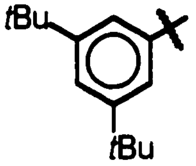
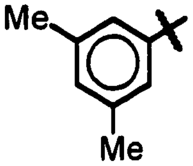
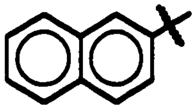
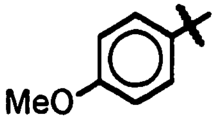
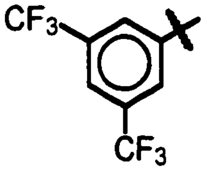
After many failed attempts, the use of methyl fluorosulphonyldifluoroacetate (**2.28**) proved to be an excellent method for the preparation of **2.48**. Reaction of (*R*)-**2.36**, methyl fluorosulphonyldifluoroacetate and CuI in DMF/HMPA at 60-70 °C gave (*R*)-**2.48** in 93% yield (Scheme 2.27). The product was readily purified by column chromatography.

Scheme 2.27



Scheme 2.28



R	product/yield	R	product/yield
	(±)- & (*R*)-**2.4** 89%		(*R*)-**2.53** 98%
	(±)- & (*R*)-**2.49** 93%	CF_3	(*R*)-**2.54** 98%
	(±)- & (*R*)-**2.50** 91%	Br	(*R*)-**2.15** 96%
	(±)- & (*R*)-**2.51** 90%	I	(*R*)-**2.41** 94%
	(*R*)-**2.52** 97%	Me	(*R*)-**2.55** 100%
		CN	(*R*)-**2.40** 96%

2.3.3.5. Preparation of 3,3'-Disubstituted-2,2'-Dihydroxy-1,1'-Binaphthyls

3,3'-Disubstituted-2,2'-bis(methoxymethoxy)-1,1'-binaphthyls were treated with Amberlyst 15 resin in MeOH/THF under reflux condition to give deprotected 3,3'-disubstituted-2,2'-dihydroxy-1,1'binaphthyls (Scheme 2.28). All reactions carried out gave excellent yields of products. The purification for the deprotected binaphthyls was performed *via* either crystallization or column chromatography followed by crystallization depending on how pure the individual reaction mixture was and the solubility of the product.

2.4. Conclusion

Application of Suzuki cross-coupling methodology proved to be efficient for the preparation of a number of 3,3'-diaryl-2,2'-bis(methoxymethoxy)-1,1'-binaphthyls **2.7** and **2.43-2.47**. Preparation of the dibromide **2.6** by the DoM method, followed by trapping with $BrCl_2CCCl_2Br$ instead of BrF_2CCF_2Br was successful and practical. However, the Suzuki cross-coupling reaction of aryl bromide and 2,2'-bis(methoxymethoxy)-1,1'-binaphthyl-3,3'-diboronic acid **(2.31f)** was not successful. In the future, further variation of the reaction conditions might improve the yield. Then Stille cross-coupling method was tried on the reaction of (3,5-dimethylphenyl)tributylstannane and **2.6**, resulting in low yield of product. Fujita and co-workers[4b] reported an excellent Stille reaction between **2.2** and **2.10** by the addition of LiCl, so it might be worthwhile to try their catalyst system in our future attempts.

To furnish 3,3'-dicyanated binaphthyl **2.39**, trapping the dilithiated intermediate **2.32** in the DoM process by phenyl cyanate (**2.21**) was successful. 3,3'-Bis(trifluoromethyl) binaphthyl **2.48** was effectively prepared by the reaction between methyl fluorosulphonyldifluoroacetate (**2.28**) and the diiodide **2.36**.

2.5. Experimental

2.5.1. General

IR spectra were recorded on a Bomem MB-100 infrared spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded using a Bruker AM-250 spectrometer. Chemical shifts are given in parts per million (ppm) downfield from tetramethylsilane (TMS). The ^{1}H NMR samples were run in deuteriochloroform containing ca. 0.01% TMS as an internal standard ($\delta = 0.0$). Spectra are tabulated in the order: chemical shift, assignment, numbers of protons, multiplicity, coupling constant. The spectral reference for ^{13}C NMR spectra was $CDCl_3$ ($\delta = 77.0$). The spectral reference for ^{19}F NMR spectra was CF_3COOH ($\delta = 76.53$ upfield of $CFCl_3$). The melting points of newly synthesized materials are uncorrected. Elemental analyses were conducted by M-H-W Laboratories, Phoenix, Arizona. Mass spectra were recorded on a GC-MS (Hewlett Packard G 1800A GCD System) or a Kratos MA890 mass spectrometer using electron impact (EI, 70 ev) ionization if the mass was over 430.

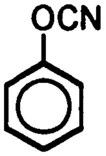
All reactions involving air or moisture sensitive reagents were performed under an argon or nitrogen atmosphere on the bench using standard Schlenk techniques. Reactions were monitored (where necessary) by thin-layer chromatography (TLC) on commercial silica pre-coated aluminum plates (silica gel 60, F_{254}).

2.5.2. Materials

Solvents were dried prior to use. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were dried by distillation from sodium/benzophenone. Dichloromethane (CH_2Cl_2), DMF, HMPA and *n*-pentane were dried by distillation from calcium hydride. Boron trifluoride ethyl etherate ($BF_3{\cdot}OEt_2$) was treated with a small quantity of ethyl ether (to ensure an excess of this component, ca. 5 ml/100 mL $BF_3{\cdot}OEt_2$) and distilled (60-62 °C/aspirator vacuum). Chloromethyl methyl ether was prepared according to the literature.[28] $BrCl_2CCCl_2Br$ was prepared in 85% yield from the reaction of dichloroethene and bromine in dichloromethane under reflux condition for 3 days, followed by the removal of organic solvent. Unless otherwise noted, chemicals were purchased from the Aldrich Chemical Company.

2.5.3. Synthesis

2.5.3.1. Preparation of Phenyl Cyanate (2.21)



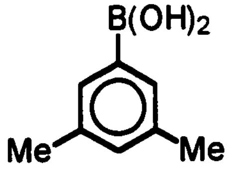
The procedure was adapted from the literature.[11] To a dry 250-mL two-necked round-bottomed flask equipped with a magnetic stirrer, thermometer and a rubber septum, was placed phenol (18.8 g, 0.20 mol), *n*-pentane (100 mL), and anhydrous diethyl ether (40 mL) under an argon atmosphere. The reaction mixture was cooled in an ice bath, then it was treated with cyanogen bromide (42.0 mL of a 5 M solution in CH_3CN). While vigorously stirring, triethylamine (29.3 mL, 0.21 mol) was added dropwise *via* a syringe at a rate such as to prevent the temperature of the reaction mixture from rising above 30 °C. The resulting white slurry was stirred vigorously for an additional 1 h at 0 °C, then the precipitated triethylamine hydrobromide was filtered on a Buchner funnel. The solid was washed with *n*-pentane (4 x 50 mL) and the combined organic solution was evaporated under reduced pressure to remove solvent. The resulting slight yellow oil was distilled to give 27.2 g of **2.21** (93%). The reagent was stored at 4 °C under argon. **2.21**: IR (neat): 2251, 1585, 1480, 1176 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.20-7.58 (ArH, 5 H, m); ^{13}C NMR ($CDCl_3$): δ 152.3, 130.0, 126.3, 114.6, 108.1.

2.5.3.2. Preparation of Arylboronic Acids (2.31a-2.31f)

2.5.3.2.1. General Precedure: Preparation of Arylboronic Acids (2.31a-2.31e)

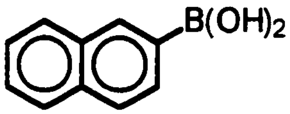
To a solution of aryl bromide (1 mmol) in THF or Et_2O (4 mL) at -78 °C, was added *t*BuLi (2.2 mmol). After 15 min, $B(OiPr)_3$ (3 mmol) was added and the resulting mixture was allowed to warm to room temperature for 3 h. Aqueous 2 M HCl (2.2 mmol) was added to the reaction mixture, and it was stirred at room temperature for 30 min. Water (4 mL) and Et_2O (4 mL) were added to the mixture and mixed well, then the organic layer was separated, washed with brine (4 mL), dried over Na_2SO_4, filtered and the organic solvent was removed under reduced pressure to afford arylboronic acid. All aryl boronic acids prepared were used without further purification in the following Suzuki cross-coupling reaction.

(a) 3,5-Dimethylphenylboronic Acid (2.31a)



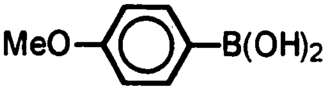
3,5-Dimethylphenyl bromide (1.0 g, 5.4 mmol) in THF (20 mL) was treated with *t*BuLi (7.0 mL of 1.7 M solution in hexane, 11.9 mmol) at -78 °C, followed by trapping with $B(OiPr)_3$ (3.7 mL, 16.2 mmol), acidification with 2 M HCl (6.0 mL), and workup giving 0.77 g of **2.31a** as a white fluffy solid (95%).

(b) 2-Naphthylboronic Acid (2.31b)



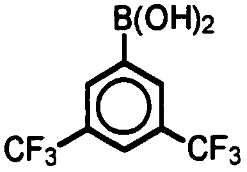
2-Naphthyl bromide (1.12 g, 5.4 mmol) in THF (20 mL) was treated with *t*BuLi (7.0 mL of 1.7 M solution in hexane, 11.9 mmol) at -78 °C, followed by trapping with $B(OiPr)_3$ (3.74 mL, 16.2 mmol), acidification with 2 M HCl (6.0 mL), and workup giving 0.89 g of **2.31b** as a white fluffy solid (96%).

(c) 4-Methoxyphenylboronic Acid (2.31c)



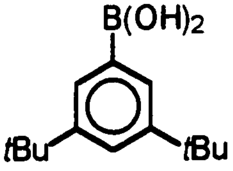
4-Methoxyphenyl bromide (0.7 mL, 5.4 mmol) in THF (20 mL) was treated with *t*BuLi (7.0 mL of 1.7 M solution in hexane, 11.9 mmol) at -78 °C, followed by trapping with $B(OiPr)_3$ (3.7 mL, 16.2 mmol), acidification with 2 M HCl (6.0 mL), and workup giving 0.77 g of **2.31c** as a white solid (94%).

(d) 3,5-Bis(trifluoromethyl)phenylboronic Acid (2.31d)



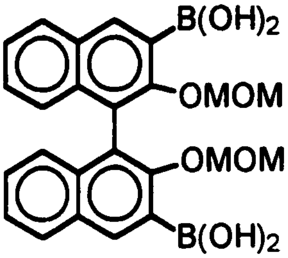
3,5-Bis(trifluoromethyl)phenyl bromide (4.9 g, 16.7 mmol) in Et_2O (90 mL) was treated with *t*BuLi (21.6 mL of 1.7 M solution in hexane, 36.8 mmol) at -78 °C, followed by trapping with $B(OiPr)_3$ (8.5 mL, 36.8 mmol), acidification with 2 M HCl (18.5 mL), and workup giving 4.0 g of **2.31d** as a white fluffy solid (93%).

(e) 3,5-Bis(*tert*-butyl)phenylboronic Acid (2.31e)



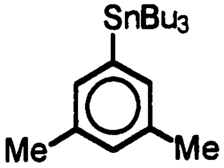
3,5-Bis(*tert*-butyl)phenyl bromide (4.5 g, 16.7 mmol) in Et_2O (90 mL) was treated with *t*BuLi (21.6 mL of 1.7 M solution in hexane, 36.8 mmol) at -78 °C, followed by trapping with $B(OiPr)_3$ (8.48 mL, 36.8 mmol), acidification with 2 M HCl (18.5 mL), and workup giving 3.85 g of **2.31e** as a white fluffy solid (99%).

2.5.3.2.2. Preparation of (±)-2,2'-Bis(methoxymethoxy)-1,1'-Binaphthyl-3,3'-Diboronic Acid (2.31f)



(±)-2,2'-Bis(methoxymethoxy)-1,1'-binaphthyl (**2.5**) (0.25 g, 0.67 mmol) was dissolved in dry Et_2O (12 mL) in a 50 mL round bottom flask under an argon atmosphere. To the mixture with stirring, was added *n*BuLi (1.0 mL of 1.41 M solution in hexane, 1.47 mmol) at room temperature by syringe injection. After the reaction mixture was stirred for 3 h, THF (8 mL) was injected into the flask and then the mixture was stirred for 1 h. The resulting mixture was treated with $B(OiPr)_3$ (0.34 mL, 1.47 mmol). Acidification with 4 M HCl (0.42 mL), and the same workup as that for other arylboronic acids gave 0.28 g of **2.31f** as an off-white solid (91%).

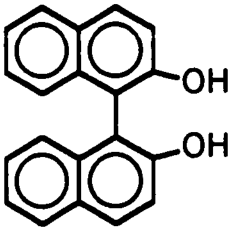
2.5.3.3. Prepartion of 3,5-Dimethylphenyltributylstannane (2.33)



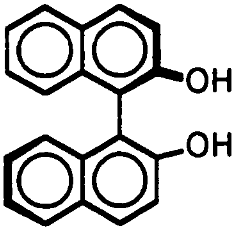
A solution of 3,5-dimethylphenyl bromide (**2.34**) (0.68 mL, 5.0 mmol), magnesium (0.28 g, 11.5 mmol), 1,2-dibromoethane (0.47 mL, 5.5 mmol), and bis(tributyltin)oxide (2.55 mL, 5.0 mmol) in THF (20 mL) was sonicated for 1 h in a commercial ultrasonic cleaning bath (Crest 575HT, 39 kHz) at around 45 °C. After the reaction was complete (monitored by TLC), 75 mL of water was added and extracted with EtOAc (3 x 50 mL). The organic layer was collected, washed with brine (75 mL), dried with Na_2SO_4, filtered and the organic solvent removed under reduced pressure to give an oily liquid. Purification was achieved by flash column chromatography (hexane) to provide 1.82 g of **2.33** (92%) as an oil: ^{1}H NMR ($CDCl_3$): δ 6.88-7.20 (ArH, 3 H, m), 2.30 ($ArCH_3$, 6 H, s), 1.20-1.68 (CH_2, 12 H, m), 0.95-1.18 (CH_2, 6 H, m), 0.89 (CH_3, 9 H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 141.6, 137.0, 134.3, 134.1, 133.8, 129.8, 29.1, 28.9, 27.8, 27.4, 26.9, 21.4, 13.7, 12.2, 9.5, 6.9.

2.5.3.4. Preparation of Binaphthyls

2.5.3.4.1. (±)- and (*R*)-2,2'-Dihydroxy-1,1'-Binaphthyl (2.1)



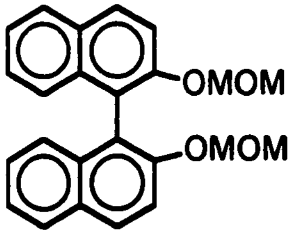
(±)-**2.1**



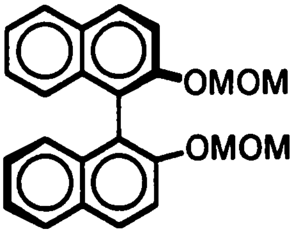
(*R*)-**2.1**

(±)-**2.1** was synthesized following a procedure from the literature[1a,b] and was resolved according to the literature[2b] to give enantiomeric pure (*R*)- and (*S*)-**2.1**. The sample of (*R*)-**2.1** showed $[\alpha]^{25}_{578}$ +36.7° (c = 1.0, THF) [lit[2b] $[\alpha]^{25}_{546}$ +35.4° (c = 1.0, THF)].

2.5.3.4.2. (±)- and (*R*)-2,2'-Bis(methoxymethoxy)-1,1'-Binaphthyl (2.5)



(±)-**2.5**



(*R*)-**2.5**

The preparation followed literature procedures[5a,b] with some modification.

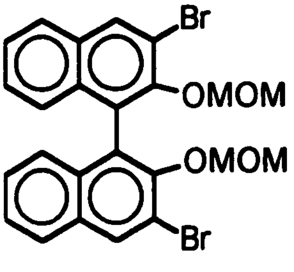
NaH (2.92 g, 60% in oil, 73.0 mmol) was mixed in dry THF (150 mL) in a 500-mL round-bottom flask at 0 °C under an argon atmosphere. To the mixture with stirring, was added a solution of (±)-2,2'-dihydroxy-1,1'-binaphthyl (**2.1**) (9.50 g, 33.2 mmol) in THF (50 mL) in a dropping funnel. After the addition, the mixture was stirred at 0 °C for 1 h, then allowed to warm up to room temperature for 15 min. After the mixture was re-cooled to 0 °C, chloromethyl methyl ether (5.54 mL, 73.0 mmol) was slowly added from the dropping funnel. After the addition, the reaction mixture was warmed to room temperature and stirred for 4.5 h. Saturated aqueous NH_4Cl (50 mL) was added to the flask, then the solvent was removed *in vacuo*. The residue was extracted with CH_2Cl_2 (50 mL x 3). The organic layers were combined, washed with brine (50 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography (EtOAc/hexane: 1/10) and crystallized from CH_2Cl_2/hexane to give a white crystalline product (±)-**2.5** in quantitative yield: mp 89-92 °C (lit[5a] mp 88-91 °C); IR, ^1H NMR, ^{13}C NMR, and MS were similar to that of (±)-**2.5** in the literature.[5a] IR (KBr): υ (max) 1236, 1144, 1028 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.88-8.14 (ArH, 2 H, m), 7.76-7.84 (ArH, 2 H, m), 7.10-7.62 (ArH, 8 H, m), 4.97, 5.08 (OCH_2O, 4 H, d, AB, J_{AB} = 8.5 Hz), 3.10 (OCH_3, 6 H, s); ^{13}C NMR ($CDCl_3$): δ 152.6, 130.0, 129.9, 129.3, 127.8, 126.3, 125.5, 124.0, 121.3, 117.3, 95.2, 55.7; MS *m/e* (relative intensity): 374 (M^+, 100), 298 (90), 270 (71), 239 (23); Anal. Calcd for $C_{24}H_{22}O_4$: C, 76.99; H, 5.92. Found: C, 77.02; H, 5.94. (R)-2,2'-Dihydroxy-1,1'-binaphthyl was used to afford (R)-**2.5** in quantitative yield. mp 98-100 °C. The sample showed $[\alpha]^{25}_{589}$ +95.0° (c = 1.0, THF).

2.5.3.4.3. General Precedure: Preparation of 3,3'-Disubsituted-2,2'-Bis(methoxymethoxy)-1,1'-Binaphthyls (2.6, 2.36, 2.37, and 2.39)

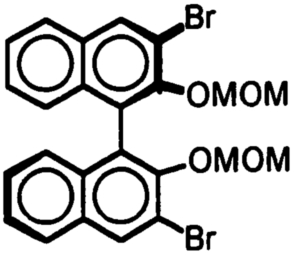
The preparation of the 3,3'-disubstituted binaphthyl compounds followed literature procedures[5a,b] with some modification.

(±)- or (*R*)-2,2'-Bis(methoxymethoxy)-1,1'-binaphthyl (**2.5**) (1 equiv) was dissolved in dry Et_2O (17 mL/1 mmol of **2.5**) in a round bottom flask under an argon atmosphere. To the mixture, with stirring, was added *n*BuLi (3 equiv) at room temperature by syringe injection. After the reaction mixture was stirred for 3 h, THF (11 mL/1 mmol of **2.5**) was injected into the flask and then the mixture was stirred for 1 h. After the flask was cooled in an ice water bath for 5 min, electrophile (3 equiv) was quickly added in one portion. The reaction mixture was stirred for 15 min, quenched with saturated aqueous NH_4Cl and water. The two phases were separated. The aqueous layer was extracted with Et_2O twice. All organic solutions were combined, washed with brine, dried over Na_2SO_4 and concentrated. Subsequent work-up gave the product.

(a) (±)- and (*R*)-3,3'-Dibromo-2,2'-Bis(methoxymethoxy)-1,1'-Binaphthyl (2.6)



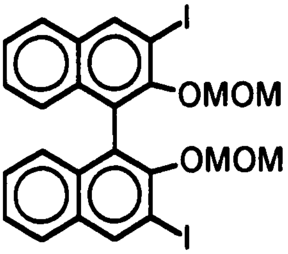
(±)-**2.6**



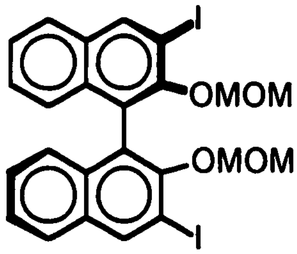
(*R*)-**2.6**

(±)-2,2'-Bis(methoxymethoxy)-1,1'-binaphthyl (**2.5**) (8.80 g, 23.5 mmol) was treated with *n*BuLi (44.10 mL of a 1.6 M solution in hexane, 70.5 mmol) at room temperature and the resulting mixture was quenched with dibromotetrachloroethane (23.0 g, 70.5 mmol). Crude product was purified by column chromatography (EtOAc/hexane: 1/10) and crystallized from Et_2O/hexane to give a white crystalline product (±)-**2.6** (10.60 g) in 85% yield: mp 125-126 °C (lit[5a] mp 124-126 °C); IR, ^1H NMR, ^{13}C NMR, and MS were similar to that of (±)-**2.6** in the literature.[5a] IR (KBr): υ (max) 1235, 1157, 1026 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.25-8.30 (ArH, 2 H, m), 7.78-7.82 (ArH, 2 H, m), 7.18-7.48 (ArH, 6 H, m), 4.81, 4.82 (OCH_2O, 4 H, d, AB, J_{AB} = 6.0 Hz), 2.56 (OCH_3, 6 H, s); ^{13}C NMR ($CDCl_3$): δ 153.2, 141.0, 133.6, 131.8, 131.6, 127.2, 126.7, 126.6, 126.2, 125.6, 99.8, 92.8, 56.6; MS *m/e* (relative intensity): 535 (M^++3, 20), 534 (M^++2, 18), 533 (M^++1, 4), 532 (M^+, 9), 457 (24), 455 (47), 453 (28), 376 (20), 268 (23), 45 (100); Anal. Calcd for $C_{24}H_{20}Br_2O_4$: C, 54.16; H, 3.79. Found: C, 54.10; H, 3.87. (*R*)-2,2'-Bis(methoxymethoxy)-1,1'-binaphthyl was used to afford (*R*)-**2.6** in 84% yield. mp 123-124 °C. The sample showed $[\alpha]^{25}_{589}$ +28.3° (c = 1.0, THF).

(b) (±)- and (*R*)-3,3'-Diiodo-2,2'-Bis(methoxymethoxy)-1,1'-Binaphthyl (2.36)



(±)-**2.36**

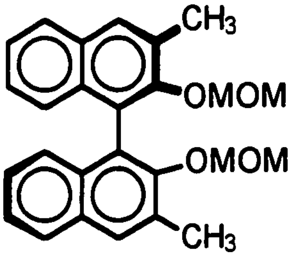


(*R*)-**2.36**

(±)-2,2'-Bis(methoxymethoxy)-1,1'-binaphthyl (**2.5**) (6.50 g, 17.4 mmol) was treated with *n*BuLi (33.0 mL of a 1.6 M solution in hexane, 52.8 mmol) at room temperature and the resulting mixture was quenched with iodine (13.20 g, 52.0 mmol). Crude product was purified by column chromatography (EtOAc/hexane: 1/10) and crystallized from CH_2Cl_2/hexane to give a white crystalline product (**2.36**) (9.60 g) in 88% yield: mp 129-131 °C (lit[5a] mp 127-128 °C); IR, ^1H NMR, ^{13}C NMR, and MS were similar to that of (±)-**2.36** in the literature.[5a] IR (KBr): υ (max) 1232, 1156, 1026 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.50-8.62 (ArH, 2 H, m), 7.70-7.85 (ArH, 2 H, m), 7.10-7.54 (ArH, 6 H, m), 4.81, 4.69 (OCH_2O, 4 H, d, AB, J_{AB} = 5.7 Hz), 2.59 (OCH_3, 6 H, s); ^{13}C NMR ($CDCl_3$): δ 152.2, 140.0, 133.8, 132.8, 132.2, 127.1, 126.7, 126.5, 126.2, 125.8, 99.4, 92.5, 56.5; MS *m/e* (relative intensity): 626 (M^+, 35), 550 (20), 549 (100), 422 (60), 268 (45), 239 (46), 237 (28), 226 (37), 224 (45); Anal.

Calcd for $C_{24}H_{20}I_2O_4$: C, 46.03; H, 3.22. Found: C, 46.05; H, 3.20. (*R*)-2,2'-Bis(methoxymethoxy)-1,1'-binaphthyl was used to afford (*R*)-**2.36**. mp 45-47 °C. The sample showed $[\alpha]^{25}_{589}$ -5.31° (c = 1.0, THF).

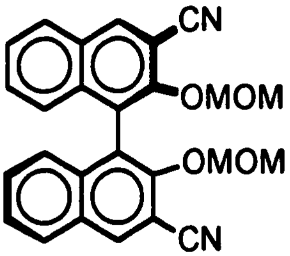
(c) (*R*)-3,3'-Dimethyl-2,2'-Bis(methoxymethoxy)-1,1'-Binaphthyl (2.37)



(*R*)-2,2'-Bis(methoxymethoxy)-1,1'-binaphthyl [(R)-**2.5**] (2.0 g, 5.3 mmol) was treated with *n*-BuLi (10.0 mL of a 1.6 M solution in hexane, 16.0 mmol) at room temperature and the resulting mixture was quenched with iodomethane (1.0 mL, 16.0 mmol). The crude product was purified by column chromatography (EtOAc/hexane: 1/10) and crystallized from CH_2Cl_2/hexane to give a white crystalline product (*R*)-**2.37** (2.1 g) in 96% yield: mp 91-92 °C (lit[5a] (*S*)-**2.37** mp 90.5-91.5 °C); IR, ^1H NMR, ^{13}C NMR, and MS were similar to that of (±)-**2.37** in the literature[5a]. IR (KBr): υ (max) 1238, 1155, 1035 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.72-7.80 (ArH, 4 H, m), 7.26-7.38 (ArH, 2 H, m), 7.14-7.20 (ArH, 4 H, m), 4.46, 4.58 (OCH_2O, 4 H, d, AB, J_{AB} = 5.8 Hz), 2.83 (OCH_3, 6 H, s), 2.57 ($ArCH_3$, 6 H, s); ^{13}C NMR ($CDCl_3$): δ 153.1, 133.0, 131.6, 131.0, 129.6, 127.1, 126.1, 125.5, 125.4, 124.7, 98.5, 56.4, 17.8; MS *m/e* (relative intensity): 402 (M^+, 30), 327 (29), 326 (100), 309 (26), 298 (36), 297

(50), 296 (45), 283 (29), 252 (20), 239 (30), 119 (27), 111 (25); Anal. Calcd for $C_{26}H_{26}O_4$: C, 77.59; H, 6.51. Found: C, 77.55; H, 6.47. The sample showed $[\alpha]^{25}_{589}$ -86.56° (c = 1.0, THF).

(d) (*R*)-3,3'-Dicyano-2,2'-Bis(methoxymethoxy)-1,1'-Binaphthyl (2.39)



(*R*)-2,2'-Bis(methoxymethoxy)-1,1'-binaphthyl [(*R*)-**2.5**] (2.99 g, 8.0 mmol) was treated with *n*BuLi (16.7 mL of a 1.44 M solution in hexane, 24.0 mmol) at room temperature and the resulting mixture was quenched with phenyl cyanate (**2.21**) (2.72 mL, 24.0 mmol). Crude product was purified by column chromatography (EtOAc/hexane: 1/4) to give a slightly yellow syrup (*R*)-**2.39** (2.4 g) in 67% yield: IR (KBr): υ (max) 2245, 1608, 1385, 1235, 1177 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.25-8.60 (ArH, 2 H, m), 7.80-8.14 (ArH, 2 H, m), 7.02-7.75 (ArH, 6 H, m), 4.94, 4.78 (OCH_2O, 4 H, d, AB, J_{AB} = 6.3 Hz), 2.87 (OCH_3, 6 H, s); ^{13}C NMR ($CDCl_3$): δ 152.5, 136.9, 135.3, 129.8, 129.5, 128.6, 126.7, 126.1, 125.5, 116.6, 107.6, 99.7, 56.9; MS *m/e* (relative intensity): 424 (M^+, 4), 349 (19), 348 (71), 333 (15), 320 (22), 319 (22), 318 (30), 209 (14), 208 (22), 207 (100), 191 (13), 133 (10), 96 (20); Anal. Calcd for

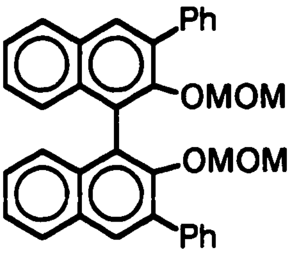
$C_{26}H_{20}O_4N_2$: C, 73.57; H, 4.75, N, 6.60. Found: C, 73.55; H, 4.69; N, 6.68. The sample showed $[\alpha]^{25}_{589}$ +34.49° (c = 1.1, THF).

2.5.3.4.4. General Procedure: Preparation of 3,3'-Diaryl-2,2'-Bis(methoxymethoxy)-1,1'-Binaphthyls (2.7, and 2.43-2.47)

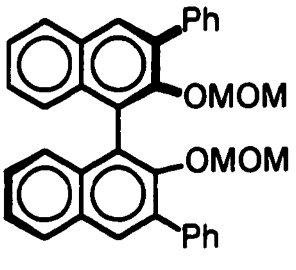
The preparation of the 3,3'-disubstituted binaphthyl compounds followed literature procedures[5a,b] with some modification.

(*R*)-3,3'-Dibromo-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl [(R)-**2.6**] (1 equiv) and $Pd(PPh_3)_4$ (10 mol%) were mixed in DME (6.7 mL/1 mmol of **2.6**) in a round-bottomed flask at room temperature under an argon atmosphere. To the mixture, with stirring, were added arylboronic acid (3.5 equiv) and 2 M aqueous Na_2CO_3 solution (5.2 equiv). The resulting mixture was stirred and heated to reflux for 10 h, cooled to room temperature, and passed through a pad of celite. The organic solution was evaporated to give a residue. The residue was dissolved in CH_2Cl_2, washed with saturated aqueous NH_4Cl, water, brine, dried over Na_2SO_4, and concentrated to give a crude product. Subsequent purification gave the product.

(a) (±)- and (*R*)-3,3'-Diphenyl-2,2'-Bis(methoxymethoxy)-1,1'-Binaphthyl (2.7)



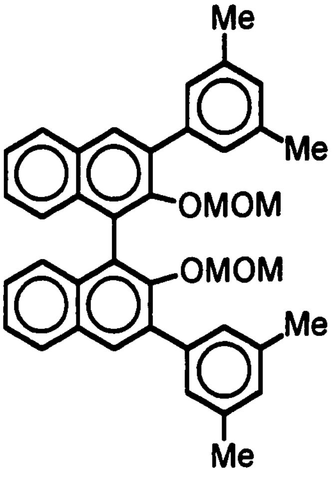
(±) -**2.7**



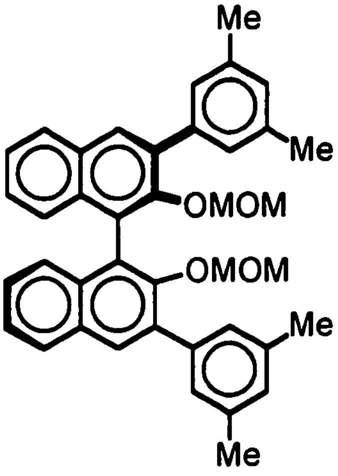
(*R*)-**2.7**

(±)-3,3'-Dibromo-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl (**2.6**) (8.0 g, 15.0 mmol) was treated with $Pd(PPh_3)_4$ (1.73 g, 1.5 mmol), phenylboronic acid (6.40 g, 52.6 mmol) and 2 M aqueous Na_2CO_3 solution (39 mL) in DME (100 mL) in a 500-mL round-bottomed flask. Purification was carried out by column chromatography (EtOAc/hexane: 1/10) to give a foamy product (±)-**2.7** (6.7 g) in 85% yield. The product was directly used for deprotection of the MOM group with only ^{1}H NMR and ^{13}C NMR being examined: ^{1}H NMR ($CDCl_3$): δ 7.65-8.05 (ArH, 8 H, m), 7.22-7.55 (ArH, 12 H, m), 4.40, 4.37 (OCH_2O, 4 H, d, AB, J_{AB} = 5.8 Hz), 2.34 (OCH_3, 6 H, s); ^{13}C NMR ($CDCl_3$): δ 139.0, 135.5, 133.6, 130.9, 130.6, 129.6, 128.3, 127.9, 127.3, 126.5, 126.4, 126.3, 125.2, 98.5, 55.8. (*R*)-3,3'-Dibromo-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl was used to afford (*R*)-**2.7**.

(b) (±)- and (*R*)-3,3'-Bis(3,5-dimethylphenyl)-2,2'-Bis(methoxymethoxy)-1,1'-Binaphthyl (2.43)



(±)-**2.43**

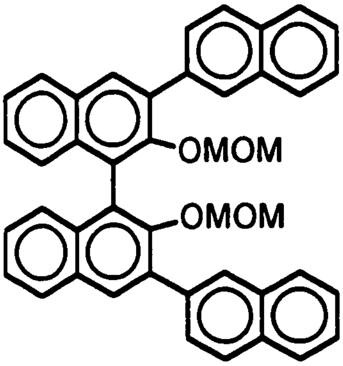


(*R*)-**2.43**

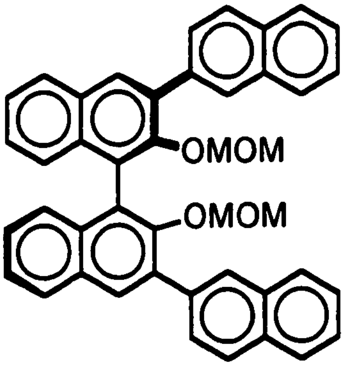
(±)-3,3'-Dibromo-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl (**2.6**) (2.0 g, 3.76 mmol) was treated with $Pd(PPh_3)_4$ (0.43 g, 0.372 mmol), 3,5-dimethylphenylboronic acid (2.0 g, 13.34 mmol) and 2 M aqueous Na_2CO_3 solution (10 mL) in DME (40 mL) in a 100-mL round-bottomed flask. Purification was carried out by column chromatography (CH_2Cl_2/hexane: 1/1)) and crystallization from CH_2Cl_2/hexane to give colorless crystals (**2.43**) (2.25 g) in 93% yield: mp 84-85 °C; IR (KBr): υ (max) 1600, 1389, 1233, 1157 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.80-7.97 (ArH, 4 H, m), 7.18-7.48 (ArH, 10 H, m), 7.02-7.08 (ArH, 2 H, m), 4.69, 4.44 (OCH_2O, 4 H, d, AB, J_{AB} = 5.8 Hz), 2.40 ($ArCH_3$, 12 H, s), 2.36 (OCH_3, 6 H, s); ^{13}C NMR ($CDCl_3$): δ 151.4, 139.0, 137.7, 135.7, 133.6, 130.8, 130.5, 128.9, 127.7, 127.4, 126.4, 126.1, 125.0, 98.5, 55.8, 21.4; MS *m/e* (relative intensity): 585 (M^++3, 1), 584

(M^++2, 4), 583 (M^++1, 15), 582 (M^+, 35), 518 (12), 507 (41), 506 (100), 478 (28); Anal. Calcd for $C_{40}H_{38}O_4$: C, 82.44; H, 6.57. Found: C, 82.55; H, 6.50. (*R*)-3,3'-Dibromo-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl was used to afford (*R*)-**2.43**. mp 81-83 °C. The sample showed $[\alpha]^{25}_{578}$ -36.85° (c = 1.1, THF).

(c) (±)- and (*R*)-3,3'-Bis(2-naphthyl)-2,2'-Bis(methoxymethoxy)-1,1'-Binaphthyl (2.43)



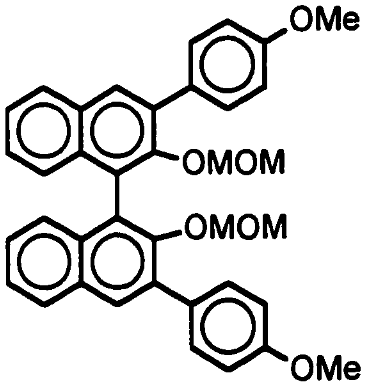
(±) -**2.44**



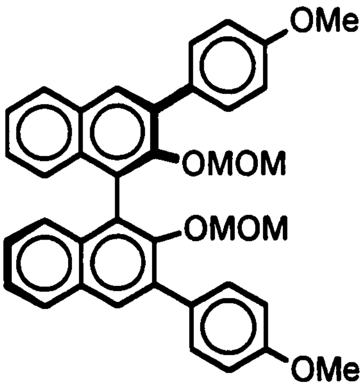
(*R*)-**2.44**

(±)-3,3'-Dibromo-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl (**2.6**) (1.2 g, 2.25 mmol) was treated with $Pd(PPh_3)_4$ (0.26 g, 0.225 mmol), 2-naphthylboronic acid (2.02 g, 11.76 mmol) and 2 M aqueous Na_2CO_3 solution (5.9 mL) in DME (25 mL) in a 100-mL round-bottomed flask. Purification was carried out by column chromatography (CH_2Cl_2/hexane: 1/1) and crystallization from CH_2Cl_2/hexane to give colorless crystals (**2.44**) (1.4 g) in 85% yield: mp 103-104 °C; IR (KBr): υ (max) 1597, 1154 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.14-8.28 (ArH, 2 H, m), 8.01-8.10 (ArH, 2 H, m), 7.70-8.01 (ArH, 10 H, m), 7.22-7.66 (ArH, 10 H, m), 4.45, 4.44 (OCH_2O, 4 H, d, AB, J_{AB} = 5.9 Hz), 2.32 (OCH_3, 6 H, s); ^{13}C NMR ($CDCl_3$): δ 151.5, 136.7, 135.3, 133.7, 133.5, 132.5, 130.9, 128.1, 128.0, 127.9, 127.7, 127.6, 126.6, 126.5, 126.4, 126.1, 126.0, 125.2, 98.6, 55.9; MS *m/e* (relative intensity): 627 (M^+, 1), 271 (22), 270 (100), 269 (30), 268 (15), 239 (22); Anal. Calcd for $C_{44}H_{34}O_4$: C, 84.32; H, 5.47. Found: C, 84.23; H, 5.38. (*R*)-3,3'-Dibromo-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl was used to afford (*R*)-**2.44** as a yellowish syrup. The sample showed $[\alpha]^{25}_{578}$ -110.02° (c = 1.1, THF).

(d) (±)- and (*R*)-3,3'-Bis(4-methoxyphenyl)-2,2'-Bis(methoxymethoxy)-1,1'-Binaphthyl (2.45)



(±)-**2.45**

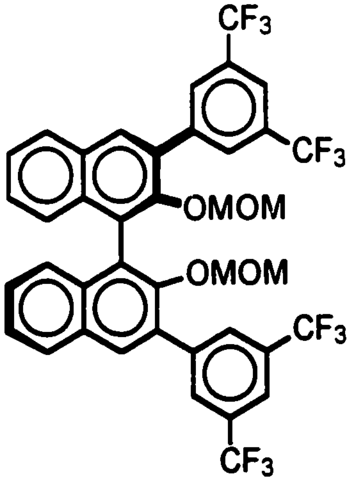


(*R*)-**2.45**

(±)-3,3'-Dibromo-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl (**2.6**) (1.0 g, 1.88 mmol) was treated with $Pd(PPh_3)_4$ (0.22 g, 0.188 mmol), 4-methoxyphenylboronic acid (1.0 g, 6.58 mmol) and 2 M aqueous Na_2CO_3 solution (4.9 mL) in DME (20 mL) in a 50-mL round-bottomed flask. Purification was carried by column chromatography (EtOAc/hexane: 1/10) and crystallization from

CH_2Cl_2/hexane to give colorless crystals (**2.45**) (1.53 g) in 92% yield: mp 75-76 °C; IR (KBr): υ (max) 1608, 1513, 1247 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.82-7.96 (ArH, 4 H, m), 7.63-7.78 (ArH, 4 H, m), 7.18-7.47 (ArH, 6 H, m), 6.90-7.08 (ArH, 4 H, m), 4.42, 4.37 (OCH_2O, 4 H, d, AB, J_{AB} = 5.7 Hz), 3.87 (OCH_3, 6 H, s), 2.35 (OCH_3, 6 H, s); ^{13}C NMR ($CDCl_3$): δ 159.0, 151.3, 135.0, 133.4, 131.4, 130.9, 130.7, 130.2, 127.7, 126.6, 126.4, 126.1, 125.1, 113.8, 98.3, 55.9, 55.3; Anal. Calcd for $C_{38}H_{34}O_6$: C, 77.80; H, 5.84. Found: C, 77.68; H, 5.78. (*R*)-3,3'-Dibromo-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl was used to afford (*R*)-**2.45**. mp 68-70 °C. The sample showed $[\alpha]^{25}_{578}$ -109.65° (c = 1.0, THF).

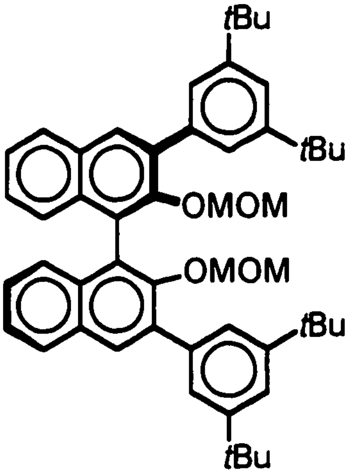
(e) (*R*)-3,3'-Bis[3,5-bis(trifluoromethyl)phenyl]-2,2'-Bis(methoxymethoxy)-1,1'-Binaphthyl (2.46)



(*R*)-3,3'-Dibromo-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl [(*R*)-**2.6**] (2.36 g, 4.43 mmol) was treated with $Pd(PPh_3)_4$ (0.512 g, 0.443 mmol), 3,5-

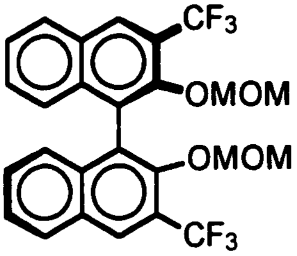
bis(trifluoromethyl)phenylboronic acid (4.0 g, 15.50 mmol) and 2 M aqueous Na_2CO_3 solution (11.7 mL) in DME (50 mL) in a 100-mL round-bottomed flask. Purification was carried out by column chromatography (CH_2Cl_2/hexane: 2/3) and crystallization from CH_2Cl_2/hexane to give slightly yellow crystals (*R*)-**2.46** (3.0 g) in 85% yield: mp 69-71 °C; IR (KBr): υ (max) 1621, 1377, 1281, 1153 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.20-8.32 (ArH, 4 H, m), 7.86-8.08 (ArH, 6 H, m), 7.20-7.56 (ArH, 6 H, m), 4.43, 4.37 (OCH_2O, 4 H, d, AB, J_{AB} = 6.0 Hz), 2.50 (OCH_3, 6 H, s); ^{13}C NMR ($CDCl_3$): δ 151.3, 141.2, 134.2, 132.8, 132.0, 131.5, 131.1, 130.7, 130.0, 128.3, 127.5, 126.4, 126.3, 125.9, 125.6, 121.1, 99.2, 56.2; ^{19}F NMR ($CDCl_3$): δ -63.43; Anal. Calcd for $C_{40}H_{26}F_{12}O_4$: C, 60.16; H, 3.28. Found: C, 60.35; H, 3.17. The sample showed $[\alpha]^{25}_{578}$ -83.62° (c = 1.1, THF).

(f) (*R*)-3,3'-Bis[3,5-di(*tert*-butyl)phenyl]-2,2'-Bis(methoxymethoxy)-1,1'-Binaphthyl (2.47)



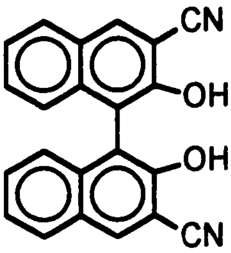
(*R*)-3,3'-Dibromo-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl [(*R*)-**2.6**] (2.50 g, 4.70 mmol) was treated with $Pd(PPh_3)_4$ (0.54 g, 0.470 mmol), 3,5-di(*tert*-butyl)phenylboronic acid (3.85 g, 16.40 mmol) and 2 M aqueous Na_2CO_3 solution (12.5 mL) in DME (50 mL) in a 100-mL round-bottomed flask. Purification was carried out by column chromatography (CH_2Cl_2/hexane: 1/1) and crystallization from CH_2Cl_2/hexane to give colorless crystals [(R)-**2.47**] (3.5 g) in 99% yield: mp 97-99 °C; IR (KBr): υ (max) 1595, 1390, 1244, 1157 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.84-8.02 (ArH, 4 H, m), 7.54-7.64 (ArH, 4 H, m), 7.20-7.50 (ArH, 8 H, m), 4.42, 4.40 (OCH_2O, 4 H, d, AB, J_{AB} = 5.7 Hz), 2.37 (OCH_3, 6 H, s), 1.39 ($(CH_3)_3$, 18 H, s); ^{13}C NMR ($CDCl_3$): δ 151.6, 150.6, 138.2, 136.4, 133.5, 130.8, 130.2, 127.8, 126.5, 126.4, 126.0, 124.9, 123.9, 121.0, 98.3, 55.7, 34.9, 31.5; Anal. Calcd for $C_{52}H_{62}O_4$: C, 83.16; H, 8.32. Found: C, 82.96; H, 8.19. The sample showed $[\alpha]^{25}_{578}$ -73.78° (c = 1.1, THF).

2.5.3.4.5. Preparation of (*R*)-3,3'-Bis(trifluoromethyl)-2,2'-Bis(methoxymethoxy)-1,1'-Binaphthyls (2.48)



A mixture of $FSO_2CF_2CO_2Me$ (1.63 mL, 12.8 mmol), CuI (1.46 g, 7.67 mmol), HMPA (2.22 mL, 12.8 mmol) and (*R*)-3,3'-diiodo-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl [(*R*)-**2.36**] (2.0 g, 3.2 mmol) in DMF (40 mL) was stirred under argon atmosphere for 6 h at 70 °C. The reaction mixture was then cooled to room temperature. It was diluted with CH_2Cl_2 (400 mL), the solution washed with water (3 x 200 mL), dried over Na_2SO_4, and concentrated to afford a syrup. The purification was done by column chromatography (EtOAc/hexane: 1/20) to give 1.51 g of pure product (*R*)-**2.48** (93%): mp 43-45 °C; IR (KBr): υ (max) 1230, 1165, 1035 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.22-8.32 (ArH, 2 H, m), 7.85-7.98 (ArH, 2 H, m), 7.25-7.55 (ArH, 4 H, m), 7.08-7.25 (ArH, 2 H, m), 4.68, 4.44 (OCH_2O, 4 H, d, AB, J_{AB} = 5.5 Hz), 2.63 (OCH_3, 6 H, s); ^{13}C NMR ($CDCl_3$): δ 150.8, 140.3, 135.6, 129.2, 129.1, 129.0, 128.9, 126.9, 126.2, 126.0, 123.9 (q, J = 30.4 Hz), 123.6 (q, 272.7 Hz), 99.7, 56.2; 19F NMR (CDCl3): δ -61.7; Anal. Calcd for $C_{26}H_{20}F_6O_4$: C, 61.18; H, 3.95, F, 22.33. Found: C, 61.10; H, 3.76; F, 22.43. The sample showed $[\alpha]^{25}_{589}$ –57.00° (c = 1.0, THF).

2.5.3.4.6. (±)-3,3'-Dicyano-2,2'-Dihydroxy-1,1'-Binaphthyl (2.40)

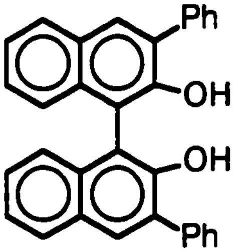


A stirred mixture of (*R*)-3,3'-dibromo-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl [(*R*)-**2.6**] (5.0 g, 9.4 mmol), cuprous cyanide (1.94 g, 21.6 mmol) and DMF (20 mL) was refluxed under argon atmosphere for 4 h. TLC was checked and showed complete reaction. The resulting brown mixture was poured into a solution of KCN (20 g) and water (60 mL) and stirred thoroughly for 10 min. The lower aqueous layer was separated, extracted with EtOAc (4 x 40 mL). All organic layers were combined and washed with 10% aqueous KCN (40 mL), water (4 x 40 mL) and brine (40 mL), and dried over Na_2SO_4. The solution was concentrated *in vacuo* to give a brown solid. Purification was carried out by column chromatography three times (twice with $MeOH/CH_2Cl_2$: 1/20; once with THF/hexane: 1/4), then by recrystallization from CH_3CN/CH_2Cl_2 to afford 1.0 g of the product as yellow needles (±)-**2.40** (32%): mp 318 °C (dec.); IR (KBr): υ (max) 3498, 2247, 1560, 1350, 1178 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.81 (OH, 2 H, s), 8.55-8.78 (ArH, 2 H, m), 7.95-8.14 (ArH, 2 H, m), 7.26-7.52 (ArH, 4 H, m), 6.78-6.88 (ArH, 2 H, m); ^{13}C NMR (DMSO-d_6): δ 153.1, 136.8, 135.7, 129.6, 128.9, 127.4, 124.2, 123.9, 117.2, 114.5, 103.2; Anal. Calcd for $C_{22}H_{12}N_2O_2$: C, 78.56; H, 3.60; N, 8.33. Found: C, 78.66; H, 3.70; N, 8.17.

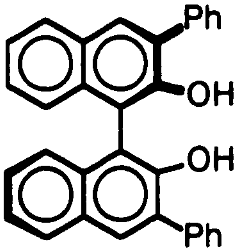
2.5.3.4.7. General Procedure: Preparation of 3,3'-Disubstituted-2,2'-Dihydroxy-1,1'-Binaphthyls (2.4, 2.15, 2.40, 2.41, and 2.49-2.55)

A mixture of 3,3'-disubstituted-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl (2.0 mmol) and Amberlyst 15 resin (1.0 g) in THF/MeOH (1:1, 10 mL) was stirred and heated to reflux under argon atomosphere for 15 h. It was then cooled to room temperature, the resin was filtered off, and the filtrate was concentrated. Subsequent purification gave the product.

(a) (±)- and (*R*)-3,3'-Diphenyl-2,2'-Dihydroxy-1,1'-Binaphthyl (2.4)



(±)-**2.4**

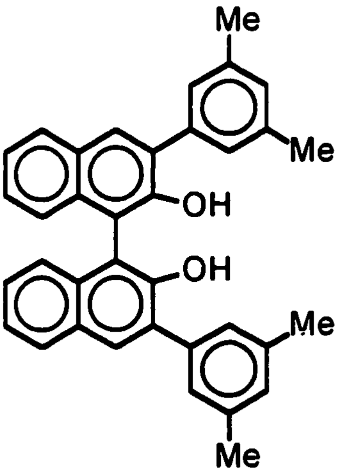


(*R*)-**2.4**

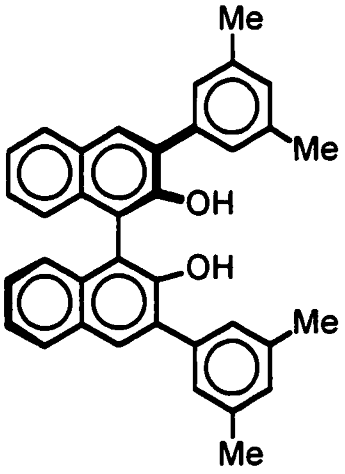
(±)-3,3'-Diphenyl-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl (**2.7**) (6.4 g, 12.2 mmol) was treated with Amberlyst 15 (6.0 g) in THF/MeOH (200 mL, 1:1). Purification was carried out by column chromatography (EtOAc/hexane: 1:10), followed by crystallization (CH_2Cl_2/hexane) to afford 4.70 g of a white crystalline product (±)-**2.4** (89%): mp 209-210 °C [lit[29] mp 204-205 °C; lit[5a] mp 210-211 °C]; IR, ^1H NMR, ^{13}C NMR were identical to that of (±)-(**2.4**) in the literature[30]; Anal. Calcd for $C_{32}H_{22}O_2$: C, 87.65; H, 5.06. Found C, 87.55; H, 4.99. (*R*)-3,3'-Diphenyl-2,2'-

bis(methoxymethoxy)-1,1'-binaphthyl was used to afford (*R*)-**2.4**: mp 200-202 °C [lit[30] mp 197-198 °C]; The sample showed $[\alpha]^{25}_{589}$ +135.0° (c = 1.0, THF) [lit[30] $[\alpha]^{25}_{546}$ +132.4° (c = 1.0, THF)].

(b) (±)- and (*R*)-3,3'-Bis(3,5-dimethylphenyl)-2,2'-Dihydroxy-1,1'-Binaphthyl (2.49)



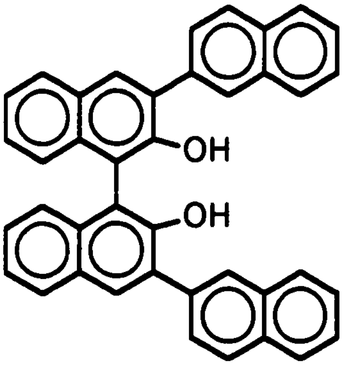
(±)-**2.49**



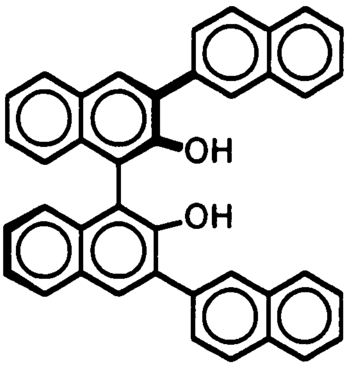
(*R*)-**2.49**

(±)-3,3'-Bis(3,5-dimethylphenyl)-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl (**2.43**) (2.20 g, 3.8 mmol) was treated with Amberlyst 15 (2.0 g) in THF/MeOH (100 mL, 1:1). Purification was carried out by crystallization (THF/hexane) to afford 1.74 g of a light yellow crystalline product (±)-**2.49** (93%): mp 299-301 °C; IR (KBr): υ (max) 3476, 1600, 1497, 1411, 1252, 1211 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 7.82-8.08 (ArH, 4 H, m), 7.18-7.48 (ArH, 10 H, m), 6.98-7.15 (ArH, 2 H, m), 5.39 (OH, 2 H, s), 2.40 (ArCH$_3$, 12 H, s); ^{13}C NMR (CDCl$_3$): δ 150.0, 138.1, 137.3, 133.0, 130.9, 129.5, 129.4, 128.3, 127.3, 127.1, 124.4, 124.1, 112.8, 21.4; Anal. Calcd for $C_{36}H_{30}O_2$: C, 87.42; H, 6.11. Found: C, 87.35; H, 5.98. (*R*)-3,3'-Bis(3,5-dimethylphenyl)-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl was used to afford (*R*)-**2.49**: mp 124-125 °C. The sample showed $[\alpha]^{25}_{578}$ +53.16° (c = 1.1, THF).

(c) (±)- and (*R*)-3,3'-Bis(2-naphthyl)-2,2'-Dihydroxy-1,1'-Binaphthyl (2.50)



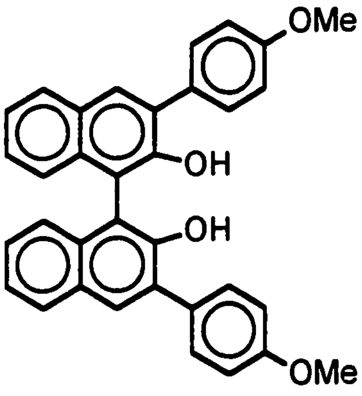
(±)-**2.50**



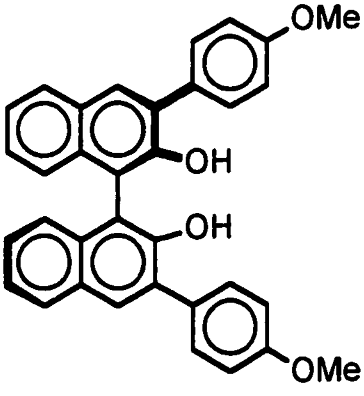
(*R*)-**2.50**

(±)-3,3'-Bis(2-naphthyl)-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl (**2.44**) (1.35 g, 2.2 mmol) was treated with Amberlyst 15 (1.1 g) in THF/MeOH (80 mL, 1:1). Purification was carried out by column chromatography (CH$_2$Cl$_2$/hexane: 1:1), then by crystallization (CH$_2$Cl$_2$/hexane) to afford 1.05 g of a light yellow crystalline product (±)-**2.50** (91%): mp 184-185 °C; IR (KBr): υ (max) 3478, 1615, 1501, 1384, 1226, 1169, 1118 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 7.70-8.40 (ArH, 14 H, m), 7.15-7.60 (ArH, 10 H, m), 5.46 (OH, 2 H, s); ^{13}C NMR (CDCl$_3$): δ 150.3, 135.0, 133.5, 133.0, 132.8, 131.7, 130.6, 129.6, 128.5, 128.2, 127.9, 127.7, 127.4, 126.3, 124.4, 124.3, 112.5; Anal. Calcd for $C_{40}H_{26}O_2$: C, 89.19; H, 4.86. Found: C, 88.98; H, 5.05. (*R*)-3,3'-Bis(2-naphthyl)-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl was used to afford (*R*)-**2.50**: mp 217-218 °C (dec.). The sample showed $[\alpha]^{25}_{578}$ -32.92° (c = 1.0, THF).

(d) (±)- and (*R*)-3,3'-Bis(4-methoxyphenyl)-2,2'-Dihydroxy-1,1'-Binaphthyl (2.51)



(±)-**2.51**

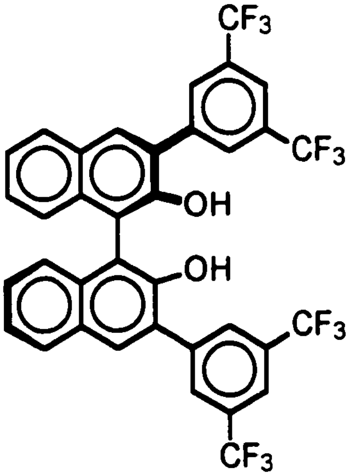


(*R*)-**2.51**

(±)-3,3'-Bis(4-methoxyphenyl)-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl (**2.45**) (1.50 g, 2.6 mmol) was treated with Amberlyst 15 (1.3 g) in THF/MeOH (80 mL, 1:1). Purification was carried out by crystallization (EtOAc/hexane) to afford 1.15 g of a light yellow crystalline product (±)-**2.51** (90%): mp 224-225 °C; IR (KBr): υ (max) 3480, 1606, 1512, 1244, 1177 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.80-8.10 (ArH, 4 H, m), 7.56-7.75 (ArH, 4 H, m), 7.12-7.45 (ArH, 6 H, m), 6.90-7.06 (ArH, 4 H, m), 5.36 (OH, 2 H, s), 3.83 (OCH_3, 6 H, s); ^{13}C NMR ($CDCl_3$): δ 159.3, 150.2, 132.7, 130.9, 130.7, 130.3, 129.8, 129.5, 128.3, 127.1, 124.2, 113.9, 112.4, 55.3; Anal. Calcd for $C_{34}H_{26}O_4$: C, 81.91; H, 5.26. Found: C, 82.02; H, 5.16. (*R*)-3,3'-Bis(4-

methoxyphenyl)-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl was used to afford (*R*)-**2.51**: mp 109-111 °C. The sample showed $[\alpha]^{25}_{578}$ +50.10° (c = 1.0, THF).

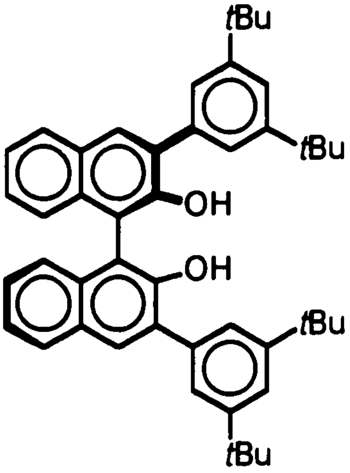
(e) (*R*)-3,3'-Bis[3,5-bis(trifluoromethyl)phenyl]-2,2'-Dihydroxy-1,1'-Binaphthyl (2.52)



(*R*)-3,3'-Bis[3,5-bis(trifluoromethyl)phenyl]-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl [(*R*)-**2.46**] (3.0 g, 3.8 mmol) was treated with Amberlyst 15 (2.0 g) in THF/MeOH (100 mL, 1:1). Purification was carried out by column chromatography (EtOAc/hexane: 1:10), and by crystallization (EtOAc/hexane) to afford 2.60 g of a light yellow crystalline product (*R*)-**2.52** (97%): mp 97-99 °C; IR (KBr): υ (max) 3477, 1603, 1385, 1203, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.80-8.35 (ArH, 10 H, m), 7.10-7.60 (ArH, 6 H, m), 5.37 (OH, 2 H, s); ^{13}C NMR ($CDCl_3$): δ 150.0, 139.7, 133.4, 132.4, 131.7 (q, J = 33.9 Hz), 129.9, 129.6, 128.9, 128.6, 127.9 (q, J = 275.5 Hz), 125.2, 124.1, 121.3, 112.0; ^{19}F NMR ($CDCl_3$): δ -63.49; Anal. Calcd for $C_{36}H_{18}F_{12}O_2$:

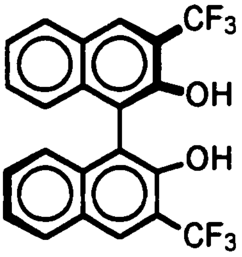
C, 60.86; H, 2.55; F, 32.09. Found: C, 60.80; H, 2.48; F, 31.99. The sample showed $[\alpha]^{25}_{589}$ -11.87° (c = 1.1, in THF).

(f) (*R*)-3,3'-Bis[3,5-di(*tert*-butyl)phenyl]-2,2'-Dihydroxy-1,1'-Binaphthyl (2.53)



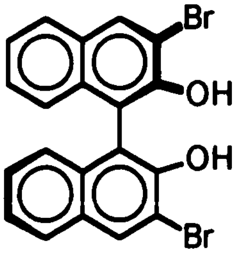
(*R*)-3,3'-Bis[3,5-di(*tert*-butyl)phenyl]-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl [(*R*)-**2.47**] (3.0 g, 3.8 mmol) was treated with Amberlyst 15 (2.0 g) in THF/MeOH (100 mL, 1:1). Purification was carried out by column chromatography (EtOAc/hexane: 1:10), and by crystallization (EtOAc/hexane) to afford 2.60 g of a white crystalline product (*R*)-**2.53** (98%): mp 142-144 °C; IR (KBr): υ (max) 3490, 1601, 1360, 1209 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.85-8.05 (ArH, 4 H, m), 7.15-7.62 (ArH, 12 H, m), 5.47 (OH, 2 H, s), 1.38 ($C(CH_3)_3$, 36 H, s); ^{13}C NMR ($CDCl_3$): δ 151.0, 150.1, 136.5, 133.0, 131.6, 130.9, 129.4, 128.3, 127.0, 124.5, 124.1, 123.9, 121.9, 113.0, 35.0, 31.5; Anal. Calcd for $C_{48}H_{54}O_2$: C, 86.96; H, 8.21. Found: C, 86.86; H, 8.17. The sample showed $[\alpha]^{25}_{589}$ +27.45° (c = 1.0, in THF).

(g) (*R*)-3,3'-Bis(trifluoromethyl)-2,2'-Dihydroxy-1,1'-Binaphthyls (2.54)



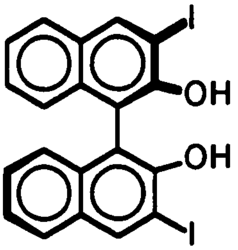
(*R*)-3,3'-Bis(trifluoromethyl)-2,2'-bis(methoxymethoxy)-1,1'-binaphthyls [(R)-**2.48**] (1.60 g, 3.1 mmol) was treated with Amberlyst 15 (1.6 g) in THF/MeOH (80 mL, 1:1). Purification was carried out by column chromatography (EtOAc/hexane: 1:10), and by crystallization (CH_2Cl_2/hexane) to afford 1.30 g of a white crystalline product (*R*)-**2.54** (98%): mp 240-242 °C; IR (KBr): υ (max) 3490, 1545, 1365, 1179 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.30-8.48 (ArH, 2 H, m), 7.90-8.10 (ArH, 2 H, m), 7.00-7.62(ArH, 6 H, m), 5.30 (OH, 2 H, s); ^{13}C NMR ($CDCl_3$): δ 149.4, 134.6, 130.4 (q, J = 5.5 Hz), 130.0, 129.7, 127.9, 125.5, 123.9, 123.3 (q, J = 272.2 Hz), 118.9 (q, J = 30.9 Hz), 112.2; ^{19}F NMR (CDCl3): δ -63.38; Anal. Calcd for $C_{22}H_{12}F_6O_2$: C, 62.57; H, 2.86; F, 26.99. Found: C, 62.50; H, 2.82; F, 26.88. MS *m e* (relative intensity): 423 (M^++1, 16), 422 (M^+, 78), 403 (13), 385 (17), 208 (23), 207 (100), 191 (29), 177 (20), 168 (42), 167 (35), 166 (22), 162 (20), 153 (46), 152 (35), 144 (25), 138 (37), 127 (23), 119 (21), 113 (22), 96 (27), 75 (19), 73 (23), 69 (20). The sample showed $[\alpha]^{25}_{589}$ +72.83° (c = 1.0, in THF).

(h) (*R*)-3,3'-Dibromo-2,2'-Dihydroxy-1,1'-Binaphthyls (2.15)



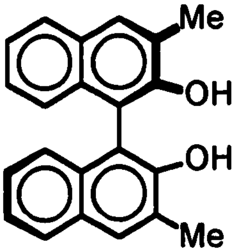
(*R*)-3,3'-Dibromo-2,2'-bis(methoxymethoxy)-1,1'-binaphthyls [(*R*)-**2.6**] (2.0 g, 3.8 mmol) was treated with Amberlyst 15 (2.0 g) in THF/MeOH (100 mL, 1:1). Purification was carried out by crystallization (CH_2Cl_2/hexane) to afford 1.6 g of a white crystalline product (*R*)-**2.15** (96%): mp 256-257 °C; IR (KBr): υ (max) 3479, 1616, 1577, 1499, 1448, 1421, 1382, 1359, 1255, 1195, 1138 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.20-8.35 (ArH, 2 H, m), 7.74-7.88 (ArH, 2 H, m), 7.05-7.50 (ArH, 6 H, m), 5.53 (OH, 2 H, s); ^{13}C NMR ($CDCl_3$): δ 148.1, 132.8, 129.8, 127.6, 127.4, 124.9, 124.6, 114.7, 112.3; Anal. Calcd for $C_{20}H_{12}Br_2O_2$: C, 54.09; H, 2.72. Found: C, 54.05; H, 2.68. The sample showed $[\alpha]^{25}_{589}$ +104.68° (c = 1.0, in THF).

(i) (*R*)-3,3'-Diiodo-2,2'-Dihydroxy-1,1'-Binaphthyls (2.41)



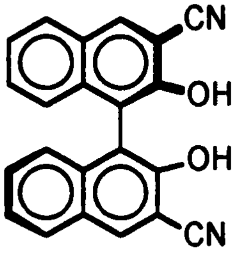
(*R*)-3,3'-Diiodo-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl [(*R*)-**2.36**] (3.7 g, 5.9 mmol) was treated with Amberlyst 15 (3.0 g) in THF/MeOH (160 mL, 1:1). Purification was carried out by column chromatography (EtOAc/hexane: 1:10), and by crystallization (EtOAc/hexane) to afford 3.0 g of a light yellow crystalline product (*R*)-**2.41** (94%): mp 312-314 °C; IR (KBr): υ (max) 3483, 1565, 1355, 1177, 1141 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.40-8.60 (ArH, 2 H, m), 7.70-7.90 (ArH, 2 H, m), 7.02-7.50 (ArH, 6 H, m), 5.41 (OH, 2 H, s); ^{13}C NMR ($CDCl_3$): δ 152.0, 140.4, 133.4, 130.7, 128.0, 127.3, 126.8, 125.2, 124.8, 124.4; Anal. Calcd for $C_{20}H_{12}I_2O_2$: C, 44.64; H, 2.25. Found: C, 44.58; H, 2.27. The sample showed $[\alpha]^{25}_{589}$ +102.66° (c = 1.0, in THF).

(j) (*R*)-3,3'-Dimethyl-2,2'-Dihydroxy-1,1'-Binaphthyls (2.55)



(*R*)-3,3'-Dimethyl-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl [(*R*)-**2.37**] (1.80 g, 4.5 mmol) was treated with Amberlyst 15 (2.5 g) in THF/MeOH (80 mL, 1:1). Purification was carried out by column chromatography (EtOAc/hexane: 1:10), and by crystallization (CH_2Cl_2/hexane) to afford 1.40 g of a slightly yellow crystalline product (*R*)-**2.55** (100%): mp 201-202 °C [lit[3a] for (*S*)-**2.55**, mp 200-202]; IR, ^1H NMR, and ^{13}C NMR were identical with that of (±)-**2.55**.[3a,5a] Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 84.01; H, 5.78. The sample showed $[\alpha]^{25}_{589}$ +43.40° (c = 1.0, in THF).

(k) (*R*)-3,3'-Dicyano-2,2'-Dihydroxy-1,1'-Binaphthyls [(*R*)-2.40]



(*R*)-3,3'-Dicyano-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl [(*R*)-**2.39**] (1.0 g, 2.4 mmol) was treated with Amberlyst 15 (0.5 g) in THF/MeOH (40 mL, 1:1). Purification was carried out by crystallization (CH_3CN/hexane) to afford 0.76 g of a light yellow crystalline product (*R*)-**2.40** (96%): mp 309 °C (dec.); IR, ^{1}H NMR, and ^{13}C NMR are identical with (±)-**2.40**. The sample showed $[\alpha]^{25}_{589}$ +141.50° (c = 1.1, in THF).

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CHAPTER 3. PREPARATION OF *B*-1-ALKYNYL BINAPHTHYLBORONATES

3.1. Introduction

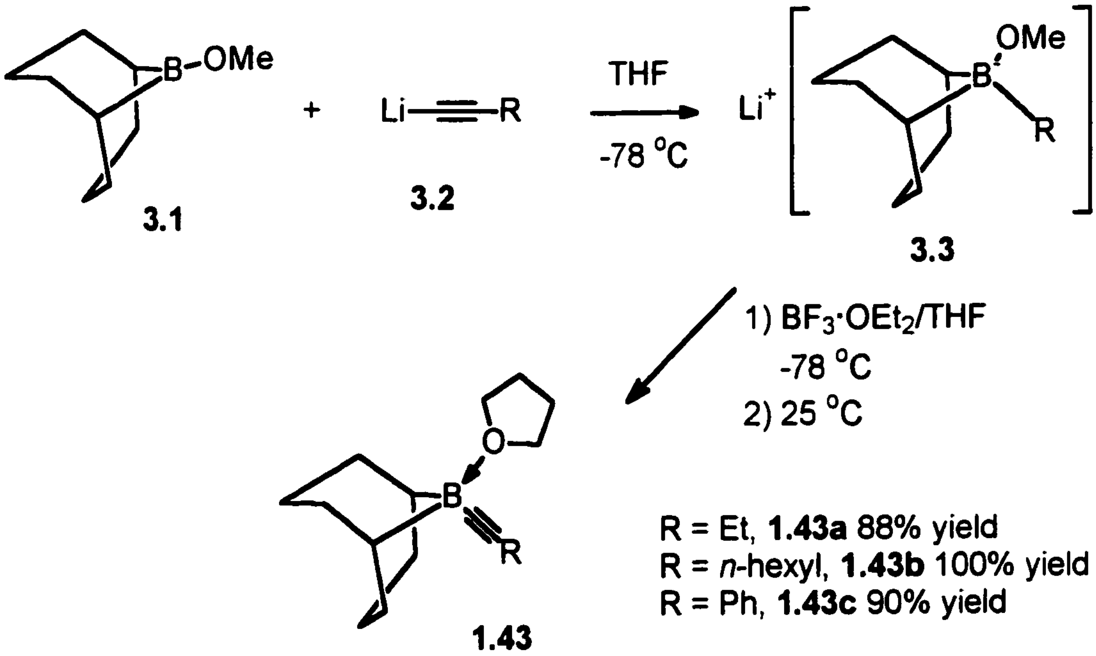
There is no literature method for direct preparation of *B*-1-alkynylbinaphthylboronates. However, many methods for the preparation of related compounds have appeared and might provide hints for furnishing the target compounds. Some of these preparative procedures will be reviewed in the following sections.

3.1.1. Preparation of *B*-1-Alkynyldialkylboranes

The reaction of alkynyllithium reagents with methyl dialkylborinates in tetrahydrofuran to form lithium methyl alkynyldialkylborinates was reported by Brown.[1] Examples of such preparations are depicted in Scheme 3.1. Treatment of *B*-methoxy-9-BBN (**3.1**) in tetrahydrofuran with an alkynyllithium reagent (**3.2**) at -78

°C resulted in the formation of the ate complex **3.3**. Treatment of this complex with 1.33 equiv of boron trifluoride diethyl etherate at -78 °C, followed by warming, resulted in the desired *B*-1-alkynyl-9-BBN **1.43**. Overall yields were excellent.

Scheme 3.1



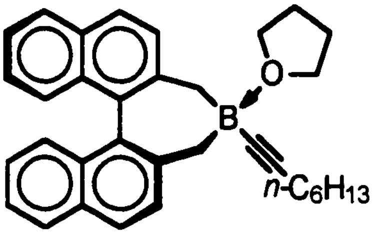
R = Et, **1.43a** 88% yield
R = *n*-hexyl, **1.43b** 100% yield
R = Ph, **1.43c** 90% yield

3.1.2. Preparation of *B*-1-Octynylbinaphthylborane

To add alkynyl groups to enones in an asymmetrical way, the first synthesis of enantiomerically pure (*S*)-*B*-1-octynylbinaphthylborane **1.82** (Figure 3.1) was carried out in our laboratory.[2]

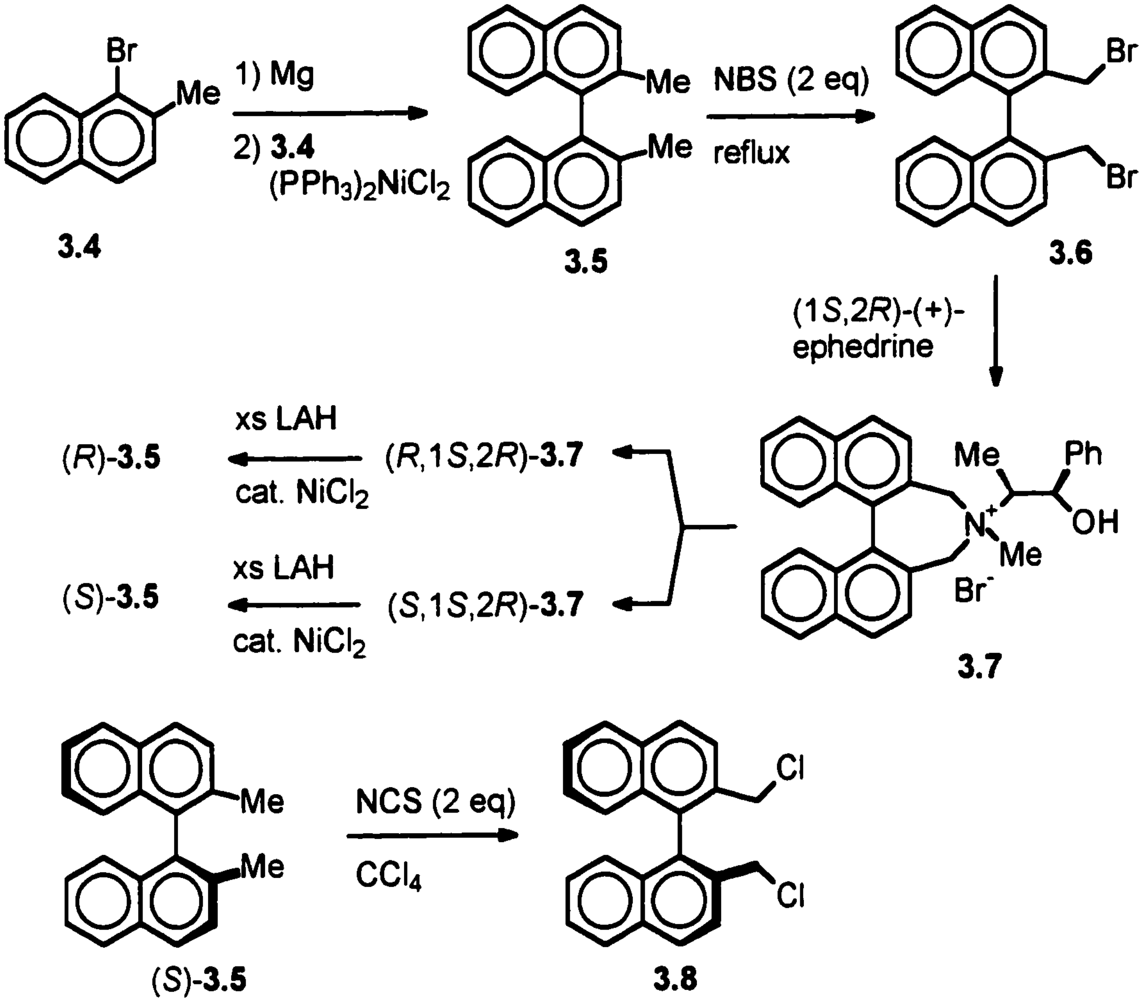
The synthesis of **1.82** required several steps starting from 1-bromo-2-methylnaphthalene (**3.4**). First, following a synthesis and resolution procedure developed by Maigrot and Mazaleyrat,[3] (*S*)-2,2'-dimethyl-1,1'-binaphthyl (**3.5**) was synthesized in 4 steps from **3.4**, which in turn was treated with N-chlorosuccinimide (NCS) to give (*S*)-2,2'-bis(chloromethyl)-1,1'-binaphthyl (**3.8**) (Scheme 3.2).

*Figure 3.1. (S)-B-1-Octynylbinaphthylborane **1.82**.*

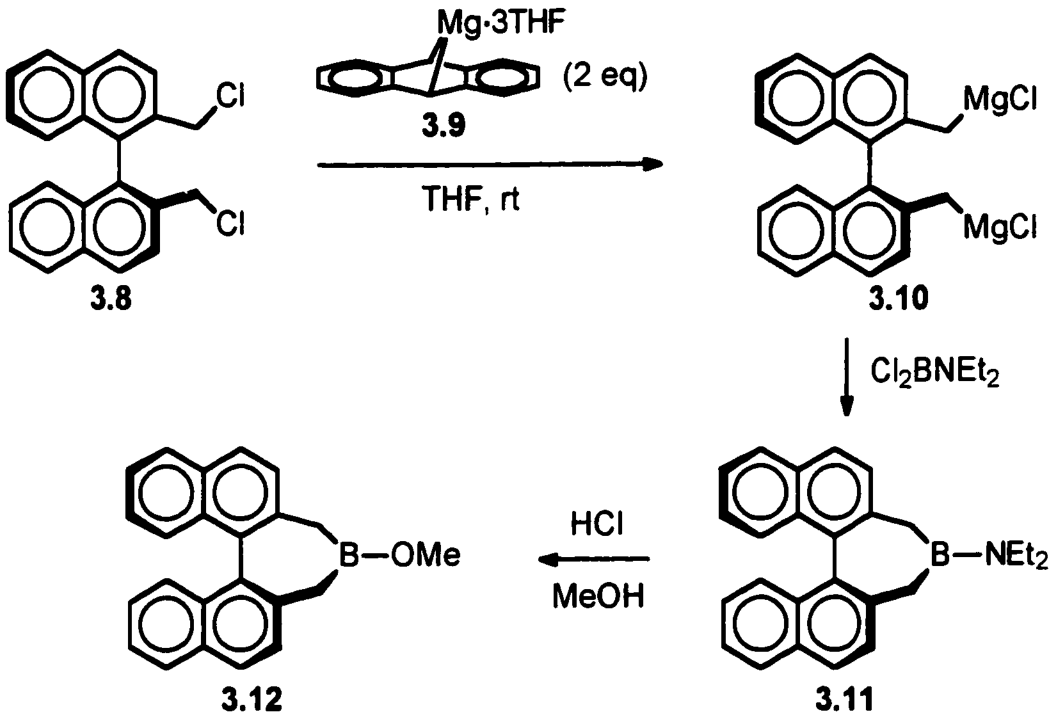


The dichloride **3.8** was reacted with 2 equiv of magnesium-anthracene (**3.9**) to provide di-Grignard **3.10** (Scheme 3.3). The di-Grignard **3.10** was cyclized with Cl_2BNEt_2; the resulting aminoborane **3.11** was stirred with 1.25 equiv of HCl in MeOH at -78 °C to give the methyl binaphthylborinate **3.12**.

Scheme 3.2

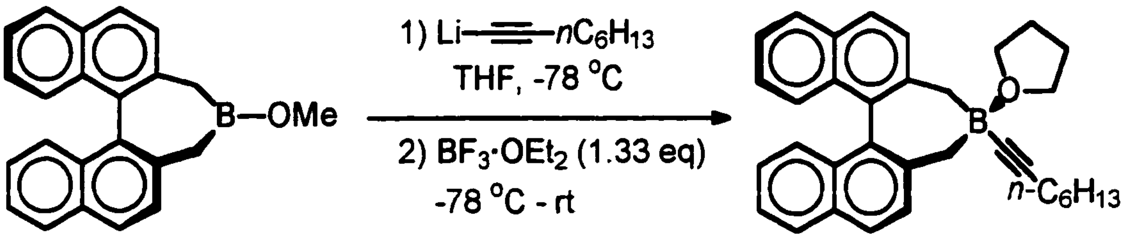

Br
Me
3.4
1) Mg
2) 3.4
(PPh3)2NiCl2
Me
Me
3.5
NBS (2 eq)
reflux
Br
Br
3.6
(1S,2R)-(+)-
ephedrine
Me
Ph
N+
OH
Me
Br-
3.7
xs LAH
cat. NiCl2
(R)-3.5
(R,1S,2R)-3.7
xs LAH
cat. NiCl2
(S)-3.5
(S,1S,2R)-3.7
Me
Me
(S)-3.5
NCS (2 eq)
CCl4
Cl
Cl
3.8

Scheme 3.3



Following the procedure for the preparation of the alkynyldialkylboranes[1] (section 3.1.1), the desired *B*-1-octynylbinaphthylborane **1.82** was prepared from **3.12** in 90% yield (Scheme 3.4).

Scheme 3.4



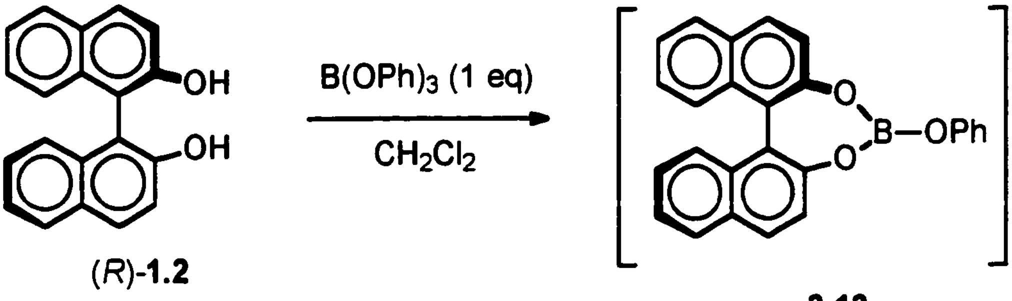
3.12 **1.82**

The octynylbinaphthylborane **1.82** was then reacted with various enones as discussed in section 1.4.2.4 of this thesis.

3.1.3. Generation of Arylbinaphthyl Boron Complex

Yamamoto and co-workers reported an *in situ* generation of chiral boron complex **3.13**.[4] The complex **3.13** was conveniently prepared *in situ* simply by mixing a 1:1 molar ratio of optically active binaphthol (*R*)-**1.2** and triphenyl borate in CH_2Cl_2 at ambient temperature for 1 h (Scheme 3.5). The complex was used in an aza-Diels-Alder reaction without isolation and characterization.

Scheme 3.5



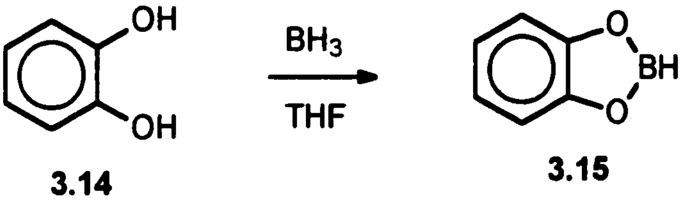
3.13

3.1.4. Preparation of Aryloxyboranes

3.1.4.1. Catecholborane

Decades ago, Brown and Gupta reported the procedure for synthesis of catecholborane (**3.15**).[5] It was simply prepared by the rapid reaction of *o*-dihydroxybenzene (catechol) (**3.14**) with borane in THF (Scheme 3.6).

Scheme 3.6



3.1.4.2. Binaphtholborane

Kelly and co-workers postulated the intermediacy of a *B*-aryloxy substituted dioxaborepine of the structural type **3.17** in the reaction of juglone (**3.16**) with borane-tetrahydrofuran and (*S*)-3,3'-diphenyl-2,2'-dihydroxy-1,1'-binaphthyl [(*S*)-**2.4**] (Scheme 3.7).[6] Though lacking spectroscopic proof for the structure **3.17**, there are three experimental observations pointing to its existence. First, replacement of the two phenyl substituents in **3.17** by (smaller) methyls gives under identical reaction conditions the same enantiomeric product but in only 70% (*vs.* >98%) ee as it is predicted. Second, asymmetric induction is achievable with other dienes and other *peri*-hydroxyquinones. Third, the absolute stereochemistry of the adduct shows that the complex **3.17** is operative. With the similarity to the synthesis of catecholborane (**3.15**), the structure would be quite reasonable, because the first step would form the binaphtholborane.

Scheme 3.7

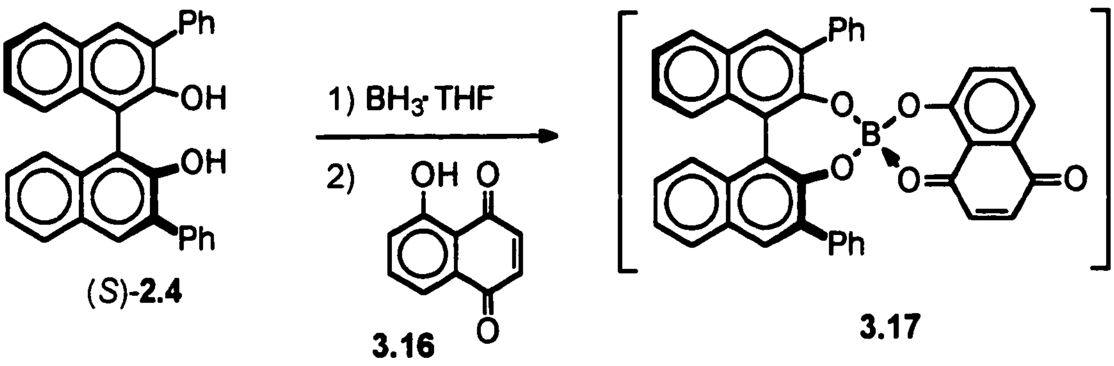
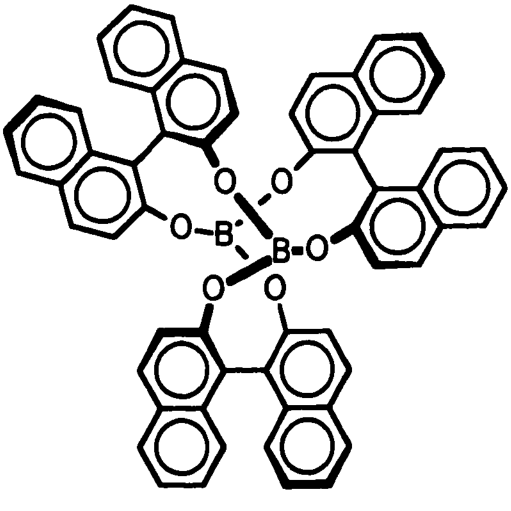


Figure 3.2. Structure of the tetradecacyclic diborate 3.18.



However, a few years later, Kaufmann and Boese discovered formation of a C_3-symmetric tetradecacyclic diborate **3.18** (Figure 3.2) from the reaction of (±)-2,2'-dihydroxy-1,1'-binaphthyl (**1.2**) and monobromoborane dimethylsulfide in dichloromethane.[7] The unit cell was shown to contain both enantiomers of the compound. The tetradecacyclic diborate **3.18** was characterized by X-ray structural analysis.

3.1.5. Synthesis of 1-Alkynyldiisopropoxyboranes

Brown and co-workers reported a preparative method for 1-alkynyldiisopropoxyboranes **3.20**.[8] The reaction of 1-lithio-1-alkynes and triisopropoxyborane (triisopropylborate) in Et_2O at -78 °C gave an ate complex **3.19**, which was treated with hydrogen chloride to afford 1-alkynyldiisopropoxyboranes **3.20** in excellent yields (Scheme 3.8).

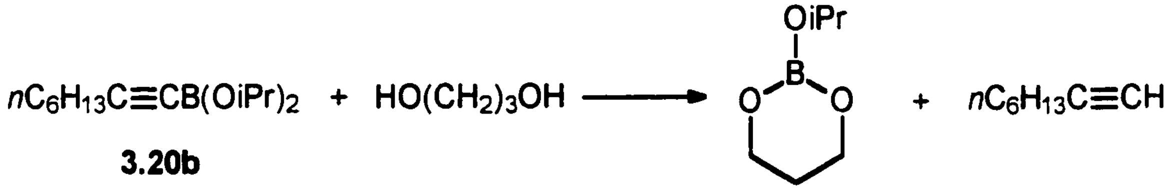
Scheme 3.8

$$\mathrm{RC{\equiv}CLi} \xrightarrow[\mathrm{Et_2O,\ -78\ ^{\circ}C}]{\mathrm{B(OiPr)_3}} \underset{\textbf{3.19}}{\mathrm{Li^{+}[RC{\equiv}CB(OiPr)_3]^{-}}} \xrightarrow{\mathrm{HCl/Et_2O}} \underset{\textbf{3.20}}{\mathrm{RC{\equiv}CB(OiPr)_2}}$$

R = $n\mathrm{C_4H_9}$, **3.20a** 85% yield
R = $n\mathrm{C_6H_{13}}$, **3.20b** 95% yield
R = *t*Bu, **3.20c** 90% yield
R = Ph, **3.20d** 86% yield

Unexpectedly, transesterification of **3.20** with various alcohols proved impossible to achieve. Thus an attempt to prepare the 1,3,2-dioxaborinane derivative from 1-octynyldiisopropoxyborane (**3.20a**) with 1,3-propanediol resulted in an almost instaneous cleavage of the alkynyl-boron bond to form the borate **3.21** and regenerated the alkyne (Scheme 3.9).[8]

Scheme 3.9

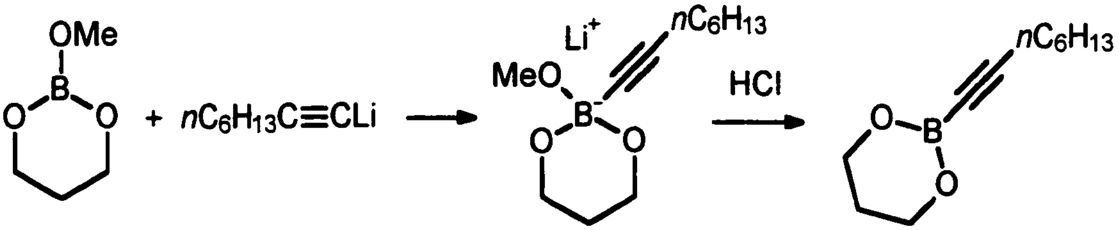


3.20b

3.21

An alternative procedure was used to synthesize different 1-alkynylboronic esters starting with a different borate.[8] For instance, the reaction of 1-lithio-1-octyne with 2-methoxy-1,3,2-dioxaborinane **3.22** furnishing the ate complex **3.23**, followed by treatment with anhydrous HCl, cleanly afforded the cyclic 1-alkynylboronate **3.24** in 85% overall yield (Scheme 3.10).

Scheme 3.10

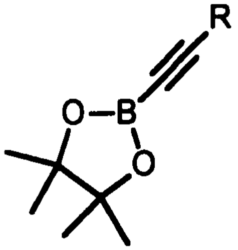


3.22 **3.23** **3.24**

overall 85% yield

Following the latter procedure, Srebnik and Deloux prepared 1-alkynyl boronates **3.25** (Figure 3.3) by reaction of 1-lithioalkynes and either 2-methoxy or 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.[9]

*Figure 3.3. 1-Alkynyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3.25**).*

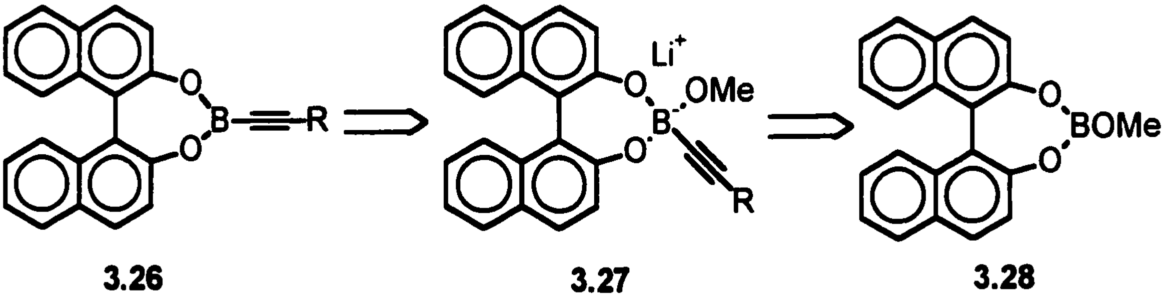


3.2. Proposal

3.2.1. *B*-Methoxybinaphtholborane Route

Considering all of the synthetic methods for the preparation of other related alkynyl boron compounds, a route starting from *B*-methoxybinaphtholborane **3.28** to prepare the *B*-1-alkynylbinaphthylboronates **3.26** was proposed (Scheme 3.11). Reaction of **3.28** with 1-lithio-1-alkyne following Brown's methods[1,8] could provide the ate complex **3.27**, and treatment of the complex **3.27** with $BF_3{\bullet}OEt_2$ or HCl could afford the target molecule **3.26**. The key point for this route to succeed was the preparation of **3.28**.

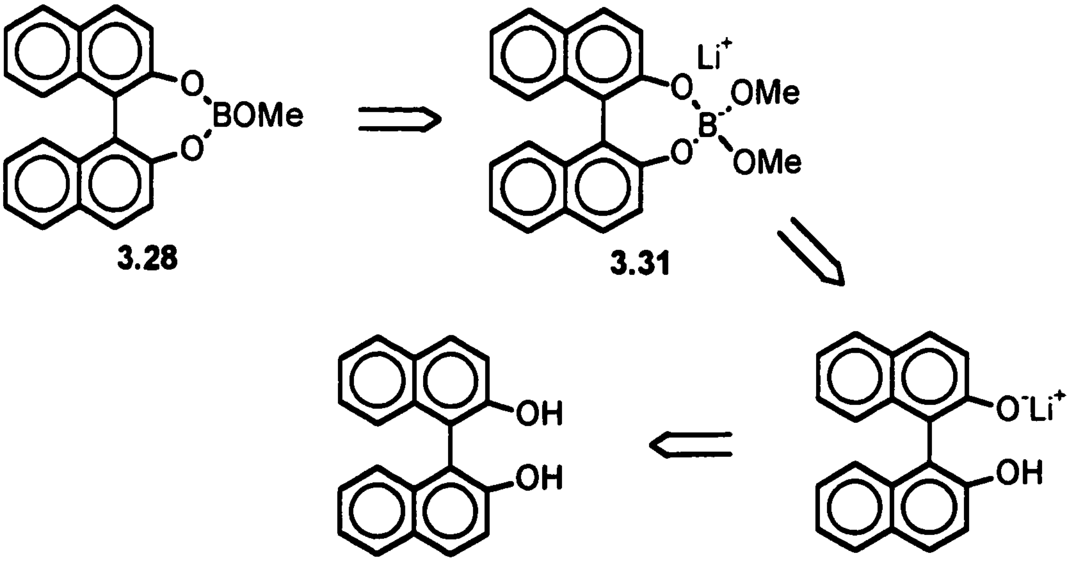
Scheme 3.11



Three different approaches were envisioned to obtain **3.28**. The first one was based on Yamamoto's method for preparation of binaphthylphenylborate (Scheme

3.5) but using trimethyl borate instead of triphenyl borate. The second was to adapt the method for preparation of the *B*-aryloxy substituted dioxaborepine developed by Kelly (Scheme 3.7). The initial product, binaphtholborane **3.29**, could be treated with methanol instead of juglone to give **3.28**. Finally, a more complicated route would involve treatment of binaphthol (**1.2**) with 1 equiv of *n*BuLi to give a mono lithium salt **3.30** which could react with trimethyl borate to afford an ate complex **3.31** (Scheme 3.12). By analogy with Brown's previous work, treatment of the complex **3.31** with $BF_3{\cdot}OEt_2$ or HCl might provide the compound **3.28**.

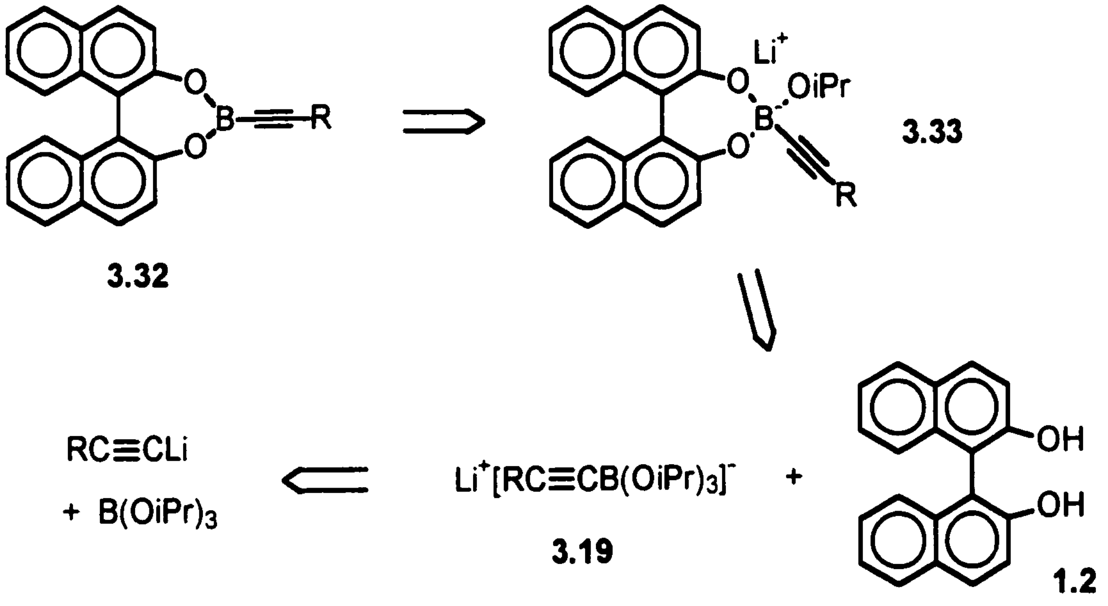
Scheme 3.12



3.2.2. Other Possible Route

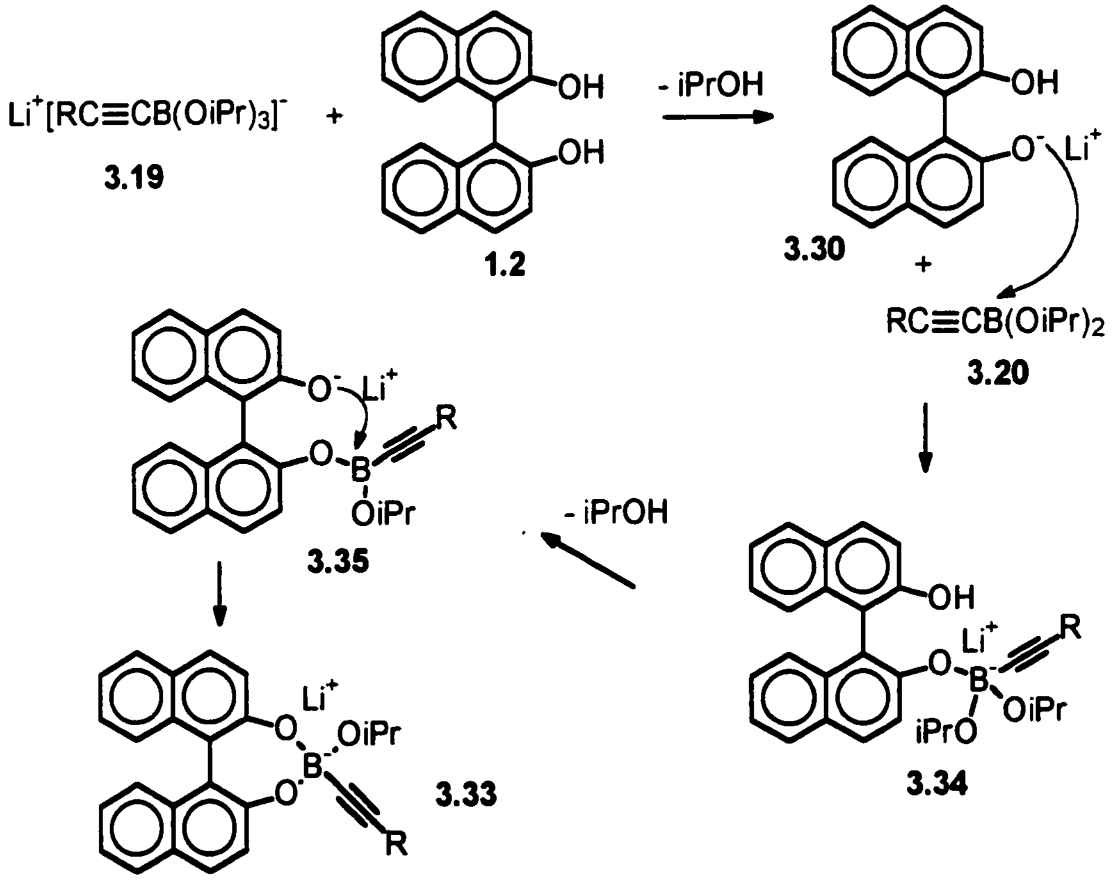
Another possible route to reach *B*-1-alkynylbinaphthylboronates **3.32** was proposed. Due to the acidic nature of OH groups of binaphthol and the fact that the ate complex **3.19** in Scheme 3.8 could be decomposed by HCl, a new complex **3.33** might be synthesized by just mixing **3.19** and binaphthol **1.2** (Scheme 3.13).

Scheme 3.13



The theoretical basis of this transesterification is depicted in Scheme 3.14. By losing one mole of 2-propanol, the exchange reaction between the ate complex **3.19** and binaphthol **1.2** could form a mono lithium salt **3.30** of binaphthol and the alkynyldiisopropylboronate **3.20**. The formed lithium salt **3.30** as a Lewis base could react with **3.20** as a Lewis acid to give the ate complex **3.34**. By losing another mole of isopropanol, the intramolecular exchange reaction of **3.34** should supply an intermediate **3.35**. The intramolecular acid-base reaction of **3.35** should give rise to the target complex **3.33**.

Scheme 3.14



3.3. Results and Discussion

The binaphthols that were used in initial trials to prepare alkynylbinaphthylboronates were racemic. After a general method was found, the enantiomerically pure binaphthols were employed to prepare enantiomerically pure alkynyl binaphthyl boron reagents for asymmetric syntheses. If there is no absolute configuration sign, the binaphthols in this section were racemic.

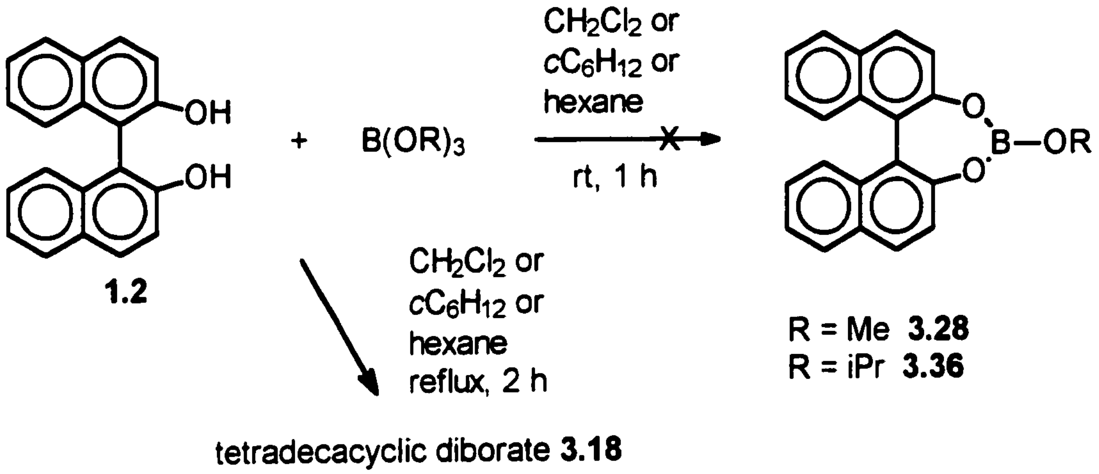
3.3.1. Preparation of *B*-Methoxy-Binaphtholborane 3.28

3.3.1.1. Attempted Reactions of Binaphthol with Trialkyl Borates

Attempts to prepare *B*-methoxy-binaphtholborane **3.28** by Yamamoto's method[4] were unsuccessful. Reactions between binaphthol (**1.2**) and trimethyl borate or triisopropyl borate in different solvents were attempted. The attempted reactions were carried out by mixing **1.2** and trimethyl borate or triisopropyl borate in dichloromethane at room temperature under argon atmosphere for 1 h, followed by removal of volatiles *in vacuo* and drying under reduced pressure at room temperature overnight. The resulting products were examined by ^{1}H NMR spectroscopy. However, no reaction was detected for all trials, and the NMR spectra showed that the starting materials remained unchanged (Scheme 3.15). Use of cyclohexane or hexane as reaction solvent did not improve the reaction under the same reaction conditions.

When the reactions were run under reflux conditions for 2 h, the tetradecacyclic diborate **3.18** (Figure 3.2) was formed exclusively.

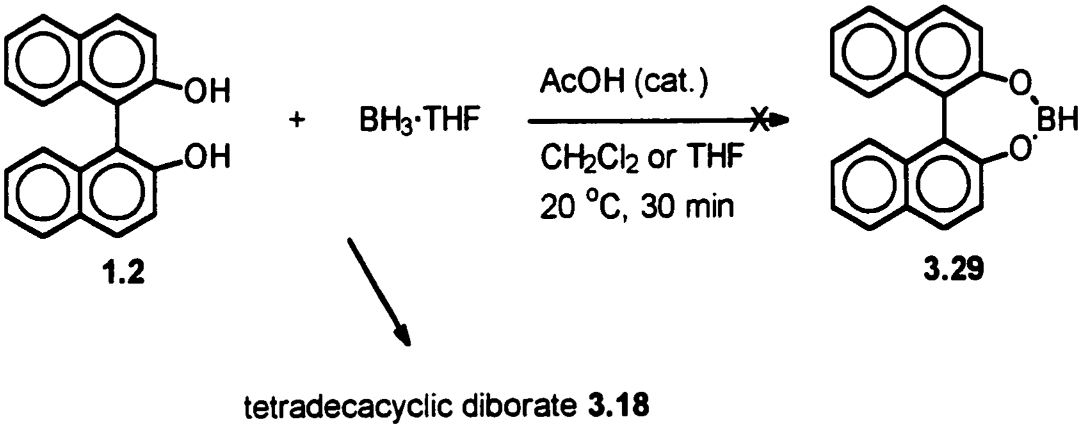
Scheme 3.15



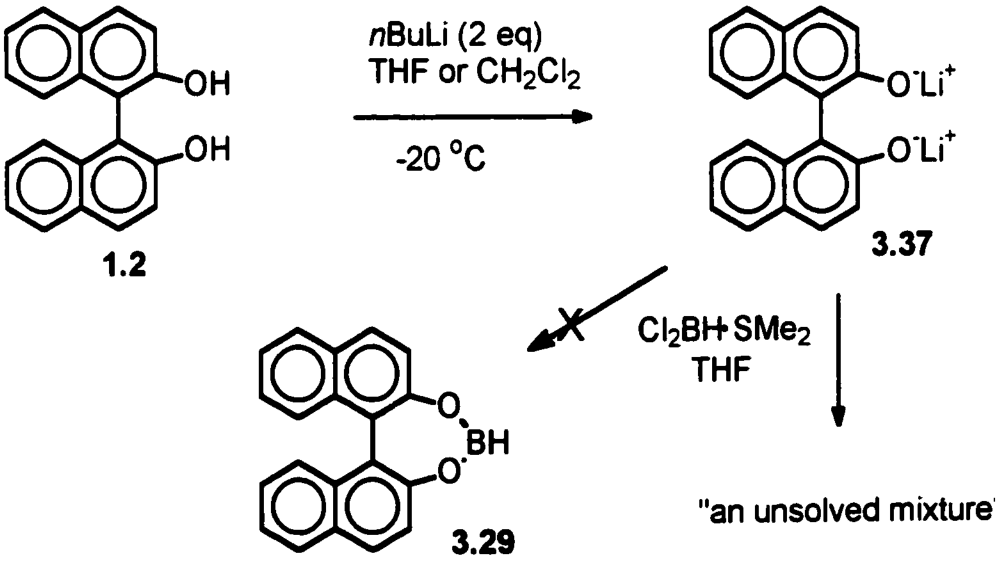
3.3.1.2. Attempted Preparation of Binaphtholborane

Preparation of binaphtholborane was attempted following the method for preparation of the *B*-aryloxy substituted dioxaborepine developed by Kelly[6] (Scheme 3.7). Thus, a mixture of binaphthol **1.2**, BH_3•THF and catalytic amount of AcOH in THF was stirred at 20 °C for 30 min, followed by removal of volatiles under high vacuum to give a white residue which was examined by ^1H NMR spectroscopy. To our surprise, no binaphtholborane **3.29** was detected, and NMR spectra revealed exclusive formation of the tetradecacyclic diborate **3.18** (Scheme 3.16). Changing the reaction solvent to Et_2O gave the same result. This result was consistent with Kaufmann's finding.[7]

Scheme 3.16



Scheme 3.17

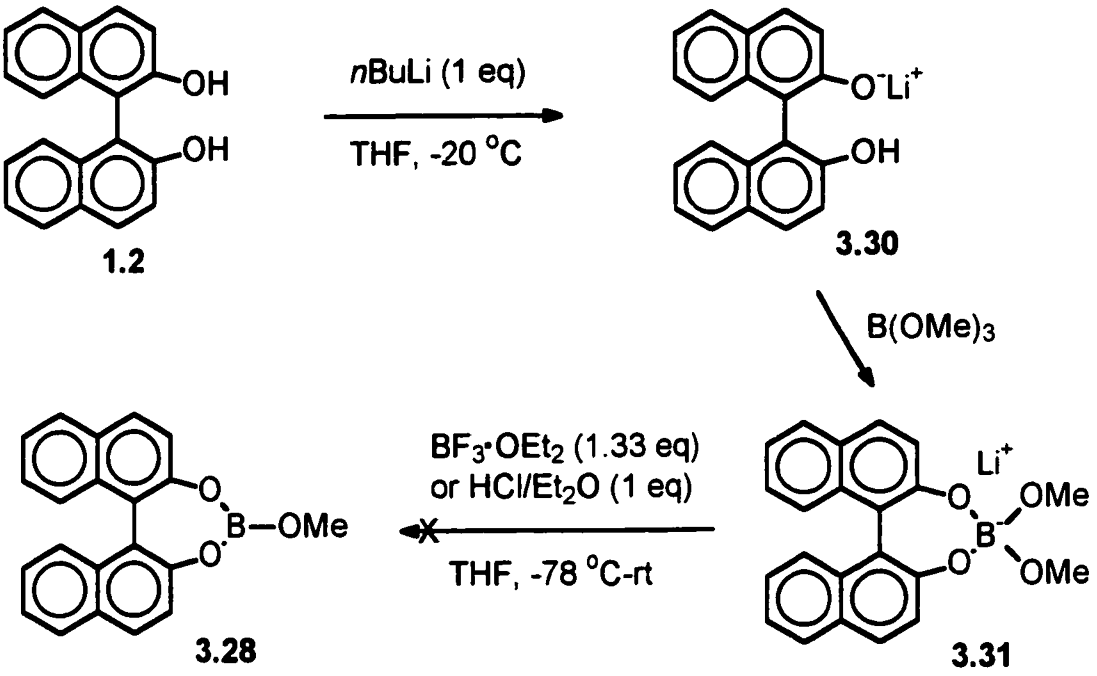


To obtain binaphtholborane, another method was tried. Treatment of binaphthol with 2 equiv of *n*BuLi at -20 °C in THF gave a dilithium salt of binaphthol **3.37** which was used to react with $Cl_2BH{\cdot}SMe_2$. However, a complex mixture resulted from this procedure (Scheme 3.17).

3.3.1.3. *Via* Substitution

Treatment of binaphthol (**1.2**) with 1 equiv of *n*BuLi gave a monolithium salt **3.30**, which in turn, reacted with trimethyl borate to afford an ate complex **3.31** in quantitative yield (Scheme 3.18). However, following Brown's method, treatment of the complex **3.31** with $BF_3{\cdot}OEt_2$ or HCl provided, after removal of solvent under high vacuum, a complex mixture. It is possible that the desired compound **3.28** is unstable under the reaction conditions, or that competing reaction pathways were operating.

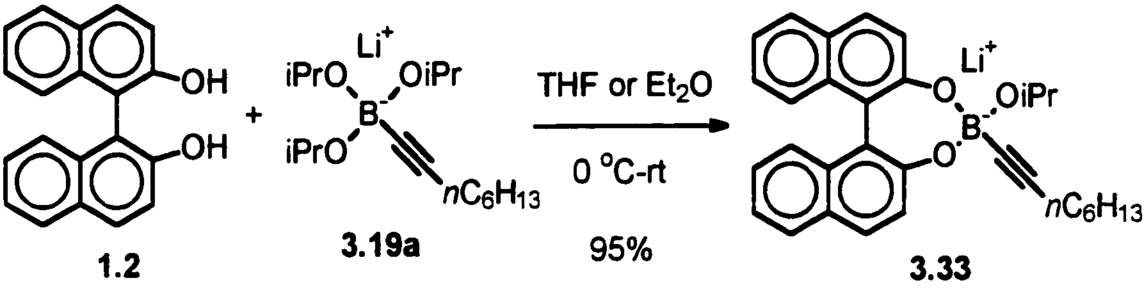
Scheme 3.18



3.3.2. Preparation of Lithium 2,2'-(1,1'-Binaphthyl)isopropyl *B*-1-Alkynylboronate

The successful preparation of **3.31**, nevertheless, provided a lead for further research. The transformation in the preparation of **3.31** is similar to the proposed transesterification method which is depicted in Scheme 3.14. So, we were encouraged to attempt the proposed transesterification. In fact, when the exchange reaction between complex **3.19a** and binaphthol **1.2** was carried out, the reaction did provide the ate complex **3.33** in 95% yield (Scheme 3.19). The mechanism for this type of transformation is outlined in Scheme 3.14.

Scheme 3.19

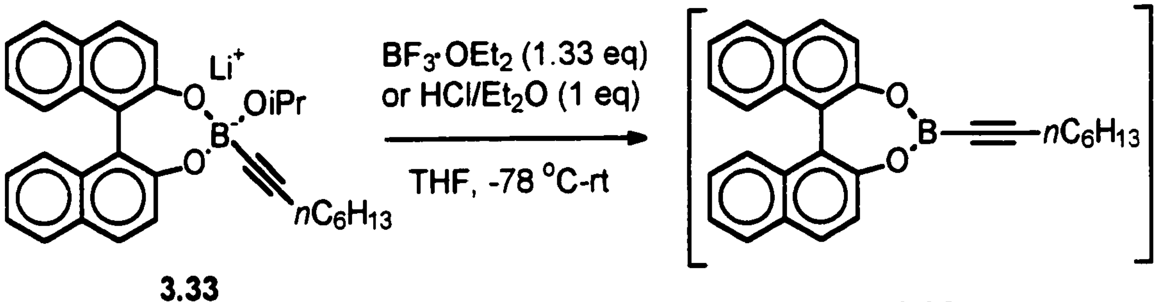


3.3.3. Preparation of 2,2'-(1,1'-Binaphthyl)-*B*-1-Octynylboronate

Attempts to obtain PURE 2,2'-(1,1'-binaphthyl)-*B*-1-octynylboronate (**3.32a**) by decomposition of the complex **3.33** with BF_3•OEt_2 or HCl were not successful. Treatment of **3.33** with 1.33 equiv of BF_3•OEt_2 or HCl in THF, followed by removal of solvent and drying under high vacuum for a short period of time (1 h) afforded mostly **3.32a** (Scheme 3.20), as determined by ^{1}H NMR spectroscopy. The NMR results from reactions with different reaction times were very similar. However, as the drying process went longer, the NMR spectra showed that more and more unexpected compounds appeared in the samples. This suggested that compound **3.32a** did form in the reaction mixtures, and was stable in the solution but was not stable during the isolation and drying process. Since our initial goal was to prepare alkynyl binaphthyl boron reagents and employ such reagents for asymmetric syntheses, further isolation and purification of **3.32a** and its derivatives were not of great importance to us. In

Chapters 4 and 5, use of **3.32a** and its derivatives formed *in situ* from their ate complexes in asymmetric conjugate addition to enones and 1,2-addition to aldehydes, respectively, will be discussed.

Scheme 3.20



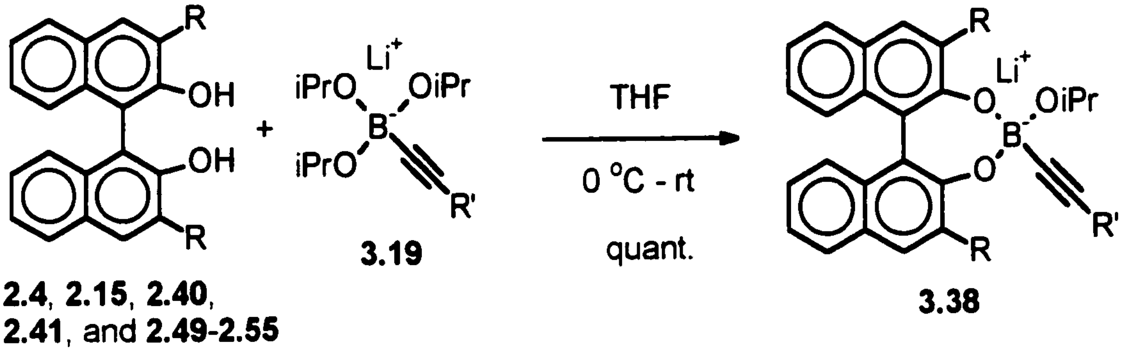
3.33

3.32a

3.3.4. Preparation of *B*-1-Alkynyl 3,3'-Disubstituted-Binaphthyl Boronates

Lithium (3,3'-disubstituted-binaphthyl)isopropylalkynylboronates **3.38** were prepared using a procedure which was the same as that for the preparation of lithium 2,2'-(1,1'-binaphthyl)isopropyl *B*-1-alkynylboronate (**3.33**). Thus reaction of the 3,3'-disubstituted binaphthols (**2.4**, **2.15**, **2.40**, **2.41**, and **2.49-2.55**) with the ate complex (**3.19**) in THF provided lithium (3,3'-disubstituted-binaphthyl)isopropylalkynylboronates (**3.38**) (Scheme 3.21). These compounds (**3.38**) were also used in the asymmetric conjugate addition and 1,2-addition by decomposition with 1.33 equiv of $BF_3{\bullet}OEt_2$ or HCl to produce *B*-1-alkynyl 3,3'-disubstituted binaphthyl boronates (**3.39**) *in situ*.

Scheme 3.21



R	R'	product	R	R'	product
Br	nC_6H_{13}	**3.38a**	3,5-$(CF_3)_2$-C_6H_3	nC_6H_{13}	**3.38i**
I	nC_6H_{13}	**3.38b**	3,5-$(tC_4H_9)_2$-C_6H_3	nC_6H_{13}	**3.38j**
CN	nC_6H_{13}	**3.38c**	C_6H_5	nC_6H_{13}	**3.38k**
CF_3	nC_6H_{13}	**3.38d**	C_6H_5	C_6H_5	**3.38l**
CH_3	nC_6H_{13}	**3.38e**	C_6H_5	CH_2OBn	**3.38m**
3,5-$(CH_3)_2$-C_6H_3	nC_6H_{13}	**3.38f**	C_6H_5	$SiMe_3$	**3.38n**
4-(CH_3O)-C_6H_4	nC_6H_{13}	**3.38g**	C_6H_5	tC_4H_9	**3.38o**
2-Naph	nC_6H_{13}	**3.38h**			

3.4. Conclusion

Attempts to obtain *B*-methoxybinaphtholborane **3.28** by a few related literature methods failed. Trials on the preparation of binaphtholborane **3.29** were also unsuccessful.

Lithium binaphthylisopropylalkynylboronate **3.33** was successfully prepared using a simple procedure that required only one step from binaphthol **1.2** and lithium alkynyltriisopropylboronate **3.19**. The procedure could be used as a general method to synthesize lithium (3,3'-disubstituted-binaphthyl)isopropylalkynylboronate **3.38**. Decomposing the boronates by $BF_3 \cdot OEt_2$ or HCl produced the corresponding alkynylbinaphthylboronates. However, the boronates were unstable after isolation from the reaction solution. It was possible to employ the boronates *in situ* in the asymmetric syntheses such as conjugate addition to enones and 1,2-addition to aldehydes.

3.5. Experimental

3.5.1. General

Nuclear magnetic resonance (NMR) spectra were recorded using a Bruker AM-250 spectrometer. Chemical shifts are given in parts per million (ppm) downfield from tetramethylsilane (TMS). The ^{1}H NMR samples were run in a mixture of deuteriochloroform/deuterio-DMSO (10:1) containing ca. 0.01% TMS as an internal standard (δ = 0.0). Spectra are tabulated in the order: chemical shift, assignment, numbers of protons, multiplicity, coupling constant. The spectral reference for ^{13}C NMR spectra was $CDCl_3$ (δ = 77.0). Melting points are uncorrected.

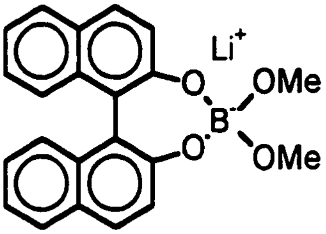
All reactions were performed under an argon or nitrogen atmosphere on the bench using standard Schlenk techniques.

3.5.2. Materials

Solvents were dried prior to use. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were dried by distillation from sodium/benzophenone ketyl. Dichloromethane (CH_2Cl_2) was dried by distillation from calcium hydride. Boron trifluoride ethyl etherate ($BF_3{\bullet}OEt_2$) was treated with a small quantity of diethyl ether (to ensure an excess of this component, ca. 5 mL/100 mL $BF_3{\bullet}OEt_2$) and distilled (60-62 °C/aspirator vacuum). Binaphthol **1.2** and all 3,3-disubstutited binaphthols were synthesized by the procedures discussed in Chapter 2. Unless noted, chemicals were purchased from Aldrich Chemical Company.

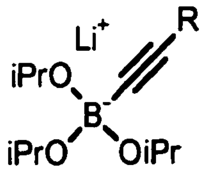
3.5.3. Preparation of the alkynyl boronates

3.5.3.1. Lithium Dimethylbinaphthylborate (3.31)



A solution of (±)-2,2'-dihydroxy-1,1'-binaphthyl (**1.2**) (0.10 g, 0.35 mmol) in THF (2 mL) was cooled to -20 °C in a 10-mL round-bottomed flask fitted with a septum, stir bar and an argon inlet. To the mixture, with stirring, was added *n*BuLi (0.22 mL of a 1.6 M solution in hexane, 0.35 mmol) and the mixture was stirred for 10 min. Trimethyl borate (44 μl, 0.39 mmol) was injected into the flask and the resulting solution was stirred at -20 °C for 1 h. Then it was allowed to warm up to room temperature. Volatiles were removed under high vacuum, and the white residue was dried under high vacuum overnight to provide compound **3.31** in quantitative yield. ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ 7.45-7.90 (ArH, 4 H, m), 6.80-7.35 (ArH, 8 H, m), 2.82 (OCH_3, 6 H, s).

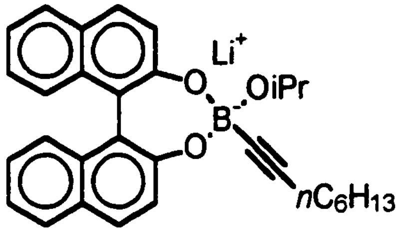
3.5.3.2. Lithium triisopropyl-*B*-1-alkynylboronate (3.19)



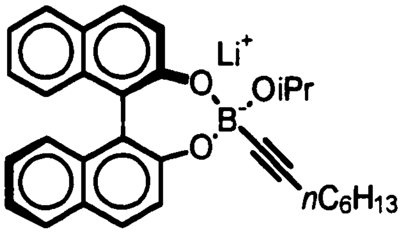
R = nC_6H_{13}, C_6H_5, CH_2OBn, $SiMe_3$, *t*Bu

The method for the preparation of the compounds (**3.19**) was analogous to the literature preparation of lithium triisopropyl-*B*-1-octynylboronate.[8] A general procedure follows. A solution of 1-alkyne (30.0 mmol) in Et_2O (42 mL) was cooled to -78 °C in a 100-mL round-bottomed flask fitted with a septum, stir bar and an argon or nitrogen inlet. To the mixture, with stirring, was added *n*BuLi (19.7 mL of a 1.52 M solution in hexane, 30.0 mmol) and the mixture was stirred for 30 min. In another 250-mL round-bottomed flask, triisopropyl borate (6.92 mL, 30.0 mmol) was mixed in Et_2O (100 mL) and the flask was cooled to -78 °C. The alkynyllithium solution from the first flask was cannulated into the triisopropyl borate flask. The resulting reaction mixture was stirred at -78 °C for 1 h and then at room temperature for 4 h. The solvent was removed *in vacuo* and the resulting white solid was dried *in vacuo* overnight to give the product **3.19** in quantitative yield. It was used in the next step without further purification and characterization.

3.5.3.3. Lithium (±) and (*R*)-2,2'-(1,1'-binaphthyl)isopropyl-*B*-1-octynylboronate (3.33)



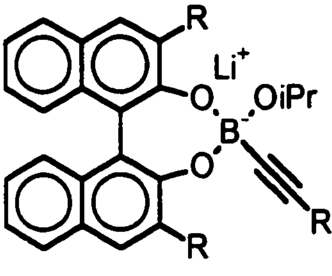
(±)-**3.33**



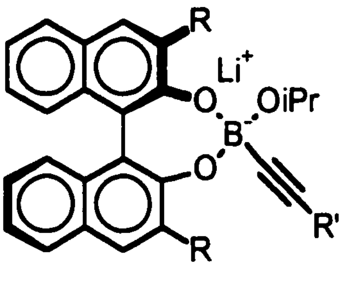
(*R*)-**3.33**

(±)-2,2'-Dihydroxy-1,1'-binaphthyl (**1.2**) (0.119 g, 0.416 mmol), lithium triisopropyl-*B*-1-octynylboronate (**3.19a**) (0.105 g, 0.345 mmol), and a stir bar were added in a 25-mL round-bottomed flask under an argon or nitrogen atmosphere. While the flask was cooled to 0 °C, THF (15 mL) was added slowly by syringe into the flask. After addition, the mixture was stirred at 0 °C for 1 h, then at room temperature for 3 h. The solvent was removed and the resulting white solid was dried *in vacuo* overnight to give compound **3.33** in quantitative yield: ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ 7.54-8.02 (ArH, 4 H, m), 6.88-7.50 (ArH, 8 H, m), 4.41 (Me_2CH-O, 1 H, sept, J = 6.1 Hz), 2.08 ($C{\equiv}C{-}CH_2$, 2 H, t, J = 6.4 Hz), 1.02-1.60 ($(CH_2)_4$, 8 H, m), 1.24 (CH_3, 3 H, d, J = 6.0 Hz), 1.23 (CH_3, 3 H, d, J = 6.0 Hz), 0.88 (CH_3, 3 H, t, J = 6.7 Hz). It was used for conjugate addition without further purification and characterization. (*R*)-2,2'-Dihydroxy-1,1'-binaphthyl was used to afford (*R*)-2,2'-(1,1'-binaphthyl)isopropyl-*B*-1-octynylboronate [(*R*)-**3.33**] in quantitative yield.

3.5.3.4. Lithium (*R*)-2,2'-(3,3'-Disubstituted-1,1'-Binaphthyl)isopropyl-*B*-1-Alkynylboronate (3.38)



(±)-**3.38**



(*R*)-**3.38**

R	R'		R	R'	
Br	$n\mathrm{C_6H_{13}}$	**3.38a**	3,5-$(\mathrm{CF_3})_2$-$\mathrm{C_6H_3}$	$n\mathrm{C_6H_{13}}$	**3.38i**
I	$n\mathrm{C_6H_{13}}$	**3.38b**	3,5-$(t\mathrm{C_4H_9})_2$-$\mathrm{C_6H_3}$	$n\mathrm{C_6H_{13}}$	**3.38j**
CN	$n\mathrm{C_6H_{13}}$	**3.38c**	$\mathrm{C_6H_5}$	$n\mathrm{C_6H_{13}}$	**3.38k**
$\mathrm{CF_3}$	$n\mathrm{C_6H_{13}}$	**3.38d**	$\mathrm{C_6H_5}$	$\mathrm{C_6H_5}$	**3.38l**
$\mathrm{CH_3}$	$n\mathrm{C_6H_{13}}$	**3.38e**	$\mathrm{C_6H_5}$	$\mathrm{CH_2OBn}$	**3.38m**
3,5-$(\mathrm{CH_3})_2$-$\mathrm{C_6H_3}$	$n\mathrm{C_6H_{13}}$	**3.38f**	$\mathrm{C_6H_5}$	$\mathrm{SiMe_3}$	**3.38n**
4-$(\mathrm{CH_3O})$-$\mathrm{C_6H_4}$	$n\mathrm{C_6H_{13}}$	**3.38g**	$\mathrm{C_6H_5}$	$t\mathrm{C_4H_9}$	**3.38o**
2-Naph	$n\mathrm{C_6H_{13}}$	**3.38h**			

The procedure was the same as that of preparation of (**3.33**) and it was a general method for preparation of (**3.38**) with different 1-alkynyl groups. (±)-3,3'-Disubstituted-2,2'-dihydroxy-1,1'-binaphthyl (0.416 mmol) and lithium triisopropyl-*B*-1-alkynylboronate (**3.19**) (0.345 mmol) were required to afford a white solid (**3.38**) in quantitative yield. All compounds were used for conjugate addition without further purification and characterization. (*R*)-3,3'-Disubstituted-2,2'-dihydroxy-1,1'-binaphthyl was used to afford (*R*)-**3.38**.

3.6. References

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CHAPTER 4. ASYMMETRIC CONJUGATE ADDITION

4.1. Introduction

4.1.1. Conjugate Addition

The conjugate addition of nucleophiles to enones has been reviewed in Section 1.4 of Chapter 1.

Conjugate addition with cuprates represents a powerful method for selective C-C bond formation. Use of zincates provides an additional tool for conjugate addition. However, cuprates usually do not transfer alkynyl groups in conjugate addition reactions; they are rather used as residual ligands (or so called dummy ligands). The conjugate addition of alkynyl groups to enones by alkynylalanes and alkynylboranes provides a solution to such problem.

Since the reaction introduces a chiral carbon on the β position of prochiral enones, many asymmetric conjugate additions by cuprates and zincates are known. The enantioselective conjugate addition of alkynyl groups by cuprates and zincates is not known, even though the introduction of the versatile alkynyl group is quite useful for further modification of the molecule. There is only one example of enantioselective conjugate additions of alkynyl groups to enones in which a chiral alkynylborane has been employed from previous work in our group (Scheme 1.34).[1] The reactions gave excellent yields of 1,4-adducts, but with poor enantioselectivities.

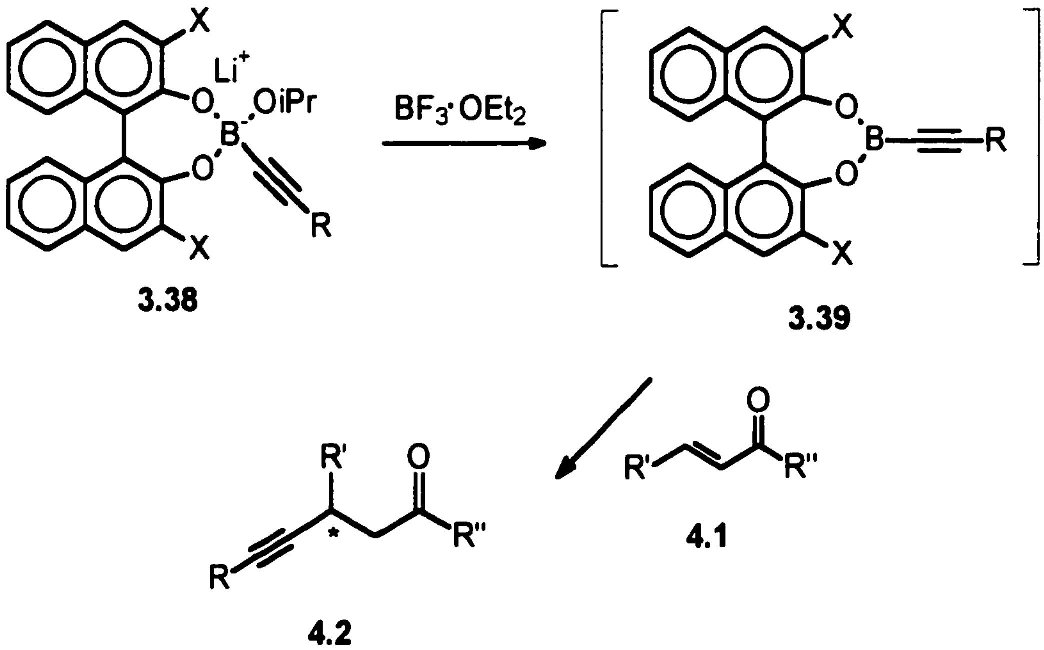
4.2. Proposal

To obtain high enantioselectivities in the conjugate addition of alkynyl groups to enones, novel alkynyl binaphthyl boron reagents were proposed and synthesized. The synthesis of these reagents has been discussed in Chapter 3. With these chiral reagents, asymmetric conjugate additions might be performed (Scheme 4.1).

Following Brown's procedure[2], the ate complex **3.38** can be decomposed to form alkynylbinaphthylboronate **3.39** *in situ*, which can react with enone **4.1** to provide enantioselectively the 1,4-adduct **4.2**.

Besides the historical advantages of using binaphthyl groups and boron reagents in asymmetric synthesis, it has additional features for the proposal. Since chiral octynylbinaphthylborane **1.82** (see Scheme 1.34) reacted with enones very quickly it usually took only a few minutes for the reaction to be completed. The reaction did provide 1,4-adducts in excellent yield, but with poor enantioselectivities. Now the main difference between the reagent **3.39** and **1.82** is that the reagent **3.39** has two oxygen atoms connecting boron to the binaphthyl group while **1.82** has two methylene groups. We wish to promote slow reactions because the oxygen atom may partially donate their electronic density to boron atom, and such donation would reduce the boron atom's ability to coordinate with the carbonyl oxygen of enones. A slower reaction might provide the 1,4-adducts with good enantioselectivities.

Scheme 4.1



3.38 **3.39** **4.1** **4.2**

where X = H, Br, I, CN, CF_3, CH_3, Aryl, etc
R = Alkyl, C_6H_5, CH_2OBn, $SiMe_3$, etc

Other advantages of the reagent **3.39** over **1.82** are its easy synthesis and the possibility of introducing 3,3'-substituents in order to increase stereo-induction (see Chapter 2 for details).

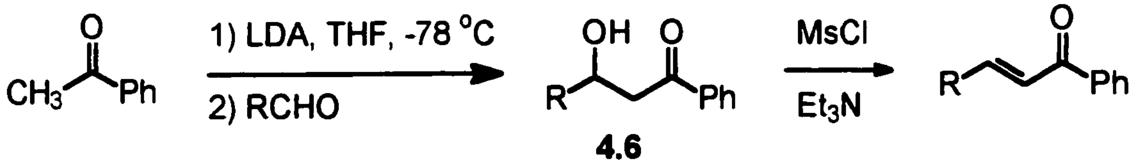
4.3. Results and Discussion

4.3.1. Synthesis of α,β-Unsaturated Ketones

A series of acyclic enones were prepared to study the asymmetric conjugate addition of alkynyl groups. Several different methods were required to obtain these enones with different substituents in place.

Following a literature method,[3] *E*-1-phenyl-2-nonen-1-one (**4.3**), *E*-4-methyl-1-phenyl-2-penten-1-one (**4.4**) and *E*,*E*-1-phenyl-2,4-hexadien-1-one (**4.5**) were prepared in good yields *via* an aldol-dehydration sequence (Scheme 4.2). The aldol **4.6** resulting from the aldol condensation step was not purified and was simply treated with mesyl chloride and triethylamine to provide the enones.

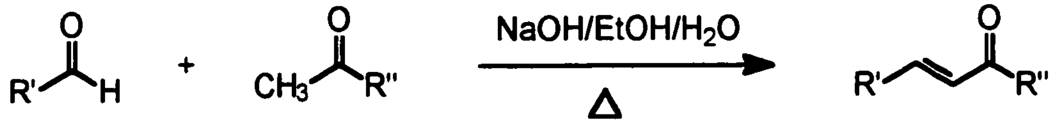
Scheme 4.2.



R	enone	overall yield / %
$n\mathrm{C_6H_{13}}$	**4.3**	75
$i\mathrm{C_3H_7}$	**4.4**	81
1-propenyl	**4.5**	85

By the Claisen-Schmidt condensations of methyl aryl ketones and aldehydes without α hydrogens, fourteen enones were prepared successfully (Table 4.1). Except in the case of *E*-4,4-dimethyl-1-phenyl-2-penten-1-one (**4.11**), all enones were obtained in excellent yields. The reaction sequence using acetophenone and trimethylacetaldehyde had a notable quantity of the aldol compound as a by-product. The aldol compound might require longer reaction time to be dehydrated to the enone **4.11**. However, optimization was not attempted since there was a sufficient amount of enone **4.11** from the reaction for further use in the conjugate addition experiments.

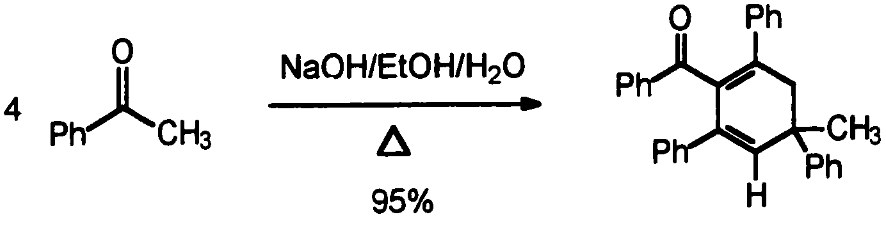
Table 4.1. Claisen-Schmidt condensation for enone proparation.



entry	R'	R"	enone	overall yield / %
1	1-Naph	C_6H_5	**4.7**	89
2	$pClC_6H_4$	C_6H_5	**4.8**	94
3	$pMeOC_6H_4$	C_6H_5	**4.9**	85
4	2-furyl	C_6H_5	**4.10**	95
5	tC_4H_9	C_6H_5	**4.11**	43
6	$pBrC_6H_4$	$pBrC_6H_4$	**4.12**	96
7	C_6H_5	$pClC_6H_4$	**4.13**	90
8	C_6H_5	$pMeOC_6H_4$	**4.14**	92
9	$pMeOC_6H_4$	$pMeOC_6H_4$	**4.15**	87
10	$pClC_6H_4$	$pMeOC_6H_4$	**4.16**	90
11	1-Naph	$pMeOC_6H_4$	**4.17**	86
12	$pClC_6H_4$	$pClC_6H_4$	**4.18**	91
13	1-Naph	$pClC_6H_4$	**4.19**	88
14	$pMeOC_6H_4$	$pClC_6H_4$	**4.20**	90

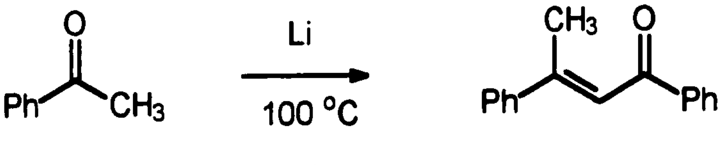
An attempt made to prepare *E*-1,3-diphenyl-2-buten-1-one (dypnone) (**4.21**) by the Claisen-Schmidt condensation failed. The Claisen-Schmidt condensation of acetophenone exclusively gave (±)-2-benzoyl-1,3,5-triphenyl-5-methyl-1,3-cyclohexadiene (**4.22**) (Scheme 4.3). The enone **4.21** was prepared by a method reported by Samuel and Setton (Scheme 4.4).[4] Acetophenone was treated with lithium metal at 100 °C to give the enone **4.21** in 81% yield based on the recovery of unreacted acetophenone.

Scheme 4.3



4.22

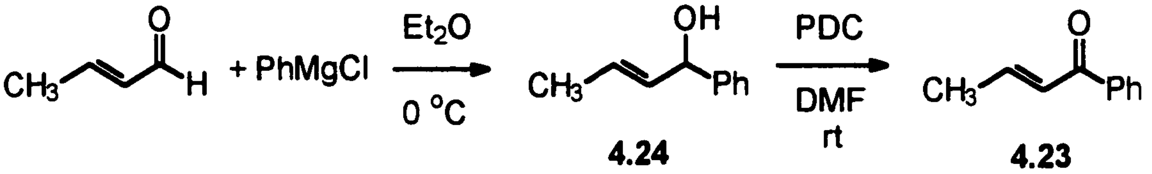
Scheme 4.4



4.21

E-1-Phenyl-2-buten-1-one (**4.23**) was prepared by the addition of crotonaldehyde to phenylmagnesium chloride, followed by oxidation of the resulting carbinol **4.24** with pyridinium dichromate (PDC) in DMF to furnish the desired compound **4.23** in 80% overall yield (Scheme 4.5).

Scheme 4.5



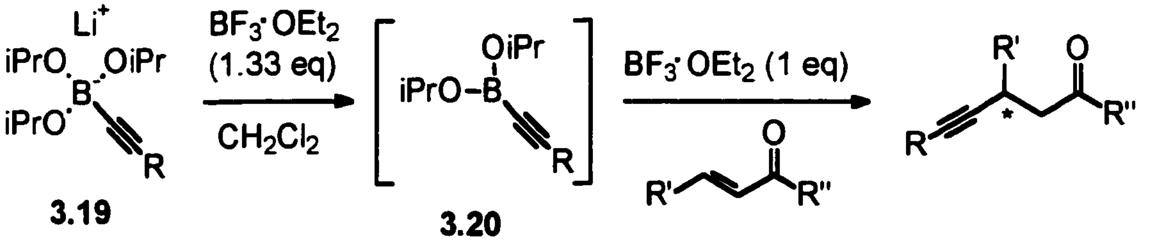
overall 80% yield

4.3.2. Synthesis of Racemic 1,4-Adducts

The racemic 1,4-adducts of these enones were prepared by following a literature method (Scheme 1.17).[5] This method was selected since the required alkynyl boron reagents for the 1,4-addition of alkynyl groups to enones were also the intermediates in the preparation of the chiral alkynyl boron reagents for asymmetric conjugate addition. Once the alkynyl boron reagents were prepared, they could be stored in the freezer and used as required.

A total of twenty two racemic 1,4-adducts were synthesized directly following the procedure without further optimization (Table 4.2). Most yields were good to excellent, except for the compound **4.46** where a yield of 15% was obtained. The low yield possibly resulted from the instability of the starting material and product under the reaction conditions since silyl compounds are often reactive to fluoride reagents.

Table 4.2. Preparation of racemic 1,4-adducts.



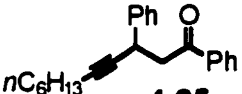
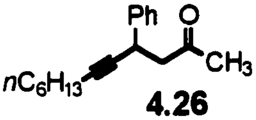
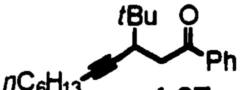
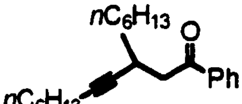
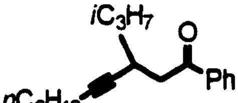
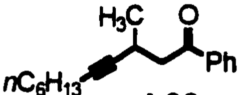
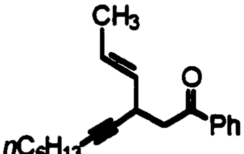
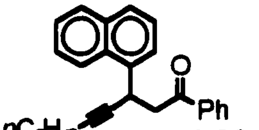
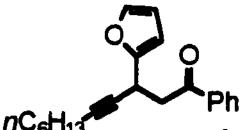
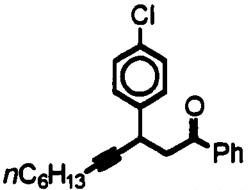
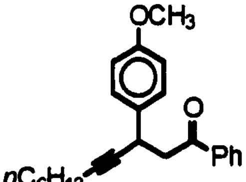
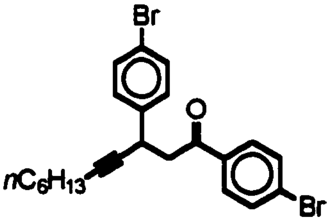
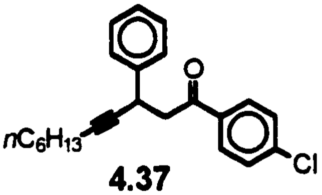
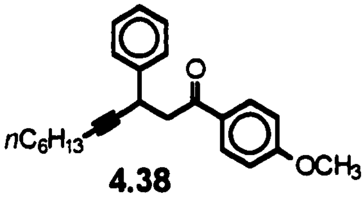
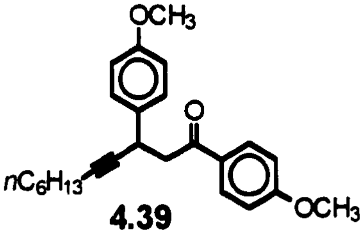
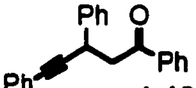
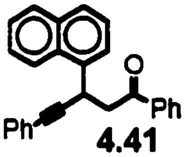
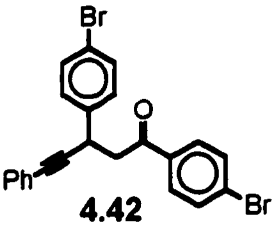
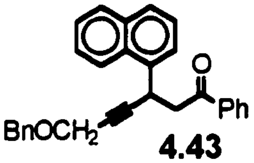
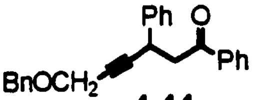
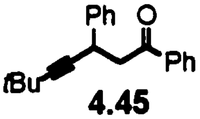
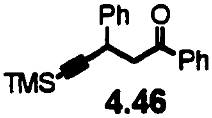
entry	1,4-adduct	yield/%
1	 **4.25**	75
2	 **4.26**	40
3	 **4.27**	40
4	 **4.28**	42
5	 **4.29**	62
6	 **4.30**	59
7	 **4.31**	48
8	 **4.32**	86
9	 **4.33**	42
10	 **4.34**	77
11	 **4.35**	78
12	 **4.36**	70

Table 4.2 (continued)

entry	1,4-adduct	yield/%
13	 **4.37**	75
14	 **4.38**	78
15	 **4.39**	72
16	 **4.40**	82
17	 **4.41**	96

entry	1,4-adduct	yield/%
18	 **4.42**	88
19	 **4.43**	72
20	 **4.44**	70
21	 **4.45**	52
22	 **4.46**	15

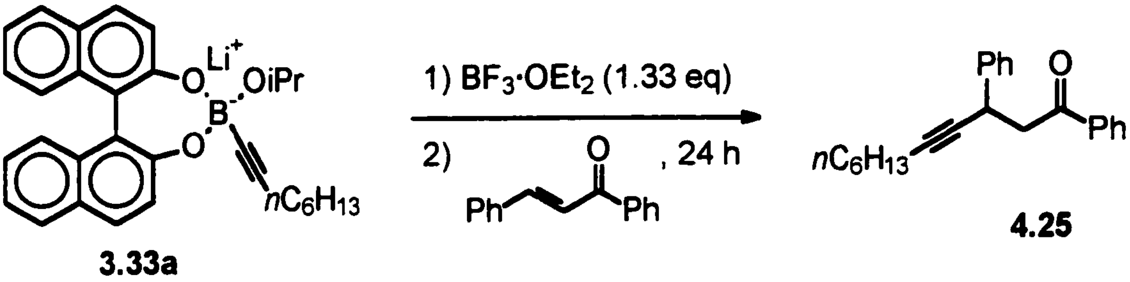
4.3.3. Conjugate Addition with Racemic Binaphthyl Alkynyl Boron Reagents

4.3.3.1. With Racemic Binaphthyl-1-octynylboronate 3.33a

Reactions between chalcone and racemic binaphthyl-1-octynylboronate **3.33a** were performed in order to test and search for the optimum reaction conditions (Table 4.3). At room temperature, either methylene chloride, cyclohexane, tetrahydrofuran or acetonitrile were used as the reaction solvent, and each reaction was conducted for 24 h. The reaction was quenched with sat. aqueous NH_4Cl solution, then examined by TLC, followed by work-up and purification by column chromatography to afford the pure 1,4-adduct **4.25**. For all reactions, the binaphthol was recovered by column chromatography in quantitative yield.

The reactions performed in methylene chloride and acetonitrile gave the best results in providing the 1,4-adduct **4.25** in 82% and 90% yield, respectively (entry 1 and 4 of Table 4.3). However, the reaction in THF gave no conjugate addition product, and in cyclohexane afforded the 1,4-adduct **4.25** in only 10% yield (entry 3 and 2, respectively). The reason for no reaction occurring in THF might be that the reaction requires a non-coordinating solvent for reactivity. THF could coordinate with the boron reagent to form a Lewis acid-base adduct which would be unreactive towards the enone. The low yield in cyclohexane could be understood in terms of a solubility problem since the boron reagent **3.33a** did not dissolve in cyclohexane and was not consumed appreciably during the reaction.

Table 4.3. Conjugate addition to chalcone with racemic binaphthyl-1-octynylboronate.



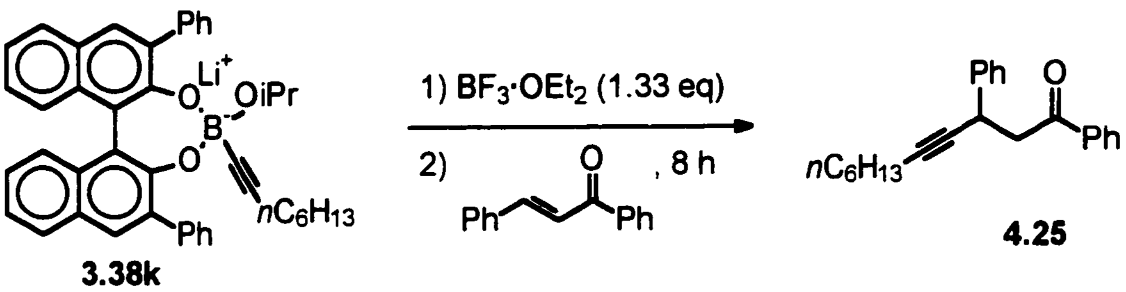
entry	solvent	react. temp./°C	yield/%
1	CH_2Cl_2	rt	82
2	cC_6H_{11}	rt	10
3	THF	rt	0
4	CH_3CN	rt	90
5	CH_2Cl_2	-78-0	0
6	CH_3CN	-78-0	0

Cooling the reaction to -78 °C in methylene chloride or acetonitrile prevented the addition from occurring. Acetonitrile freezes at -48 °C which may prevent the reaction occurring. Furthermore, no reaction was observed when warming to 0 °C and stirring overnight (Entry 5 and 6 of Table 4.3). The reason for these results is not clear.

4.3.3.2. Use of Racemic (3,3'-Diphenylbinaphthyl)-1-Octynylboronate 3.38k

The reactions of racemic (3,3'-diphenylbinaphthyl)-1-octynylboronate **3.38k** and chalcone were also examined under different conditions and are summarized in Table 4.4. Acetonitrile and methylene chloride, the two best solvents for the reaction of **3.33a** and chalcone were also satisfactory for the reaction of **3.38k** and chalcone. However, the reaction of **3.38k** was faster and complete within 8 h at room temperature (entry 1 and 2). The reaction in THF also gave no 1,4-adduct (entry 3). One more feature of the reaction with **3.38k** was that in methylene chloride a higher yield resulted than in acetonitrile. The yield in methylene chloride was 88% *vs.* 70% in acetonitrile. Cooling the reaction to -78 °C in methylene chloride or acetonitrile also prevented the addition from occurring and no reaction was observed when warmed to 0 °C and left overnight (Entry 4 and 5 of Table 4.4). The temperature effect was similar to the reaction with **3.33a**.

*Table 4.4. Conjugate addition of racemic (3,3'-diphenylbinaphthyl)-1-octynylboronate **3.38k** and chalcone.*



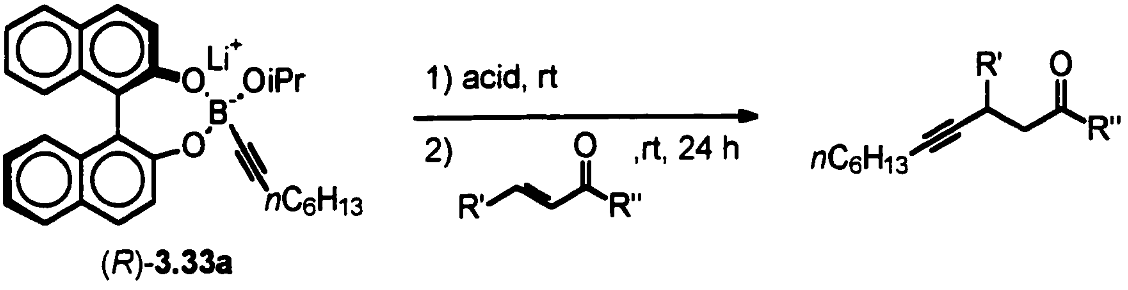
entry	solvent	react. temp./°C	yield/%
1	CH_2Cl_2	rt	88
2	CH_3CN	rt	70
3	THF	rt	0
4	CH_2Cl_2	-78-0	0
5	CH_3CN	-78-0	0

4.3.4. Conjugate Addition with Chiral Alkynylbinaphthylboronates

4.3.4.1. Addition with Alkynylbinaphthylboronate

The first examples of asymmetric conjugate additions were the reactions of (*R*)-binaphthyl-1-octynylboronate [(*R*)-**3.33a**] with several enones (Table 4.5). Chalcone was used as a standard, in order to investigate different conditions in the asymmetric additions. The enantioselectivity was determined by ^{13}C NMR spectroscopic analysis of the diastereomers formed by ketalization of the 1,4-adduct with (*R*,*R*)-2,3-butanediol.[6] The conjugate addition of the octynyl group to chalcone in CH_2Cl_2 occurred with 0% ee in 82% yield when BF_3•OEt_2 was used to decompose the lithium (*R*)-binaphthyl-1-octynylisopropylboronate [(*R*)-**3.33a**] (entry 1). When a solution of HCl in ether was used to decompose (*R*)-**3.33a** (entry 3), the 1,4-adduct was formed in 79% yield and with 34% ee. The absence of any enantioselectivity in entry 1 was quite puzzling since the two reactions (entry 1 and 3) are supposed to undergo the same pathway, and thus should provide similar results. Another two reactions (entries 2 and 4) in acetonitrile were performed and provided ee's between 31-51% in 90% yields when BF_3•OEt_2 was used to decompose (*R*)-**3.33a** (entry 2). A 31% ee and 78% yield was achieved when HCl was used (entry 4). It should be noticed that the 31-51% ee of entry 2 was determined by the ^{13}C NMR. The inconsistency of the ^{13}C NMR method might be the reason for observing no selectivity in entry 1.

Table 4.5. Asymmetric conjugate addition of (R)-binaphthyl-1-octynylboronate [(R)-3.33a].



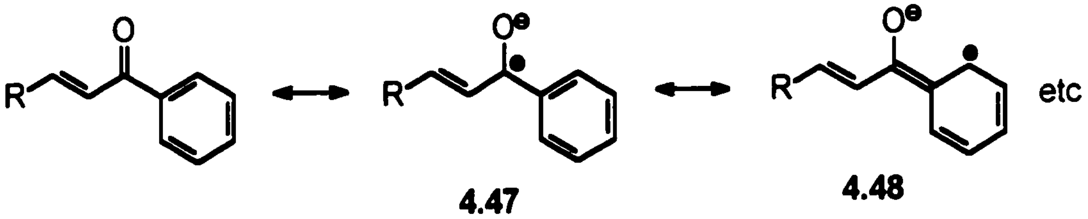
entry	R'	R''	solvent	acid	yield/%	%ee
1	C_6H_5	C_6H_5	CH_2Cl_2	BF_3/OEt_2	82	~0[a]
2	C_6H_5	C_6H_5	CH_3CN	BF_3/OEt_2	90	31-51[a]
3	C_6H_5	C_6H_5	CH_2Cl_2	HCl/OEt_2	79	34[a]
4	C_6H_5	C_6H_5	CH_3CN	HCl/OEt_2	78	31[a]
5	C_6H_5	CH_3	CH_3CN	BF_3/OEt_2	38	31[a],21[b]
6	CH_3	C_6H_5	CH_3CN	BF_3/OEt_2	88	~0[c]
7	iC_3H_7	C_6H_5	CH_3CN	BF_3/OEt_2	90	3[c]
8	nC_6H_{13}	C_6H_5	CH_3CN	BF_3/OEt_2	88	6[c]

a. measured by ^{13}C NMR; b. measured by GC; c. measured by HPLC with a Chiracel OD column.

4.3.4.2. Effects of Substituents of Enones on Reaction Rate and Enantioselectivity

Table 4.5 also demonstrates the effect that substituents on the enones have on reaction rates and enantioselectivities. When enones with a phenyl R'' group were used (all entries except 5), reactions gave good to excellent yields of 1,4-adducts within a certain period of time. In entry 5, the reaction of the enone with methyl R'' group gave a moderate yield of product. These results indicated that the phenyl group directly on the carbonyl group of the enone was important for ensuring high yields. These high yields might be explained by the resonance structures of the enones (Figure 4.1). Structures **4.47** and **4.48** are contributing resonance structures. Conjugate additions normally occur *via* a six-membered ring transition state, and require co-ordination between the carbonyl oxygen and boron atom for transfer of the alkynyl group to the β carbon of the enone.[7] The resonance contributions suggest that the carbonyl oxygen is more Lewis basic and would coordinate to the boron atom better. Therefore, one might expect an increase in reaction rates. In this specific case, increasing the reaction rate enhanced the yield of the 1,4-adducts.

Figure 4.1. Resonance structures of the 1-phenyl enones.



The steric bulk of the R' group was not the only factor for obtaining enantioselectivity, but the electronic nature of the R' group played a role as well. By comparison of entries 2, 6-8 of Table 4.5, it is observed that an increase in the R' group size correlated with an increase in enantioselectivity. However by comparison of entries 2 and 7, it is clear that electronic factors are also important. The reaction of the enone with a phenyl R' group gave 31-51% ee; however under the same reaction conditions the enone with the isopropyl R' group provided only 3% ee. Since isopropyl groups and phenyl groups have almost the same size in terms of A values, enones with the two groups should afford a similar enantioselectivity. The very different enantioselectivities observed might be explained by the electronic effect of the R' group since a phenyl group has π electrons and isopropyl does not. This topic will be discussed in more detail in Section 4.3.4.7.

4.3.4.3. Addition with Alkynyl(3,3'-disubstituted-binaphthyl)boronates

4.3.4.3.1. 3,3'-Diaryl-binaphthyl Alkynyl Boronates

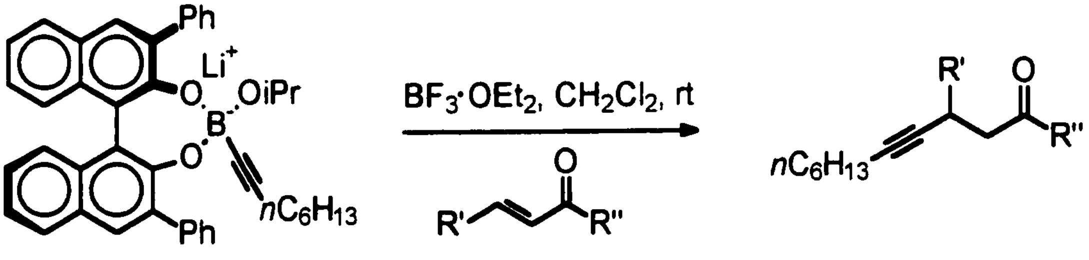
Based on the binaphthyl moiety, six kinds of 3,3'-diaryl-binaphthyl alkynyl boronates were prepared (see Chapter 3) and used in the asymmetric conjugate addition of alkynyl groups to enones. The following are the results from the additions of these boronates to enones.

(a) Using (*R*)-alkynyl-(3,3'-diphenylbinaphthyl)-boronates

The results from using (*R*)-(3,3'-diphenylbinaphthyl)octynylboronate [(*R*)-**3.38k**] in addition to a variety of enones are recorded in Table 4.6. With the exception of the reaction in entry 2, the reactions of enones with a phenyl group directly attached to the carbonyl group provided the 1,4-adducts in excellent yields. A reaction of the enone with a methyl group attached to the carbonyl group in entry 2 gave a lower yield. This trend was the same as that observed for the reactions of (*R*)-binaphthyl-1-octynylboronate [(*R*)-**3.33a**] with enones (Table 4.5). Therefore this phenomenon might also be explained by the stability of the resonance structures **4.47** and **4.48** resulting from the extra resonances with the aromatic ring in Figure 4.4. Based on reaction times (amount of time required to complete the reactions), further differences in reactivity of the enones were observed. Both reactions in entries 12,13 needed a time of 3 h for completion. The fast reactions might result from further resonance contributions of the *para* chloro and bromo substituents. The further resonance contributions increased the Lewis basicity of the carbonyl oxygen and made the coordination between the oxygen atom and the boron atom better. In entry 7 of Table 4.6, the reaction involving *E*,*E*-1-phenyl-2,4-hexadien-1-one (**4.5**) required a time period of 24 h to reach completion, while the reactions of most enones took 5-8 h. Why a longer reaction time was required in this case is not clear. However, an extra double bond on the β carbon might be responsible for the slow reaction. Contrary to the slow reaction, a naphthyl group on the β carbon caused a fast reaction (entry 10). This was confusing since enones with a naphthyl group on the β carbon as in *E*-3-(1-naphthyl)-1-phenyl-2-propen-1-one (**4.7**) and a phenyl group on the β carbon as in chalcone were aromatic and supposed to have similar reactivity towards the octynyl boron reagent (*R*)-**3.38k**. It was speculated that the extra aromatic ring of the naphthyl group provided some kind of interactions during the reaction, such as π-

π stacking interactions between the extra ring of the naphthyl group and the binaphthyl ring(s) of the boron reagent (*R*)-**3.38k**. This type of interaction could promote a faster conjugate addition.

Table 4.6. Conjugate addition of (R)-(3,3'-Diphenylbinaphthyl)octynylboronate [(R)-3.38k] with enones.



(*R*)-**3.38k**

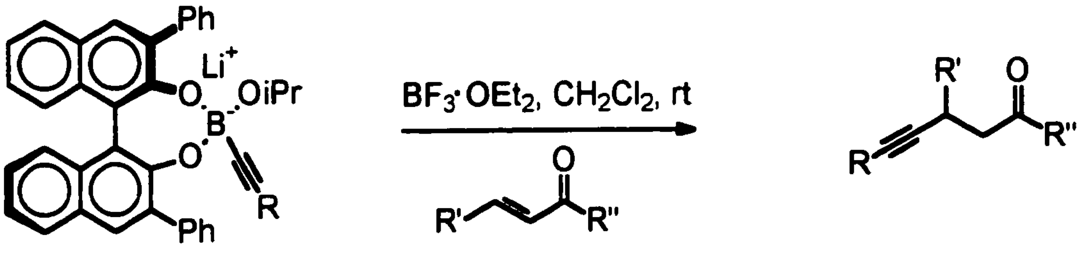
entry	R'	R''	react. time/h	yield/%	%ee[a]
1	C_6H_5	C_6H_5	5-8	88	85
2	C_6H_5	CH_3	5-8	50	85
3	CH_3	C_6H_5	5-8	85	9
4	$n C_6H_{13}$	C_6H_5	5-8	80	16
5	iC_3H_7	C_6H_5	5-8	85	41
6	tC_4H_9	C_6H_5	8	87	82
7	1-propenyl	C_6H_5	24	82	74
8	pCl-C_6H_4	C_6H_5	5	90	87
9	pMeO-C_6H_4	C_6H_5	5	90	82
10	1-Naph	C_6H_5	2	91	95
11	2-furyl	C_6H_5	8	91	>98
12	pBr-C_6H_4	pBr-C_6H_4	3	93	75
13	C_6H_5	pCl-C_6H_4	3	92	82
14	C_6H_5	pMeO-C_6H_4	8	85	82
15	pMeO-C_6H_4	pMeO-C_6H_4	8	86	85

[a] measured by HPLC with a Chiracel OD column.

The enantioselectivities obtained for enones with the aromatic group on the β carbon were excellent (entries 1,2, and 8-15 of Table 4.6). The extreme cases were the reactions of *E*-3-(1-naphthyl)-1-phenyl-2-propen-1-one (**4.7**) (entry 10) and *E*-3-(2-furyl)-1-phenyl-2-propen-1-one (**4.10**) (entry 11) which afforded 95% ee and >98% ee, respectively. With enones containing an alkyl group on the β carbon (entries 3-6), the enantioselectivity of the conjugate addition increased with an increase in size of the alkyl group. Among these examples, *E*-1-phenyl-2-buten-1-one (**4.23**) gave the lowest enantioselectivity (9% ee, entry 3), while *E*-4,4-dimethyl-1-phenyl-2-penten-1-one (**4.11**) afforded the highest (82% ee, entry 6). This trend was understood by the argument that the steric bulk of the alkyl group was an important factor for achieving stereoselectivity. By comparing the enantioselectivities of entries 1,5, and 6, a confusing observation also existed. Since an isopropyl group and a phenyl group have almost the same size, enones with these two groups should afford a similar level of enantioselectivity. However the reaction of an enone with a phenyl group as in *R*' gave higher enantioselectivity (85% ee, entry 1) than the one with an isopropyl group (41% ee, entry 5). By the same argument, since a *t*Bu group is even larger than a phenyl group, the former should afford a higher level of enantiomeric excess. However, the level of selectivity actually achieved was opposite to what was expected. This unexpected result might also be explained by the electronic difference of the *R*' group because a phenyl group has π bonding electrons while isopropyl and *t*Bu do not. The result of the conjugate addition with enone **4.5** (entry 7) supported the hypothesis of the existence of an electronic effect. Since a 1-propenyl group is smaller than an isopropyl group, an enone with a 1-propenyl group should afford a lower level of enantioselectivity. However, the electronic effect due to the presence of π electrons in 1-propenyl should be responsible for the observed higher enantioselectivity (74% ee).

The results of a select few reactions with other (*R*)-alkynyl-(3,3'-diphenylbinaphthyl)-boronates and enones are recorded in Table 4.7. Varying the substituent on the triple bond dramatically caused the conjugate additions to vary in reaction time, product yield, and enantiomeric excess of the product. When a phenyl group was on the triple bond, the reactions of the alkynyl boron reagent (*R*)-**3.38l** with three enones afforded excellent yields of products with great enantioselectivities (entries 1-3 of Table 4.7). The reactions were fast, and all the three enones completely reacted with (*R*)-**3.38l** at room temperature within 3 h. The conjugate additions of the boron reagent (*R*)-**3.38m** which had a CH_2OBn group on the triple bond gave good yields and excellent stereoselectivities as well (entries 4 and 5). However, these reactions required longer times to reach completion, normally 24 h. When the reagent (*R*)-**3.38o** reacted with chalcone, both the yield and enantiomeric excess were depressed (entry 6). Although it was unclear, probably the large size of *t*Bu group on the triple bond was the cause for such a low yield and for a low level of stereoselectivity. The worst case occurred in the reaction of reagent (*R*)-**3.38n** with chalcone (entry 7). The reaction gave a very low yield of 1,4-adduct (<10%). The reason for such a poor yield might be due to the instability of the product under fluoride conditions. The enantiomeric excess was not determined, due to such a poor yield.

Table 4.7. Conjugate addition of (R)-alkynyl-(3,3'-diphenylbinaphthyl)-boronates.



entry	R/reagent	R'	R"	react. time/h	yield/%	%ee[a]
1	C_6H_5/**3.38l**	C_6H_5	C_6H_5	3	90	90
2	C_6H_5/**3.38l**	1-Naph	C_6H_5	2	99	98
3	C_6H_5/**3.38l**	pBr-C_6H_4	pBr-C_6H_4	3	87	90
4	CH_2OBn/**3.38m**	C_6H_5	C_6H_5	24	84	80
5	CH_2OBn/**3.38m**	1-Naph	C_6H_5	24	81	>98
6	tC_4H_9/**3.38o**	C_6H_5	C_6H_5	24	62	20
7	TMS/**3.38n**	C_6H_5	C_6H_5	18	<10	ND

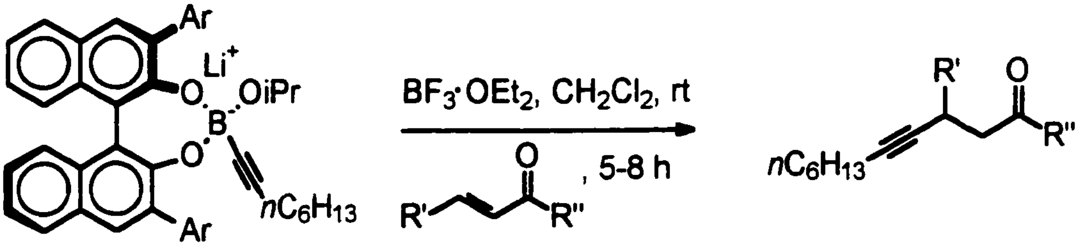
a. measured by HPLC with a Chiracel OD column.

(b) Using (*R*)-(3,3'-diarylbinaphthyl)-octynyl-boronates

Although a 3,5-dimethylphenyl group, a naphthyl group, a 4-methoxyphenyl group, and a 3,5-bis(trifluoromethyl)phenyl group are larger than a phenyl group, the conjugate addition of reagents (*R*)-**3.38f-3.38i**, which had substituted phenyl groups on 3,3'-positions of binaphthyl moieties, gave similar results to those obtained with (*R*)-**3.38k** (by comparison between entries 1,2, 5 of Table 4.6 and entries 1-10 of

Table 4.8). The groups on the 3,5-positions of the phenyl group were too far away from the reaction site to affect the outcome of the reaction. The second aromatic rings of the naphthyl groups on the 3,3'-positions of binaphthyl group of reagent (*R*)-**3.38h** might point away from the reaction site, far enough to not affect the outcome of the reaction. The conjugate addition of (*R*)-{3,3'-bis[3,5-bis(trifluoromethyl)-phenyl]binaphthyl}-octynyl-boronate [(*R*)-**3.38i**] to chalcone provided the 1,4-adduct **4.25** in 90% yield and with 82% ee (entry 10), and was completed within 2 h. The short reaction time for the reagent (*R*)-**3.38i** could be due to the electron deficient nature of the 3,3'-disubstituents and these effects will be discussed in Section 4.3.4.4. However, the reaction between (*R*)-{3,3'-bis[3,5-di(*tert*-butyl)-phenyl]binaphthyl}-octynyl-boronate [(*R*)-**3.38j**] and chalcone required 24 h to be completed to afford only a 53% yield of product with 10% ee (entry 11). The question remaining here was why the reaction of reagent (*R*)-**3.38j** gave such a poor result. To answer the question, one has to consider the effect the large size of the *t*butyl group has on this reaction. The reaction site might be hindered by the four *t*-butyl groups which surround the site. The result of this interaction prevents the reaction process, or in other terms, creates a slow reaction. Of course, although unclear, other reasons could not be excluded.

Table 4.8. Conjugate additions of (R)-(3,3'-diarylbinaphthyl)-octynyl-boronates.



Ar = 3,5-dimethyl-C_6H_3, (*R*)-**3.38f**; 2-Naph, (*R*)-**3.38h**;
4-methoxy-C_6H_4, (*R*)-**3.38g**; 3,5-bis(trifluoromethyl)-C_6H_3, (*R*)-**3.38i**;
3,5-di(*tert*-butyl)-C_6H_3, (*R*)-**3.38j**

entry	reagent	R'	R''	yield/%	%ee[a]
1	(*R*)-**3.38f**	C_6H_5	C_6H_5	93	85
2	(*R*)-**3.38f**	C_6H_5	CH_3	67	84
3	(*R*)-**3.38f**	iC_3H_7	C_6H_5	91	50
4	(*R*)-**3.38h**	C_6H_5	C_6H_5	88	80
5	(*R*)-**3.38h**	C_6H_5	CH_3	66	80
6	(*R*)-**3.38h**	iC_3H_7	C_6H_5	89	50
7	(*R*)-**3.38g**	C_6H_5	C_6H_5	93	85
8	(*R*)-**3.38g**	C_6H_5	CH_3	68	83
9	(*R*)-**3.38g**	iC_3H_7	C_6H_5	91	50
10[b]	(*R*)-**3.38i**	C_6H_5	C_6H_5	90	82
11[c]	(*R*)-**3.38j**	C_6H_5	C_6H_5	53	10

a. measured by HPLC with a Chiracel OD column. b. reacted for 2 h. c. reacted for 24 h.

4.3.4.4. Effect of 3,3'-Substituents of Binaphthyl on Reaction Rate and Enantioselectivity

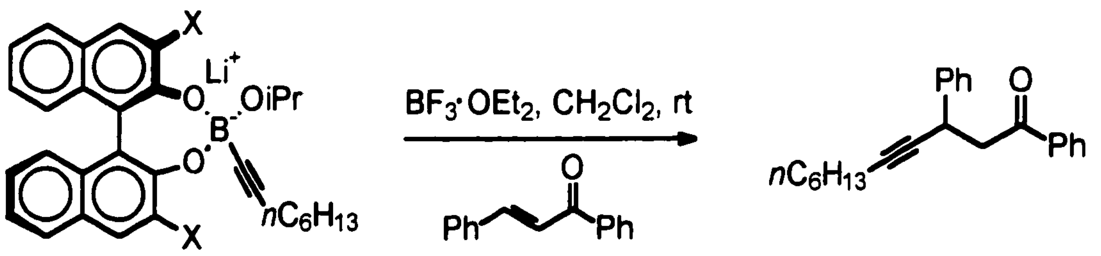
4.3.4.4.1. 3,3'-Dimethyl, Dibromo, Diiodo, Dicyano, and Bis(trifluoromethyl)-binaphthyl Alkynyl Boronates

To study the effect of 3,3'-substituents of binaphthyl on reaction rate and enantioselectivity, conjugate additions of 3,3'-dimethyl, dibromo, diiodo, dicyano, and bis(trifluoromethyl)-binaphthyl alkynyl boronates with chalcone were performed (Table 4.9).

All the reactions afforded the 1,4-adduct **4.25** in excellent yield. When 3,3'-substituents were electron withdrawing groups such as bromine, iodine, trifluoromethyl, and cyano groups, the reactions were fast, and usually took 1-3 h to complete (entries 2,3,4, and 6 of Table 4.9). The times were comparable to the reaction times required for the conjugate additions of reagent (*R*)-**3.38i** which also had electron withdrawing group on the 3,3'-positions of the binaphthyl moiety (entry 10 of Table 4.8). Reactions with reagent (*R*)-**3.38e**, which had 3,3'-dimethyl groups on binaphthyl moiety, required a period of 12 h to complete (entry 1 of Table 4.9). In Section 4.3.4.3, it was noticed that all the conjugate additions of (*R*)-**3.38f-3.38h**, and **3.38k** with chalcone required 5-8 h to complete. Therefore, electron withdrawing groups on the 3,3'-positions of the binaphthyl moiety increase the reaction rate.

An increase in reaction rate may be due to the electron withdrawing groups taking away electron density from the binaphthol oxygens so that they are less available for donation to boron, thus resulting in greater availability of boron's empty orbital to accept co-ordination of the carbonyl oxygen of chalcone. As a result, the six-member ring intermediate (possibly transition state) of the addition reaction formed more easily and the addition proceeded faster.

Table 4.9. Conjugate additions of 3,3'-dimethyl, dibromo, diiodo, dicyano, and bis(trifluoromethyl)-binaphthyl alkynyl boronates.



entry	X/reagent	react. time/h	yield/%	%ee[a]
1	CH$_3$/**3.38e**	12	90	67
2	Br/**3.38a**	1	97	63
3	I/**3.38b**	1	95	86
4	CF$_3$/**3.38d**	1	97	83
5[b]	CF$_3$/**3.38d**	20	96	88
6	CN/**3.38c**	3	95	14

a. measured by HPLC with a Chiracel OD column; b. run at -30- -20 °C for 10 h, then rt for 10 h.

At room temperature, the reagent (*R*)-**3.38e** gave **4.25** with 67% ee (entry 1 of Table 4.9). This enantiomeric excess was comparable to what was obtained with reagent (*R*)-**3.38a**. Since bromine is smaller than a methyl group, one might consider that not only the steric bulk of the 3,3'-substituents on the binaphthyl moiety was important for the stereoselectivity, but other factor(s) such as electronegativity and the bond distance could not be ruled out. In entry 3, when reagent (*R*)-**3.38b**, having iodine on the 3,3'-positions reacted with chalcone, the enantiomeric excess of the product was 86%, which was larger than what was obtained for both (*R*)-**3.38a** and (*R*)-**3.38e**. The reason why the enantiomeric excess was larger than that for (*R*)-**3.38a** can be explained by the size of the 3,3'-substituents since iodine is larger than bromine. However, the fact that the enantioselectivity of (*R*)-**3.38b** was larger than that of (*R*)-**3.38e** could not be reasoned by the size of the 3,3'-subsitituent, since a methyl group is larger than iodine (in terms of atomic radii where a methyl group has *ca.* 146 pm and iodine has 133 pm). Three factors might cause such an unusual phenomenon. One reason could be the electronegativity of the 3,3'-substituents. The others could be the way that 3,3'-substituents are connected with the binaphthyl moiety and the bond length between the substituent and the carbon of the binaphthyl moiety. The connectivity of C-halogen bonds might provide an extra help to the stereoselectivity comparing to the C-C connection. The bond distance of C-I bond (210 pm for sp^2 C-I) is larger than C-C (151 pm for sp^2 C-sp^2 C) and the larger bond distance might increase the capability of stereo-induction for (*R*)-**3.38e**. The use of reagent (*R*)-**3.38d** (entry 4) to obtain an ee of 83% provided a proof for such a hypothesis. A trifluoromethyl group is larger than a methyl group or iodine (in terms of group radii where a trifluoromethyl group has *ca.* 206 pm), and the electronegativity of CF_3 is larger than that of CH_3 and iodine atom. Therefore, the reaction with reagent (*R*)-**3.38d** was expected to afford a larger ee than what was expected with (*R*)-**3.38e** and (*R*)-**3.38b**. However, the ee obtained with reagent (*R*)-**3.38d** was slightly larger than what was achieved with reagent (*R*)-**3.38e**, and only smaller than what was obtained with (*R*)-**3.38b**. This could be explained by factors which include size, electronegativity, the connection of the substituents, and the bond distance, etc. The large size and electronegativity of CF_3 was responsible for the larger ee that was obtained with (*R*)-**3.38d** than with (*R*)-**3.38e**.

By taking into account these three factors, the reason that the addition of reagent (*R*)-**3.38c** gave only a 14% ee could be understood. The electronegativity of the CN group is the largest among all groups tried. However, the enantioselectivity of the conjugate addition of (*R*)-**3.38c** suffered from the C-C connection between CN group and binaphthyl moiety, and the small size of the CN group.

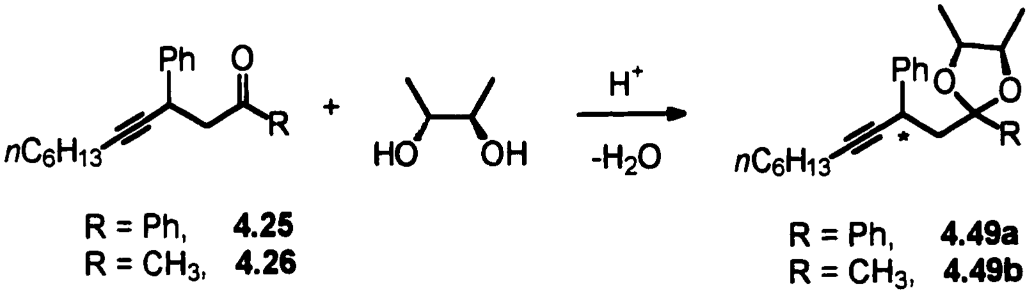
In Table 4.9, it was interesting to observe that the reagent (*R*)-**3.38d** could undergo the addition at between -30 and -20°C with the reaction improving in the amount of % ee obtained (entry 5). Increased selectivity at lower reaction temperatures is commonly observed and is consistent with standard kinetic theories.[8]

4.3.4.5. Enantiomeric Excess Measurement of 1,4-Adducts

4.3.4.5.1. NMR Method

Initially, an NMR method was used to determine the enantiomeric excesses of the 1,4-adducts **4.25** and **4.26** that were prepared by the reaction of (*R*)-**3.38a** with chalcone (entries 1-5 of Table 4.5). Reactions of the ketones **4.25** and **4.26** with (*R*,*R*)-butane-2,3-diol afforded the diastereomeric cyclic ketals **4.49a** and **4.49b**, respectively (Scheme 4.6). Subsequent ^{13}C NMR analysis of the two pairs of ketals provided integration data of the diastereomeric carbon signals of the ketals.

Scheme 4.6

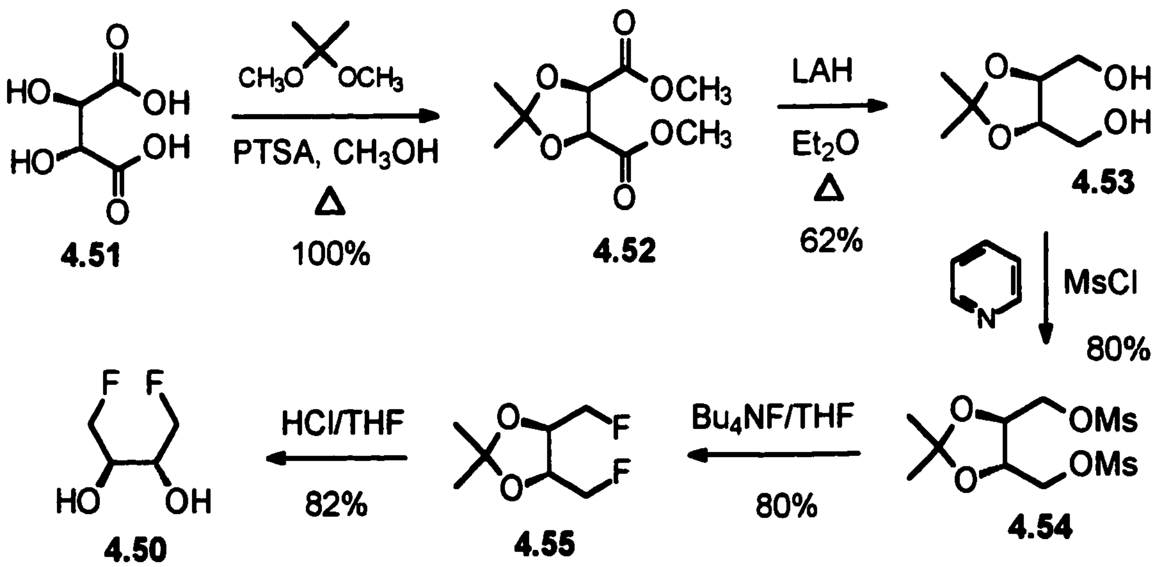


In the ^{13}C NMR spectrum, one carbon of the *n*-hexyl group of the diastereomeric ketals **4.49a** showed two peaks at 16.23 ppm and 16.09 ppm. The ratio of the diastereomeric isomers could be obtained by calculating the areas of the two signals. For the diastereomeric ketals **4.49b**, there was also one carbon from the *n*-

hexyl group which showed two peaks at 16.60 ppm and 16.48 ppm. However, the ^{13}C NMR method in this case was not accurate. Inconsistent results were achieved by this method for **4.49b** as can be seen in entry 2 of Table 4.5. Also, since the ketals **4.49b** were separable by GC, a diastereomeric ratio that was different from what was obtained in the ^{13}C NMR as seen in entry 5 of Table 4.5.

Another method consisted in using (*R*,*R*)-1,4-difluoro-butane-2,3-diol (**4.50**) as a derivatizing agent. It was expected to provide a more reliable method for the enantiomeric excess determination for our purpose. (*R*,*R*)-1,4-Difluoro-butane-2,3-diol (**4.50**) was synthesized following the preparative sequence described by Larose (Scheme 4.7).[9]

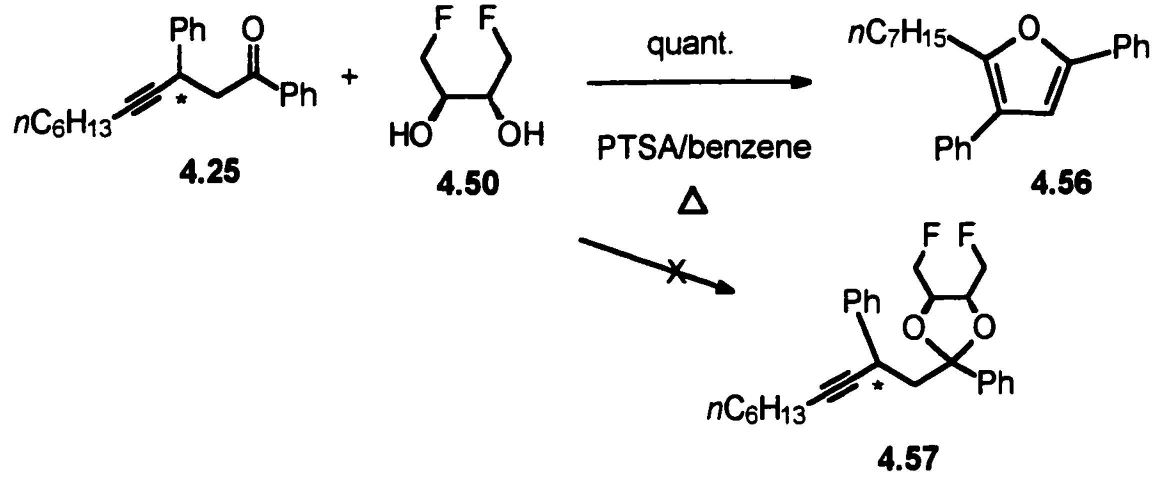
Scheme 4.7



The synthesis of the difluorodiol **4.50** started with pure (*R*,*R*)-tartaric acid (**4.51**). **4.51** was first treated with 2,2-dimethoxypropane in methanol in the presence of a catalytic amount of *p*TsOH. This reaction protected the 2,3-diol and provided the dimethyl ester **4.52** in quantitative yield. The yield obtained was comparable to that of literature cited.[10] Following a procedure reported by Feit,[11] **4.52** was reduced with LAH to the diol **4.53** in 62% yield. **4.53** then was reacted with MsCl in pyridine to afford the mesylated product **4.54** in 80% yield. The next step adapted Larose's procedure,[9] which treated **4.54** with Bu_4NF in THF in the presence of 3 Å molecular sieves. The reaction provided the difluorinated compound **4.55** in 80% yield. Finally, deprotection of **4.55** with HCl/THF furnished the difluorinated diol **4.50** in 70% yield.

Unfortunately, attempts to prepare ketals of **4.25** using diol **4.50** failed. The reaction of **4.25** in the presence of the diol **4.50** and *p*TsOH produced a trisubstituted furan **4.46** instead of the expected ketals **4.57** (Scheme 4.8). We wondered if the difluorodiol **4.50** might be a catalyst for the furan formation. An experiment was conducted consisting of a reaction of **4.25** under the same reaction conditions, with the absence of **4.50**. However, this reaction also formed the furan in quantitative yield. This result demonstrated that the competitive reaction of the ketone **4.25** forming the furan **4.56** was faster than the ketal formation under acidic conditions.

Scheme 4.8



Nevertheless, this reaction provided a new route to 2,3,5-trisubstituted furans which might be useful for organic synthesis.[12]

4.3.4.5.2. HPLC with Chiracel OD Column

An HPLC method proved to be a very useful means for the determination of the enantiomeric excess of the 1,4-adducts with the use of a Chiracel OD column. Except for ketone **4.31**, all ketones in Table 4.2 could be analyzed by this method. Each racemic sample was analyzed first to search for the optimal operational conditions, such as flow rate, and solvent systems. After the optimization was complete, the sample of the asymmetric conjugate product was analyzed. By comparison between both chromatograms of the racemic sample and the asymmetric sample, the two enantiomeric bands were easily identified according to their retention times. Table 4.10 records the HPLC operational conditions and retention times for each pair of 1,4-adduct enantiomers.

Table 4.10. HPLC operating conditions and retention times for each pair of 1,4-adduct enantiomers.

entry	1,4-adduct	eluent (%*i*PrOH in hexane)	eluent rate(mL/min)	retention time/min	
				A[a]	B[a]
1	**4.25**	0.1	0.5	55	M, 61
		0.3	0.5	34	M, 38
		0.3	0.35	47	M, 50
2	**4.26**	0.1	0.5	M, 54	60
3	**4.27**	0.2	0.5	M, 10	13
		0.1	0.5	M, 17	23
4	**4.28**	0.1	1.0	M, 22	25
5	**4.29**	0.2	0.5	M, 20	24
6	**4.30**	0.0	0.5	29	M, 32
7	**4.32**	0.1	0.5	29	M, 87
		0.5	1.0	17	M, 24
8	**4.33**	0.2	0.5	M, 34	36
9	**4.34**	0.05	0.5	58	M, 61

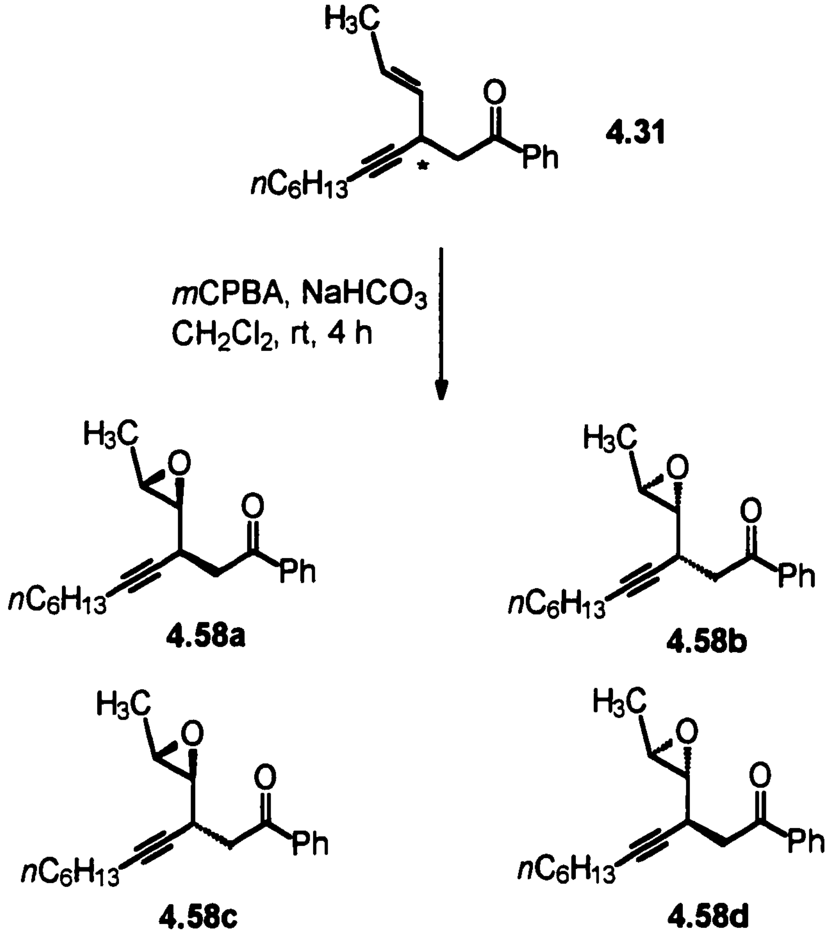
10	**4.35**	0.1	0.5	M, 53	58
11	**4.36**	0.1	0.5	39	M, 42
12	**4.37**	0.2	0.5	125	M, 142
13	**4.38**	0.1	0.5	62	M, 71
14	**4.39**	1.0	0.5	38	M, 42
15	**4.40**	0.2	0.5	M, 100	115
16	**4.41**	1.0	1.0	17	M, 22
17	**4.42**	0.5	1.0	M, 43	80
		2.0	1.0	M, 16	28
18	**4.43**	1.0	1.0	M, 58	63
19	**4.44**	3.0	1.0	M, 16	26
20	**4.45**	0.1	0.5	25	M, 28

a. A and B represent the two enantiomeric bands in the HPLC spectra; M represents the major band.

However, the order of elution for each pair of enantiomers of certain asymmetric 1,4-adduct resulting from different reactions with a variety of chiral alkynyl boron reagents was consistent.

The enantiomers of **4.31** were not separable by HPLC with the Chiracel OD column. However, after the compounds were converted to their epoxides by reacting them with *m*CPBA under basic conditions (Scheme 4.9), the two pairs of resulting diastereomers **4.58a-4.58d** could be separated by the HPLC method.

Scheme 4.9



The diastereomeric mixture resulting from racemic **4.31** showed four bands at 43, 49, 50, and 66 min with intensities in the ratio of 2:1:2:1, respectively, occurring with an elution rate of 0.5 mL/min and with composition of 0.25% of iPrOH in hexane. The mixture resulting from the asymmetric compound **4.31** (entry 7 of Table 4.6) also showed four peaks at retention times the same as above but with intensities in the ratio of 2.1:6.7:13.5:1. Considering that the epoxidation had a diastereoselectivity of 33%, the enantiomeric excess of the asymmetric compound

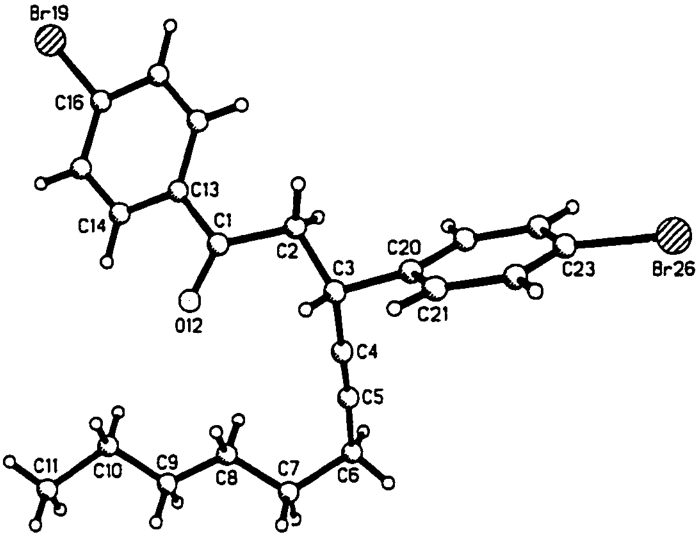
4.31 was (6.7 - 1)/(6.7 + 1) = 74%. A similar number was obtained if the calculation used the data for the other pair of enantiomers.

4.3.4.6. Absolute Configuration of 1,4-Adducts

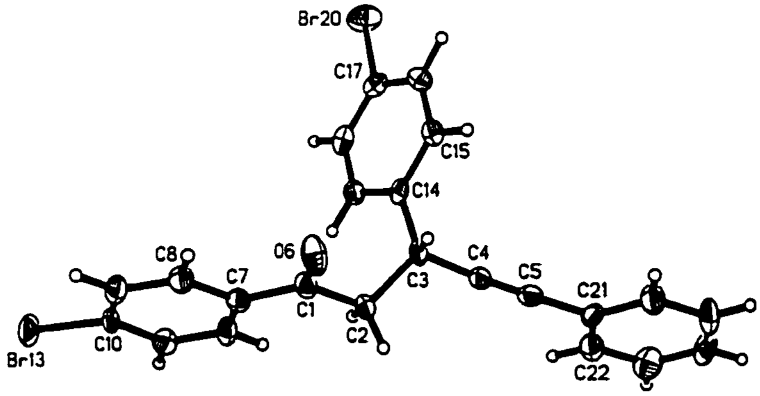
All 1,4-adducts were unknown in the literature and the determination of their absolute configuration was difficult to obtain. To determine the absolute configuration, compound **4.36** of entry 12 in Table 4.6 and **4.42** of entry 3 in Table 4.7 were designed and analyzed by X-ray crystallography.

The enantiomerically pure compounds **4.36** and **4.42** were recrystallized from CH_2Cl_2/hexane to provide crystals for X-ray crystallographic analysis (Figure 4.2). X-ray data were collected and analyzed by Dr. Nicholas J. Taylor, Department of Chemistry, University of Waterloo. Particular attention was paid to the assignment of absolute configuration; details are provided in the Appendix. The X-ray crystal structures demonstrated both the compounds **4.36** and **4.42** possessed a *R* configuration. The assignment of *R*/*S* was based on the priority of the groups directly connected to the chiral carbon. Since the phenylethynyl group and *n*-hexylethynyl group have higher priority than the phenyl group, according to the X-ray crystal structure, the absolute configuration of the compounds **4.42** and **4.36** is *R*. (Note that an ethynyl group has lower priority than a phenyl group.)

Figure 4.2 X-ray crystal structure of the enantiomerically pure 4.36 and 4.42.



(*R*)-**4.36**



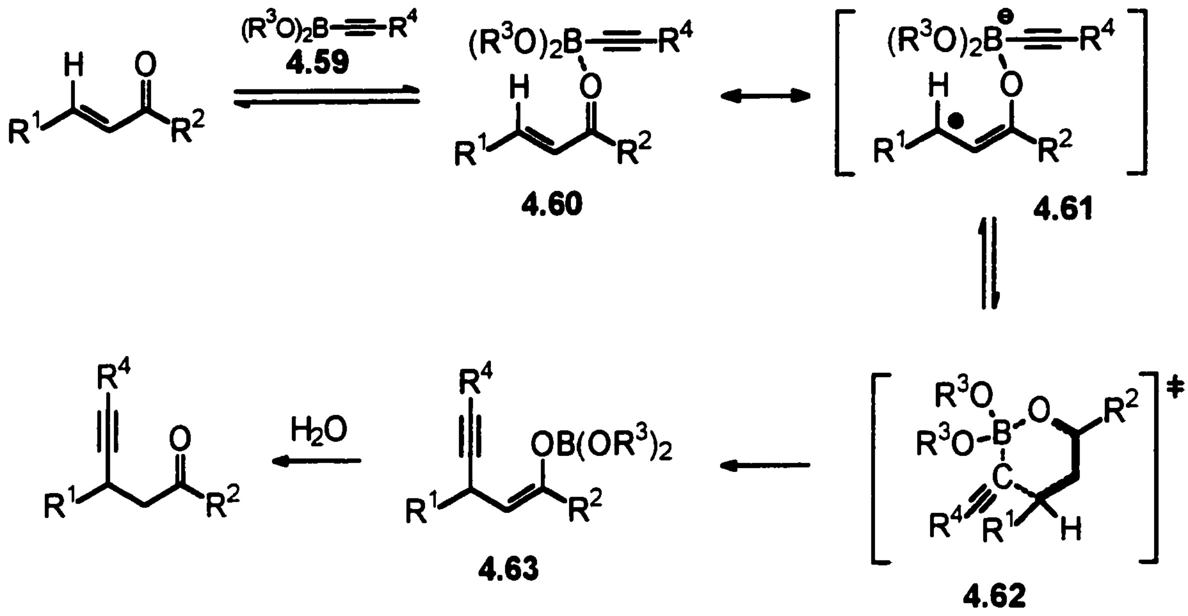
(*R*)-**4.42**

More information on the absolute configuration was needed to get a deeper understanding regarding the mechanism of the reaction. This will be discussed in the future work section.

4.3.4.7. Mechanism of Asymmetric Conjugate Addition

As discussed in Section 1.4.1.3.2, the conjugate addition of alkynyl groups to enones with alkynyldialkylboranes proceeds through a cyclic transition state (Figure 1.12).[7] It was believed that the conjugate addition of alkynyl groups to enones with alkynylboronates also proceeds *via* a cyclic transition state because of the similarity between the two reactions. The reaction pathway for the conjugate addition of alkynylboronates is depicted in Scheme 4.10. The reaction is promoted by the complexation of the boron atom of the alkynylboronate to the oxygen atom which activates the enone. A contributing resonance structure of this complex is **4.61**. The alkynyl group transfer then occurs from boron to the enone β carbon by the six membered ring transition state **4.62**. Hydrolysis of enolborate **4.63** then affords the 1,4-adduct.

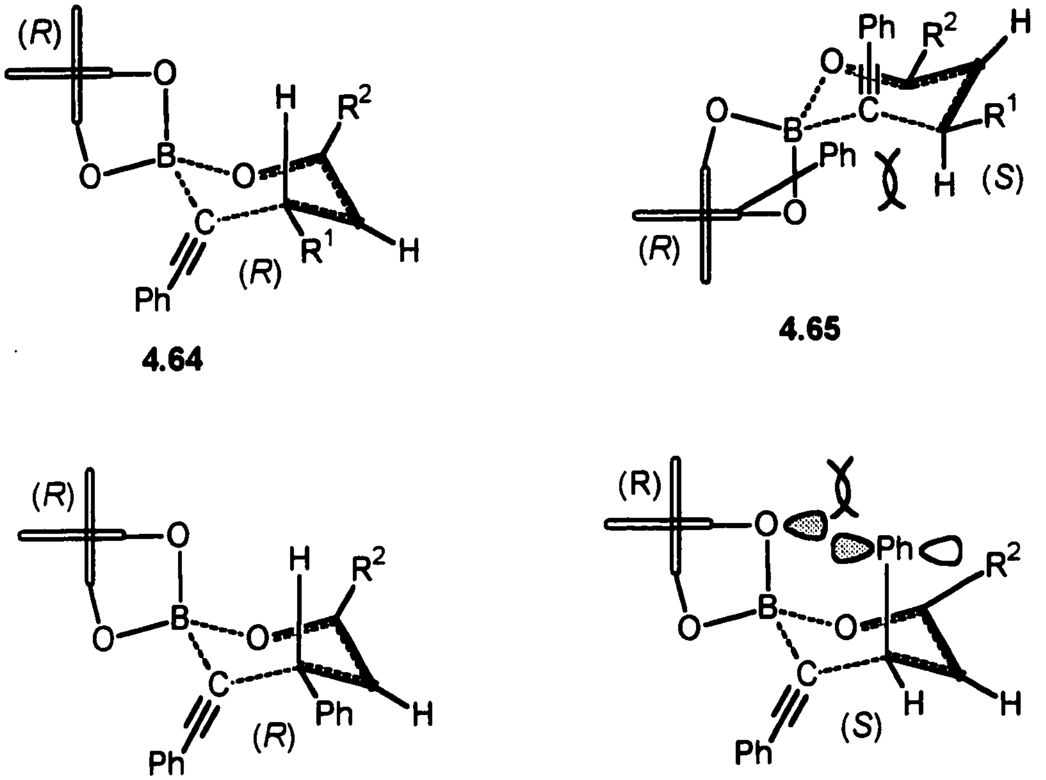
Scheme 4.10



The two binaphthyl oxygens in (*R*)-(3,3'-diphenylbinaphthyl)-(phenylethynyl)boronate are diastereotopic, and therefore two types of chair-like transition states, **4.64** and **4.65** are possible (Figure 4.3). There are two possible diastereomeric structures for **4.65** if the positions of the hydrogen and R^1 are switched. However, the structure **4.65** was unfavorable because this structure suffered severe steric repulsion between the 3,3'-diphenyl-binaphthyl moiety and β subsitituents (either R^1 or H). This could be easily understood by model inspection. In the model, the 2,6-hydrogen of 3,3'-phenyl group collided with the axial β substituent. There are also two possible diastereomeric transition states, **4.66** and **4.67** that are based on **4.64**. Now let us consider phenyl group as R^1. Since the X-ray analysis of the crystal structure of chiral **4.42** indicated that it had the *R* configuration, one would expect that the *R*-generating transition state **4.66** was generally favored over the *S*-generating transition state **4.67**. Two effects are responsible for this expectation. First, the phenyl group should favor occupying the equatorial position over H. Second, as described in BINAL-H reduction,[13] a n/π type electronic repulsion between the axially oriented binaphyl oxygen and the unsaturated moiety is responsible for the high enantioselectivity of reduction. So the second effect here was the n/π type electronic repulsion between the axially oriented binaphthyl oxygen and the phenyl group. Such electronic repulsion is absent in **4.66**. The first effect could explain that increasing the size of the group on enone β carbon increased the enantioselectivity (entries 3-6 of Table 4.6). The second effect could explain that the phenyl and alkenyl group on the β carbon (entries 1 and 7 of Table 4.6, respectively) gave better enantioselectivity than the alkyl ones with equal or larger size than phenyl group (entries 5 and 6).

The proposed mechanism could also explain why the conjugate addition of the boronate reagents with 3,5-dimethylphenyl, 2-naphthyl, 4-methoxyphenyl, 3,5-bis(trifluoromethyl)phenyl, and 3,5-di(*tert*-butyl)phenyl groups gave similar enantioselectivities to the reaction of the 3,3'-diphenylboronate: all these groups have a similar steric environment on the carbon next to the carbon connected to the binaphthyl group.

Figure 4.3. Proposed chair-like transition states of the asymmetric conjugate addition.



4.64

4.65

4.66

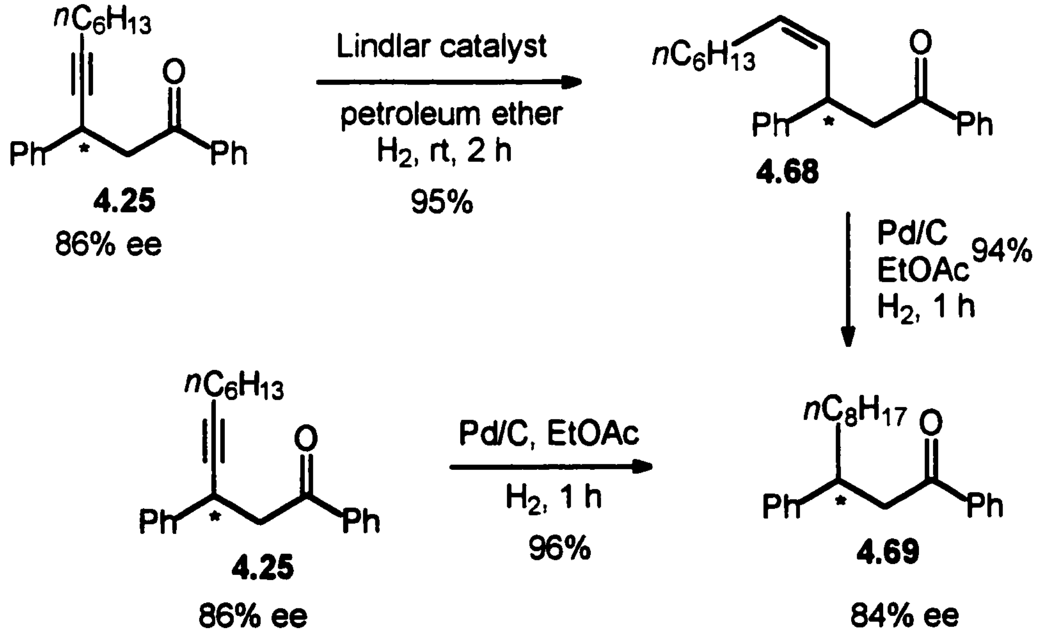
4.67

4.3.4.8. Hydrogenation of 1,4-Adduct

To examine if the chirality of 1,4-adduct formed by the asymmetric conjugate addition could be retained during chemical conversion to some derivatives, hydrogenation of **4.25** was carried out (Scheme 4.11). Hydrogenation of the triple bond of both racemic and enantiomerically enriched **4.25** under Lindlar catalysis[16] afforded the *cis* alkenone **4.68** in 95% yield. Unfortunately, the two enantiomers of

4.68 could not be separated by the HPLC method, so the enantiomeric excess of **4.68** could not be determined. The alkenone was further hydrogenated to the saturated ketone **4.69** by Pd/C catalysis. The enanatiomers of **4.69** could be separated by the HPLC method and showed two bands at 27.0 and 34.0 min when the HPLC was run at a rate of 0.5 mL/min using an eluent of 0.2% iPrOH in hexane. When a chiral compound **4.25** (86% ee) was used, after the two hydrogenation steps, the enantiomeric excess was retained in the product **4.69** which showed 84% ee. Therefore, this demonstrated that the chirality of 1,4-adduct could withstand the hydrogenation conditions and remain unchanged.

Scheme 4.11

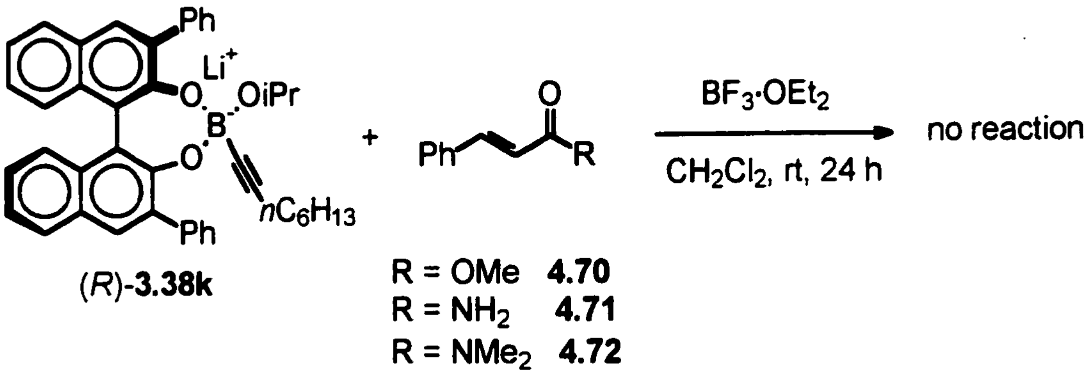


Enantiomerically enriched **4.25** (86% ee) could be hydrogenated directly to **4.69** with Pd/C catalyst, and the product also showed an enantiomeric excess of 84%.

4.3.5. Attempted Addition to Other Conjugated Systems

Attempts at addition to α,β-unsaturated ester and α,β-unsaturated amides failed (Scheme 4.12). No conjugate addition was observed by treatment of methyl *trans*-cinnamate (**4.70**), *trans*-cinnamamide (**4.71**), and *N,N*-dimethylcinnamamide (**4.72**) with the boronates (*R*)-**3.38d** and (*R*)-**3.38k** for 24 h. The lower nucleophilicity of the oxygen of the ester than that of the enone might be the main reason for the non-reactivity since the reaction pathway initially involves the coordination between the oxygens of substrates and the boron of the reagents. The reason for the non-reactivity of these amides is not clear. Since amides may be more basic than ketones (e.g. borane reacts with amides fast, with ketones slowly, with esters very slowly), they should be expected to be reactive towards the boronate.

Scheme 4.12



We also tried to effect a conjugate addition to *E*-1,3-diphenyl-2-buten-1-one (dypnone) (**4.21**) with (*R*)-**3.38k**, but it was unsuccessful. No 1,4-adduct was detected by TLC after 24 h and the starting material remained unchanged in the reaction. The β methyl group might deny the approach of the alkynyl group to the β carbon of **4.21**, thus preventing the reaction from occurring.

4.4. Conclusions and Future Work

Asymmetric conjugate addition of alkynyl groups to prochiral enones with chiral boronates was carried out. In order to accomplish a high level of asymmetric transformation, a variety of alkynyl binaphthyl boronates with different groups on 3,3'-positions of the binaphthyl moiety were designed and utilized in the conjugate addition. All enantiomeric excesses of products from the addition with the chiral boron reagents have significantly increased by changing ligands from (*R*)-2,2'-binaphthyl to (*R*)-3,3'-diaryl-2,2'-binaphthyl groups. The boronates having iodo and trifluoromethyl groups on 3,3'-positions of binaphthyl moiety provided comparable enantioselectivities to the 3,3'-diarylbinaphthyl boronates.

The enantioselectivity of the conjugate addition was dependent on the bulkiness and electronegativity of the 3,3'-substituents, as well as the connectivity between the binaphthyl and the substituents. Electron withdrawing groups on 3,3'-positions of binaphthyl moiety increased the rate of the conjugate addition.

HPLC with a Chiracel OD column could be used as an efficient analytical means in the determination of enantiomeric excesses of the 1,4-adducts.

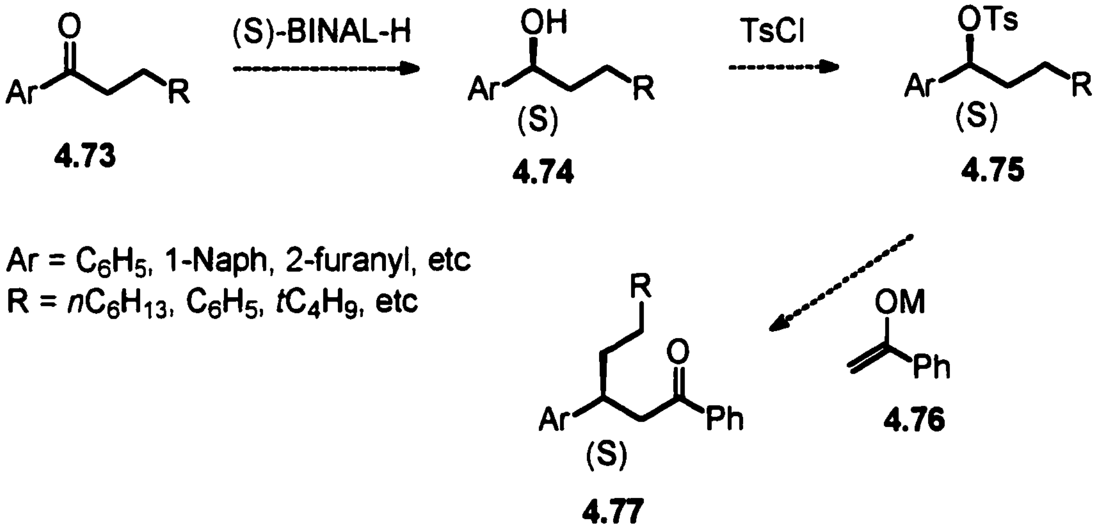
As to the origin of the efficiency of the enantiofacial differentiation, arguments based on both the simple steric approach control and electronic difference of the substituents attached to β carbon of enones were of significance in determining the steric course of the reaction.

The only information on the absolute configuration of the 1,4-adducts was the X-ray crystal structures of the enantiomerically pure **4.36** and **4.42**. To make this methodology useful to the synthetic community and to understand the reaction in more detail, more work on determination of the absolute configuration has to be done. The following is a plan that might be used to determine the absolute configuration for 1,4-adducts (Scheme 4.13). Following Noyori's reducing procedure[13], alkyl aryl ketone **4.73** could be reduced to a (*S*) secondary alcohol **4.74** using (*S*)-BINAL-H. Treatment of **4.74** with TsCl would provide a tosylate **4.75**. A SN2 substitution of

4.75 with enolate **4.76** might give (*S*) ketone **4.77**. Compound **4.77** can then be analyzed by the HPLC or optical rotation measurement.

Products from the asymmetric conjugate addition could be converted to **4.77** following the procedures described in Scheme 4.11. Compound **4.77** resulted from the hydrogenation also could be analyzed by HPLC or measurement of optical rotation. By comparison of the retention times of two enantiomers in the HPLC spectra or the optical rotation signs (plus or minus) of the samples, the absolute configuration should be readily deduced.

Scheme 4.13



Ar = C_6H_5, 1-Naph, 2-furanyl, etc
R = $n C_6H_{13}$, C_6H_5, $t C_4H_9$, etc

As described in Section 4.3.4.7, the 2,6-hydrogens on the 3,3'-aryl substituents interfere with the β substituent of the enone and make the transition state **4.65** unfavorable. To increase the enantioselectivities, especially for the conjugate addition of enones with β alkyl groups, more modification of the binaphthyl moiety might be useful. For example, 2,6-dimethylphenyl or 2,6-difluorophenyl groups could be introduced on 3,3'-positions of binaphthyl group. With this modification, the possible transition state **4.65** might be further reduced to promote higher enantioselectivities.

4.5. Experimental

4.5.1. General

The general procedures previously described in Section 2.5.1 are applicable here.

4.5.2. Materials

Solvents were dried prior to use. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were dried by distillation from sodium wire. Dichloromethane (CH_2Cl_2), DMF, acetonitrile (CH_3CN) and diisopropylamine were dried by distillation from calcium hydride. Boron trifluoride ethyl etherate ($BF_3{\bullet}OEt_2$) was treated with a small quantity of ethyl ether (to ensure an excess of this component, ca. 5 mL/100 mL $BF_3{\bullet}OEt_2$) and distilled (60-62 °C/aspirator vacuum).

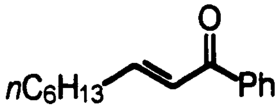
All alkynyl boron reagents used in this Chapter are from Chapter 3 and each of them has the same number as that described in Chapter 3. Unless otherwise pointed out, chemicals were purchased from the Aldrich Chemical Company.

4.5.3. Preparation of enones

4.5.3.1. General Procedure A

A procedure from the literature[3] was followed. Diisopropylamine (14.70 mL, 105.0 mmol) was mixed in THF (160 mL) in a 500-mL round-bottomed flask fitted with a stir bar and an argon inlet and the flask was cooled to -20 °C. To the mixture, with stirring, was syringed *n*BuLi (69.0 mL of 1.52 M solution in hexane, 105.0 mmol). After addition, the reaction was stirred at -20 °C for 30 min. The reaction mixture was chilled to -78 °C and acetophenone (11.70 mL, 100.0 mmol) was added to the flask. The reaction was stirred at -78 °C for 30 min. To the resulting mixture was added an aldehyde (110.0 mmol). After the reaction was stirred for 30 min at -78 °C, it was quenched with saturated aqueous $NaHCO_3$ (65 mL) and the mixture was allowed to warm up to room temperature. The layers were separated and the aqueous layer was extracted with Et_2O (100 mL x 2). All organic layers were combined and washed with cold 1% HCl (120 mL), saturated aqueous $NaHCO_3$ (120 mL), brine (120 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford a slightly yellow oil. The oil was dissolved in pyridine (75 mL) in a 300-mL round-bottomed flask and treated with mesyl chloride (7.70 mL, 100.0 mmol) at 0 °C under a nitrogen atmosphere for 16 h. Water (200 mL) was added to the flask and the mixture was extracted with Et_2O (150 mL x 3). The organic phase was washed with saturated aqueous $CuSO_4$ (100 mL x 4), and brine (150 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give an oil. The oil was mixed with Et_3N (14.50 mL, 104.0 mmol) and Et_2O (250 mL) in a 500 mL round bottom flask and stirred at room temperature for 18 h. Water (100 mL) was added to the flask and the mixture was stirred for 10 min. Then the organic layer was washed with cold 1% HCl (100 mL), saturated aqueous $NaHCO_3$ (100 mL), brine (100 mL), and dried over Na_2SO_4. The solvent was removed to afford the crude product. Purification was carried out by column chromatography (EtOAc/hexane: 1:10) to provide an enone.

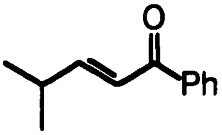
(a) *E*-1-Phenyl-2-nonen-1-one (4.3)



Following procedure A, heptaldehyde (15.40 mL, 110.0 mmol) was used to provide 16.20 g of **4.3** (75%): IR (neat): C=O 1671 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.85-8.05 (ArH, 2 H, m), 7.40-7.67 (ArH, 3 H, m), 7.04 (HC=C, 1 H, dt, J = 15.4; 6.8 Hz), 6.88 (C=CH-CO, 1 H, d, J = 15.4 Hz), 2.31 (CH_2C=C, 2 H, ddt, J = 7.1, 0, 7.1 Hz), 1.18-1.66 ($(CH_2)_4$, 8 H, m), 0.89 (CH_3, 3 H, t, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$): δ 190.9, 150.0, 138.0, 132.5, 128.4, 125.9, 32.8, 31.5, 28.8, 28.1, 22.5, 14.0; MS *m/e* (relative intensity): 216 (3, M$^+$), 159 (16), 145 (15), 133 (19), 131 (10), 121 (18), 120

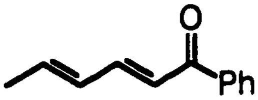
(46), 105 (100), 91 (10), 77 (47), 55 (26), 51 (11), 43 (14), 41 (14). Anal. Calcd for $C_{15}H_{20}O$: C, 83.29; H, 9.32. Found C, 83.16; H, 9.35.

(b) *E*-4-Methyl-1-phenyl-2-penten-1-one (4.4)



Following procedure A, isobutyraldehyde (10.0 mL, 110.0 mmol) was used to provide 14.10 g of **4.4** (81%): IR (neat): 1676 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.88-8.02 (ArH, 2 H, m), 7.43-7.62 (ArH, 3 H, m), 7.04 (HC=C, 1 H, dd, J = 15.4; 6.6 Hz), 6.83 (C=CH-CO, 1 H, dd, J = 15.5; 1.3 Hz), 2.58 (CH-C=C, 1 H, ddq, J = 1.3; 6.7; 6.6 Hz), 1.13 (CH_3, 6 H, d, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$): δ 191.1, 155.8, 138.0, 132.4, 128.3, 123.0, 31.3, 21.2; MS *m e* (relative intensity): 174 (30, M^+), 159 (18), 105 (100), 91 (7), 77 (56), 51 (17), 43 (9), 41 (15), 39 (7). Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found C, 82.66; H, 8.12.

(c) *E,E*-1-phenyl-2,4-hexadien-1-one (4.5)



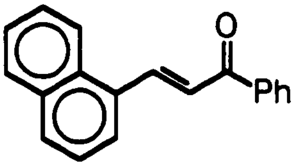
Following procedure A, crotonaldehyde (12.76 mL, 110.0 mmol) was used to provide 16.10 g of **4.5** (85%): mp 43-45 °C; IR (KBr): 1662 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.85-8.10 (ArH, 2 H, m), 7.30-7.70 (ArH, HC=C, 4 H, m), 6.87 (HC=C-CO, 1 H, d, J = 15.1 Hz), 6.18-6.45 (HC=CH, 2 H, m), 1.90 (CH_3, 3 H, d, J = 5.5 Hz); ^{13}C NMR ($CDCl_3$): δ 190.5, 144.9, 140.8, 138.1, 132.3, 130.4, 128.3, 128.1, 123.2, 18.6; MS *m/e* (relative intensity): 172 (25, M^+), 158 (13), 157 (100), 129 (20), 128 (18), 105 (27), 95 (14), 77 (56), 67 (23), 65 (10), 51 (24), 41 (19), 39 (16). Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found C, 83.86; H, 7.00.

4.5.3.2. General Procedure B

Aryl- or *t*-butyl-aldehyde (18.4 mmol), arylmethylketone (18.4 mmol), and NaOH (73.6 mg, 1.84 mmol) were mixed with water (20 mL) and MeOH (20 mL) in a 150-mL round-bottomed flask. The mixture was heated at reflux for 2 h. After it was cooled to room temperature, 6 M HCl (0.32 mL, 1.92 mmol) was added to the flask to neutralize NaOH. The resulting mixture was extracted with CH_2Cl_2 (50 mL x 3) and the organic solution was washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried over Na_2SO_4, and concentrated to give a crude product.

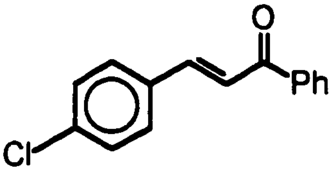
Subsequent purification by crystallization from MeOH/H_2O or column chromatograph provided the pure product.

(a) *E*-3-(1-Naphthyl)-1-phenyl-2-propen-1-one (4.7)



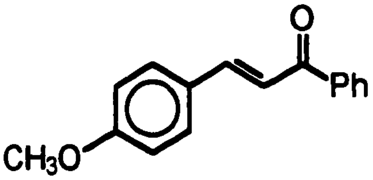
Following procedure B, 1-naphthaldehyde (2.50 mL, 18.4 mmol) and acetophenone (2.15 mL, 18.4 mmol) were used to give a yellow solid. It was crystallized from MeOH/H_2O to provide the pure product **4.7** (4.23 g, 89%): mp: 78-79 °C; IR (KBr): C=O 1661 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.67 (HC=C, 1 H, d, J = 15.5 Hz), 7.30-8.35 (ArH, HC=C, 13 H, m); ^{13}C NMR ($CDCl_3$): δ 190.1, 141.5, 138.1, 133.6, 132.8, 132.2, 131.6, 130.7, 128.6, 128.5, 126.9, 126.2, 125.3, 125.0, 124.5, 123.4; MS *m e* (relative intensity): 258 (77, M^+), 257 (84), 229 (14), 181 (20), 153 (51), 152 (74), 151 (24), 128 (33), 114 (11), 105 (100), 77 (80), 51 (17). Anal. Calcd for $C_{19}H_{14}O$: C, 88.34; H, 5.46. Found C, 88.43; H, 5.43.

(b) *E*-3-(4'-Chlorophenyl)-1-phenyl-2-propen-1-one (4.8)



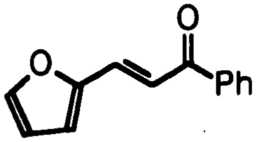
Following procedure B, 4-chlorobenzaldehyde (2.59 g, 18.4 mmol) and acetophenone (2.15 mL, 18.4 mmol) were used to give a yellow solid. It was crystallized from MeOH/H_2O to provide the pure product **4.8** (4.20 g, 94%): mp: 109-110 °C; IR (KBr): 1658, 1588, 1487, 1401, 1312, 1215, 1011 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.96-8.08 (ArH, 2 H, m), 7.76 (Ar-HC=C, 1 H, d, J = 15.7 Hz), 7.32-7.66 (ArH, CO-HC=C, 8 H, m); ^{13}C NMR ($CDCl_3$): δ 190.0, 143.1, 137.9, 136.3, 133.3, 132.8, 129.5, 129.1, 128.6, 128.4, 122.3; MS *m/e* (relative intensity): 243 (21, M$^+$), 242 (58), 241 (41), 207 (53), 179 (29), 178 (24), 167 (14), 165 (41), 137 (24), 130 (23), 105 (63), 102 (42), 101 (35), 89 (25), 77 (100), 76 (25), 75 (30), 51 (38), 50 (16). Anal. Calcd for $C_{15}H_{11}ClO$: C, 74.23; H, 4.57. Found C, 73.98; H, 4.80.

(c) *E*-3-(4'-Methoxyphenyl)-1-phenyl-2-propen-1-one (4.9)



Following procedure B, 4-methoxybenzaldehyde (2.24 mL, 18.4 mmol) and acetophenone (2.15 mL, 18.4 mmol) were used to give a yellow solid. It was crystallized from MeOH/H_2O to provide the pure product **4.9** (3.73 g, 85%): mp: 67-68 °C; IR (KBr): 1657, 1589, 1511, 1283, 1213, 1176, 1017 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.94-8.08 (ArH, 2 H, m), 7.78 (Ar-HC=C, 1 H, d, J = 15.6 Hz), 7.34-7.66 (ArH, CO-HC=C, 6 H, m), 6.84-7.02 (ArH, 2 H, m), 3.82 (OCH_3, 3 H, s); ^{13}C NMR ($CDCl_3$): δ 190.4, 161.6, 144.6, 138.4, 132.4, 130.1, 128.5, 128.3, 127.5, 119.6, 114.3, 55.3; MS *m/e* (relative intensity): 239 (14, M^{+}+1), 238 (87, M^{+}), 237 (49), 223 (21), 207 (21), 195 (11), 165 (12), 161 (63), 133 (31), 118 (15), 108 (58), 105 (37), 90 (15), 89 (21), 77 (100), 63 (13), 51 (26). Anal. Calcd for $C_{16}H_{14}O$: C, 80.65; H, 5.92. Found C, 80.77; H, 6.07.

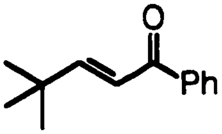
(d) *E*-3-(2-Furyl)-1-phenyl-2-propen-1-one (4.10)



Following procedure B, 2-furancarboxaldehyde (furfural) (1.77 g, 18.4 mmol) and acetophenone (2.15 mL, 18.4 mmol) were used to give a yellow solid. It was crystallized from MeOH/H_2O to provide the desired product **4.10** (3.47 g, 95%): IR(neat): 1663 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.95-8. 15 (ArH, 2 H, m), 7.42-7.65 (ArH, furanH, HC=CH, 6 H, m), 6.72 (furanH, 1 H, d, J = 3.4 Hz), 6.52 (furanH, 1 H, dd, J = 3.4; 1.8 Hz); ^{13}C NMR ($CDCl_3$): δ 189.2, 151.3, 144.6, 137.8, 132.4, 130.2, 128.2, 128.0, 118.9, 115.9, 112.4; MS *m/e* (relative intensity): 198 (59, M^+), 169 (10), 144

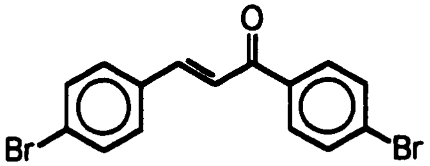
(22), 141 (28), 121 (35), 115 (14), 105 (100), 77 (60), 65 (33), 51 (21), 39 (25). Anal. Calcd for $C_{13}H_{10}O_2$: C, 78.77; H, 5.08. Found C, 78.70; H, 5.12.

(e) *E*-4,4-Dimethyl-1-phenyl-2-penten-1-one (4.11)



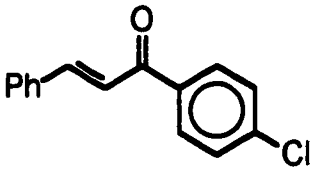
Following procedure B, trimethylacetaldehyde (2.15 mL, 18.4 mmol) and acetophenone (2.15 mL, 18.4 mmol) were used to afford a slightly yellow oil. Since both ^{1}H NMR and TLC showed that there was some aldol product in the crude oil, the purification was performed by column chromatography (EtOAc/hexane: 1:10) to afford the desired product **4.11** (1.50 g, 43%): IR (neat): C=O 1672 cm $^{-1}$; ^{1}H NMR ($CDCl_3$): δ 7.85-7.98 (ArH, 2 H, m), 7.40-7.62 (ArH, 3 H, m), 7.05 (HC=C, 1 H, d, J = 15.6 Hz), 6.78 (HC=C-CO, 1 H, d, J = 15.6 Hz), 1.16 (CH_3, 9 H, s); ^{13}C NMR ($CDCl_3$): δ 191.1, 159.2, 138.0, 132.3, 128.3, 120.8, 33.9, 28.5; MS *m e* (relative intensity): 188 (7, M^+), 173 (38), 145 (12), 129 (11), 105 (100), 77 (51), 55 (14), 51 (17), 43 (20), 41 (16). Anal. Calcd for $C_{13}H_{16}O$: C, 82,94; H, 8.56. Found C, 83.07; H, 8.61.

(f) *E*-1,3-Bis(4-bromophenyl)-2-propen-1-one (4.12)



Following procedure B, 4-bromobenzaldehyde (3.40 g, 18.4 mmol) and 4'-bromoacetophenone (3.66 g, 18.4 mmol) were used to give a yellow solid. It was crystallized from MeOH/H_2O to provide the desired product **4.12** (6.47 g, 96%): mp: 177-178 °C; IR (KBr): C=O 1656 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.85-7.95 (ArH, 2 H, m), 7.75 (HC=C, 1 H, d, J = 15.7 Hz), 7.40-7.75 (ArH, HC=CCO, 7 H, m); ^{13}C NMR ($CDCl_3$): δ 189.0, 143.9, 136.7, 133.6, 132.3, 132.0, 130.0, 129.8, 128.1, 125.1, 121.9; MS *m e* (relative intensity): 366 (27, M^+), 287 (77), 285 (85), 185 (38), 183 (50), 178 (50), 155 (42), 102 (100), 89 (69), 76 (88), 75 (58). Anal. Calcd for $C_{15}H_{10}Br_2O$: C, 49.22; H, 2.75. Found C, 49.26; H, 2.61.

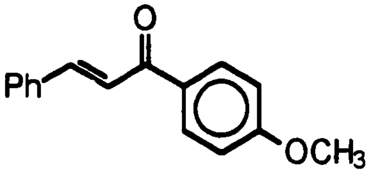
(g) *E*-1-(4'-Chlorophenyl)-3-phenyl-2-propen-1-one (4.13)



Following procedure B, benzaldehyde (1.95 g, 18.4 mmol) and 4'-chloroacetophenone (2.84 g, 18.4 mmol) were used to give a yellow solid. It was crystallized from MeOH/H_2O to provide the desired product **4.13** (4.02 g, 90%): mp:

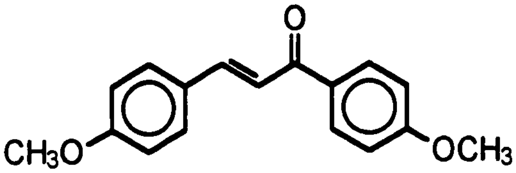
93-94 °C; IR (KBr): 1681, 1592, 1448, 1335, 1217, 1010 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.90-8.06 (ArH, 2 H, m), 7.82 (Ar-HC=C, 1 H, d, J = 15.7 Hz), 7.32-7.75 (ArH, HC=C-CO, 8 H, m); ^{13}C NMR ($CDCl_3$): δ 188.9, 145.2, 139.1, 136.4, 134.6, 130.6, 129.8, 128.9, 128.8, 128.4, 121.4; MS *m/e* (relative intensity): 245 (2, M^++2), 244 (20, M^++1), 243 (40, M^+), 242 (63), 241 (100), 207 (53), 179 (16), 178 (23), 141 (14), 139 (48), 131 (48), 113 (16), 111 (50), 103 (46), 102 (12), 89 (24), 77 (52), 76 (28), 75 (34), 51 (23), 50 (12). Anal. Calcd for $C_{15}H_{11}ClO$: C, 74.23; H, 4.57. Found C, 74.25; H, 4.50.

(h) *E*-1-(4'-Methoxyphenyl)-3-phenyl-2-propen-1-one (4.14)



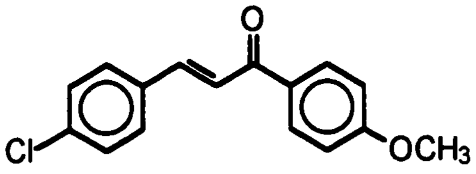
Following procedure B, benzaldehyde (1.95 g, 18.4 mmol) and 4'-methoxyacetophenone (2.76 g, 18.4 mmol) were used to give a yellow solid. It was crystallized from MeOH/H_2O to provide the desired product **4.14** (4.03 g, 92%): mp: 99-100 °C; IR (KBr): 1655, 1603, 1572, 1384, 1335, 1258, 1183 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.98-8.12 (ArH, 2 H, m), 7.80 (Ar-HC=C, 1 H, d, J = 15.7 Hz), 7.58-7.72 (ArH, 2 H, m), 7.56 (HC=C-CO, 1 H, d, J = 15.7 Hz), 7.32-7.50 (ArH, 3 H, m), 6.80-7.10 (ArH, 2 H, m), 3.89 (OCH_3, 3 H, s); ^{13}C NMR ($CDCl_3$): δ 188.4, 163.2, 143.7, 134.9, 130.9, 130.6, 130.1, 128.7, 128.2, 121.7, 113.7, 55.3; MS *m/e* (relative intensity): 240 (2, M^++2), 239 (14, M^++1), 238 (98, M^+), 237 (79), 223 (16), 210 (12), 207 (11), 195 (13), 167 (10), 165 (12), 135 (100), 131 (22), 107 (15), 103 (30), 92 (31), 77 (83), 64 (16), 63 (15), 51 (17). Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found C, 80.67; H, 6.00.

(i) *E*-1,3-Bis(4'-methoxyphenyl)-2-propen-1-one (4.15)



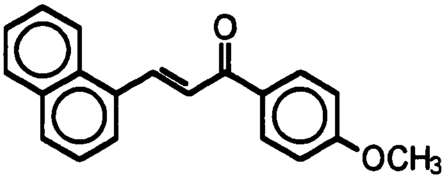
Following procedure B, 4-methoxybenzaldehyde (2.24 mL, 18.4 mmol) and 4'-methoxyacetophenone (2.76 g, 18.4 mmol) were used to give a yellow solid. It was crystallized from MeOH/H_2O to provide the desired product **4.15** (4.30 g, 87%): mp: 95-96 °C; IR (KBr): 1656, 1591, 1508, 1419, 1334, 1253, 1215, 1166, 1015 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.95-8.15 (ArH, 2 H, m), 7.78 (Ar-HC=C, 1 H, d, J = 15.6 Hz), 7.52-7.70 (ArH, 2 H, m), 7.44 (HC=C-CO, 1 H, d, J = 15.6 Hz), 6.82-7.09 (ArH, 4 H, m), 3.89 (OCH_3, 3 H, s), 3.86 (OCH_3, 3 H, s); ^{13}C NMR ($CDCl_3$): δ 188.5, 163.1, 161.4, 143.6, 131.2, 130.5, 129.9, 127.6, 119.4, 114.2, 113.6, 55.3, 55.2; MS *m/e* (relative intensity): 269 (7, M^++1), 268 (36, M^+), 267 (14), 253 (15), 161 (14), 135 (30), 92 (12), 77 (22), 32 (45), 28 (100). Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found C, 75.89; H, 6.10.

(j) *E*-3-(4'-Chlorophenyl)-1-(4'-methoxyphenyl)-2-propen-1-one (4.16)



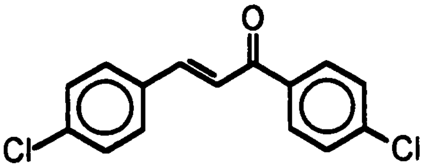
Following procedure B, 4-chlorobenzaldehyde (2.59 g, 18.4 mmol) and 4'-methoxyacetophenone (2.76 g, 18.4 mmol) were used to give a yellow solid. It was crystallized from MeOH/H_2O to provide the desired product **4.16** (4.52 g, 90%): mp: 123-124 °C; IR (KBr): 1657, 1598, 1491, 1409, 1253, 1223, 1176, 1023 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.95-8.15 (ArH, 2 H, m), 7.74 (Ar-HC=C, 1 H, d, J = 15.7 Hz), 7.46-7.65 (ArH, 2 H, m), 7.52 (HC=C-CO, 1 H, d, J = 15.7 Hz), 7.30-7.47 (ArH, 2 H, m), 6.80-7.08 (ArH, 2 H, m), 3.89 (OCH_3, 3 H, s); ^{13}C NMR ($CDCl_3$): δ 188.1, 163.4, 142.2, 136.0, 133.5, 130.8, 130.7, 129.4, 129.1, 122.2, 113.8, 55.4; MS *m e* (relative intensity): 275 (2, M^++2), 274 (12, M^++1), 273 (10, M^+), 272 (36), 271 (15), 165 (16), 135 (56), 102 (11), 101 (12), 92 (16), 77 (25), 32 (42), 28 (100). Anal. Calcd for $C_{16}H_{13}O_2Cl$: C, 70.46; H, 4.80. Found C, 70.30; H, 4.94.

(k) *E*-1-(4'-Methoxyphenyl)-3-(1'-naphthyl)-2-propen-1-one (4.17)



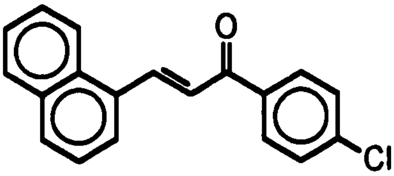
Following procedure B, 1-naphthaldehyde (2.50 mL, 18.4 mmol) and 4'-methoxyacetophenone (2.76 g, 18.4 mmol) were used to give a yellow solid. It was crystallized from MeOH/H_2O to provide the desired product **4.17** (4.56 g, 86%): mp: 79-80 °C; IR (KBr): 1650, 1590, 1509, 1348, 1310, 1253, 1175, 1016 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.66 (Ar-HC=C, 1 H, d, J = 15.4 Hz), 8.20-8.35 (ArH, 1 H, m), 7.77-8.18 (ArH, 5 H, m), 7.64 (HC=C-CO, 1 H, d, J = 15.4 Hz), 7.02-7.70 (ArH, 3 H, m), 6.95-7.10 (ArH, 2 H, m), 3.90 (OCH_3, 3 H, s); ^{13}C NMR ($CDCl_3$): δ 188.3, 163.4, 140.7, 133.6, 132.5, 131.6, 130.9, 130.8, 130.5, 128.6, 126.8, 126.1, 125.3, 124.9, 124.4, 123.4, 113.8, 55.3; MS *m/e* (relative intensity): 290 (1, M^++2), 289 (11, M^++1), 288 (57, M^+), 287 (47), 153 (12), 152 (41), 151 (14), 135 (100), 128 (16), 107 (11), 92 (19), 77 (34). Anal. Calcd for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59. Found C, 83.19; H, 5.55.

(l) *E*-1,3-Bis(4'-chlorophenyl)-2-propen-1-one (4.18)



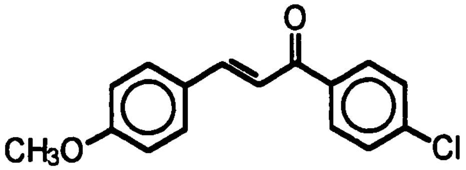
Following procedure B, 4-chlorobenzaldehyde (2.84 g, 18.4 mmol) and 4'-chloroacetophenone (2.59 g, 18.4 mmol) were used to give a yellow solid. It was crystallized from MeOH/H_2O to provide the desired product **4.18** (4.64 g, 91%): mp: 151-152 °C; IR (KBr): 1657, 1594, 1562, 1408, 1404, 1329, 1218, 1098, 1083, 1033, 1010 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.86-8.04 (ArH, 2 H, m), 7.75 (Ar-HC=C, 1 H, d, J = 15.7 Hz), 7.30-7.60 (ArH, HC=C-CO, 7 H, m); ^{13}C NMR ($CDCl_3$): δ 188.8, 143.7, 139.4, 136.6, 136.3, 133.2, 129.9, 129.6, 129.3, 129.0, 121.8; MS *m/e* (relative intensity): 280 (3, M$^+$+3), 279 (4, M$^+$+2), 278 (13, M$^+$+1), 277 (15, M$^+$), 276 (19), 275 (17), 243 (19), 242 (11), 241 (67), 178 (17), 165 (21), 139 (42), 137 (13), 113 (12), 111 (38), 106 (11), 102 (23), 101 (20), 88 (13), 76 (12), 75 (37), 51 (12), 50 (11), 32 (48), 28 (100). Anal. Calcd for $C_{15}H_{10}Cl_2O$: C, 65.01; H, 3.64. Found C, 64.98; H, 3.59.

(m) *E*-1-(4'-Chlorophenyl)-3-(1'-naphthyl)-2-propen-1-one (4.19)



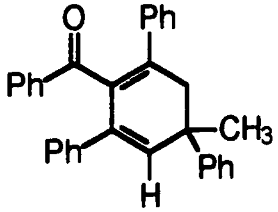
Following procedure B, 1-naphthaldehyde (2.50 mL, 18.4 mmol) and 4'-chloroacetophenone (2.84 g, 18.4 mmol) were used to give a yellow solid. It was crystallized from MeOH/H_2O to provide the desired product **4.19** (4.74 g, 88%): mp: 79-80 °C; IR (KBr): 1656, 1586, 1398, 1348, 1312, 1253, 1212, 1008 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.67 (Ar-HC=C, 1 H, d, J = 15.4 Hz), 7.30-8.35 (ArH, HC=C-CO, 12 H, m); ^{13}C NMR ($CDCl_3$): δ 188.3, 141.6, 138.9, 136.1, 133.4, 131.7, 131.5, 130.8, 129.7, 128.6, 128.5, 126.8, 126.1, 125.2, 124.9, 123.5, 123.1; MS *m e* (relative intensity): 295 (5, M^++2), 294 (24, M^++1), 293 (40, M^+), 292 (68), 291 (80), 257 (29), 229 (12), 228 (17), 181 (20), 154 (10), 153 (86), 152 (100), 151 (34), 150 (13), 141 (30), 139 (94), 128 (26), 127 (11), 126 (12), 114 (26), 113 (35), 111 (54), 101 (15), 77 (12), 76 (12), 75 (32), 32 (27), 28 (58). Anal. Calcd for $C_{19}H_{13}ClO$: C, 77.95; H, 4.48. Found C, 78.14; H, 4.49.

(n) *E*-1-(4'-Chlorophenyl)-3-(4'-methoxyphenyl)-2-propen-1-one (4.20)



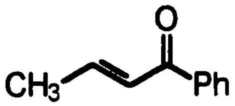
Following procedure B, 4-methoxybenzaldehyde (2.24 mL, 18.4 mmol) and 4-chloroacetophenone (2.84 g, 18.4 mmol) were used to give a yellow solid. It was crystallized from MeOH/H_2O to provide the desired product **4.20** (4.52 g, 90%): mp: 119-120 °C; IR (KBr): 1657, 1594, 1511, 1425, 1296, 1258, 1211, 1109, 1010 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.90-8.20 (ArH, 2 H, m), 7.79 (Ar-HC=C, 1 H, d, J = 15.6 Hz), 7.36-7.77 (ArH, 4 H, m), 7.37 (HC=C-CO, 1 H, d, J = 15.6 Hz), 6.85-7.05 (ArH, 2 H, m), 3.87 (OCH_3, 3 H, s); ^{13}C NMR ($CDCl_3$): δ 188.8, 161.7, 145.0, 138.7, 136.6, 130.2, 129.6, 128.7, 127.2, 118.9, 114.3, 55.2; MS *m e* (relative intensity): 274 (11, M^{+}+1), 273 (12, M^{+}), 272 (32), 271 (21), 237 (35), 165 (11), 161 (30), 139 (19), 133 (16), 111 (25), 108 (18), 89 (12), 77 (10), 75 (15), 32 (45), 28 (100). Anal. Calcd for $C_{16}H_{13}ClO_2$: C, 70.46; H, 4.80. Found C, 70.29; H, 5.03.

(o) (±)-2-benzoyl-1,3,5,-triphenyl-5-methyl-1,3-cyclohexadiene (4.22)



Following procedure B, acetophenone (2.84 g, 18.4 mmol) were used to give a white solid. It was crystallized from MeOH/H_2O to give exclusively the product **4.22** (1.86 g, 95%): mp: 134-135 °C [lit[4] mp 136 °C]. Since the paper has only the melting point of compound **4.22**, more analyses were performed as follows. IR (KBr): 1659, 1602, 1594, 1562, 1403, 1323, 1218, 1098, 1034, 1012 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.88-7.70 (ArH, 20 H, m), 6.19 (HC=C, 1 H, s), 3.24, 3.05 (CH_AH_B, 2 H, dd, AB, J_{AB} = 16.1 Hz), 1.63 (CH_3, 3 H, s); ^{13}C NMR ($CDCl_3$): δ 147.2, 141.0, 140.2, 139.7, 138.0, 135.5, 134.9, 132.3, 128.7, 128.1, 127.8, 127.7, 127.4, 127.3, 126.9, 126.4, 126.2, 44.6, 39.8, 28.1; MS *m/e* (relative intensity): 427 (2, M^+), 105 (100), 77 (28), 32 (20), 28 (56). Anal. Calcd for $C_{32}H_{26}O$: C, 90.11; H, 6.14. Found C, 90.32; H, 6.33.

4.5.3.3. *E*-1-Phenyl-2-buten-1-one (4.23)

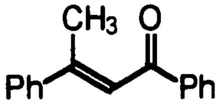


To a 300-mL round-bottomed flask fitted with a stir bar and an argon inlet, was added THF (150 mL) and phenylmagnesium chloride (25 mL of a 2.0 M solution in THF, 50.0 mmol). The flask was cooled in an ice-water bath for 10 min, crotonaldehyde (4.1 mL, 50.0 mmol) was added dropwise to the flask over a period of 10 min and the reaction was stirred for 30 min at 0 °C. The reaction was quenched with aqueous sat. NH_4Cl (20 mL), then THF was removed *in vacuo* to give an oil. The resulting oil was diluted with Et_2O (120 mL) and washed with 1 M HCl (40 mL), H_2O (2 x 40 mL), brine (30 mL), and dried over $MgSO_4$. The removal of ether *in vacuo* afforded 6.9 g of a yellow oil **4.24** which was used in next reaction without purification.

The oil **4.24** was added to pyridinium dichromate (23.5 g, 62.5 mmol) in DMF (40 mL) in a 100 mL round-bottomed flask at room temperature. The reaction was stirred at room temperature for 1 h, then diluted with ether (1200 mL), washed with water (3 x 1000 mL), brine (500 mL) and dried over $MgSO_4$. Removal of solvent to provide ca. 7.0 g of a crude oil, followed by distillation under high vacuum (82 °C/0.1 torr) gave 5.85 g of the target enone **4.23** (80%). IR (neat): 3061, 2973, 1669, 1623, 1578, 1446, 1296, 1222 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.70-8.10 (ArH, 2 H, m), 7.30-7.60 (ArH, 3 H, m), 7.08 (Me-HC=C, 1 H, dq, J = 15.3; 6.6 Hz), 6.91 (C=CH-CO, 1

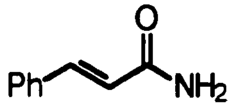
H, dq, J = 15.3; 1.1 Hz), 2.0 (CH_3, 3 H, dd, J = 6.6; 1.1 Hz); ^{13}C NMR ($CDCl_3$): δ 191.0, 155.7, 137.9, 132.5, 127.8, 123.0, 30.3; MS *m/e* (relative intensity): 147 (M^++1, 5), 146 (M^+, 51), 145 (15), 131 (45), 117 (12), 105 (100), 77 (76), 69 (56), 41 (19), 39 (16). Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.89. Found C, 82.10; H, 7.02.

4.5.3.4. *E*-1,3-Diphenyl-2-buten-1-one (dypnone) (4.21)

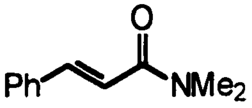


The preparation of **4.21** followed a literature procedure.[4] Lithium (0.12 g, 17.3 mmol) and acetophenone (10.0 mL, 85.7 mmol) were placed in a 25-mL round-bottomd flask and the mixture was heated to 100 °C with stirring for 3 h under an argon atmosphere. After the reaction mixture was cooled to room temperature, aqueous sat. NH_4Cl (5 mL) was added slowly. The resulting mixture was diluted with CH_2Cl_2 (25 mL), washed with water (2 x 25 mL), brine (25 mL), dried over Na_2SO_4. Removal of solvent *in vacuo* afforded a crude oil. Purification by column chromatograph (EtOAc/hexane: 1/20) provided the desired product **4.21** (1.2 g, 81% based on the recovery of acetophenone): IR (neat): 3063, 2973, 1667, 1603, 1456, 1298, 1225 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.92-8.06 (ArH, 2 H, m), 7.28-7.66 (ArH, 8 H, m), 7.17 (CO-HC=C, 1 H, q, J = 1.2 Hz), 2.60 (CH_3, 3 H, d, J = 1.2 Hz); ^{13}C NMR ($CDCl_3$): δ 188.5, 156.7, 137.9, 132.5, 128.6, 126.9, 126.2, 125.3, 125.0, 124.5, 123.0, 32.3; MS *m/e* (relative intensity): 223 (M^++1, 10), 222 (M^+, 67), 221 (100), 207 (11), 145 (23), 131 (14), 117 (15), 116 (11), 115 (47), 105 (23), 91 (21), 77 (55), 51 (20). Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found C, 86.54; H, 6.32.

4.5.4. *trans*-Cinnamamide (4.71) and *N,N*-dimethylcinnamide (4.72)



4.71



4.72

Ammonium hydroxide (15 mL of 28-30% solution in water, ca. 0.22 mol) was placed in a 50-mL round-bottomed flask equipped with a magnetic stirrer. While the flask was cooled in an ice-water bath, a solution of cinnamoyl chloride (3.33 g, 0.02 mol) in ether (10 mL) was added to the flask slowly. After the addition, the reaction was heated to reflux for 10 min. Ether was carefully removed by gentle heating. After the mixture was cooled to room temperature, the resulting white precipitate was filtered off, washed with water (3 x 20 mL), and air dried. Crystallization from ethanol provided the pure amide **4.71** (2.7 g, 92%): ^{1}H NMR ($CDCl_3$): δ 7.65 (Ar-CH=C, 1 H, d, J = 15.7 Hz), 7.25-7.65 (ArH, 5 H, m), 6.47 (CO-HC=C, 1 H, d, J = 15.7 Hz), 5.40-6.12 (NH_2, 2 H, br); MS *m/e* (relative intensity): 148 (M^++1, 4), 147 (M^+, 46), 146 (100), 131 (46), 130 (18), 129 (15), 103 (55), 102 (19), 77 (47), 51 (26), 32 (25), 28 (65).

The same procedure was used to prepare **4.72**. Dimethylamine (40 mL of 25% of solution in water, ca. 0.22 mol) was reacted with cinnamoyl chloride (3.33 g, 0.02

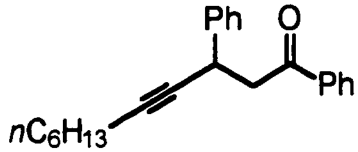
mol) to provide 3.30 g of white crystalline product **4.72** (95%): mp: 94-95 °C; IR (KBr): 1651, 1594, 1501, 1415, 1286, 1231, 1100, 1011 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.66 (Ar-HC=C, 1 H, d, J = 15.5 Hz), 7.20-7.65 (ArH, 5 H, m), 6.90 (HC=C-CO, 1 H, d, J = 15.5 Hz), 3.18 (CH_3, 3 H, s), 3.07 (CH_3, 3 H, s); ^{13}C NMR ($CDCl_3$): δ 166.3, 141.9, 135.1, 129.2, 128.5, 127.5, 117.3, 37.1, 35.6; MS *m/e* (relative intensity): 176 (5, M$^+$+1), 175 (39, M$^+$), 174 (19), 132 (11), 131 (100), 103 (69), 102 (12), 98 (15), 77 (40), 51 (16). Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found C, 75.32; H, 7.56; N, 8.04.

4.5.5. Achiral Conjugate Addition Products

4.5.5.1. General procedure

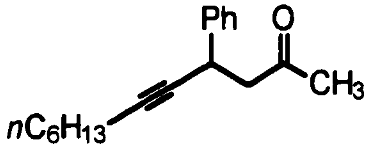
The method for preparation of racemic addition products was adapted from a procedure reported by Suzuki[5] with some modification. A mixture of **3.19** (1.5 mmol), enone (1.0 mmol), and CH_2Cl_2 (20 mL) was placed in a 50-mL round-bottomed flask under an argon or nitrogen atmosphere. To the mixture, with stirring, was syringed BF_3•OEt_2 (0.43 mL, 3.5 mmol). After addition, the reaction was stirred at room temperature for 1 h, then heated to reflux for 12 h. Saturated aqueous NH_4Cl (5 mL) and water (10 mL) were added to the flask. The mixture was separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL x 2). The organic phases were combined, dried over Na_2SO_4, and concentrated. Purification was performed by column chromatography (EtOAc/hexane or CH_2Cl_2/hexane) to afford the 1,4-addition product.

(a) 1,3-Diphenyl-4-undecyn-1-one (4.25)



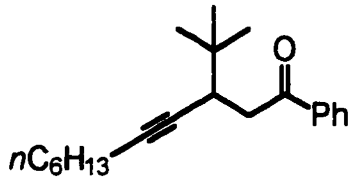
Following the general procedure, chalcone (0.208 g, 1.0 mmol) and lithium triisopropyl-*B*-1-octynylboronate (**3.19a**) (0.456 g, 1.5 mmol) were used to provide 0.239 g of compound **4.25** in 75% yield after column purification (EtOAc/hexane: 1:10): IR (neat): C=O 1684 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.85-8.05 (ArH, 2 H, m), 7.15-7.70 (ArH, 8 H, m), 4.39 (CH-C≡C, 1 H, ddt, J = 8.3; 6.0, 2.2 Hz), 3.52, 3.26 (CO-CH_AH_B, 2H, dd, ABX, J_{AB} = 16.4, J_{AX} = 8.3, J_{BX} = 6.0 Hz), 2.14 (C≡C-CH_2, 2 H, dt, J = 6.8; 2.2 Hz), 1.02-1.50 ($(CH_2)_4$, 8 H, m), 0.86 (CH_3, 3 H, t, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 197.2, 141.9, 136.9, 132.9, 128.4, 128.0, 127.4, 126.7, 83.5, 80.9, 47.5, 33.2, 31.2, 28.7, 28.3, 22.4, 18.7, 13.9; MS *m/e* (relative intensity): 318 (1, M^+), 247 (13), 234 (11), 233 (33), 129 (15), 128 (20), 115 (15), 105 (100), 91 (27), 77 (53), 55 (11), 41 (11). Anal. Calcd for $C_{23}H_{26}O$: C, 86.75; H, 8.23. Found C, 86.55; H, 8.20.

(b) 4-Phenyl-5-dodecyn-2-one (4.26)



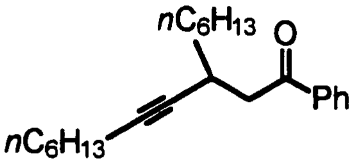
Benzalacetone (0.146 g, 1.0 mmol) and lithium triisopropyl-*B*-1-octynylboronate (**3.19a**) (0.456 g, 1.5 mmol) were used to provide compound **4.26** (0.104 g, 40%) after column purification (EtOAc/hexane: 1:15): IR (neat): C=O 1706 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.05-7.45 (ArH, 5 H, m), 4.02-4.15 (CH-C≡C, 1 H, m), 2.84, 2.67 (CO-CH_AH_B, 2 H, dd, ABX, J_{AB} = 16.1, J_{AX} = 8.5, J_{BX} = 6.1 Hz), 2.11 (C≡C-CH_2, 2 H, dt, J = 4.7; 2.1 Hz), 2.06 (CH_3-CO, 3 H, s), 1.10-1.65 ($(CH_2)_4$, 8 H, m), 0.81 (CH_3, 3 H, t, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$): δ 206.1, 141.6, 128.5, 127.3, 126.8, 83.8, 80.5, 52.3, 33.2, 31.3, 30.6, 28.8, 28.5, 22.5, 18.7, 14.0; MS *m/e* (relative intensity): 256 (1, M^+), 185 (52), 171 (49), 157 (13), 143 (21), 141 (13), 129 (39), 128 (41), 127 (10), 115 (22), 91 (28), 77 (11), 55 (15), 43 (100), 41 (15). Anal. Calcd for $C_{18}H_{24}O$: C, 84.32; H, 9.44. Found C, 84.26; H, 9.32.

(c) 3-(1,1-Dimethylethyl)-1-phenyl-4-undecyn-1-one (4.27)



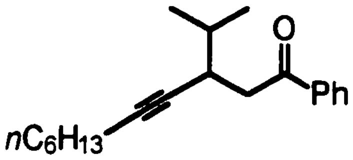
Enone **4.11** (0.188 g, 1.0 mmol) and lithium triisopropyl-*B*-1-octynylboronate (**3.19a**) (0.456g, 1.5 mmol) were used to provide compound **4.27** (0.119 g, 40%) after column purification (CH_2Cl_2/hexane: 1:2): IR (neat): C=O 1687 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.92-8.02 (ArH, 2 H, m), 7.42-7.62 (ArH, 3 H, m), 3.17, 2.94 (CO-CH_AH_B, 2 H, dd, ABX, J_{AB} = 15.2, J_{AX} = 10.1, J_{BX} = 3.8 Hz), 2.87 (CH-C≡C, 1 H, ddt, J = 10.1; 3.8; 1.9 Hz), 2.04 (C≡C-CH_2, 2 H, dt, J = 1.9; 6.6 Hz), 1.10-1.45 ($(CH_2)_4$, 8 H, m), 1.03 (CH3, 9 H, s), 0.85 (CH_3, 3 H, t, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 199.3, 137.5, 132.7, 128.4, 128.2, 83.0, 81.0, 39.8, 39. 1, 33.4, 31.2, 28.9, 28.3, 27.3, 22.4, 18.6, 13.9; MS *m/e* (relative intensity): 298 (0, M^+), 241 (36), 171 (33), 157 (26), 105 (100), 77 (49), 57 (36), 41 (18). Anal. Calcd for $C_{21}H_{30}O$: C, 84.51; H, 10.13. Found C, 84.60; H, 10.10.

(d) 3-Hexyl-1-phenyl-4-undecyn-1-one (4.28)



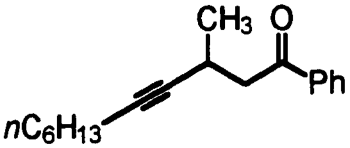
Enone **4.3** (0.216 g, 1.0 mmol) and lithium triisopropyl-*B*-1-octynylboronate (**3.19a**) (0.456 g, 1.5 mmol) were used to provide compound **4.28** (0.137 g, 42%) after column purification (EtOAc/hexane: 1:15): IR (neat): C=O 1689 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.75-8.05 (ArH, 2 H, m) 7.25-7.60 (ArH, 3 H, m), 2.75-3.30 (CO-CH_AH_B-CH_X, 3H, m,), 1.95-2.10 (C≡C-CH_2, 2 H, m), 1.05-1.60 ((CH_2)$_9$, 18 H, m), 0.65-0.95 (CH_3, 6 H, m); ^{13}C NMR ($CDCl_3$): δ 198.5, 137.3, 132.9, 128.5, 128.2, 82.5, 81.8, 44.4, 35.3, 31.8, 31.3, 29.0, 28.4, 27.7, 27.3, 22.6, 22.5, 18.7, 14.0; MS *m/e* (relative intensity): 326 (1, M^+), 242 (11), 241 (57), 157 (23), 105 (100), 77 (43), 55 (12), 43 (12), 41 (12). Anal. Calcd for $C_{23}H_{34}O$: C, 84.60; H, 10.50. Found C, 84.65; H, 10.60.

(e) 3-Isopropyl-1-phenyl-4-undecyn-1-one (4.29)



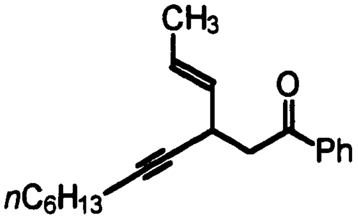
Enone **4.4** (0.174 g, 1.0 mmol) and lithium triisopropyl-*B*-1-octynylboronate (**3.19a**) (0.456 g, 1.5 mmol) were used to provide compound **4.29** (0.176 g, 62%) after column purification (CH_2Cl_2/hexane: 1:5): IR (neat): C=O 1682 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.75-8.05 (ArH, 2 H, m), 7.20-7.60 (ArH, 3 H, m), 2.75-3.25 (CO-CH$_A$H$_B$-CH$_X$, 3H, m,), 1.90-2.15 (C≡C-CH$_2$, 2 H, m), 1.55-1.82 (CH, 1 H, m), 0.95-1.45 ((CH_2)$_4$, 8 H, m), 0.94 (CH_3, 3 H, d, J = 6.8 Hz), 0.90 (CH_3, 3 H, d, J = 6.7 Hz), 0.78 (CH_3, 3 H, t, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$): δ 198.7, 137.3, 132.8, 128.4, 128.1, 82.8, 80.3, 42.1, 34.3, 31.3, 31.2, 28.9, 28.3, 22.4, 21.1, 18.6, 18.0, 13.9; MS *m e* (relative intensity): 284 (1, M^+), 171 (17), 157 (34), 105 (100), 97 (10), 77 (49), 55 (9), 43 (9), 41 (9). Anal. Calcd for $C_{20}H_{28}O$: C, 84.45; H, 9.92. Found C, 84.56; H, 9.98.

(f) 3-Methyl-1-phenyl-4-undecyn-1-one (4.30)



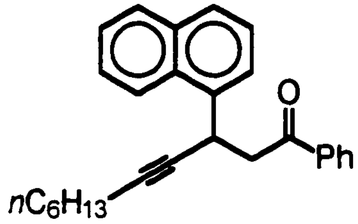
Enone **4.23** (0.146 g, 1.0 mmol) and lithium triisopropyl-*B*-1-octynylboronate (**3.19a**) (0.456 g, 1.5 mmol) were used to provide compound **4.30** (0.151 g, 59%) after column purification (EtOAc/hexane: 1/20): IR (neat): 3061, 2924, 1686, 1601, 1431, 1361, 1230, 1103 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.92-8.02 (ArH, 2 H, m), 7.40-7.62 (ArH, 3 H, m), 2.90-3.30 (CO-CH_AH_B-CH_X, 3H, m,), 2.10 (C≡C-CH_2, 2 H, dt, J = 1.8, 6.8 Hz), 1.12-1.60 ($(CH_2)_4$, CH_3, 11 H, m), 0.87 (CH_3, 3 H, t, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$): δ 198.0, 137.0, 132.8, 128.4, 128.0, 83.6, 80.7, 45.7, 31.2, 28.8, 28.3, 22.4, 22.0, 21.3, 18.6, 13.9; MS *m/e* (relative intensity): 256 (1, M^+), 185 (16), 171 (21), 157 (10), 136 (13), 105 (100), 91 (6), 77 (55), 55 (8), 43 (11), 41 (11). Anal. Calcd for $C_{18}H_{24}O$: C, 84.32; H, 9.43. Found C, 84.22; H, 9.46.

(g) 3-(1-*E*-Propenyl)-1-phenyl-4-undecyn-1-one (4.31)



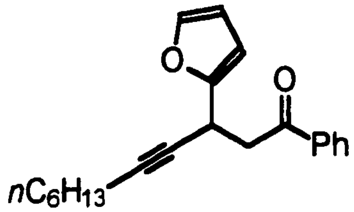
Enone **4.5** (0.172 g, 1.0 mmol) and lithium triisopropyl-*B*-1-octynylboronate (**3.19a**) (0.456 g, 1.5 mmol) were used to provide compound **4.31** (0.136 g, 48%) after column purification (EtOAc/hexane: 1:15): IR (neat): C=O 1685 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 7.92-8.02 (ArH, 5 H, m), 7.40-7.62 (ArH, 3 H, m), 5.66-5.87, 5.40-5.56 (HC=CH, 2 H, m), 3.64-3.82 (HC-C≡C, 1 H, m), 3.25, 3.07 (CO-CH$_A$H$_B$, 2 H, dd, ABX, J_{AB} = 16.4, J_{AX} = 7.0, J_{BX} = 7.1 Hz), 2.13 (C≡C-CH$_2$, 2 H, dt, J = 2.2; 6.9 Hz), 1.67 (CH$_3$-C=C, 3 H, ddd, J = 6.4; 1.3; 1.3 Hz), 1.10-1.60 ((CH$_2$)$_4$, 8 H, m), 0.87 (CH$_3$, 3 H, t, J = 6.7 Hz); ^{13}C NMR (CDCl$_3$): δ 197.9, 137.1, 133.0, 130.3, 128.5, 128.2, 126.2, 83.5, 80.4, 45.0, 31.3, 30.2, 28.9, 28.4, 22.5, 18.7, 17.5, 14.0; MS *m e* (relative intensity): 282 (0, M^+), 267 (1), 197 (15), 105 (100), 91 (16), 77 (45), 55 (11), 41 (10). Anal. Calcd for $C_{20}H_{26}O$: C, 85.06; H, 9.28. Found C, 85.10; H, 9.32.

(h) 3-(1-Naphthyl)-1-phenyl-4-undecyn-1-one (4.32)



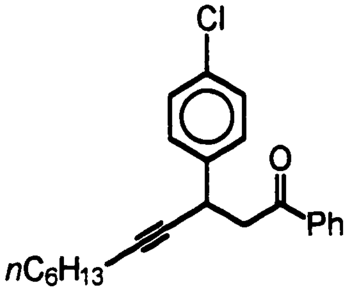
Enone **4.7** (0.258 g, 1.0 mmol) and lithium triisopropyl-*B*-1-octynylboronate (**3.19a**) (0.456 g, 1.5 mmol) were used to provide compound **4.32** (0.317 g, 86%) after column purification (EtOAc/hexane: 1:15): IR (neat): C=O 1684 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 8.12-8.22 (ArH, 1 H, m), 7.68-8.02 (ArH, 5 H, m), 7.35-7.60 (ArH, 6 H, m), 5.10-5.35 (C≡C-CH, 1 H, m), 3.67, 3.30 (CO-CH$_A$H$_B$, 2 H, dd, ABX, J_{AB} = 16.7, J_{AX} = 9.8, J_{BX} = 3.9 Hz), 2.16 (C≡C-CH$_2$, 2 H, dt, J = 2.2; 6.8 Hz), 1.02-1.58 ((CH$_2$)$_4$, 8 H, m), 0.84 (CH$_3$, 3 H, t, J = 5.2 Hz); ^{13}C NMR (CDCl$_3$): δ 197.6, 137.4, 137.0, 134.0, 133.0, 130.3, 129.0, 128.5, 128.2, 127.6, 126.2, 125.6, 125.5, 125.2, 123.0, 84.1, 80.8, 46.5, 31.2, 30.0, 29.0, 28.4, 22.5, 18.8, 14.0; MS *m/e* (relative intensity): 368 (3, M$^+$), 284 (23), 283 (83), 263 (11), 191 (15), 189 (12), 179 (48), 178 (32), 165 (30), 153 (11), 152 (17), 141 (23), 105 (100), 91 (10), 77 (64), 55 (23), 43 (13), 41 (18). Anal. Calcd for $C_{27}H_{28}O$: C, 88.00; H, 7.66. Found C, 88.10; H, 7.58.

(i) 3-(2-Furanyl)-1-phenyl-4-undecyn-1-one (4.33)



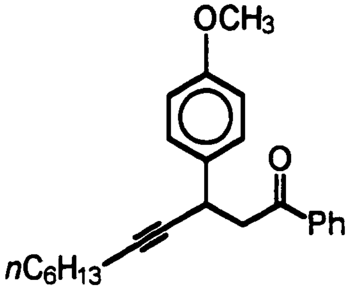
Enone **4.10** (0.198 g, 1.0 mmol) and lithium triisopropyl-*B*-1-octynylboronate (**3.19a**) (0.456 g, 1.5 mmol) were used to provide compound **4.33** (0.128 g, 42%) after column purification (EtOAc/hexane: 1:15): IR (neat): C=O 1689 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 7.90-8.05 (ArH, 2 H, m), 7.35-7.65 (ArH, 3 H, m), 7.31 (furanH, 1 H, dd, J = 1.8, 0.9 Hz), 6.29 (furanH, 1 H, dd, J = 3.2; 1.9 Hz), 6.24 (furanH, 1 H, ddd, J = 3.3; 0.9; 0.7 Hz), 4.40-4.55 (HC-C≡C, 1 H, m), 3.47 (CO-CH$_2$, 2 H, d, J = 7.0 Hz), 2.14 (C≡C-CH$_2$, 2 H, dt, J = 2.2; 6.9 Hz), 1.05-1.52 ((CH$_2$)$_4$, 8 H, m), 0.86 (CH$_3$, 3 H, t, J = 6.7 Hz); ^{13}C NMR (CDCl$_3$): δ 196.9, 154.1, 141.6, 136.9, 133.1, 128.5, 128.2, 110.3, 105.8, 86.7, 82.9, 78.3, 43.8, 31.3, 28.7, 28.4, 27.2, 22.5, 18.7, 14.0; MS *m e* (relative intensity): 308 (1, M$^+$), 223 (11), 105 (100), 91 (9), 81 (10), 77 (43). Anal. Calcd for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found C, 81.90; H, 7.76.

(j) 3-(4'-Chlorophenyl)-1-phenyl-4-undecyn-1-one (4.34)



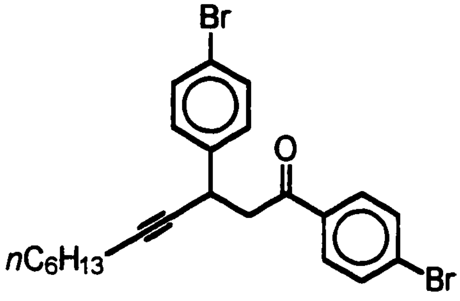
Enone **4.8** (0.243 g, 1.0 mmol) and lithium triisopropyl-*B*-1-octynylboronate (**3.19a**) (0.456 g, 1.5 mmol) were used to provide 0.272 g of compound **4.34** in 77% yield after column purification (EtOAc/hexane: 1:10): IR (neat): 3061, 2933, 1684, 1599, 1489, 1449, 1406, 1244, 1258, 1208, 1094, 1015 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.84-7.99 (ArH, 2 H, m), 7.02-7.70 (ArH, 7 H, m), 4.37 (CH-C≡C, 1 H, ddt, J = 7.6, 6.4, 2.2 Hz), 3.50, 3.25 (CO-CH_AH_B, 2 H, dd, ABX, J_{AB} = 16.7, J_{AX} = 7.6, J_{BX} = 6.4 Hz), 2.15 (C≡C-CH_2, 2 H, dt, J = 7.0, 2.2 Hz), 1.05-1.62 ($(CH_2)_4$, 8 H, m), 0.86 (CH_3, 3 H, t, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$): δ 197.1, 140.5, 136.8, 133.2, 132.9, 132.5, 129.5, 129.2, 128.9, 128.5, 128.1, 83.9, 80.5, 47.4, 32.6, 31.2, 28.7, 28.4, 22.5, 18.7, 14.0; MS *m/e* (relative intensity): 353 (1, M^+), 267 (18), 127 (10), 125 (13), 105 (100), 77 (49), 41 (10). Anal. Calcd for $C_{23}H_{25}OCl$: C, 78.28; H, 7.14. Found C, 78.23; H, 7.11.

(k) 3-(4'-Methoxyphenyl)-1-phenyl-4-undecyn-1-one (4.35)



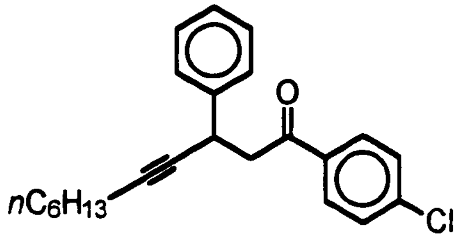
Enone **4.9** (0.238 g, 1.0 mmol) and lithium triisopropyl-*B*-1-octynylboronate (**3.19a**) (0.456 g, 1.5 mmol) were used to provide 0.271 g of compound **4.35** in 78% yield after column purification (EtOAc/hexane: 1:10): IR (neat): 3061, 2932, 1685, 1599, 1510, 1455, 1346, 1300, 1252, 1179, 1034 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.84-8.02 (ArH, 2 H, m), 7.26-7.60 (ArH, 5 H, m), 6.74-6.92 (ArH, 2 H, m), 4.35 (CH-C≡C, 1 H, ddt, J = 8.0, 6.2, 2.2 Hz), 3.77 (OCH_3, 3 H, s), 3.49, 3.24 (CO-CH_AH_B, 2 H, dd, ABX, J_{AB} = 16.4, J_{AX} = 8.0, J_{BX} = 6.2 Hz), 2.14 (C≡C-CH_2, 2 H, dt, J = 6.8, 2.2 Hz), 1.10-1.58 ($(CH_2)_4$, 8 H, m), 0.86 (CH_3, 3 H, t, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$): δ 197.5, 158.4, 137.0, 134.0, 133.0, 128.4, 128.1, 113.8, 83.3, 81.2, 55.2, 47.7, 32.5, 31.2, 28.8, 28.4, 22.4, 18.7, 14.0; MS *m/e* (relative intensity): 348 (3, M^+), 264 (15), 263 (34), 235 (11), 159 (12), 121 (28), 115 (13), 105 (100), 91 (10), 77 (48), 55 (10), 32 (30), 28 (65). Anal. Calcd for $C_{24}H_{28}O_2$: C, 82.72; H, 8.10. Found C, 82.63; H, 8.04.

(l) 1,3-Bis(4'-bromophenyl)-4-undecyn-1-one (4.36)



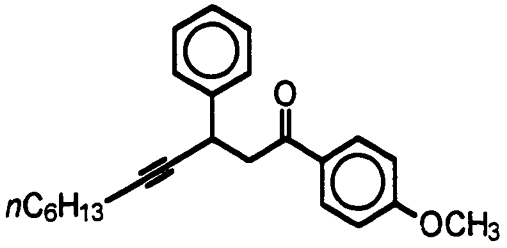
Enone **4.12** (0.366 g, 1.0 mmol) and lithium triisopropyl-*B*-1-octynylboronate (**3.19a**) (0.456 g, 1.5 mmol) were used to provide 0.333 g of compound **4.36** in 70% yield after column purification (EtOAc/hexane: 1:10): mp 40-41 °C; IR (KBr): 3062, 2932, 1686, 1582, 1485, 1400, 1350, 1260, 1204, 1177, 1071, 1010 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.14-7.94 (ArH, 8 H, m), 4.35 (CH-C≡C, 1 H, ddt, J = 7.7, 6.4, 2.2 Hz), 3.46, 3.20 (CO-CH_AH_B, 2 H, dd, ABX, J_{AB} = 16.7, J_{AX} = 7.7, J_{BX} = 6.4 Hz), 2.14 (C≡C-CH_2, 2 H, dt, J = 6.9, 2.2 Hz), 0.98-1.60 ($(CH_2)_4$, 8 H, m), 0.87 (CH_3, 3 H, t, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$): δ 196.1, 140.8, 135.5, 131.9, 131.6, 129.7, 129.3, 128.4, 120.7, 84.2, 80.2, 47.2, 32.8, 31.3, 28.7, 28.4, 22.5, 18.7, 14.0. Anal. Calcd for $C_{23}H_{24}OBr_2$: C, 58.01; H, 5.08. Found C, 58.01; H, 5.19.

(m) 1-(4'-Chlorophenyl)-3-phenyl-4-undecyn-1-one (4.37)



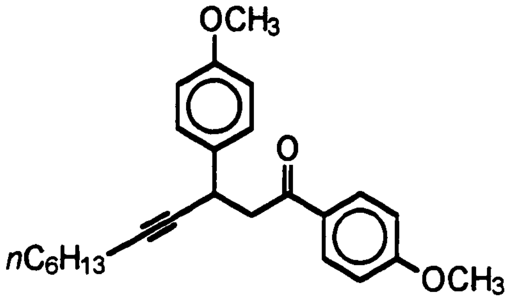
Enone **4.13** (0.243 g, 1.0 mmol) and lithium triisopropyl-*B*-1-octynylboronate (**3.19a**) (0.456 g, 1.5 mmol) were used to provide 0.265 g of compound **4.37** in 75% yield after column purification (EtOAc/hexane: 1:10): IR (neat): 3062, 3026, 2932, 1686, 1588, 1481, 1465, 1401, 1348, 1257, 1202, 1039, 1011 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.77-7.94 (ArH, 2 H, m), 7.12-7.52 (ArH, 7 H, m), 4.35 (CH-C≡C, 1 H, ddt, J = 8.3, 5.9, 2.2 Hz), 3.48, 3.21 (CO-CH_AH_B, 2 H, dd, ABX, J_{AB} = 16.3, J_{AX} = 8.3, J_{BX} = 5.9 Hz), 2.14 (C≡C-CH_2, 2 H, dt, J = 6.8, 2.2 Hz), 1.05-1.58 (($CH_2)_4$, 8 H, m), 0.86 (CH_3, 3 H, t, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$): δ 196.3, 141.7, 139.5, 135.3, 129.6, 128.8, 128.5, 127.4, 126.9, 83.8, 80.7, 47.5, 33.4, 31.3, 28.8, 28.4, 22.5, 18.7, 14.0; MS *m e* (relative intensity): 353 (1, M^+), 281 (12), 269 (12), 268 (12), 267 (31), 198 (11), 143 (10), 141 (44), 139 (100), 129 (23), 128 (30), 127 (12), 125 (10), 117 (11), 115 (21), 113 (12), 111 (36), 91 (29), 77 (10), 55 (16), 43 (13), 41 (15), 32 (17), 28 (36). Anal. Calcd for $C_{23}H_{25}OCl$: C, 78.28; H, 7.14. Found C, 78.12; H, 6.98.

(n) 1-(4'-Methoxyphenyl)-3-phenyl-4-undecyn-1-one (4.38)



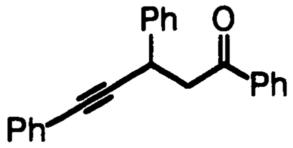
Enone **4.14** (0.238 g, 1.0 mmol) and lithium triisopropyl-*B*-1-octynylboronate (**3.19a**) (0.456 g, 1.5 mmol) were used to provide 0.271 g of compound **4.38** in 78% yield after column purification (EtOAc/hexane: 1:10): IR (neat): 3061, 3028, 2934, 1676, 1601, 1576, 1511, 1457, 1351, 1310, 1256, 1173, 1029 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.84-7.98 (ArH, 2 H, m), 7.10-7.54 (ArH, 5 H, m), 6.78-7.02 (ArH, 2 H, m), 4.39 (CH-C≡C, 1 H, ddt, J = 8.3, 6.0, 2.2 Hz), 3.83 (OCH_3, 3 H, s), 3.47, 3.18 (CO-CH_AH_B, 2 H, dd, ABX, J_{AB} = 16.2, J_{AX} = 8.3, J_{BX} = 6.0 Hz), 2.14 (C≡C-CH_2, 2 H, dt, J = 6.8, 2.2 Hz), 1.10-1.55 ($(CH_2)_4$, 8 H, m), 0.86 (CH_3, 3 H, t, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$): δ 195.9, 163.4, 142.1, 130.4, 130.1, 128.4, 127.4, 126.7, 113.6, 83.5, 81.0, 55.3, 47.2, 33.4, 31.2, 28.8, 28.4, 22.4, 18.7, 14.0; MS *m/e* (relative intensity): 348 (1, M^+), 135 (100), 91 (10), 77 (18), 32 (15), 28 (36). Anal. Calcd for $C_{24}H_{28}O_2$: C, 82.72; H, 8.10. Found C, 82.83; H, 7.98.

(o) 1,3-Bis(4'-Methoxyphenyl)-4-undecyn-1-one (4.39)



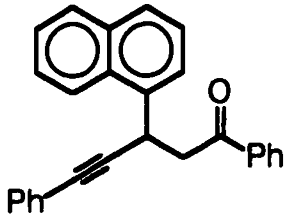
Enone **4.15** (0.268 g, 1.0 mmol) and lithium triisopropyl-*B*-1-octynylboronate (**3.19a**) (0.456 g, 1.5 mmol) were used to provide 0.273 g of compound **4.39** in 72% yield after column purification (EtOAc/hexane: 1:10): IR (neat): 3058, 3026, 2932, 1675, 1596, 1506, 1458, 1419, 1305, 1209, 1174, 1111, 1032 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.85-8.00 (ArH, 2 H, m), 7.28-7.44 (ArH, 2 H, m), 6.75-7.00 (ArH, 4 H, m), 4.35 (CH-C≡C, 1 H, ddt, J = 8.0, 6.3, 2.2 Hz), 3.82 (OCH_3, 3 H, s), 3.75 (OCH_3, 3 H, s), 3.43, 3.17 (CO-CH_AH_B, 2 H, dd, ABX, J_{AB} = 16.2, J_{AX} = 8.0, J_{BX} = 6.3 Hz), 2.14 (C≡C-CH_2, 2 H, dt, J = 6.8, 2.2 Hz), 1.02-1.58 ($(CH_2)_4$, 8 H, m), 0.86 (CH_3, 3 H, t, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 196.3, 163.4, 158.3, 134.2, 130.4, 130.1, 128.3, 113.8, 113.6, 83.2, 81.4, 55.3, 55.1, 47.3, 32.6, 31.2, 28.8, 28.4, 22.4, 18.7, 14.0; MS *m/e* (relative intensity): 379 (1, M$^+$), 293 (19), 265 (15), 135 (100), 121 (34), 77 (21), 32 (20), 28 (43). Anal. Calcd for $C_{25}H_{30}O_3$: C, 79.33; H, 7.99. Found C, 79.47; H, 7.78.

(p) 1,3,5-Triphenyl-4-pentyn-1-one (4.40)



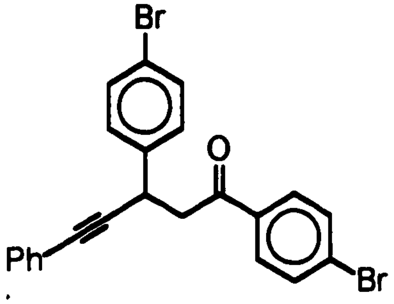
Chalcone (0.208 g, 1.0 mmol) and lithium triisopropyl-*B*-(phenylacetylenyl)boronate (**3.19b**) (0.444 g, 1.5 mmol) were used to provide compound **4.40** (0.255 g, 82%) after column purification (EtOAc/hexane: 1:10): mp: 89-90 °C; IR (KBr): C=O 1680 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.88-8.10 (ArH, 2 H, m), 7.10-7.70 (ArH, 13 H, m), 4.65 (HC-C≡C, 1 H, dd, J = 7.7; 6.3 Hz), 3.67, 3.40 (CO-CH_AH_B, 2 H, dd, ABX, J_{AB} = 16.7, J_{AX} = 7.9, J_{BX} = 6.2 Hz); ^{13}C NMR ($CDCl_3$): δ 197.0, 141.2, 136.8, 133.1, 131.6, 128.6, 128.5, 128.1, 127.8, 127.5, 127.0, 123.3, 90.7, 83.2, 47.2, 33.7; MS *m/e* (relative intensity): 310 (10, M^+), 233 (12), 206 (17), 205 (100), 204 (18), 203 (13), 202 (11), 191 (44), 189 (21), 105 (71), 77 (57), 51 (12). Anal. Calcd for $C_{23}H_{18}O$: C, 89.00; H, 5.84. Found C, 89.13; H, 5.83.

(q) 3-(1-Naphthyl)-1,5-diphenyl-4-pentyn-1-one (4.41)



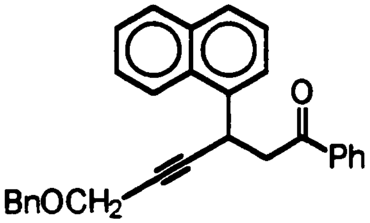
Enone **4.7** (0.258 g, 1.0 mmol) and lithium triisopropyl-*B*-(phenylacetylenyl)boronate (**3.19b**) (0.444 g, 1.5 mmol) were used to provide compound **4.41** (0.346 g, 96%) after column purification (CH_2Cl_2/hexane: 1:1): mp: 105-106 °C; IR (KBr): C=O 1686 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.10-8.35 (ArH, 17 H, m), 5.44 (HC-C≡C, 1 H, dd, J = 9.4; 4.0 Hz), 3.83, 3.47 (CO-CH_AH_B, 2 H, dd, ABX, J_{AB} = 16.8, J_{AX} = 9.5, J_{BX} = 4.1 Hz); ^{13}C NMR ($CDCl_3$): δ 197.2, 136.8, 136.7, 134.1, 133.2, 131.6, 130.3, 129.1, 128.6, 128.2, 128.1, 127.9, 127.8, 126.4, 125.7, 125.5, 125.4, 123.4, 122.9, 90.7, 83.9, 46.2, 30.5; MS *m e* (relative intensity): 360 (11, M^+), 255 (35), 253 (17), 241 (30), 240 (17), 239 (30), 209 (14), 208 (28), 207 (100), 105 (24), 96 (15), 77 (24), 44 (17), 40 (15). Anal. Calcd for $C_{27}H_{20}O$: C, 89.97; H, 5.59. Found C, 90.05; H, 5.58.

(r) 1,3-Bis(4'-bromophenyl)-5-phenyl-4-pentyn-1-one (4.42)



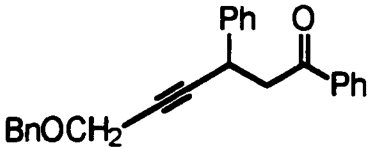
Enone **4.12** (0.366 g, 1.0 mmol) and lithium triisopropyl-*B*-(phenylacetylenyl)boronate (**3.19b**) (0.444 g, 1.5 mmol) were used to provide compound **4.42** (0.410 g, 88%) after column purification (CH_2Cl_2/hexane: 1:2): mp: 85-87 ^{o}C; IR (KBr): C=O 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.20-7.95 (ArH, 13 H, m), 4.58 (HC-C≡C, 1 H, dd, J = 7.0; 7.0 Hz), 5.50, 3.40 (CO-CH_AH_B, 2 H, dd, ABX, J_{AB} = 16.8, J_{AX} = 7.3, J_{BX} = 6.6 Hz); ^{13}C NMR ($CDCl_3$): δ 195.7, 140.0, 135.3, 131.9, 131.8, 131.6, 129.6, 129.4, 128.6, 128.2, 128.1, 122.9, 121.0, 89.9, 83.7, 46.9, 33.1; MS *m e* (relative intensity): 468 (2, M^+), 384 (20), 383 (19), 382 (35), 381 (29), 380 (21), 379 (14), 370 (15), 368 (31), 366 (18), 227 (14), 225 (13), 185 (100), 183 (99), 171 (12), 169 (11), 157 (25), 155 (27), 105 (10), 104 (20). Anal. Calcd for $C_{23}H_{16}Br_2O$: C, 59.00; H, 3.44. Found C, 58.88; H, 3.50.

(s) 6-Benzyloxy-3-naphthyl-1-phenyl-4-hexyn-1-one (4.43)



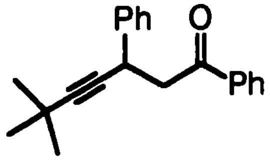
Enone **4.7** (0.258 g, 1.0 mmol) and lithium triisopropyl-*B*-(3-benzoxy-1-propynyl)-boronate (**3.19c**) (0.510 g, 1.5 mmol) were used to provide compound **4.43** (0.290 g, 72%) after column purification (CH_2Cl_2/hexane: 1:1): IR (neat): C=O 1683 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.72-8.24 (ArH, 6 H, m), 7.05-7.66 (ArH, 11 H, m), 5.30 (HC-C≡C, 1 H, ddt, J = 9.6, 4.0, 2.0 Hz),), 4.53 (OCH_2Ph, 2 H, s), 4.19 (OCH_2-C≡C, 2 H, d, J = 2.0 Hz), 3.76, 3.42 (CO-CH_AH_B, 2 H, dd, ABX, J_{AB} = 17.1, J_{AX} = 9.6, J_{BX} = 4.0 Hz); ^{13}C NMR ($CDCl_3$): δ 197.1, 137.5, 136.7, 136.4, 134.1, 133.3, 130.3, 129.1, 128.6, 128.3, 128.2, 128.1, 127.9, 127.7, 126.4, 125.7, 125.5, 125.3, 122.9, 87.9, 79.4, 71.2, 57.6, 46.0, 29.8; MS *m/e* (relative intensity): 404 (0, M^+), 296 (17), 295 (12), 191 (24), 178 (10), 106 (10), 105 (100), 91 (33), 77 (33). Anal. Calcd for $C_{29}H_{24}O_2$: C, 86.11; H, 5.98. Found C, 85.99; H, 5.91.

(t) 6-Benzyloxy-1,3-diphenyl-4-hexyn-1-one (4.44)



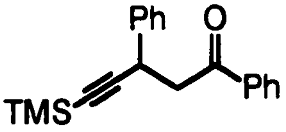
Chalcone (0.208 g, 1.0 mmol) (0.258 g, 1.0 mmol) and lithium triisopropyl-*B*-(3-benzoxy-1-propynyl)boronate (**3.19c**) (0.510 g, 1.5 mmol) were used to provide compound **4.44** (0.248 g, 70%) after column purification (CH_2Cl_2/hexane: 1:1): IR (neat): 3062, 3030, 2232, 1684, 1598, 1495, 1450, 1352, 1255, 1205, 1072, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.85-8.02 (ArH, 2 H, m), 7.12-7.64 (ArH, 13 H, m), 4.53 (OCH_2Ph, 2 H, s), 4.48 (HC-C≡C, 1 H, ddt, J = 8.1, 6.0, 2.0 Hz), m), 4.17 (OCH_2-C≡C, 2 H, d, J = 2.0 Hz), 3.59, 3.33 (CO-CH_AH_B, 2 H, dd, ABX, J_{AB} = 16.9, J_{AX} = 8.1, J_{BX} = 6.0 Hz); ^{13}C NMR ($CDCl_3$): δ 196.8, 141.0, 137.6, 136.7, 133.2, 128.6, 128.3, 128.1, 127.7, 127.5, 127.1, 87.9, 78.8, 71.3, 57.6, 47.1, 33.1; MS *m e* (relative intensity): 354 (0, M$^+$), 324 (7), 128 (18), 105 (100), 91 (25), 77 (31), 28 (10). Anal. Calcd for $C_{25}H_{22}O_2$: C, 84.72; H, 6.26. Found C, 84.98; H, 6.17.

(u) 1,3-Diphenyl-6,6-dimethyl-4-heptyn-1-one (4.45)



Chalcone (0.208 g, 1.0 mmol) (0.258 g, 1.0 mmol) and lithium triisopropyl-*B*-(3,3-dimethyl-1-butynyl)boronate (**3.19d**) (0.414 g, 1.5 mmol) were used to provide compound **4.45** (0.150 g, 52%) after column purification (CH_2Cl_2/hexane: 1:2): IR (neat): 3062, 3029, 1685, 1598, 1494, 1450, 1353, 1258, 1206, 1024 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.86-8.02 (ArH, 2 H, m), 7.14-7.64 (ArH, 8 H, m), 4.36 (H_XC-C≡C, 1 H, dd, ABX, J_{AX} = 8.1, J_{BX} = 6.2 Hz), 3.49, 3.21 (CO-CH_AH_B, 2 H, dd, ABX, J_{AB} = 15.9, J_{AX} = 8.3, J_{BX} = 6.2 Hz), 1.14 ($(CH_3)_3$, 9 H, s); ^{13}C NMR ($CDCl_3$): δ 197.6, 142.0, 137.1, 132.9, 128.4, 128.2, 127.4, 126.7, 92.2, 79.2, 47.7, 33.5, 31.0, 27.3; MS *m e* (relative intensity): 290 (1, M^+), 275 (42), 234 (20), 233 (35), 220 (17), 129 (11), 128 (13), 115 (13), 105 (100), 91 (23), 77 (50), 57 (10), 28 (17). Anal. Calcd for $C_{21}H_{22}O$: C, 86.86; H, 7.64. Found C, 87.00; H, 7.85.

(v) 1,3-Diphenyl-5-trimethylsilyl-4-hexyn-1-one (4.46)



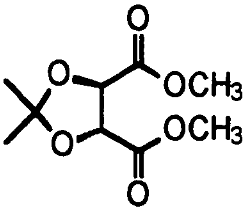
Chalcone (0.208 g, 1.0 mmol) (0.258 g, 1.0 mmol) and lithium triisopropyl-*B*-(trimethylsilylethynyl)boronate (**3.19e**) (0.440 g, 1.5 mmol) were used to provide compound **4.46** (0.045 g, 15%) after column purification (CH_2Cl_2/hexane: 1:2): IR (neat): 3062, 3031, 1686, 1599, 1494, 1450, 1349, 1252, 1018 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.85-8.02 (ArH, 2 H, m), 7.12-7.64 (ArH, 8 H, m), 4.45 (H_XC-C≡C, 1 H, dd, ABX, J_{AX} = 7.0, J_{BX} = 7.0 Hz), 3.55, 3.30 (CO-CH_AH_B, 2 H, dd, ABX, J_{AB} = 16.5, J_{AX} = 7.5, J_{BX} = 6.5 Hz), 0.11 ($Si(CH_3)_3$, 9 H, s); ^{13}C NMR ($CDCl_3$): δ 197.1, 141.0, 137.0, 133.1, 128.6, 128.2, 127.6, 127.0, 107.4, 87.5, 47.3, 34.1, 0.0; MS *m/e* (relative intensity): 309 (1, M^++3), 308 (1, M^++2), 307 (5, M^++1), 306 (19, M^+), 291 (11), 234 (15), 233 (83), 215 (16), 217 (29), 202 (12), 159 (24), 105 (37), 91 (8), 83 (13), 77 (41), 75 (15), 73 (100). Anal. Calcd for $C_{20}H_{22}OSi$: C, 78.38; H, 7.24. Found C, 78.52; H, 7.04.

4.5.6. Asymmetric Conjugate Addition

The general procedure for the asymmetric conjugate addition was as follows. Lithium binaphthyl isopropyl *B*-1-alkynylboronate (0.345 mmol) (*R*)-**3.19** or (*R*)-**3.38** and enone (0.232 mmol) were placed in CH_2Cl_2 (15 mL) in a 25 mL round bottom flask under an argon or nitrogen atmosphere. To the mixture with stirring, was added $BF_3{\cdot}OEt_2$ (58 µl, 0.461 mmol). The reaction was stirred at room temperature for different lengths of time depending on the nature of the boron reagent and enone used. TLC was performed to determine the reaction progress. After reaction was complete (or no further change on the TLC), saturated aqueous NH_4Cl (2 mL) and water (2 mL) were added to quench the reaction. The mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (5 mL x 2). The organic phase was washed with water (5 mL), dried over Na_2SO_4, and concentrated. Most of the binaphthol was collected by crystallization from CH_2Cl_2/hexane and the remaining residue from the mother liquor was purified by column chromatography (EtOAc/hexane or CH_2Cl_2/hexane, the ratio depending on R_f's from TLC) to give the 1,4-addition product and the other portion of the binaphthol. The binaphthol was recovered in quantitative yield from all trials. The reaction time and yield for all cases are recorded in the tables in Section 4.3.

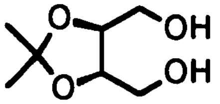
4.5.7. Synthesis of (*R*,*R*)-1,4-Difluorobutane-2,3-diol (4.50)

4.5.7.1. Dimethyl 2,3-*O*-isopropylidene-L-tartrate (4.52)



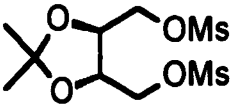
(*R*,*R*)-Tartaric acid (**4.51**) (101.0 g, 0.67 mol), 2,2-dimethoxypropane (160.0 g, 1.54 mol), *p*-toluenesulfonic acid (0.4 g, 2.1 mmol), and methanol (40 mL) were placed in a 1000-mL round-bottomed flask under an argon atmosphere. The mixture was stirred and heated to reflux for 1.5 h. More 2,2-dimethoxypropane (79.5 g, 0.76 mol) was added to the reaction, as well as cyclohexane (450 mL). The reaction was further stirred and heated as acetone and methanol were removed by azeotropic distillation with cyclohexane. After the vapor temperature reached 79 °C (about 36 h), anhydrous potassium carbonate (1.0 g) was added to neutralize the acid catalyst. The solid was filtered off and the solvent was evaporated in vacuo. The resulting dark yellow oil was fractionally distilled under high vacuum to afford 146.0 g of **4.52** as a light yellow oil (83-89 °C, 100%): ^{1}H NMR ($CDCl_3$): δ 4.78 (OCHCHO, 2 H, s), 3.76 (OCH_3, 6 H, s), 1.45 ($C(CH_3)_2$, 6 H, s).

4.5.7.2. 2,3-*O*-isopropylidene-L-threitol (4.53)



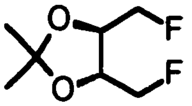
A suspension of LiAlH$_4$ (55.1 g, 1.45 mol) in ether (500 mL) in a 2000-mL round-bottomed flask was stirred at reflux for 30 min, then cooled to room temperature. To the mixture was added dropwise a solution of **4.52** (144.0 g, 0.66 mol) in ether (600 mL). After the addition, the reaction was heated for 3.5 h, then EtOAc (60 mL) was slowly added. The reaction was cooled in an ice-water bath, water (55 mL), 15% NaOH (55 mL), and water (165 mL) were carefully added. The resulting white inorganic precipitate was filtered off and washed with EtOAc (1000 mL). The filtrate was evaporated in vacuo to give a crude oil, which was Kugelrohr distilled to give 66.3 g of product **4.53** (62%): ^{1}H NMR (CDCl$_3$): δ 4.02 (OCHCHO, 2 H, m), 3.60-3.90 (OCH$_2$, 4 H, m), 1.44 (C(CH$_3$)$_2$, 6 H, s).

4.5.7.3. 2,3-*O*-isopropylidene-L-threitol 1,4-di(methanesulfonate) (4.54)



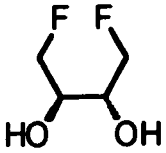
To a solution of **4.53** (66.0 g, 0.41 mol) in pyridine (300 mL) in a 1000-mL round-bottomed flask cooled in an ice-water bath, was added dropwise methanesulfonyl chloride (95.0 mL, 1.23 mol). After addition, the reaction was stirred at -10 °C for 20 h. Then the reaction was poured into ice-water (1200 mL). The resulting off-white precipitate was filtered and washed with water (2 x 1000 mL). The solid was dried *in vacuo* overnight. The crude product was crystallized from $CHCl_3$/ether to give 104.6 g of **4.54** (80%): ^{1}H NMR ($CDCl_3$): δ 4.30-4.45 (OCH_2, 4 H, m), 4.14-4.25 (OCHCHO, 2 H, m), 3.10 (OSO_2CH_3, 6 H, s), 1.45 ($C(CH_3)_2$, 6 H, s).

4.5.7.4. 2,3-*O*-isopropylidene-L-threitol-1,4-difluoride (4.55)



Tetrabutylammonium fluoride (440.0 mL of 1 M solution in THF, 0.44 mol), crushed 3 Å molecular sieves (80 g), and THF (300 mL) were placed in a 2000-mL round-bottomed flask. To the mixture, was added a solution of **4.54** (40.0 g, 0.125 mol) in THF (100 mL). The reaction mixture was stirred and heated to reflux for 48 h. After filtration, the filtrate was washed with water (400 mL), 1 M HCl (400 mL), and sat. $NaHCO_3$ (400 mL). The organic phase was dried over $MgSO_4$, concentrated *in vacuo* to give a crude oil. The oil was purified by Kugelrohr distillation to give 16.6 g of **4.55** as a colorless oil (80%): ^{1}H NMR ($CDCl_3$): δ 4.38-4.76 (FCH_2, 4 H, m), 4.05-4.30 (OCHCHO, 2 H, m), 1.45 ($C(CH_3)_2$, 6 H, s).

4.5.7.5. (*R*,*R*)-1,4-Difluorobutane-2,3-diol (4.50)



Compound **4.55** (3.2 g, 19.3 mmol) was treated with 1 M HCl (6.4 mL) in THF (6.4 mL) under reflux condition for 2 days. Then the reaction mixture was extracted with ether (3 x 20 mL). The organic phase was neutralized with sat. $NaHCO_3$ (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was recrystallized from chloroform to furnish the desired product **4.50** as needle-like crystals (2.0 g, 82%): ^1H NMR ($CDCl_3$): δ 4.36-4.76 (FCH_2, 4 H, m), 3.92-4.10 (OCHCHO, 2 H, m), 2.48 (OH, 2 H, br).

4.5.8. Enantiomeric Excess Determination of 1,4-Adducts

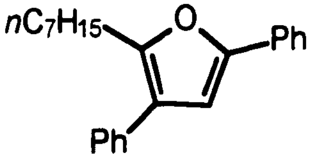
Enantiomeric excesses were determined by HPLC (Waters 600 Pump, Waters 486 Tunable Absorbance Detector, and Waters 600 Controller) with a Chiracel OD column (purchased from Chiral Technologies, Inc., Exton, PA) using a solvent system of 2-propanol in hexane (usually 0.1%-0.5% isopropanol in hexane). Isopropanol was pre-mixed in hexane to prevent fluctuations in solvent composition (experienced without pre-mixing). Flow rate was kept at 0.5 mL/min for all trials. Except for compound **4.31**, the enantiomers of the 1,4-products could be separated by the HPLC method. The racemic compound was run parallel to the asymmetric 1,4-addition product so that the two enantiomers could be identified according to their retention times. The enantiomeric excess was calculated by the area difference of the two enantiomeric peaks.

Compound **4.31** was converted to its epoxides first, and the resulted four epoxides could be separated by the above HPLC method. A basic two-phase epoxidation procedure for converting **4.31** to the epoxides was applied since the formed epoxides undergo very facile rearrangement to intramolecular ketals.[15] To a magnetically stirred mixture of **4.31** (10.0 mg, 0.0354 mmol) in CH_2Cl_2 (0.5 mL) and 0.5 M aqueous $NaHCO_3$ (0.4 mL), was added solid *m*-chloroperbenzoic acid (22.0 mg, 0.0708 mmol). The mixture was stirred at room temperature for 4 h and the two phases were separated. The organic phase was washed successively with 1 N aqueous NaOH (0.2 mL) and water (1 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give ca. 10 mg of crude product which was run through a short column (silica gel, CH_2Cl_2/hexane 1:1). The eluate containing product was concentrated to afford quite pure oil which was used as a HPLC sample directly.

Enantiomeric excesses of compounds **4.25** and **4.26** were also determined by ^{13}C NMR. They were converted to their diastereomeric ketals, then the ketals were analyzed by ^{13}C NMR spectra. The following is a general procedure for the conversion.

The 1,4-adduct (0.251 mmol) was treated with (*R*,*R*)-butane-2,3-diol (25.0 mg, 0.276 mmol) and a catalytic amount of *p*TsOH in benzene (5 mL). The reaction was heated to reflux with a Dean-Stark apparatus filled with 3 Å molecular sieves for 3 h while monitoring reaction progress by TLC analysis. At completion the reaction was quenched with $KHCO_3$ and diluted with ether (25 mL). The organic phase was washed with water (2 x 10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated to give a residue. The residue was purified by column chromatography (ether/hexane: 1/24) and analyzed by ^{13}C NMR. The ketals formed from compound **4.26** were also analyzed by gas chromatography.

4.5.9. Preparation of 2-heptyl-3,5-diphenylfuran (4.56)



Compound **4.25** (65.0 mg, 0.204 mmol) and *p*TsOH (5.0 mg) were mixed in benzene (4 mL) in a 10 mL round bottom flask. The mixture was stirred and heated to reflux for 3 h. The reaction mixture was neutralized with $NaHCO_3$ (10 mg), then washed with water (5 mL) and brine (5 mL), and dried with $MgSO_4$. Removal of solvent gave a yellow residue. Purification was done by column chromatography (EtOAc/hexane: 1/20) to afford 62.0 mg of furan **4.56** (95%): IR (neat): 3047, 2931, 2855, 1601, 1554, 1492, 1454, 1136 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.60-7.80 (ArH, 2 H, m), 7.06-7.55 (ArH, 8 H, m), 6.74 (furanH, 1 H, s), 2.81 (furan-CH_2, 2 H, t, J = 7.6

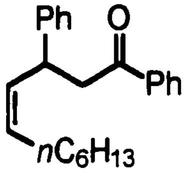
Hz), 1.75 (CH_2, 2 H, tt, J = 7.6, 6.8 Hz), 1.02-1.58 ($(CH_2)_4$, 8 H, m), 0.87 (CH_3, 3 H, t, J = 5.4 Hz); ^{13}C NMR ($CDCl_3$): δ 151.9, 151.5, 134.3, 131.0, 128.6, 127.7, 126.9, 126.5, 123.4, 122.9, 106.6, 31.8, 29.3, 29.0, 28.6, 27.0, 22.6, 14.1; MS *m/e* (relative intensity): 318 (5, M^+), 235 (25), 233 (20), 105 (37), 77 (18), 32 (32), 28 (71), 18 (100), 17 (21). Anal. Calcd for $C_{23}H_{26}O$: C, 86.75; H, 8.23. Found C, 86.58; H, 8.13.

4.5.10. Absolute Configuration of the Asymmetric 1,4-Adducts

The compounds **4.36** and **4.42** were designed to determine the absolute configuration of the asymmetric 1,4-addition products. After the preparation of **4.36** and **4.42** using the reagent (*R*)-**3.38k**, the crystals of **4.36** and **4.42** in good quality (one enantiomer) could be achieved by two crystallizations from CH_2Cl_2/hexane. X-ray crystallography was performed by Dr. Nicholas J. Taylor in the Department of Chemistry, the University of Waterloo, Ontario. The X-ray data are provided in the Appendix. It was indicated that the absolute configuration of the pure crystals was (*R*) for both **4.36** and **4.42**. With the assumption that the reaction should undergo the same mechanism, we shall extend the result to all other asymmetric 1,4-addition products, which were described in this paper.

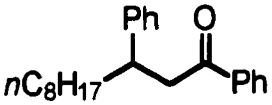
4.5.11. Hydrogenation of 1,4-Adduct

4.5.11.1. Preparation of (*Z*)-1,3-Diphenyl-4-Undecen-1-one (4.68)



To a 25-mL round-bottomed flask equipped with magnetic stirrer, was added racemic **4.25** (50.0 mg, 0.157 mmol), petroleum ether (10 mL, 60-80 °C) and Pd/$CaCO_3$/$Pd(OAc)_2$ (Lindlar catalyst)[14] (25.0 mg). The mixture was stirred under a hydrogen atmosphere at room temperature for 2 h. The reaction mixture was passed through a pad of Celite. The filtrate was evaporated *in vacuo* to give a crude residue. Purification was done by a pipette column (EtOAc/hexane: 1/20) to give 47.8 mg of racemic **4.68** (95%): IR (neat): 3039, 2930, 2856, 1686 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.80-7.92 (ArH, 2 H, m), 7.02-7.56 (ArH, 8 H, m), 5.20-5.62 (HC=CH, 2 H, m), 4.20-4.42 (ArCH, 1 H, m), 3.32, 3.21 (CH_AH_B, 2 H, dd, ABX, J_{AX} = 6.3; J_{BX} = 7.9; J_{AB} = 16.1 Hz), 1.88-2.15 (C=C-CH_2, 2 H, m), 0.85-1.38 ($(CH_2)_4$, 8 H, m), 0.78 (CH_3, 3 H, t, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$): δ 198.4, 144.6, 137.2, 132.9, 131.7, 130.9, 128.5, 128.1. 127.2, 126.2, 45.7, 39.2, 31.6, 29.4, 28.9, 27.5, 22.5, 14.0; MS *m/e* (relative intensity): 320 (0, M^+), 210 (18), 105 (100), 77 (42), 51 (13). Enantiomerically enriched **4.25** (86% ee) was also used to give enantiomerically enriched **4.68** (84% ee).

4.5.11.2. Preparation of 1,3-Diphenylundecan-1-one (4.69)



To a 25-mL round-bottomed flask equipped with magnetic stirrer was added racemic **4.25** (50.0 mg, 0.157 mmol), ethyl acetate (5 mL) and Pd/C (5%) (5.0 mg). The mixture was stirred under a hydrogen atmosphere at room temperature for 1 h. The reaction mixture was passed through a pad of Celite. The filtrate was evaporated *in vacuo* to give a crude residue. Purification was done by a pipette column (EtOAc/hexane: 1/20) to give 48.6 mg of racemic **4.69** (96%): IR (neat): 3041, 2932, 2854, 1683 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.76-7.88 (ArH, 2 H, m), 7.02-7.55 (ArH, 8 H, m), 3.10-3.35 ($COCH_2CHAr$, 3 H, m), 0.82-1.85 ($(CH_2)_7$, 14 H, m), 0.78 (CH_3, 3 H, t, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$): δ 199.2, 145.0, 137.3, 132.8, 128.5, 128.4, 128.0, 127.6, 126.2, 46.0, 41.3, 36.3, 31.8, 29.5, 29.4, 29.2, 27.5, 22.6, 14.0; MS *m/e* (relative intensity): 322 (1, M$^+$), 209 (50), 202 (41), 117 (19), 105 (100), 104 (55), 91 (38), 77 (51). Following the same procedure, use of enantiomerically enriched **4.25** (86% ee) gave **4.69** (84% ee).

Following the procedure, enantiomerically enriched **4.68** (19.3 mg, 0.060 mmol) in EtOAc (1 mL) catalyzed by Pd/C (2.0 mL) gave 18.2 mg of **4.69** (94%).

4.6. References

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CHAPTER 5. ENANTIOSELECTIVE ALKYNYLATION OF ALDEHYDES

5.1. Introduction

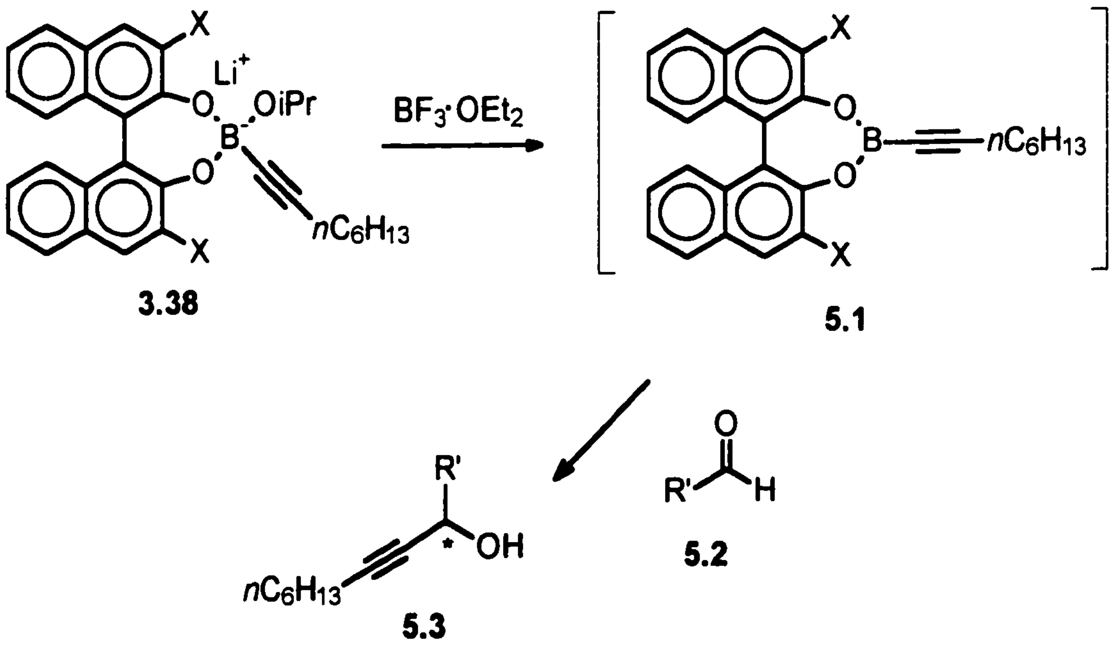
Asymmetric 1,2-additions onto aldehydes have been reviewed in Section 1.5 of this thesis.

Considerable progress has been made in the enantioselective addition of dialkyl- and alkenylzinc compounds to aldehydes using chiral amino alcohols as ligands (see Sections 1.5.1-1.5.3). However, in contrast to alkylation and alkenylation, there are few examples on the enantioselective alkynylation in the literature (Section 1.5.4). Among them, the one using chiral oxazaborolidines as promoters is quite successful (Table 1.3).[1] The nucleophilic alkynylation of aldehydes is an important synthetic method whose utility would be considerably enhanced if practical enantioselective versions were available. To make this alkynylation synthetically useful, more reliable methodologies on the enantioselective alkynylation of aldehydes will be required.

5.2. Proposal

With the encouragement of the successful asymmetric conjugate addition of alkynyl groups to enones with alkynyl binaphthyl boronates, it was felt that it might be possible to extend the chemistry to include asymmetric alkynylation of aldehydes using the same boronates (Scheme 5.1). Several boronates and aldehydes were selected to see if the boronates could add enantioselectively to prochiral aldehydes.

Scheme 5.1



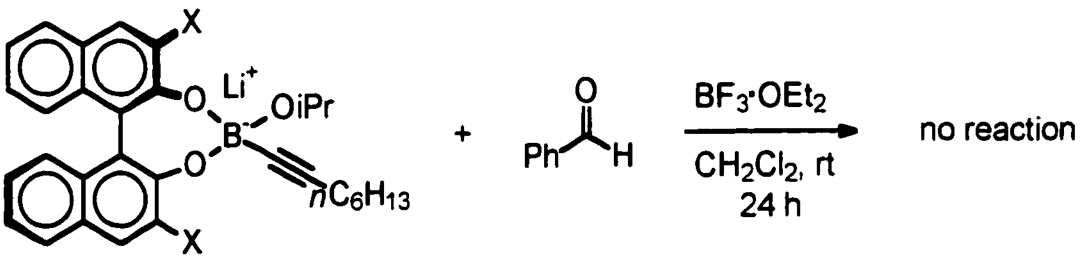
where X = Br, I, CN, CF_3, Aryl, etc.
R' = Alkyl, C_6H_5, etc.

5.3. Results and Discussion

5.3.1. Addition to Benzaldehyde and *trans*-Cinnamaldehyde

Attempts to alkynylate benzaldehyde failed. No product was observed from the reactions of alkynyl binaphthyl boronates **3.38a-3.38c**, **3.38i**, and **3.38k** with benzaldehyde (Scheme 5.2). In all attempts, benzaldehyde was isolated unchanged from the reaction mixture.

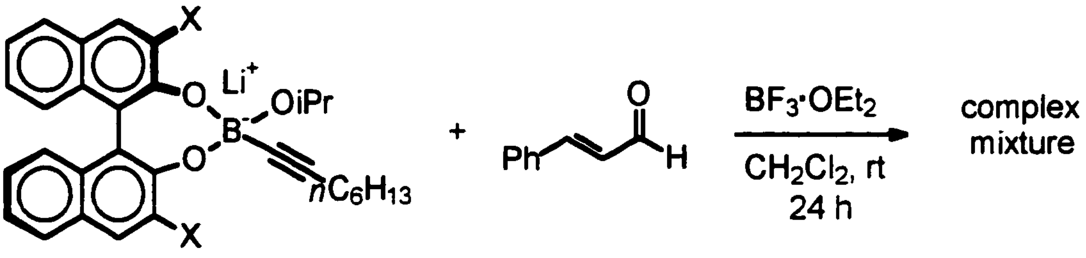
Scheme 5.2



X = Br, I, CF_3, 3,5-$(CF_3)_2C_6H_3$, C_6H_5
3.38a-3.38c, **3.38i**, and **3.38k**

However, the reaction of boronates **3.38a**, **3.38i**, and **3.38k** and *trans*-cinnamaldehyde resulted in a complex mixture (Scheme 5.3). This may be indicative of 1,2-addition along with some 1,4-addition and other products which imply that the reaction of the boronates with aldehydes is possible if suitable aldehydes are selected.

Scheme 5.3

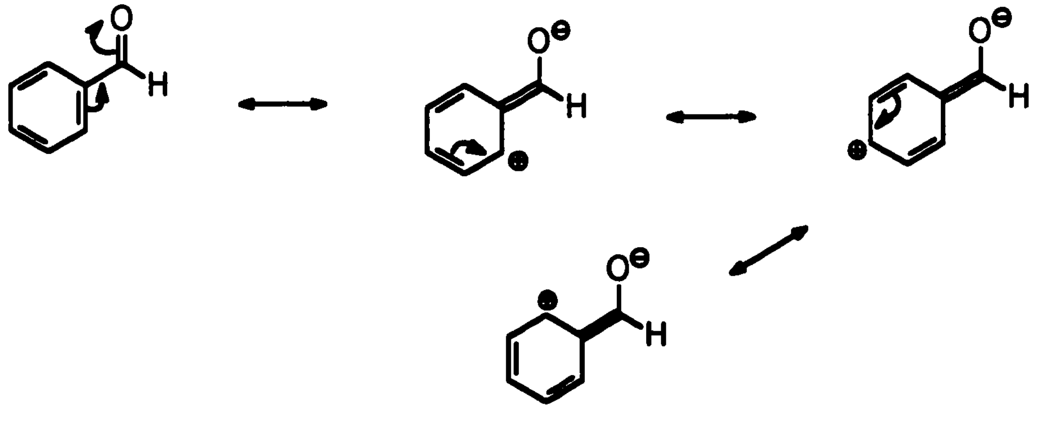


X = Br, C_6H_5, 3,5-$(CF_3)_2C_6H_3$

3.38a, **3.38i**, and **3.38k**

There are two possible factors for the lack of reaction with benzaldehyde. One is the relatively large size of the phenyl group, the other is resonance contributions from the phenyl group (Figure 5.1). The phenyl group might prevent the aldehyde from approaching the boron reagent. The resonance reduces the electrophilicity of the carbonyl carbon of the aldehyde.

Figure 5.1. Resonance structures of benzaldehyde.

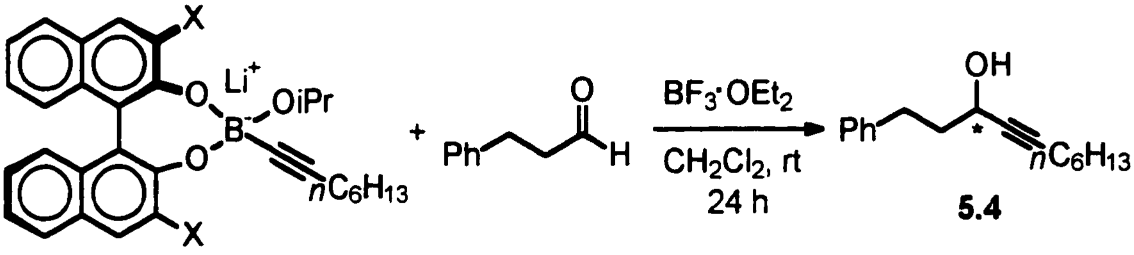


5.3.2. Alkynylation of Hydrocinnamaldehyde

In an attempt to observe 1,2-additions, we decided to use hydrocinnamaldehyde in alkynylations as the phenylethyl group on the carbonyl group would avoid the two problematic factors. The reaction of hydrocinnamaldehyde occurred as expected (Table 5.1). As predicted, the reaction of hydrocinnamaldehyde occurred and provided 1,2-addition product **5.4** although the yields and enantioselectivities were low. The best yield (53%) was obtained with the boronate bearing iodine on the 3,3'-positions of the binaphthyl moiety (entry 6) while the reaction with the boronate having 3,3'-diphenyl groups on the binaphthyl moiety gave the highest enantioselectivity (entry 1).

Changing the reaction solvent from CH_2Cl_2 to CH_3CN did not improve the yield or enantioselectivity (comparing entry 3 to entry 2). The reaction in CH_3CN provided the product in even lower yield and with poorer enantioselectivity. Quite interestingly, the reaction also formed a very large amount of an unexpected isopropyl ether **5.5** (84%). The ether was not examined for its chirality. The *in situ* decomposition of the boron ate complex forming the reactive boronate leaves one mole of 2-propanol which can then give rise to ether formation. The proposed mechanism for the formation of the ether **5.5** is outlined in Scheme 5.4. 2-Propanol reacted as a nucleophile attacking the intermediate **5.6** formed from 1,2-addition. The result was the formation of the ether **5.5** which might be a more stable species than the intermediate. However, without further study, other mechanisms could not be ruled out.

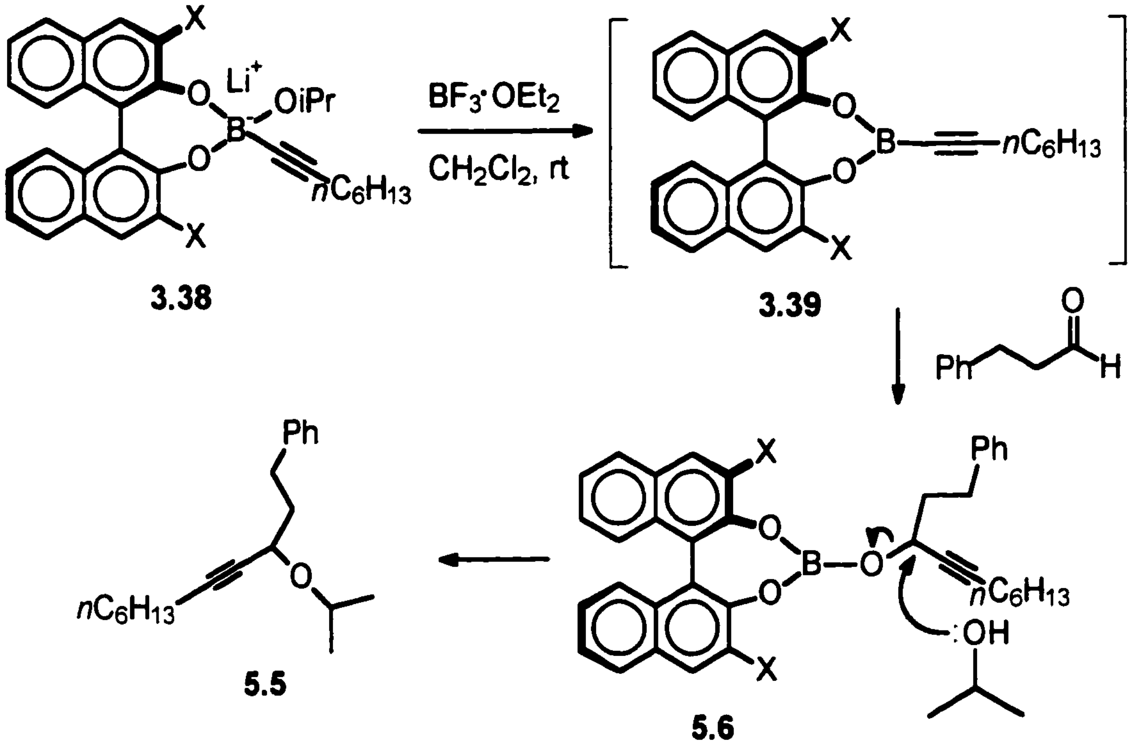
Table 5.1. Chiral alkynylation of hydrocinnamaldehyde



entry	X	yield/%	ee/%
1	Ph	26	40
2	CF_3	35	24
3*	CF_3	9	10
4	CN	44	10
5	Br	46	4
6	I	53	7
7	3,5-$(CF_3)_2$Ph	18	35

* CH_3CN was used as reaction solvent.

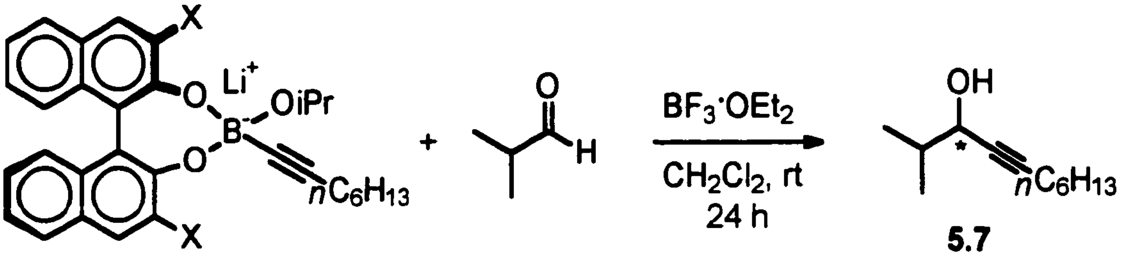
Scheme 5.4



5.3.3. Alkynylation of Isobutyraldehyde

To examine the effect of the substituent on the carbonyl group, isobutyraldehyde was employed as a substrate for alkynylation. The results were recorded in Table 5.2, which were similar to those for hydrocinnamaldehyde. The larger size of the isopropyl group did not increase the enantioselectivity.

Table 5.2. Alkynylation of isobutyraldehyde.



5.7

entry	X	yield/%	ee/%
1	Ph	20	45
2	CF_3	35	25
3*	CF_3	21	17
4	CN	38	15

*CH_3CN was used as reaction slovent.

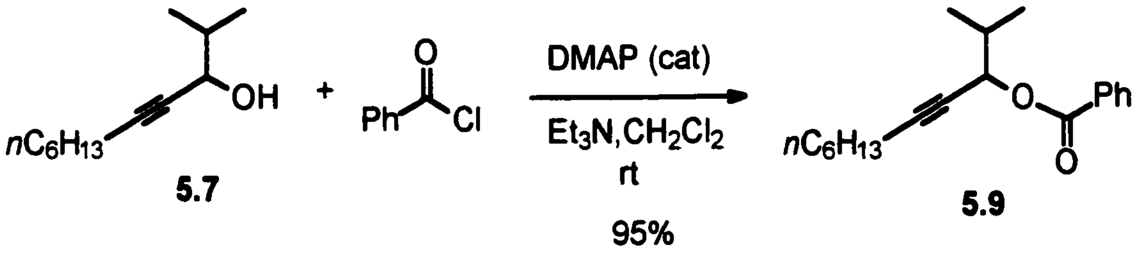
Changing the solvent to CH_3CN also did not improve the reaction yield or selectivity. The reaction in CH_3CN provided a large quantity of isopropyl ether **5.8** (83%) as well.

5.3.4. Determination of Enantiomeric Excess

Enantiomeric excess of the 1,2-addition products was determined by HPLC using a Chiracel OD column. The HPLC spectra of racemic compound **5.4** showed two bands at 9.1 and 13.1 min with equal area percentage when the HPLC was operated at a rate of 1 mL/min and with an eluent of 5% iPrOH in hexane. Products from asymmetric 1,2-addition of hydrocinnamaldehyde gave two bands at the two retention times. The band at 9.1 min was consistently larger than the other band. The order of elution for each pair of asymmetric 1,4-adducts was consistent, even from different reactions with a variety of chiral alkynyl boron reagents.

Compound **5.7** was not separable on the HPLC and showed very a weak band in the chromatogram due to its low absorbance in the UV region. The problem was easily solved by converting **5.7** into its benzoate ester **5.9** by the reaction of **5.7** and benzoyl chloride in CH_2Cl_2 catalyzed by DMAP (Scheme 5.5). The racemic ester was separable by HPLC and its chromatogram showed two bands at 12.9 and 17.4 min when the HPLC was operated at a rate of 0.5 mL/min and with an eluent of 0.1% iPrOH in hexane. The ester from asymmetric 1,2-addition showed two bands at the two retention times. The band at 17.4 min was consistently larger than the earlier band.

Scheme 5.5



5.4. Conclusion and Future Work

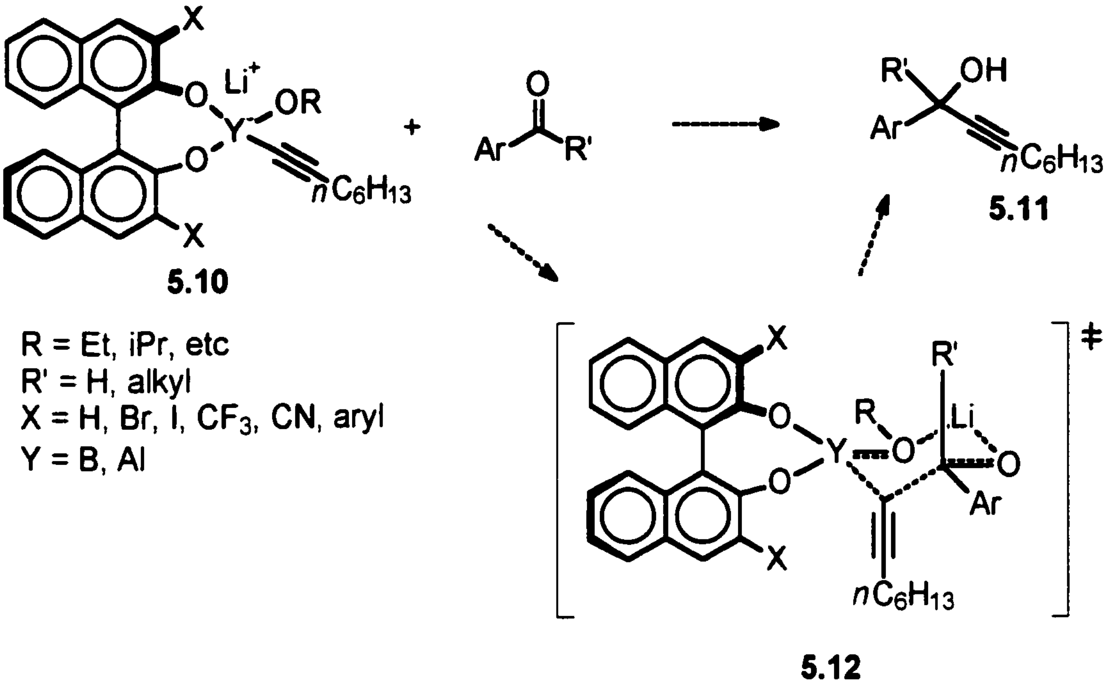
The asymmetric alkynylation of hydrocinnamaldehyde and isobutyraldehyde was successfully carried out using a series of boronates. However, the 1,2-adduct yields were low and enantioselectivities were poor. Nevertheless, these initial results will provide the basis for further improvement of the reaction.

Attempts to perform 1,2-addition on benzaldehyde using the boronates failed. The failure was probably due to the weak electrophilicity of benzaldehyde to the boronates.

Noyori *et al.* introduced the use of BINAL-H for the enantioselective reduction of alkyl aryl ketones; the corresponding secondary alcohols are obtained in ee of up to 100%.[2] Asymmetric alkynylation of arylaldehydes and alkyl aryl ketones might occur using lithium alkynyl-binaphthyl-isopropyl-boronates (**5.10**) (Scheme 5.6). Based on the proposed mechanism of the reduction using BINAL-H (see Figure 1.3), a six-membered ring transition state **5.12** might exist in the alkynylation, and the reaction should provide 1,2-addition product **5.11** in an enantioselective fashion. Both boron and aluminum reagents might be used to achieve such a goal.

Since the alkynylation described in this chapter occurred at a very slow rate, asymmetric alkynylation of aldehydes and ketones might be achieved by the catalysis with some chiral Lewis acids **5.13** (Figure 5.2). Some reports on the use of Lewis acids to achieve other asymmetric reactions have appeared in the literature (see Section 1.2.3).

Scheme 5.6



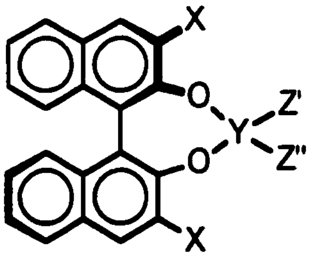
5.10

5.11

5.12

R = Et, iPr, etc
R' = H, alkyl
X = H, Br, I, CF$_3$, CN, aryl
Y = B, Al

Figure 5.2. Proposed Lewis acids.

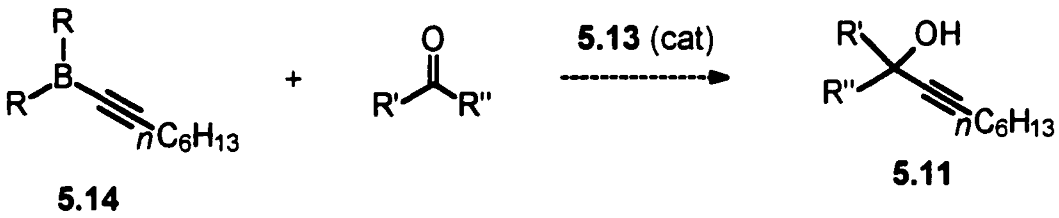


5.13

X = H, Br, I, CF$_3$, CN, aryl
Y = Sn, Ti with Z' and Z'' = Cl
Y = Al with Z' = Cl, but without Z''

In the presence of the chiral Lewis acids **5.13**, the alkynyl boron reagent **5.14** might react with aldehydes and ketones to give 1,2-adducts **5.11** in good yield with good enantioselectivity (Scheme 5.7).

Scheme 5.7



R = alkyl, alkoxy, etc
R', R'' = H, alkyl, aryl

5.5. Experimental

5.5.1. General

The general procedures previously described in Section 2.5.1 are applicable here.

5.5.2. Materials

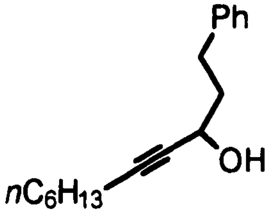
Solvents were dried prior to use. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were dried by distillation from sodium wire. Dichloromethane (CH_2Cl_2), acetonitrile (CH_3CN) and triethylamine were dried by distillation from calcium hydride. Boron trifluoride ethyl etherate ($BF_3{\bullet}OEt_2$) was treated with a small quantity of ethyl ether (to ensure an excess of this component, *ca.* 5 mL/100 mL $BF_3{\bullet}OEt_2$) and distilled (60-62 °C/aspirator vacuum).

All alkynyl boron reagents used in this Chapter are from Chapter 3 and each of them has the same numbering as that described in Chapter 3. Unless otherwise stated, the chemicals were purchased from Aldrich Chemical Company. All aldehydes were distilled before they were used in the alkynylation.

5.5.3. Preparation of Racemic 1,2-Addition Products

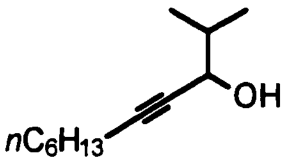
A general procedure was used. In a 50-mL round-bottomed flask equipped with argon inlet and magnetic stirrer, 1-octyne (1.34 mL, 9.1 mmol) and ether (20 mL) were added. The flask was cooled to -78 ^{0}C in a dry-ice acetone bath for 10 min, then *n*BuLi (6.1 mL of 1.49 M solution in hexane, 9.1 mmol) was added into the flask slowly *via* a syringe. The resulting mixture was stirred at -78 ^{0}C for 30 min. To the flask was added aldehyde (9.1 mmol) *via* a syringe. After the addition, the reaction was allowed to warm to room temperature and stirred for 30 min. Sat. NH_4Cl (5 mL) was added to the reaction, and stirred for 5 min. The organic phase was separated, washed with sat. aq. $NaHCO_3$ (5 mL) and brine (2 x 5 mL), and dried over Na_2SO_4. Removal of solvent gave a crude oil. Purification was carried out by column chromatography (EtOAc/hexane: 1/10).

5.5.3.1. 1-Phenyl-4-undecyn-3-ol (5.4)



Following the general procedure, hydrocinnamaldehyde (1.20 mL, 9.1 mmol) was used to afford 2.13 g of compound **5.4** (96%): IR (neat): 3378, 3022, 2933, 2859, 2228, 1603, 1496, 1455, 1036 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.10-7.72 (ArH, 5 H, m), 4.36 (OCH-C≡C, 1 H, tt, J = 1.9, 6.5 Hz), 2.79 ($ArCH_2$, 2 H, t, J = 7.9 Hz), 2.22 (CH_2-C≡C, 2 H, dt, J = 1.9, 6.9 Hz), 1.85-2.10 (CH_ACH_B, 2 H, AB, m), 1.68-1.82 (OH, 1 H, br), 1.02-1.62 ($(CH_2)_4$, 8 H, m), 0.89 (CH_3, 3 H, t, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 141.4, 128.3, 128.2, 125.6, 85.6, 81.0, 61.7, 39.5, 31.4, 31.2, 28.5, 28.4, 22.4, 18.5, 13.9; MS *m/e* (relative intensity): 244 (2, M^+), 159 (33), 156 (10), 155 (15), 141 (15), 129 (14), 105 (29), 104 (13), 95 (14), 93 (13), 92 (71), 91 (100), 83 (11), 81 (15), 79 (27), 78 (20), 77 (23), 70 (10), 69 (23), 67 (21), 65 (19), 57 (11), 55 (35), 53 (10), 51 (12). Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found C, 83.73; H, 10.01.

5.5.3.2. 2-Methyl-4-undecyn-3-ol (5.7)



Following the general procedure, isobutyraldehyde (0.82 mL, 9.1 mmol) was used to afford 1.65 g of compound **5.7** (99%): IR (neat): 3371, 2940, 2865, 2233, 1484, 1376, 1023 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.16 (OCH-C≡C, 1 H, td, J = 2.0, 5.5 Hz), 2.21 (CH_2-C≡C, 2 H, dt, J = 2.0, 6.8 Hz), 1.74-1.94 (CH, 1 H, m), 1.65-1.74 (OH, 1 H, br), 1.15-1.64 ($(CH_2)_4$, 8 H, m), 0.99 (CH_3, 3 H, d, J = 6.7 Hz), 0.97 (CH_3, 3 H, d, J = 6.7 Hz), 0.89 (CH_3, 3 H, t, J = 5.5 Hz); ^{13}C NMR ($CDCl_3$): δ 85.5, 79.8, 67.6, 34.4, 31.1, 28.5, 28.3, 22.3, 18.4, 17.9, 17.1, 13.7; MS *m/e* (relative intensity): 182 (0, M^+), 139 (58), 112 (20), 97 (39), 96 (12), 95 (95), 93 (41), 91 (12), 83 (38), 81 (34), 79 (53), 77 (17), 71 (14), 70 (24), 69 (70), 68 (26), 67 (49), 57 (64), 55 (100), 53 (19). Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found C, 78.97; H, 12.13.

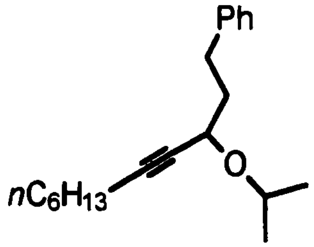
5.5.4. Enantioselective alkynylation of aldehydes

5.5.4.1. General procedure

The general procedure for the enantioselective alkynylation of aldehydes was as follows. Lithium binaphthyl isopropyl *B*-1-alkynylboronate (0.35 mmol) (**3.38a-**

3.38d, **3.38i**, and **3.38k**) and aldehyde (0.23 mmol) were placed in CH_2Cl_2 (15 mL) in a 25-mL round-bottomed flask under a nitrogen atmosphere. To the mixture, with stirring, was added $BF_3{\cdot}OEt_2$ (58 µl, 0.46 mmol). The reaction was stirred at room temperature for 24 h. Sat. aq. NH_4Cl (2 mL) and water (2 mL) were added to quench the reaction. The mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (5 mL x 2). The organic phase was washed with water (5 mL), dried over Na_2SO_4, and concentrated. Most of the binaphthol was collected by crystallization from CH_2Cl_2/hexane and the remaining residue from mother liquor was purified by column chromatography (EtOAc/hexane or CH_2Cl_2/hexane, the ratio depending on R_f's from TLC) to give the 1,4-addition product and the other portion of the binaphthol. The binaphthol was recovered in quantitative yield for all trials. The reaction yields for all cases are recorded in Table 5.1.

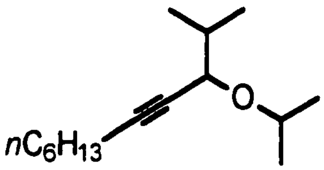
5.5.4.2. 3-Isopropoxy-1-phenyl-4-undecyne (5.5)



Following the general procedure, when acetonitrile was the reaction solvent instead of CH_2Cl_2, hydrocinnamaldehyde (30.5 µL, 0.23 mmol) was used to afford 56.0 mg of compound **5.5** (84%) and 5.0 mg of **5.4** (9%): ^{1}H NMR ($CDCl_3$): δ 7.10-

7.38 (ArH, 5 H, m), 4.06 (OCH-C≡C, 1 H, tt, J = 1.8, 6.5 Hz), 3.89 (OCH, 1 H, sept, J = 6.1 Hz), 2.77 (ArCH$_2$, 2 H, t, J = 8.0 Hz), 2.22 (CH$_2$-C≡C, 2 H, dt, J = 1.8, 6.8 Hz), 1.82-2.14 (CH$_A$CH$_B$, 2 H, AB, m), 1.18-1.64 ((CH$_2$)$_4$, 8 H, m), 1.22 (CH$_3$, 3 H, d, J = 6.2 Hz), 1.11 (CH$_3$, 3 H, d, J = 6.0 Hz), 0.89 (CH$_3$, 3 H, t, J = 6.7 Hz); ^{13}C NMR (CDCl$_3$): δ 141.9, 128.5, 128.3, 125.7, 85.6, 79.9, 69.4, 66.3, 38.1, 31.6, 31.3, 28.7, 28.5, 23.3, 22.5, 21.4, 18.7, 14.0; MS *m/e* (relative intensity): 286 (0, M$^+$), 216 (8), 174 (10), 159 (15), 156 (8), 155 (11), 141 (12), 139 (45), 129 (15), 105 (16), 96 (10), 95 (35), 93 (15), 92 (16), 91 (100), 81 (12), 79 (23), 77 (11), 69 (23), 67 (16), 65 (14), 57 (17), 55 (24).

5.4.4.3. 3-Isopropoxy-2-methyl-4-undecyne (5.8)



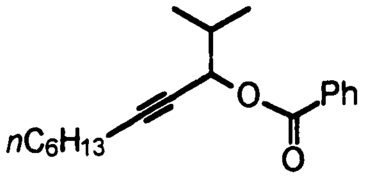
Following the general procedure, when acetonitrile was the reaction solvent instead of CH$_2$Cl$_2$, isobutyraldehyde (21.0 μL, 0.23 mmol) was used to afford 43.0 mg of compound **5.8** (83%) and 9.0 mg of **5.7** (21%): ^{1}H NMR (CDCl$_3$): δ 3.86 (OCH, 1 H, sept, J = 6.1 Hz), 3.82 (OCH-C≡C, 1 H, td, J = 2.0, 5.9 Hz), 2.21 (CH$_2$-C≡C, 2 H, dt, J = 2.0, 6.9 Hz), 1.70-1.92 (CH, 1 H, m), 1.18-1.65 ((CH$_2$)$_4$, 8 H, m), 1.20 (CH$_3$, 3 H, d, J = 6.2 Hz), 1.11 (CH$_3$, 3 H, d, J = 6.1 Hz), 0.98 (CH$_3$, 3 H, d, J = 6.6 Hz), 0.95 (CH$_3$, 3 H, d, J = 5.8 Hz), 0.89 (CH$_3$, 3 H, t, J = 6.8 Hz); ^{13}C NMR

(CDCl$_3$): δ 85.7, 78.9, 72.9, 69.5, 33.5, 31.3, 28.8, 28.5, 23.2, 22.6, 21.3, 18.7, 14.0; MS *m/e* (relative intensity): 224 (0, M$^+$), 181 (56), 140 (10), 139 (100), 109 (12), 97 (16), 95 (75), 93 (26), 83 (17), 81 (26), 79 (34), 77 (13), 69 (41), 68 (15), 67 (30), 57 (35), 55 (46).

5.5.5. Enantiomeric Excess Determination of 1,2-Adducts

Enantiomeric excesses were determined by HPLC (Waters 600 Pump, Waters 486 Tunable Absorbance Detector (λ = 254 nm), and Waters 600 Controller) with a Chiracel OD column (purchased from Chiral Technologies, Inc., Exton, PA) using a solvent system of 0.1-5% isopropanol in hexane. Isopropanol was pre-mixed in hexane to prevent fluctuations in solvent composition. Flow rate was kept at 0.5 mL/min for all trials. The enantiomers of compound **5.7** could not be separated by the HPLC method. The racemic compound was run parallel to the asymmetric 1,4-addition product, so that the two enantiomers could be identified according to their retention times. The enantiomeric excess then was calculated by the area difference of the peaks corresponding to the two enantiomers.

Compound **5.7** was converted to its benzoate ester **5.9** first, and the ester could easily be separated by the above HPLC method. A procedure for converting racemic **5.7** to the ester follows.



5.9

To a magnetically stirred mixture of racemic **5.7** (0.182 g, 1.0 mmol), triethylamine (0.153 mL, 1.1 mmol), and a catalytic amount of DMAP in CH_2Cl_2 (5 mL), was added benzoyl chloride (0.128 mL, 1.1 mmol) slowly. After the reaction was stirred at room temperature under a nitrogen atmosphere for 3 h, sat. $NaHCO_3$ (3 mL) was added to the reaction. The organic phase was separated, washed with water (3 mL), and dried over Na_2SO_4. Removal of solvent *in vacuo* gave a crude oil. Purification by column chromatography (EtOAc/hexane: 1/20) afforded 0.272 g of **5.9** as a colorless oil (95%): IR (neat): 3030, 2930, 2865, 2232, 1724, 1457, 1265, 1100 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.05-8.15 (ArH, 2 H, m), 7.36-7.64 (ArH, 3 H, m), 5.45 (OCH-C≡C, 1 H, td, J = 2.0, 5.5 Hz), 2.22 (CH_2-C≡C, 2 H, dt, J = 2.0, 6.8 Hz), 2.02-2.20 (CH, 1 H, m), 1.15-1.60 ($(CH_2)_4$, 8 H, m), 1.09 (CH_3, 3 H, d, J = 7.1 Hz), 1.07 (CH_3, 3 H, d, J = 7.0 Hz), 0.87 (CH_3, 3 H, t, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 165.5, 132.8, 130.3, 129.6, 128.2, 86.8, 76.2, 69.9, 32.8, 31.2, 28.4, 28.3, 22.4, 18.6, 18.2, 17.6, 13.9; MS *m/e* (relative intensity): 286 (1, M^+), 105 (100), 77 (19). Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found C, 79.83; H, 9.30.

5.6. References

1. Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 3151.

2. Noyori, R.; Tomino, I.; Tanimoto, Y. *J. Am. Chem. Soc.* **1979**, *101*, 3129. (b) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709.

APPENDIX X-RAY CRYSTALLOGRAPHIC DATA

I. X-Ray Crystallographic Data of (*R*)-1,3-Bis(4'-Bromophenyl)-4-Undecyn-1-one [(*R*)-4.36]

STRUCTURE DETERMINATION SUMMARY

Crystal Data

Empirical Formula	$C_{23}H_{24}Br_2O$
Color; Habit	Colourless needle prism fragment
Crystal Size (mm)	0.08{100}x0.25{001}x0.40{0$\bar{1}$0}x0.24($\bar{2}$10)
	Distances from common centre
Crystal System	Monoclinic
Space Group	$P2_1$
Unit Cell Dimensions	$\underline{a}$ = 11.644(2) Å
	$\underline{b}$ = 5.770(1) Å
	$\underline{c}$ = 15.757(3) Å
	β = 96.182(6)°
Volume	1052.6(4) $Å^3$
Z	2
Formula Weight	476.2
Density(calc.)	1.503 g/cm^3
Absorption Coefficient	38.59 cm^{-1}
F(000)	480

Data Collection

Diffractometer Used	Siemens P4
Radiation	$MoK\alpha$ (λ = 0.71073 Å)
Temperature (K)	190
Monochromator	Highly oriented graphite crystal
2θ Range	4.0 to 56.0°
Scan Type	ω
Scan Speed	Variable; 3.00 to 30.00°/min. in ω
Scan Range (ω)	1.20°
Background Measurement	Stationary crystal and stationary counter at beginning and end of scan, each for 25.0% of total scan time
Standard Reflections	3 measured every 100 reflections
Index Ranges	$0 \le h \le 15$, $0 \le k \le 7$ $-20 \le \ell \le 20$
Reflections Collected	2899
Independent Reflections	2770 (R_{int} = 1.13%)
Observed Reflections	2077 ($F > 4.0\sigma(F)$)
Absorption Correction	Face-indexed numerical
Min./Max. Transmission	0.1748 / 0.5593

Solution and Refinement

System Used	Siemens SHELXTL IRIS
Solution	Patterson and Fourier
Refinement Method	Full-Matrix Least-Squares
Quantity Minimized	$\sum w(F_o-F_c)^2$
Absolute Structure	*
Extinction Correction	$\chi = 0.00078(10)$, where $F^* = F\ [\ 1 + 0.002\chi F^2/\sin(2\theta)\ ]^{-1/4}$
Hydrogen Atoms	Riding model, refined isotropic U
Weighting Scheme	$w^{-1} = \sigma^2(F) + 0.0001F^2$
Number of Parameters Refined	270
Final R Indices (obs. data)	R = 2.79 %, wR = 2.67 %
(R Indices (all data)	R = 4.23 %, wR = 2.76 %)
Goodness-of-Fit	1.18
Largest and Mean Δ/σ	0.436, 0.027
Data-to-Parameter Ratio	7.7:1
Largest Difference Peak	0.36 eÅ^{-3}
Largest Difference Hole	-0.40 eÅ^{-3}

* The alternative enantiomorph gave R, wR and GoF values of 3.20, 3.14 and 1.38.

Table 1. Atomic coordinates ($x10^4$) and equivalent isotropic displacement coefficients ($Å^2x10^3$)

	x	y	z	U(eq)
C(1)	3135(3)	4834(7)	2378(2)	30(1)
C(2)	3147(3)	2975(7)	3052(2)	32(1)
C(3)	2935(3)	3971(7)	3928(2)	28(1)
C(4)	1733(3)	4790(6)	3925(2)	29(1)
C(5)	773(3)	5460(7)	3935(2)	34(1)
C(6)	-400(4)	6377(8)	3926(3)	50(1)
C(7)	-572(6)	8694(11)	3506(4)	53(1)
C(7a)	-896(9)	7503(14)	3065(7)	45(1)
C(8)	-197(4)	9012(9)	2657(3)	66(1)
C(9)	-484(5)	10976(9)	2110(3)	75(1)
C(10)	-11(7)	11278(11)	1304(4)	69(1)
C(10a)	182(9)	12401(14)	1607(7)	45(1)
C(11)	-299(5)	13671(9)	873(3)	78(1)
O(12)	3069(3)	6877(5)	2553(2)	46(1)
C(13)	3231(3)	4094(7)	1472(2)	29(1)
C(14)	2912(4)	5664(7)	824(2)	38(1)
C(15)	3033(4)	5118(7)	-23(2)	42(1)
C(16)	3470(3)	3017(7)	-204(2)	37(1)
C(17)	3799(4)	1414(7)	430(2)	42(1)
C(18)	3659(3)	1951(7)	1273(2)	34(1)
Br(19)	3654.5(4)	2217(1)	-1350.2(2)	60.8(2)
C(20)	3218(3)	2291(8)	4661(2)	25(1)
C(21)	3977(3)	2912(7)	5376(2)	33(1)
C(22)	4128(3)	1482(7)	6088(2)	30(1)
C(23)	3552(3)	-591(7)	6073(2)	28(1)
C(24)	2837(3)	-1312(7)	5363(2)	30(1)
C(25)	2679(3)	124(7)	4662(2)	30(1)
Br(26)	3662.4(4)	-2500	7071.1(2)	39.4(1)

Occupancy for C(7) and C(10) 2/3; for C(7a) and C(10a) 1/3.

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 2. Bond lengths (Å)

Br(19)-C(16)	1.899(3)	Br(26)-C(23)	1.913(4)
O(12)-C(1)	1.215(5)	C(1)-C(2)	1.509(5)
C(1)-C(13)	1.505(5)	C(2)-C(3)	1.541(5)
C(3)-C(4)	1.476(6)	C(3)-C(20)	1.517(5)
C(4)-C(5)	1.186(6)	C(5)-C(6)	1.463(6)
C(6)-C(7)	1.495(8)	C(6)-C(7a)	1.558(10)
C(7)-C(8)	1.464(8)	C(7a)-C(8)	1.396(11)
C(8)-C(9)	1.441(7)	C(9)-C(10)	1.447(9)
C(9)-C(10a)	1.428(11)	C(10)-C(11)	1.559(8)
C(10a)-C(11)	1.431(11)	C(13)-C(14)	1.386(5)
C(13)-C(18)	1.382(5)	C(14)-C(15)	1.392(5)
C(15)-C(16)	1.357(6)	C(16)-C(17)	1.384(5)
C(17)-C(18)	1.391(5)	C(20)-C(21)	1.401(4)
C(20)-C(25)	1.399(6)	C(21)-C(22)	1.389(5)
C(22)-C(23)	1.370(5)	C(23)-C(24)	1.385(5)
C(24)-C(25)	1.377(5)		

Table 3. Bond angles (°)

O(12)-C(1)-C(2)	121.7(3)	O(12)-C(1)-C(13)	120.2(3)
C(2)-C(1)-C(13)	118.0(3)	C(1)-C(2)-C(3)	112.1(3)
C(2)-C(3)-C(4)	111.1(3)	C(2)-C(3)-C(20)	113.7(3)
C(4)-C(3)-C(20)	109.6(3)	C(3)-C(4)-C(5)	179.0(4)
C(4)-C(5)-C(6)	177.5(4)	C(5)-C(6)-C(7)	114.1(4)
C(5)-C(6)-C(7a)	114.7(5)	C(6)-C(7)-C(8)	118.5(5)
C(6)-C(7a)-C(8)	118.8(7)	C(7)-C(8)-C(9)	124.9(5)
C(7a)-C(8)-C(9)	131.1(6)	C(8)-C(9)-C(10)	122.2(5)
C(8)-C(9)-C(10a)	132.9(6)	C(9)-C(10)-C(11)	113.9(5)
C(9)-C(10a)-C(11)	123.7(8)	C(1)-C(13)-C(14)	118.2(3)
C(1)-C(13)-C(18)	122.3(3)	C(14)-C(13)-C(18)	119.5(3)
C(13)-C(14)-C(15)	120.8(4)	C(14)-C(15)-C(16)	118.9(4)
Br(19)-C(16)-C(15)	120.0(3)	Br(19)-C(16)-C(17)	118.2(3)
C(15)-C(16)-C(17)	121.8(3)	C(16)-C(17)-C(18)	119.2(4)
C(13)-C(18)-C(17)	120.0(3)	C(3)-C(20)-C(21)	121.0(4)
C(3)-C(20)-C(25)	120.8(3)	C(21)-C(20)-C(25)	118.2(3)
C(20)-C(21)-C(22)	120.7(4)	C(21)-C(22)-C(23)	119.1(3)
Br(26)-C(23)-C(22)	119.9(3)	Br(26)-C(23)-C(24)	118.2(3)
C(22)-C(23)-C(24)	121.8(3)	C(23)-C(24)-C(25)	118.9(4)
C(20)-C(25)-C(24)	121.1(3)		

Table 4. Anisotropic displacement coefficients ($Å^2 x10^3$)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	26(1)	32(1)	31(1)	2(1)	4(1)	2(1)
C(2)	33(1)	33(1)	29(1)	3(1)	7(1)	-3(1)
C(3)	27(1)	24(1)	33(1)	0(1)	2(1)	-6(1)
C(4)	30(1)	28(1)	29(1)	0(1)	3(1)	-2(1)
C(5)	32(1)	37(1)	33(1)	-1(1)	3(1)	1(1)
C(6)	32(1)	67(1)	52(1)	11(1)	12(1)	0(1)
C(7)	32(1)	67(1)	60(1)	20(1)	7(1)	-4(1)
C(7a)	42(1)	41(1)	52(1)	5(2)	1(1)	14(1)
C(8)	53(1)	81(1)	65(1)	26(1)	9(1)	13(1)
C(9)	71(1)	74(1)	84(1)	27(1)	26(1)	33(1)
C(10)	64(1)	71(1)	69(1)	7(1)	-3(1)	-4(1)
C(10a)	38(1)	42(1)	53(1)	-4(2)	1(1)	-5(1)
C(11)	97(1)	66(1)	69(1)	-21(1)	7(1)	6(1)
O(12)	68(1)	34(1)	36(1)	-2(1)	10(1)	-4(1)
C(13)	26(1)	27(1)	33(1)	-1(1)	6(1)	1(1)
C(14)	44(1)	33(1)	36(1)	4(1)	6(1)	-2(1)
C(15)	48(1)	42(1)	35(1)	-1(1)	3(1)	6(1)
C(16)	39(1)	43(1)	30(1)	-9(1)	5(1)	-8(1)
C(17)	49(1)	37(1)	40(1)	-3(1)	9(1)	-10(1)
C(18)	36(1)	34(1)	34(1)	-2(1)	6(1)	-2(1)
Br(19)	74.5(3)	77.0(4)	31.8(2)	-2.5(4)	10.3(2)	-15.3(3)
C(20)	22(1)	26(1)	28(1)	3(1)	5(1)	-6(1)
C(21)	27(1)	35(1)	36(1)	0(1)	4(1)	-6(1)
C(22)	27(1)	34(1)	29(1)	6(1)	-1(1)	-6(1)
C(23)	27(1)	33(1)	25(1)	8(1)	6(1)	0(1)
C(24)	29(1)	30(1)	31(1)	1(1)	4(1)	-2(1)
C(25)	29(1)	34(1)	27(1)	-2(1)	-1(1)	-4(1)
Br(26)	44.9(2)	47.0(2)	26.5(2)	2.4(3)	4.5(2)	1.8(3)

The anisotropic displacement factor exponent takes the form:

$-2\pi^2(h^2a*^2U_{11} + ... + 2klb*c*U_{23})$

Table 5. H-Atom coordinates ($x10^4$) and isotropic displacement coefficients ($Å^2x10^3$)

	x	y	z	U
H(2x)	3877	2185	3095	54(2)
H(2y)	2549	1870	2884	46(2)
H(3)	3446	5269	4034	33(2)
H(6u)*	-584	6467	4504	60(2)
H(6v)*	-931	5303	3630	60(2)
H(6x)**	-416	7415	4401	60(2)
H(6y)**	-925	5132	4002	60(2)
H(7u)*	-200	9849	3879	69(2)
H(7v)*	-1386	9013	3443	69(2)
H(7x)**	-1500	8524	3203	69(2)
H(7y)**	-1253	6372	2675	69(2)
H(8u)*	-470	7685	2327	80(2)
H(8v)*	630	8906	2743	80(2)
H(8x)**	121	7941	2279	80(2)
H(8y)**	432	9468	3067	80(2)
H(9u)*	-252	12308	2452	83(2)
H(9v)*	-1310	11032	1994	83(2)
H(9x)**	-722	12091	2508	83(2)
H(9y)**	-1172	10558	1752	83(2)
H(10u)*	-292	10043	930	63(2)
H(10v)*	814	11154	1401	63(2)
H(10x)**	707	11327	1388	63(2)
H(10y)**	645	13460	1968	63(2)
H(11u)*	30	13785	342	82(2)
H(11v)*	-1125	13785	769	82(2)
H(11w)*	-9	14906	1244	82(2)
H(11x)**	299	14405	596	82(2)
H(11y)**	-737	12660	477	82(2)
H(11z)**	-800	14832	1068	82(2)
H(14)	2590	7129	965	50(2)
H(15)	2824	6213	-471	62(2)
H(17)	4121	-47	285	46(2)
H(18)	3848	850	1722	52(2)
H(21)	4396	4342	5361	58(2)
H(22)	4622	1934	6588	45(2)
H(24)	2454	-2785	5369	38(2)
H(25)	2203	-366	4159	53(2)

Occupancy * : ** = 2/3 : 1/3

II. X-Ray Crystallographic Data of (*R*)-1,3-Bis(4'-Bromophenyl)-5-Phenyl-4-Pentyn-1-one [(*R*)-4.42]

STRUCTURE DETERMINATION SUMMARY

Crystal Data

Empirical Formula	$C_{23}H_{16}Br_{2}O$
Color; Habit	Colourless needle plate fragment
Crystal Size (mm)	$0.13\{001\}\mathrm{x}0.18\{10\bar{2}\}\mathrm{x}0.70\{120\}\{\bar{1}\bar{2}0\}$
Crystal System	Monoclinic
Space Group	$P2_{1}$
Unit Cell Dimensions	a = 7.9517(6) Å
	b = 5.8731(5) Å
	c = 20.681(2) Å
	β = 99.651(4)°
Volume	952.2(2) $Å^{3}$
Z	2
Formula Weight	468.2
Density(calc.)	1.633 g/cm^{3}
Absorption Coefficient	42.65 cm^{-1}
F(000)	464

Data Collection

Diffractometer Used	Siemens P4
Radiation	MoKα (λ = 0.71073 Å)
Temperature (K)	200
Monochromator	Highly oriented graphite crystal
2θ Range	4.0 to 52.0°
Scan Type	ω
Scan Speed	Variable; 3.00 to 30.00°/min. in ω
Scan Range (ω)	1.20°
Background Measurement	Stationary crystal and stationary counter at beginning and end of scan, each for 25.0% of total scan time
Standard Reflections	3 measured every 100 reflections
Index Ranges	$0 \le h \le 9$, $-7 \le k \le 7$ $-25 \le \ell \le 25$
Reflections Collected	4013
Independent Reflections	3734 (R_{int} = 1.36%)
Observed Reflections	3121 ($F > 6.0\sigma(F)$)
Absorption Correction	Face-indexed numerical
Min./Max. Transmission	0.3849 / 0.6300

Solution and Refinement

System Used	Siemens SHELXTL IRIS
Solution	Patterson and Fourier
Refinement Method	Full-Matrix Least-Squares
Quantity Minimized	$\sum w(F_o - F_c)^2$
Absolute Structure	*
Extinction Correction	χ = 0.00032(4), where $F^* = F\ [\ 1 + 0.002\chi F^2/\sin(2\theta)\ ]^{-1/4}$
Hydrogen Atoms	Riding model, refined isotropic U
Weighting Scheme	$w^{-1} = \sigma^2(F)$
Number of Parameters Refined	251
Final R Indices (obs. data)	R = 2.43 %, wR = 2.15 %
(R Indices (all data)	R = 3.05 %, wR = 2.18 %)
Goodness-of-Fit	1.43
Largest and Mean Δ/σ	0.002, 0.000
Data-to-Parameter Ratio	12.4:1
Largest Difference Peak	0.71 eÅ^{-3}
Largest Difference Hole	-0.67 eÅ^{-3}

* Refinement of the other enantiomorph gave R, wR and GoF values of 4.98, 5.07 and 3.38

Table 1. Atomic coordinates ($x10^4$) and equivalent isotropic displacement coefficients ($Å^2x10^3$)

	x	y	z	U(eq)
C(1)	3287(4)	8056(6)	6367(2)	25(1)
C(2)	2830(3)	7231(7)	7014(1)	25(1)
C(3)	4278(4)	7767(6)	7584(1)	22(1)
C(4)	3705(3)	7555(6)	8227(1)	24(1)
C(5)	3327(3)	7410(6)	8757(1)	25(1)
O(6)	3997(3)	9877(4)	6349(1)	37(1)
C(7)	2826(4)	6669(5)	5757(2)	23(1)
C(8)	3281(4)	7522(7)	5179(1)	27(1)
C(9)	2954(4)	6319(6)	4599(2)	29(1)
C(10)	2169(4)	4232(6)	4599(2)	25(1)
C(11)	1671(4)	3336(5)	5158(2)	26(1)
C(12)	2016(4)	4567(6)	5735(2)	26(1)
Br(13)	1798.9(5)	2500	3813.2(2)	37.8(1)
C(14)	5881(4)	6349(5)	7587(2)	20(1)
C(15)	7420(3)	7166(6)	7933(1)	25(1)
C(16)	8903(4)	5922(5)	7977(2)	25(1)
C(17)	8859(4)	3850(5)	7679(2)	25(1)
C(18)	7366(4)	2984(6)	7327(2)	28(1)
C(19)	5882(4)	4256(6)	7281(2)	24(1)
Br(20)	10861.7(4)	2014.1(9)	7793.5(2)	43.9(1)
C(21)	2889(4)	7291(7)	9411(1)	25(1)
C(22)	2027(5)	5409(6)	9598(2)	32(1)
C(23)	1634(5)	5299(7)	10226(2)	40(1)
C(24)	2129(4)	7052(8)	10666(2)	40(1)
C(25)	2986(5)	8911(7)	10477(2)	42(2)
C(26)	3363(4)	9041(6)	9851(2)	32(1)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 2. Bond lengths (Å)

C(1)-C(2)	1.525(4)	C(1)-O(6)	1.213(4)
C(1)-C(7)	1.495(4)	C(2)-C(3)	1.535(4)
C(3)-C(4)	1.482(4)	C(3)-C(14)	1.522(4)
C(4)-C(5)	1.187(4)	C(5)-C(21)	1.453(4)
C(7)-C(8)	1.397(4)	C(7)-C(12)	1.390(5)
C(8)-C(9)	1.379(5)	C(9)-C(10)	1.375(5)
C(10)-C(11)	1.387(5)	C(10)-Br(13)	1.898(3)
C(11)-C(12)	1.383(4)	C(14)-C(15)	1.396(4)
C(14)-C(19)	1.383(4)	C(15)-C(16)	1.377(4)
C(16)-C(17)	1.362(5)	C(17)-C(18)	1.382(4)
C(17)-Br(20)	1.905(3)	C(18)-C(19)	1.386(5)
C(21)-C(22)	1.390(5)	C(21)-C(26)	1.384(5)
C(22)-C(23)	1.388(6)	C(23)-C(24)	1.386(5)
C(24)-C(25)	1.377(6)	C(25)-C(26)	1.379(5)

Table 3. Bond angles (°)

C(2)-C(1)-O(6)	119.2(3)	C(2)-C(1)-C(7)	120.5(3)
O(6)-C(1)-C(7)	120.3(3)	C(1)-C(2)-C(3)	110.5(3)
C(2)-C(3)-C(4)	111.5(2)	C(2)-C(3)-C(14)	114.3(3)
C(4)-C(3)-C(14)	109.5(2)	C(3)-C(4)-C(5)	176.7(3)
C(4)-C(5)-C(21)	178.4(4)	C(1)-C(7)-C(8)	117.6(3)
C(1)-C(7)-C(12)	123.9(3)	C(8)-C(7)-C(12)	118.5(3)
C(7)-C(8)-C(9)	121.4(3)	C(8)-C(9)-C(10)	118.4(3)
C(9)-C(10)-C(11)	122.1(3)	C(9)-C(10)-Br(13)	118.9(3)
C(11)-C(10)-Br(13)	119.0(2)	C(10)-C(11)-C(12)	118.6(3)
C(7)-C(12)-C(11)	121.0(3)	C(3)-C(14)-C(15)	118.4(3)
C(3)-C(14)-C(19)	123.4(3)	C(15)-C(14)-C(19)	118.2(3)
C(14)-C(15)-C(16)	121.3(3)	C(15)-C(16)-C(17)	119.2(3)
C(16)-C(17)-C(18)	121.5(3)	C(16)-C(17)-Br(20)	119.5(2)
C(18)-C(17)-Br(20)	118.9(2)	C(17)-C(18)-C(19)	119.0(3)
C(14)-C(19)-C(18)	120.9(3)	C(5)-C(21)-C(22)	120.3(3)
C(5)-C(21)-C(26)	119.7(3)	C(22)-C(21)-C(26)	120.0(3)
C(21)-C(22)-C(23)	119.8(3)	C(22)-C(23)-C(24)	119.7(4)
C(23)-C(24)-C(25)	120.2(3)	C(24)-C(25)-C(26)	120.3(3)
C(21)-C(26)-C(25)	120.0(3)		

Table 4. Anisotropic displacement coefficients ($Å^2$x10^3)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	26(2)	29(2)	18(2)	7(2)	-1(2)	2(1)
C(2)	24(2)	33(2)	17(2)	3(2)	0(1)	-3(2)
C(3)	26(2)	26(2)	15(2)	2(2)	1(1)	-4(2)
C(4)	19(2)	29(2)	24(2)	4(2)	0(1)	-4(2)
C(5)	17(1)	28(2)	28(2)	3(2)	1(1)	-4(2)
O(6)	60(2)	24(1)	24(1)	-9(1)	2(1)	-1(1)
C(7)	21(2)	25(2)	22(2)	8(1)	0(1)	1(1)
C(8)	28(2)	27(2)	24(2)	-1(2)	4(1)	-1(2)
C(9)	33(2)	34(2)	20(2)	-2(2)	8(2)	1(2)
C(10)	25(2)	34(2)	15(2)	3(2)	2(2)	-9(2)
C(11)	29(2)	22(2)	27(2)	-3(1)	5(2)	-3(1)
C(12)	34(2)	28(2)	16(2)	4(2)	4(2)	2(2)
Br(13)	44.4(2)	46.7(3)	23.4(2)	-8.8(2)	9.0(1)	-13.1(2)
C(14)	28(2)	23(2)	12(2)	2(1)	7(1)	5(1)
C(15)	28(2)	23(2)	22(2)	0(2)	2(1)	-3(2)
C(16)	23(2)	24(2)	27(2)	-4(2)	0(2)	1(2)
C(17)	25(2)	27(2)	27(2)	5(2)	10(2)	6(2)
C(18)	41(2)	22(2)	22(2)	2(2)	11(2)	0(1)
C(19)	25(2)	26(2)	22(2)	0(2)	3(2)	-1(2)
Br(20)	30.8(2)	35.8(2)	66.8(3)	11.0(2)	9.9(2)	-1.8(2)
C(21)	22(2)	35(2)	18(1)	8(2)	5(1)	-1(2)
C(22)	36(2)	31(2)	27(2)	1(2)	4(2)	-5(2)
C(23)	50(3)	37(2)	38(3)	-3(2)	16(2)	6(2)
C(24)	51(2)	54(3)	17(2)	14(3)	12(2)	5(2)
C(25)	57(3)	47(3)	21(2)	1(2)	5(2)	-11(2)
C(26)	37(2)	32(2)	27(2)	-4(2)	6(2)	-6(2)

The anisotropic displacement factor exponent takes the form:
$-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2klb^*c^*U_{23})$

Table 5. H-Atom coordinates ($x10^4$) and isotropic displacement coefficients ($Å^2x10^3$)

	x	y	z	U
H(2x)	2576	5632	7003	9(8)
H(2y)	1828	8041	7086	30(10)
H(3)	4594	9331	7542	32(10)
H(8)	3847	8969	5190	37(10)
H(9)	3244	6925	4201	26(8)
H(11)	1072	1913	5142	18(8)
H(12)	1701	3960	6129	40(11)
H(15)	7443	8612	8151	13(8)
H(16)	9966	6510	8204	50(12)
H(18)	7373	1533	7113	12(9)
H(19)	4829	3684	7040	47(12)
H(22)	1724	4174	9297	34(10)
H(23)	1013	4019	10353	31(10)
H(24)	1876	6964	11103	48(10)
H(25)	3326	10127	10781	34(10)
H(26)	3959	10338	9720	22(9)