Asymmetric Organic Synthesis Using Organoboron Compounds

by

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M.S. Chemistry, Seoul National University (1982)
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Submitted to the Department of
Chemistry

In Partial Fulfillment of the Requirements
for the Degree of

Doctor of Philosophy in
Organic Chemistry

at the

Massachusetts Institute of Technology

February, 1988

Signature of Author _____
Department of Chemistry, November 30, 1987

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Satoru Masamune, Thesis Adviser

Accepted by _____
Glenn A. Berchtold, Chairman,
Departmental Committee on Graduate Students

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Abstract

(*R,R*)- And (*S,S*)-2,5-dimethylborolanes {(*R,R*)-**1-1** and (*S,S*)-**1-1**} have been synthesized and applied to asymmetric synthesis of several fundamental organic reactions. An efficient separation of *trans*- from *cis*-*B*-methoxyborolane and resolution of the corresponding racemic *B*-methoxyborolane (*trans*-(±)-**2-51**) are central to the synthesis.

Asymmetric hydroboration using homochiral 3,4-diethyl- or 3,4-dicyclohexyl-borolane (**2-8** or **2-9**, respectively) with type II-IV olefins exhibits marginal degree of enantioselectivities. However, 2,5-dimethylborolanes are shown to be highly enantioselective hydroborating reagents (>98% ee). A mechanistic study on the hydroboration of **1-1** is carried out utilizing ^{11}B NMR for the first time to quantify the boron species in kinetic measurements. Three-halves order kinetics is observed for the hydroboration of **1-1** with *cis*-3-hexene; 1st order in the olefin and a half order in the borolane dimer. The kinetic data coupled with study of the hydroboration of different types of alkenes with the conformationally fixed borolanes provides valuable information about the transition state of this reaction.

It is found that the enolate prepared from *S*-3-(3-ethyl)pentyl propanethioate employing (*S,S*)-2,5-dimethylborolanyl trifluoromethanesulfonate {(*S,S*)-**3-21**} as an external chiral reagent in the presence of diisopropylethylamine undergoes aldol reaction with various aldehydes to provide *anti*-2-methyl-3-hydroxycarbonyl compounds with high diastereoselection (anti/syn >30:1) and enantioselection (>97% ee for the anti- isomer). Likewise the corresponding boron enolate derived from *S*-3-(3-ethyl)pentyl ethanethioate provides upon reaction with aldehydes 3-hydroxycarbonyl compounds with an asymmetric induction of 90-98% ee. This methodology using external boron reagents is applied to the aldol reactions of methyl ketones aiming to develop methods to couple large synthetic fragments in a stereoselective manner. Moderate to good enantioselections are observed with various homochirai boron reagents including *B*-chloroboranes, a practical alternative to the boron triflate. Rationales for the high diastereo- and enantioselectivities encountered in these reactions are given on the basis of 6-membered, cyclic transition states.

B-Allyl- and *B*-(*Z*)- and (*E*)-crotyl-2,5-dimethylborolanes (**4-1**, **4-2**, and **4-3**, respectively) are prepared from the corresponding *B*-methoxyborolane (**2-51**) with allylmagnesium bromide and (*Z*)- and (*E*)-crotylpotassium, respectively. Reactions of (*S,S*)-**4-1** with representative achiral aldehydes proceed at -78°C to provide homoallylic alcohols of 85-93% ee. In a similar manner (*R,R*)-**4-2** and (*R,R*)-**4-3**, upon reaction with achiral aldehydes, lead to the predominant formation of the *syn*- and *anti*-2-methyl-1-hydroxyl products, respectively, with an average selectivity of 20:1 and the ee's of the major product ranging between 86-97% for the **4-2** series and between 95-97% for that of **4-3**. A set of double asymmetric reactions with a chiral aldehyde (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**4-38**) are carried out to provide highly diastereo- and enantioselective syn- and anti- homoallylic units, respectively, conforming to the rule that has been established for double asymmetric synthesis. A rationale for the high selectivities observed with reagents **4-1**, **4-2**, and **4-3** is given based on steric interactions in the corresponding transition states.

Thesis Supervisor: Professor Satoru Masamune
Title: Professor of Chemistry

Acknowledgements

First of all I would like to express the deepest gratitude to my adviser, Professor Satoru Masamune, for his guidance and enthusiasm throughout this study. He shared with me his unique and inspired perspective of organic chemistry and I feel truly privileged to have had the opportunity to work with a scientist of such perception.

I also would like to extend my thanks to Professor Eun Lee for helping me get started in organic chemistry at Seoul National University. I feel thankful to Professors K. Barry Sharpless, Rick Danheiser, Glenn Berchtold, Fred Greene, and William Roush (now at Indiana University), all of whom greatly aided my development at MIT. I wish to acknowledge the financial supports from the Department of Chemistry in the form of Teaching (1983-1984) and Research Assistantships (1984-1987).

Thanks are due to all my colleagues in the Masamune research group. Special thanks to Robert Kennedy, David Writenour, and John Roberts who took pains to read this manuscript and provide numerous corrections and helpful discussions. I also would like to make grateful acknowledgements to the following people for their contribution to the work presented in this thesis: Toshiro Imai for the first separation and resolution of 2,5-dimethylborolanes and the preparation of 2,5-diethylborolane aminoalcohol complex; John Petersen for developing methods to efficiently separate and resolve 2,5-dimethylmethoxyborolanes and performing all kinetic works; Tsuneo Sato for the contribution in the hydroboration and aldol reactions using 2,5-dimethylborolane derivatives; Jordi Garcia for crotylboration and part of the aldol reaction of methyl ketones; Siem Veenstra for the hydroboration using 3,4-disubstituted borolanes; Robert Kennedy and Robert Short for the preparation of 2,5-diisopropylborolane and 2,5-bis(trimethylsilyl)borolane, and finally Shoji Nakagawa and Hiromi Tobita for the preparation of 3,4-diethyl- and 3,4-dicyclohexylborolanes.

For encouragements, friendships, and many useful discussions, I return all my thanks to the following: Jeff Davis, Jim Snow, Scott Batcheller, Peter McCarthy, Mary Blanchette, John Ellingboe, Larry Sita, Michelle Palmer, Allen Duplantier, Mike Nantz, Remo Gamboni, Ken Nakayama, Ed Differding, Hwang Shing Chen, Takeshi Kawase, Toshiro Takemasa, Hiroshi Okumoto, Atsushi Abiko, Yoshio Kabe, Yuichi Eriyama, and William Choy. I also wish to express my thanks to Jotham Coe (now at Indiana University) for his friendship and encouragement since the early days of my stay at this school.

I want to express my thanks to all members of my extended family: To my mother- and father-in-law, Soo-Ok and Seung-Moon Bahng and my sister- and brother-in-laws, I give thanks for their friendship and support throughout this study. My late mother-in-law, Soo-Ok is specially acknowledged for having stayed with us and cared for my wife and my son, Phillip, when he was born last spring. I thank my brothers and sisters for their encouragement and support. And most of all, to my parents, Jung-Keun and Jung-Young Kim, I wish to thank them for the everlasting gifts that I will never be able to repay.

Finally, I wish to give very special thanks to my wife, ChoonWon Bahng, who has shared all those good and bad times with me throughout this study. Without all the love, understanding, and support provided by her together with her prayer, this work could not have come to fruition. I must admit that she has been bringing up Phillip, my 8 month old son, almost by herself, and I can never thank her enough for that. Because of all that she is to me, I dedicate this thesis to ChoonWon.

The fear of the Lord is the beginning of knowledge;
Fools despise wisdom and instruction.

(Proverbs 1:7)

Table of Contents

List of Abbreviations

Ac	Acetyl
9-BBN	9-Borabicyclo[3.3.0.]nonane
Bn	Benzyl
Bu	Butyl
DCC	*N,N'*-Dicyclohexylcarbodiimide
DHP	3,4-Dihydro-2*H*-pyran
DIBAL	Diisobutylaluminum hydride
DMAP	4-(*N,N*-dimethylamino)pyridine
DPEA	Diisopropylethylamine
Et	Ethyl
cyc-Hex	Cyclohexyl
LAH	Lithium aluminum hydride
Me	Methyl
MoOPH	Oxodiperoxymolybdenum(pyridine)hexamethylphosphoramide
MTPA	α-Methoxy-α-trifluoromethylphenylacetic acid
Pr	Propyl
pyr	Pyridine
Red-Al®	Sodium bis(methoxyethoxy)aluminum hydride
TBS	t-Butyldimethylsilyl
TfOH	Trifluoromethanesulfonic acid
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TMS	Trimethylsilyl
p-TsOH	p-Toluenesulfonic acid

Chapter 1. INTRODUCTION

The last two decades have witnessed the rise of asymmetric synthesis to the forefront of organic chemistry.[1] Numerous chiral reagents and new methodologies have emerged for the efficient construction of molecules possessing one or more stereogenic centers.

Before the advent of highly selective "reagent controlled" synthesis based on double-asymmetric strategy,[2] the selectivities in acyclic organic reactions invariably resorted to the diastereofacial selectivities (D.S.'s[3]) of the substrates ("substrate controlled" reaction) rationalized by Cram,[4] Felkin,[5] or cyclic chelation-controlled[6] models. Except for the cases of metal-chelated reactions,[7] the selectivities in the substrate controlled reactions usually do not exceed 5:1. Double-asymmetric synthesis, which enhances ("matched"[3] case) or overrides ("mismatched"[3] case) the substrate selectivities by use of powerful homochiral[3] reagents, has made possible the construction of the desired chiral carbon units in a predictable and controlled manner. It has proven to be an extremely powerful methodology for the total synthesis of complex natural products where efficient stereochemical control is vital.[2,8]

As depicted in Scheme 1 double asymmetric synthesis can be executed by two different pathways. Reaction of the substrate A*-C(X) with a selected "internal"† chiral reagent B*-C(Y) (step a) provides a product which contains the chiral auxiliary of the reagent in addition to the newly formed chiral centers (Cn*). In order to obtain the product A*-C(Cn*)-C(Z) which is furnished with a desired functionality for further synthetic transformation, the chiral auxiliary B* must be removed (step b) with full preservation of the stereochemical integrity of the chiral centers created in step a. An alternative to this rather circuitous pathway is the employment of an "external" chiral reagent capable of converting A*-C(X) into A*-(Cn*)-C(Z) directly (step c).

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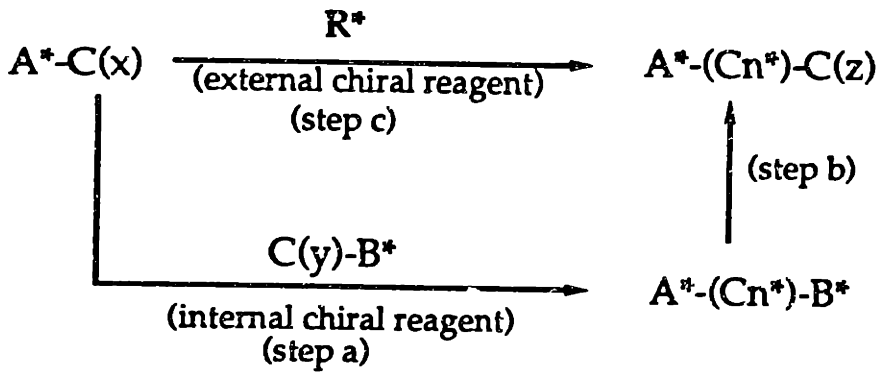
† The reaction involving a chiral reagent provides a product which either contains or does not contain the chiral moiety of the reagent. If it does, the reagent is called 'internal', and if not, 'external'.

Scheme 1

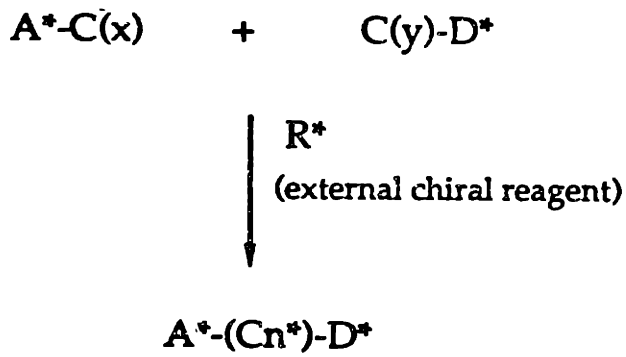


B* : chiral auxiliary
C(x, y, or z) : carbon terminus with functional groups
Cn : carbon chain
* designates chirality

In addition to the advantage of the "external" chiral reagent over the "internal" one in terms of synthetic manipulations, the crucial role of the former becomes even more obvious in a reaction which involves a coupling of two chiral fragments with concurrent generation of a stereogenic center or centers; the strategy often utilized in the total synthesis of natural products (Scheme 2).

This is best exemplified in the case where two chiral fragments are combined via an aldol reaction. Perhaps the most straightforward way to control the sterochemistry of this coupling reaction is to incorporate a third chiral component (R*) which possesses surmounting stereochemical control over the D.S.'s of the two reactants. Thus in practice D*-C(Y) may be converted to the enolate containing a chiral metal reagent and the coupling of both fragments mediated by a third chiral reagent is viewed as a "*triple asymmetric synthesis*". In the past, many convergent natural

Scheme 2



product syntheses have included the coupling of two or more major fragments in their closing stages with the risk of uncertain product stereochemistry. Although no reagents yet exist for such triple asymmetric synthesis, the development of powerful external reagents should address this significant problem.

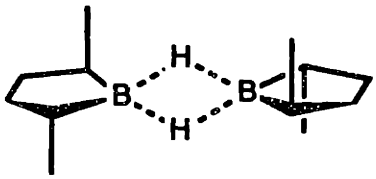
It becomes obvious that the new strategy involving double or triple asymmetric synthesis strongly demands development of homochiral reagents of high (≥100:1) diastereofacial selectivity that surpass those of substrates so that any new stereogenic center or centers can be constructed at will. In this regard the design of new reagents meeting the standard set above is of paramount importance. Because of the preference for the reagents to be external, attention is shifted toward organometallic reagents due to their capability of extra non-covalent bonding (Lewis acidity) or reversible covalent bonding through catalytic pathways (transition metals). Thus two criteria for the reagents become apparent: (1) chiral ligands of high symmetry with close proximity to the metal, and (2) high degree of reactivity usually arising from high Lewis acidity.

Relative to the design of ligands, C_2 symmetry has long been recognized[9,10] as an excellent control element for asymmetric reagents of bidentate ligands due to the fact

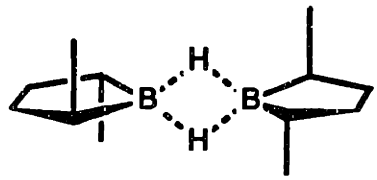
that an induction of asymmetry ultimately resolves into a facial differentiation of a prochiral compound which mostly comprises an sp^2 carbon. Numerous reagents possessing C_2 or D_2 symmetric ligands have been developed and successfully utilized in a number of asymmetric transformations.[1,10,11]

In connection with these ligands, particularly noteworthy is the introduction and rapid adaptation of organometallic reagents of main group metals as versatile reagents for selective organic reactions.[12] The recognition of several main group metals such as B, Al, and Sn as suitable metal elements with appropriate Lewis acidity has been spreading widely over the past decades. Our choice of boron was made based on the following merits: (1) strong Lewis acidity (or so-called "oxygenophilicity"[12b]) due to its empty p orbital, (2) the shortest metal-oxygen and metal-carbon bond lengths among the above mentioned metals ($D_{B\text{-}O}$ = 1.36-1.47, $D_{B\text{-}C}$ = 1.5-1.6 Å)[13], thus confering greater stereochemical control in kinetically controlled processes, (3) relatively strong metal-carbon bond compared to those of other main group metals such as Al or Sn, which have ca. 20-30 kcal/mol lower bond energies for the corresponding M-C bonds,[14] and (4) versatile applicability of the corresponding organoboranes[14-19] to various asymmetric organic reactions such as hydroboration, carbonyl reduction, hydrogenation, alkylation, allyl- or crotyl- addition to carbonyl compounds, aldol reaction, and, as a chiral Lewis acid catalyst, the Diels-Alder reaction, Michael addition, and carbonyl addition of organometallic nucleophiles, etc.

Our aim is to demonstrate the powerful control that rationally designed external reagents exert over asymmetric reactions and to establish beyond question the mechanism of the fundamental reactions examined with the aid of simple, rigid reagent systems such as (*R*,*R*)-**1-1** and (*S*,*S*)-**1-1**. It is also envisioned that this study should serve to introduce the reader in the general strategy towards the design of new asymmetric reagents.



(*R*,*R*)-1-1



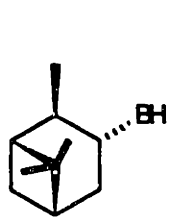
(*S*,*S*)-1-1

Three avenues of asymmetric reactions utilizing (*R*,*R*)-1-1 and (*S*,*S*)-1-1 are described in this account: (1) hydroboration, (2) aldol reaction, and (3) allyl- and crotyl-addition to aldehydes. Part of the work described in this thesis has been included in three papers in the form of preliminary communications.[20-22] Throughout this account, main emphasis is placed on the demonstration of powerful external reagents derived from (*R*,*R*)-1-1 or (*S*,*S*)-1-1 establishing the rule of double-asymmetric synthesis, and an attempt is also made to lay a foundation for triple asymmetric synthesis through the successful employment of such external boron reagents.

Chapter 2. HYDROBORATION

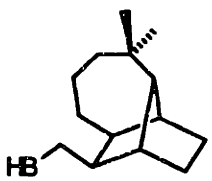
2.1 INTRODUCTION

Since the pioneering studies of H.C. Brown on asymmetric hydroboration with diisopinocampheylborane (2-1) in 1961,[23] a few other reagents (2-2 - 2-4)[24] have emerged all of which were derived from readily available natural products, monoterpenes or sesquiterpenes (2-1 and 2-4 from α-pinene (2-5), 2-2 from longifolene (2-6), and 2-3 from limonene (2-7)). Prochiral olefins can be classified into four major groups; (type I) geminally disubstituted, (type II) cis-disubstituted, (type III) trans-disubstituted, and (type IV) trisubstituted alkenes.



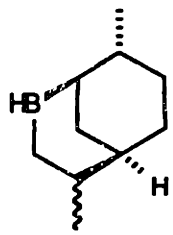
Ipc_2BH

2-1



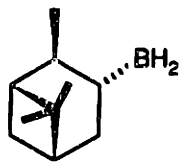
Lgf_2BH

2-2



LImBH

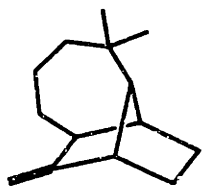
2-3



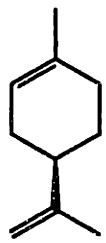
$IpcBH_2$

2-4

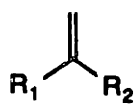
2-5



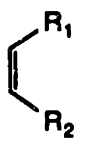
2-6



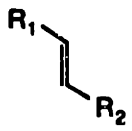
2-7



Type I



Type II



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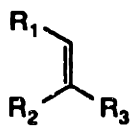


Type IV

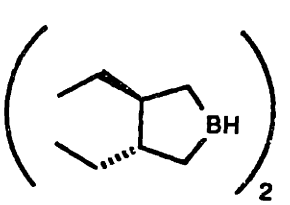
Though easily accessible, the reagents **2-1** - **2-4** are of limited application because of their specificity to certain types of olefins and because the enantioselectivities of the resulting product alcohols usually do not meet the criteria set for double-asymmetric synthesis. High selectivities observed with some reagents (such as **2-4** with type IV olefins) are obtained only after the crystallization of the reaction intermediate, trialkylboranes, inevitably resorting to the crystallinity of the trialkylboranes, thus they are inapplicable to double-asymmetric synthesis[2] or cannot be used with costly olefins (such as those very often encountered in muti-step syntheses) without a substantial loss of yield.

Various models[25-28] for the transition state of hydroboration have been proposed over the years to explain the steric relationship between the absolute configuration of the reagent **2-1** and that of the product alcohols, however understanding the exact nature of the transition state is yet to be realized. It was hoped that a simple, rationally designed reagent might greatly enhance our knowledge of the transition state.

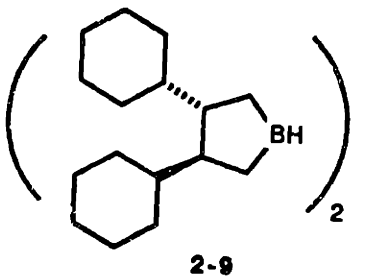
It is for these reasons that a rational step toward the design and synthesis of new asymmetric hydroborating reagents appeared to be warranted. In this regard, Chapter 2 focuses on the design, preparation, and use of two different types of reagents: (1) 3,4-disubstituted borolanes and (2) 2,5-dimethylborolane. The last section of the chapter is concerned with kinetic studies on the hydroboration of 2,5-dimethylborolane.

2.2 Preparation and Subsequent Hydroboration of 3,4-Disubstituted Borolanes.

Our initial step towards a rationally designed hydroborating reagent involved homochiral 3,4-disubstituted borolanes. The highlight in the preparation of the reagents is the preservation of C_2 symmetry in the carbon skeleton and the technically rather straightforward synthesis of the homochiral reagents. The preparation of two 3,4-disubstituted borolanes, 3,4-diehtyl- and 3,4-dicyclohexylborolanes (**2-8** and **2-9**) was made possible by Drs. S. Nakagawa, H. Tobita, and S. J. Veenstra in these laboratories. Both of the reagents were derived from 3,4-disubstituted succinic acid, adopting a general method of cyclic borane preparation originally developed by Köster.[29,30]



2-8



2-9

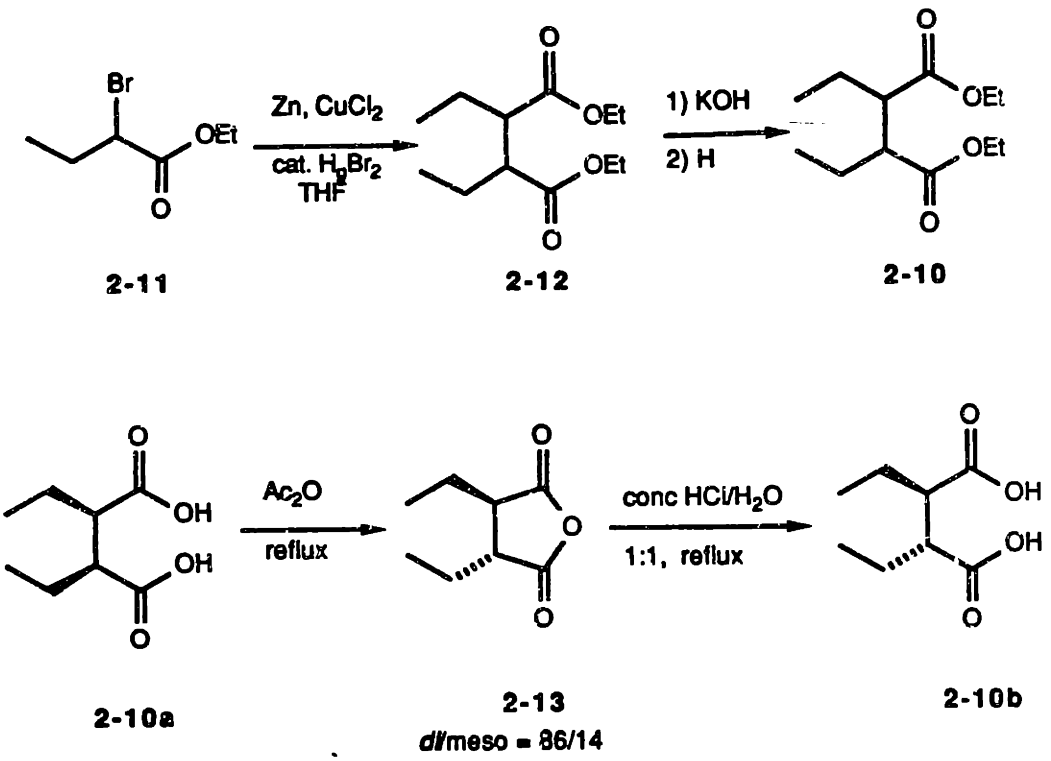
2.2.1 3,4-Diethylborolane (2-8)

The preparation of 3,4-diethylsuccinic acid (**2-10**) was accomplished according to a reported procedure[31-33] as depicted in Scheme 2.1.

Homocoupling reaction of ethyl α-bromobutyrate was affected with Zn-Cu and subsequent hydrolysis afforded the succinic acid **2-10** as a mixture of *dl*- and meso-isomers. *dl*-Isomers **2-10b** can be easily separated from the mixture by recrystallization

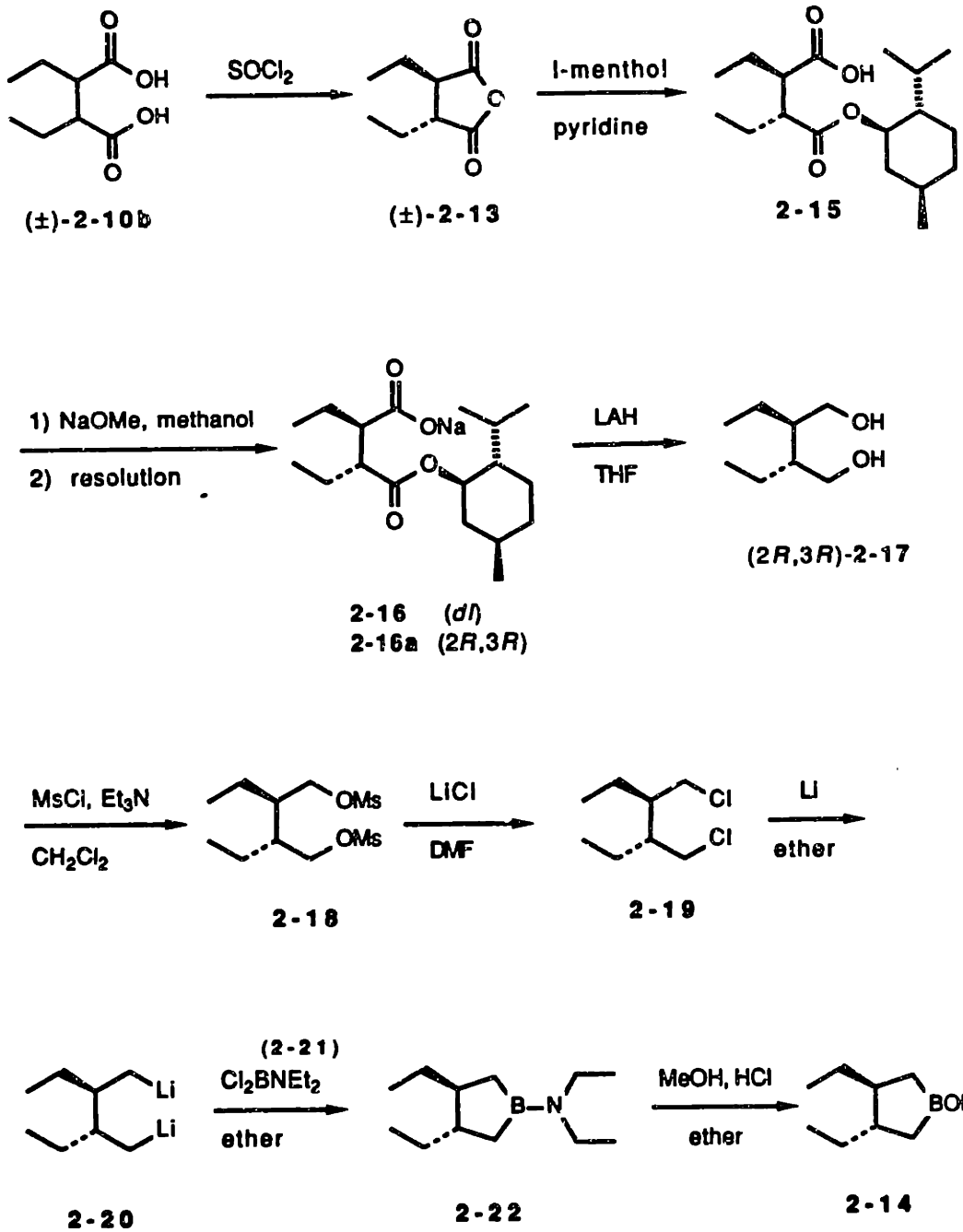
from water and remaining meso compound **2-10a** can be converted to *dl*-compounds under equilibrium condition as portrayed in Scheme 2.1.

Scheme 2.1



Depicted in Scheme 2.2 is the synthesis of *B*-methoxy-(3*S*,4*S*)-3,4-diethylborolane (**2-14**), a direct precursor to the borolane **2-8**. The resolution of the *dl*-mixture (containing ca. 20% of meso compound **2-10a**) was accomplished by a fractional crystallization of monosodium *l*-menthyl trans-3,4-diethylsuccinate (**2-16**). (3*R*,4*R*)-3,4-Diethylsuccinate (**2-16a**) came out in the first crystals (20% recovery, ~70% ee) from methanol/ether solution (1/1) and *dl*-isomer was obtained as second crystallized material in ~20% recovery.

Scheme 2.2



(±)-2-10b (±)-2-13 2-15

2-16 (*dl*)
2-16a (2*R*,3*R*)

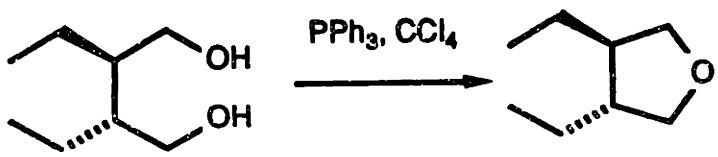
(2*R*,3*R*)-2-17

2-18 2-19

2-20 2-22 2-14

Although it is possible to obtain (3*R*,4*R*)-diethyl succinate (**2-16a**) of higher purity (>95% ee) by reiterative crystallization from ether/methanol (25/1) with a significant sacrifice in yield, the material of ca. 70% ee was carried throughout the reaction sequence in order to obtain a sizeable amount of **2-14** to test asymmetric induction in the hydroboration. Reduction of **2-16a** with excess LAH provided 1,4-diol

2-17 (~90%), which was subsequently treated with methanesulfonyl chloride to afford the bis-mesylate 2-18 quantitatively. A direct chlorination with carbon tetrachloride and triphenylphosphine resulted in tetrahydrofuran ring (2-23) formation as shown below.

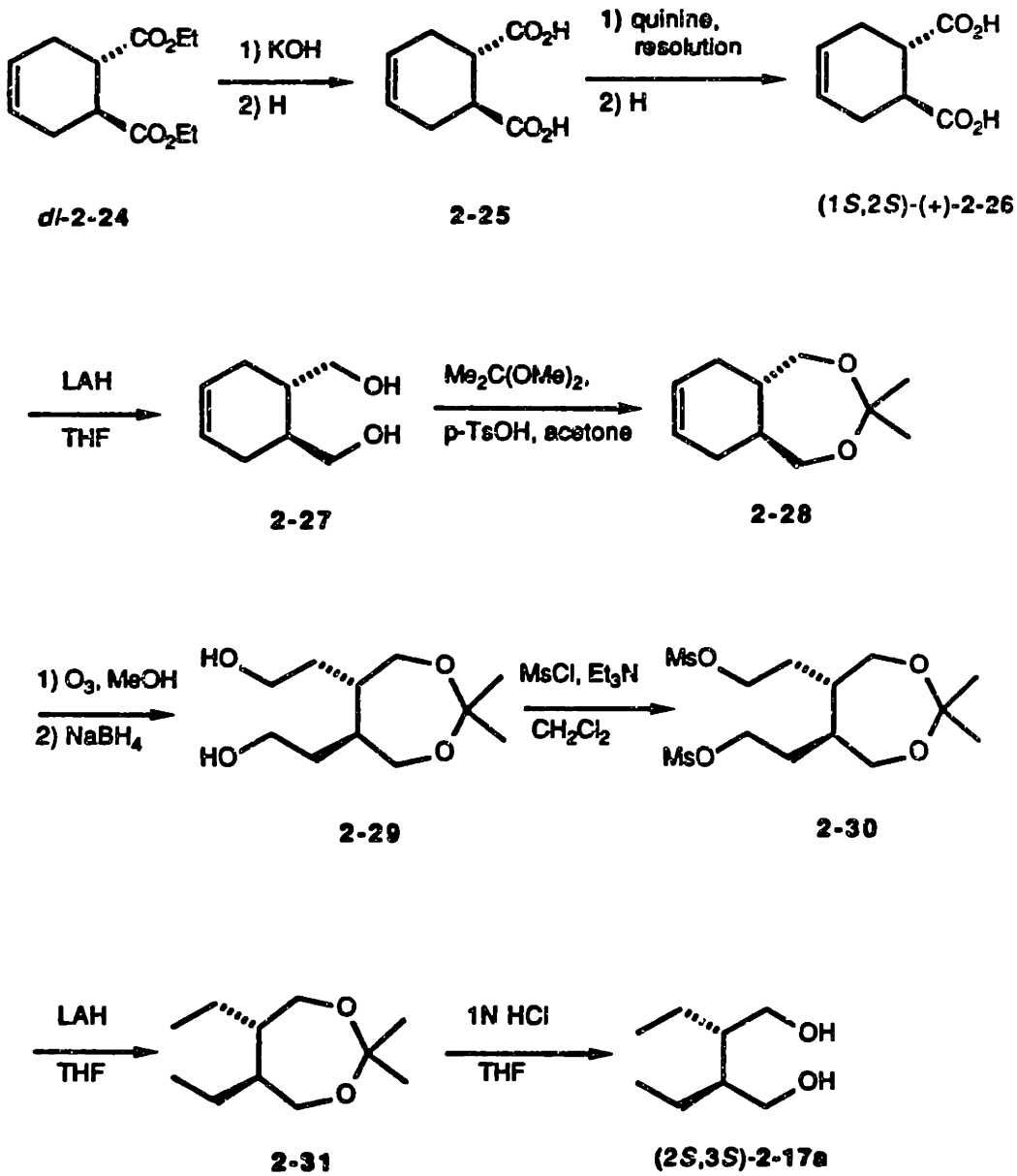


2-17 2-23

Displacement of the mesylate with chloride was smoothly effected with LiCl/DMF at 70°C. The resulting dichloride 2-19 was bis-metalated with excess lithium (as a dispersion containing 1% Na) to provide an ethereal solution of 1,4-dilithio-2,3-diethylbutane (2-20) (84%, determined by titration with sec-BuOH using bipyridyl as an indicator). Finally, cyclic borane 2-22 was obtained in the reaction of the dilithium compound 2-20 with *N,N*-diethylaminodichloroborane (2-21) in a high yield (95%). Replacement of the diethylamino moiety with a methoxy group was accomplished with HCl and furnished *B*-methoxy-(3*S*,4*S*)-3,4-diethylborolane 2-14 (90% yield), an immediate precursor to the borolane 2-8.

The absolute configuration of the reagent 2-8 was unambiguously confirmed by oxidation to the diol 2-17 and comparison with authentic material prepared independently from compounds with established absolute stereochemistry. Scheme 2.3 delineates the route to obtain (3*S*,4*S*)-diethyl-1,4-butanediol 2-17a.

Scheme 2.3



Resolution of a racemic mixture of the diol **2-25** was performed according to a published procedure using quinine.[†,34,35] Resolved diacid **2-26** (~70% ee) was reduced to diol **2-27**, which was then protected as an acetonide. The cyclohexene ring was

---

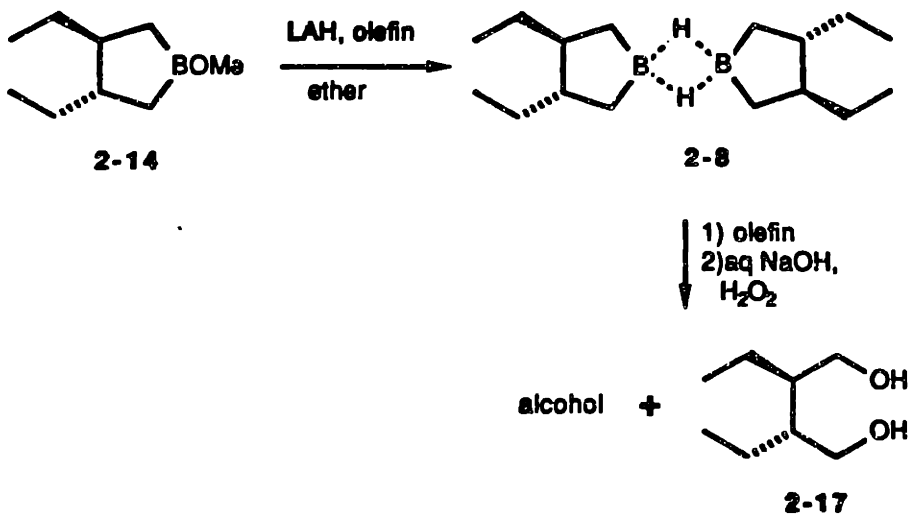
[†] An attempted resolution with *l*-(-)-α-methylbenzylamine or *l*-(+)-threo-2-amino-1-(p-nitrophenyl)-1,3-propanediol proved unsuccessful.

ultimately transformed to 3,4-diethyl moiety via a sequence of routine manipulations; ozonolysis followed by reductive workup afforded the diol **2-29**, derivatization of **2-29** with methanesulfonyl chloride provided the bis-mesylate **2-30**, and reduction with lithium aluminum hydride led to **2-31**. Removal of the acetonide protecting group provided (2*S*,3*S*)-2,3-diethyl-1,4-butanediol (**2-17a**). The diol **2-17a** exhibited a levorotatory optical rotation {$[\alpha]^{20}_D$ -2.0° (*c* 1.115, EtOH), -10.6° (*c* 0.52, $CHCl_3$)}, whereas $[\alpha]^{20}_D$ +1.58° (*c* 1.01, EtOH), +9.4° (*c* 0.50, $CHCl_3$) was observed for alcohol **2-17** (72.8% ee). That **2-17** has (2*R*,3*R*)-cofiguration was also confirmed by comparative ^1H NMR analysis of the corresponding MTPA esters of the diols **2-17** and **2-17a**.

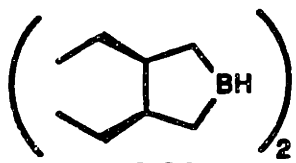
Asymmetric Hydroboration with 3,4-Diethylborolane

Depicted in Scheme 2.4 is the hydroboration of olefins using borolane **2-8** which is generated *in situ* by using 0.3 equiv of LAH in the presence of an olefin. The parent borolane **2-32** is known to be thermally unstable and easily isomerizes to yield 1,6-diboracyclodecane **2-33** which is inert to olefins.[36]

Scheme 2.4



2-32 2-33

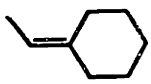


2-34

The borolane 2-8 was found to undergo the same type of isomerization only slowly, allowing sufficient hydroboration to occur before the isomerization. Additionally racemic borolane 2-34 was generated in the absence of olefin, stored for 24 h at 4°C, and allowed to react with *trans*-2-butene for 3 days (entry 2, Table 1). A respectable 62% yield of the corresponding 2-butanol was obtained after oxidative workup.

Results of asymmetric hydroboration of representative olefins with 2-8 are shown in Table 2.1.

Table 2.1.[a] Hydroboration of representative olefins with 2-34 and (*R,R*)-2-8.

entry	borolane reagent	olefin	reaction temp (°C)	reaction time (h)	yield	%ee [c] obsd	corrected %ee for the purity of 2-8
1	2-34		+4	73	56	_	_
2 [d]	2-34		+4	72	62	_	_
3	(*R,R*)-2-8		-20	65	23	16.4	22.5
4	(*R,R*)-2-8		-20	70	28	17.3	23.8
5	(*R,R*)-2-8		-20	70	22	4.6	6.3

a. Borolane (~0.4 M, 72.8% ee) was generated *in situ* with 0.3 equiv LAH in ether in the presence of an olefin.

b. Yields were determined by capillary GC analysis of the corresponding 3,3-dimethylbutanoyl ester (entries 1-4) or acetate (entry 5) using dodecane as an internal standard.

c. Values were determined by ^{1}H NMR analysis of the corresponding derivatives (see footenote b) in the presence of Eu(hfc)$_3$ as a chiral shift reagent.

d. The borolane was prepared in the absence of olefin, stored at 4°C for 24 h, and then olefin was added.

The results of hydroboration with meso borolane 2-34, shown in entries 1 and 2, indicate reasonable reactivities of the borolane system toward olefin. The asymmetric hydroborations were carried out at the lowest possible temperature (-20°C) in order to ensure the highest enantioselectivity. However, only a marginal degree of selectivities

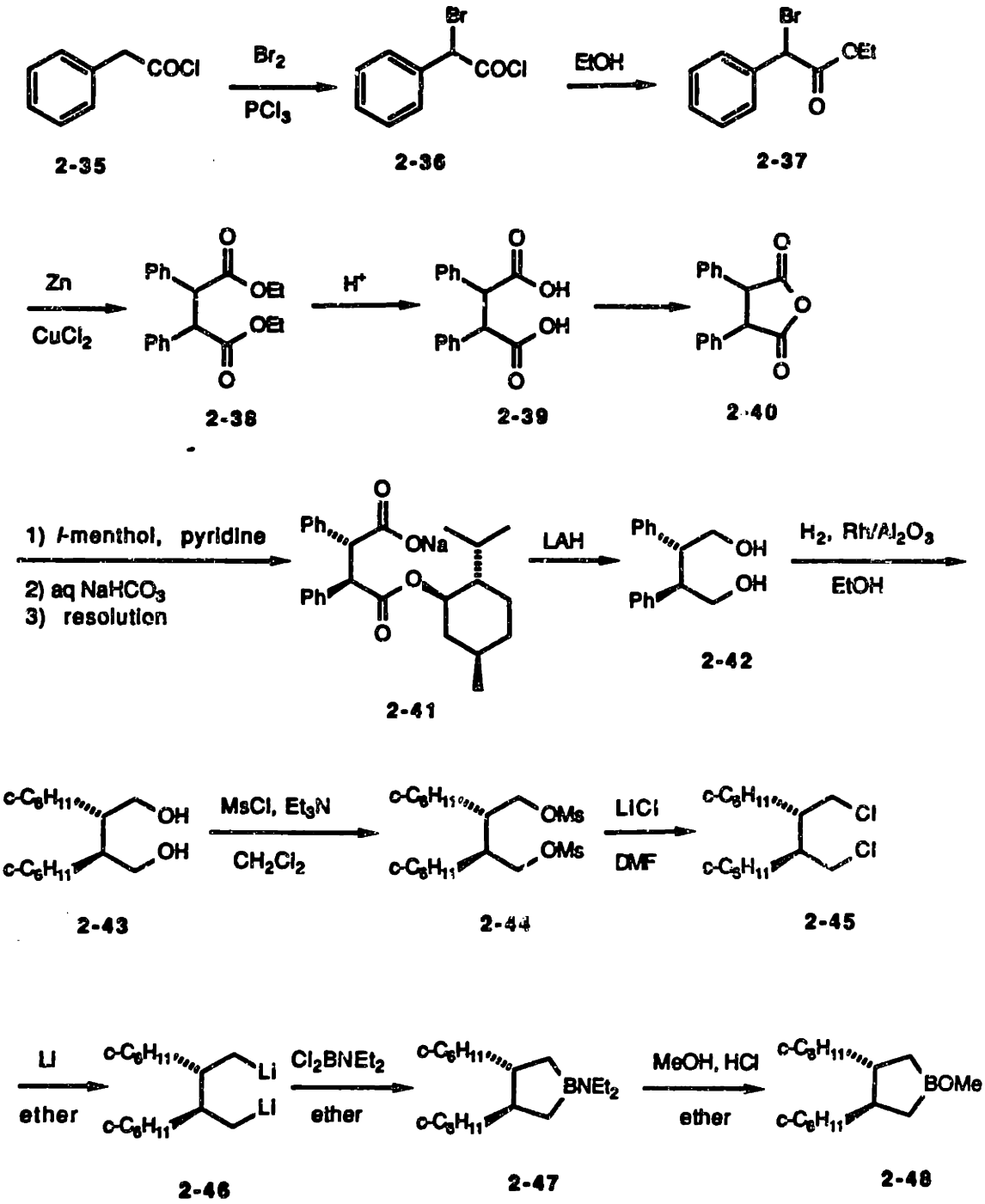
was obtained. Among the olefins tested, type IV olefin (entry 5) showed lower enantioselection compared to type II and III olefins. Concluding that the 3,4-diethyl groups can not effect significant asymmetric induction, we moved on to the borolanes with larger alkyl group.

2.2.2. 3,4-Dicyclohexylborolane (2-9)

Hoping that a bulkier substituent may effect a larger influence on asymmetric hydroboration, we undertook the synthesis of 3,4-dicyclohexylborolane (2-9). The synthetic strategy to 2-9 is patterned exactly after that for 2-8 as depicted in scheme 2.6.

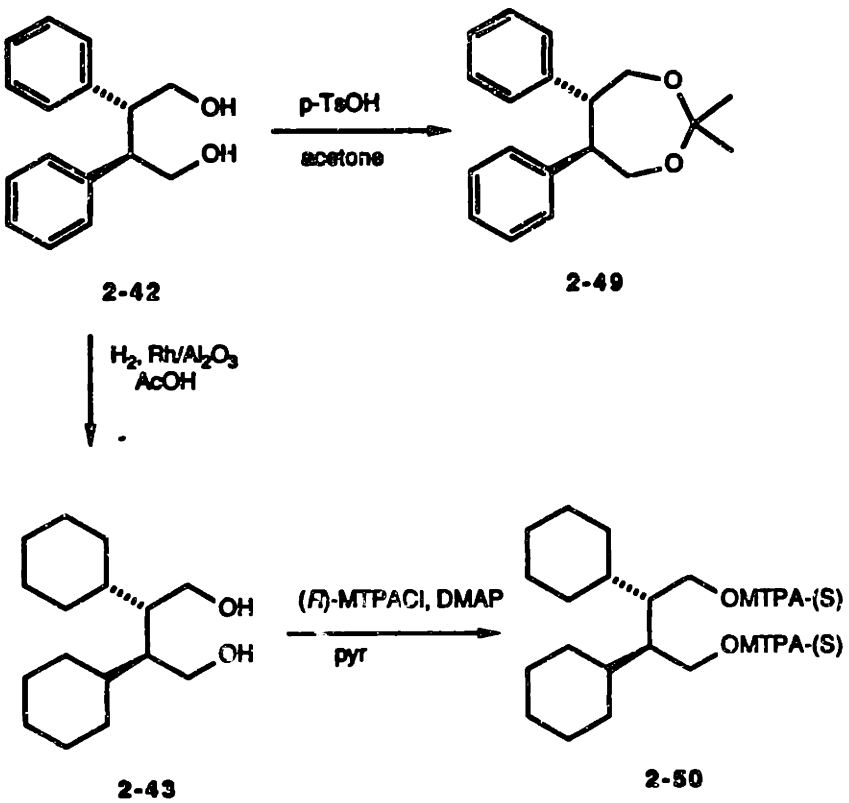
Synthesis of monosodium *l*-menthyl 2,3-trans-diphenyldicarboxylate 2-41 was accomplished according to the reported procedure.[37,38] Essentially pure (2*R*,3*R*)-isomer (>99% ee) of 2-41 was obtained by recrystallization of the mixture from methanol. Reduction of (*R*,*R*)-2-41 with LAH provided the diol (*R*,*R*)-2-42 and subsequent hydrogenation of this diol with Rh/Al_2O_3 catalyst was carried out without detectable racemization. In the same manner as that described for the preparation of *B*-methoxyborolane 2-14, the methoxyborolane 2-48 was obtained. The enantiomeric purity of 2-48 was determined at the stage of diols (2-42 and 2-43) as presented in Scheme 2.7.

Scheme 2.6


COCl
Br2
PCl3
Br
COCl
EtOH
Br
OEt
O
2-35
2-36
2-37
Zn
CuCl2
Ph
OEt
OEt
Ph
O
O
H+
Ph
OH
OH
Ph
O
Ph
O
O
2-38
2-39
2-40
1) l-menthol, pyridine
2) aq NaHCO3
3) resolution
Ph
ONa
Ph
O
O
LAH
Ph
OH
OH
Ph
H2, Rh/Al2O3
EtOH
2-41
2-42
c-C6H11
OH
OH
c-C6H11
MsCl, Et3N
CH2Cl2
c-C6H11
OMs
OMs
c-C6H11
LiCl
DMF
c-C6H11
Cl
Cl
c-C6H11
2-43
2-44
2-45
Li
ether
c-C6H11
Li
Li
c-C6H11
Cl2BNEt2
ether
c-C6H11
BNEt2
c-C6H11
MeOH, HCl
ether
c-C6H11
BOMe
c-C6H11
2-46
2-47
2-48

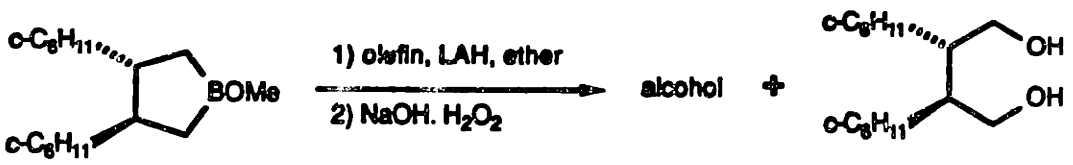
^{1}H NMR analysis of acetonide **2-49** with the aid of Eu(hfc)$_3$ indicated >99% ee of the alcohol **2-42** {[α]$^{25}_D$ -47.6° (*c* 0.500, CHCl$_3$)}. The reduced diol **2-43** {[α]$^{23}_D$ -2.3° (*c* 0.52, CHCl$_3$)} also proved to be >99% ee from the ^{1}H NMR analysis of the corresponding bis-MTPA ester **2-50** as shown in Scheme 2.7.

Scheme 2.7



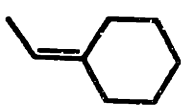
Collected in Table 2.2 are data from the hydroboration of representative olefins using borolane 2-9 which was *in situ* generated from *B*-methoxyborolane 2-48 (Scheme 2.8). The enantioselectivities obtained with the product alcohols, again, fell into a range of 4-23% ee.

Scheme 2.8



2-48 2-43

Table 2.2.[a] Asymmetric hydroboration of representative aldehyde with 2-9

entry	olefin	reaction temp (°C)	reaction time (h)	yield (%) [b]	% ee [c]
1		-20	46	42	18
2		-20	21	32	23
3		+4	38	66	15
4		+4	44	81	4

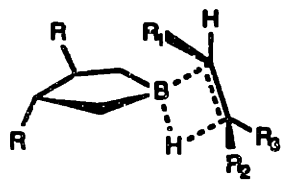
a. Borolane 2-9 (>99% ee, ~0.4 M) was generated *in situ* with 0.3 equiv LAH in ether in the presence of 2.0 equiv olefin.

b. Yield was calculated from capillary GC analysis of the corresponding 3,3-dimethylbutanoyl ester (entries 1-3) or acetate (entry 4) in the presence of an internal standard.

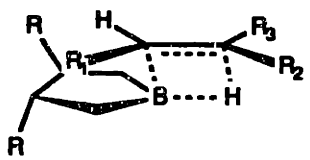
c. Values were determined by ^1H NMR analysis of the corresponding esters (see footnote b) with the aid of $Eu(hfc)_3$ as a chiral shift reagent.

2.2.3. Concluding remarks

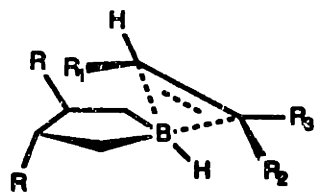
From the results of Table 2.1 and Table 2.2, it became obvious that β-substitution of the borolane ring system does not effect significant asymmetric induction. Although hydroborations with **2-8** and **2-9** did not proceed in highly stereoselective manner, data obtained from the reactions using 3,4-disubstituted borolanes shed a light on the understanding of the transition state of the reaction. Namely, the boron atom should occupy a much developed sp^3 configuration (A) rather than an sp^2 one of an earlier transition state (B)[25,26] or a position in the π-complex 3-center configuration (C).[27] In the latter two cases there must be a rather large influence of the β-substituents of the borolane system on the orientation of the incoming olefin. Therefore a strong request for the α-disubstituted borolanes emerges, the preparation of which requires a conceptually new strategy.



A



B



C

2.3. 2,5-DIMETHYLBOROLANE {(*R*,*R*)-1-1 OR (*S*,*S*)-1-1}

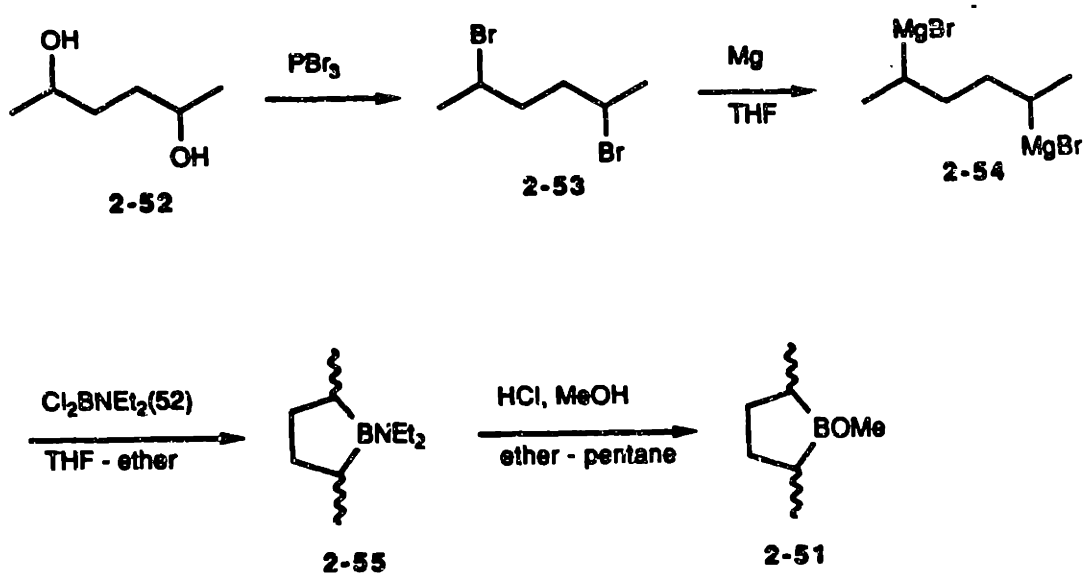
The methodology employed in the construction of the 2,5-dimethylborolane system stems in part from that of the preparation of 3,4-disubstituted borolanes in that both utilize cyclization via reaction of a 1,4-bismetallic reagent with an electrophilic borane reagent. However, the strategy to accommodate chiral substituents α to boron required an essentially different approach regarding the resolution technique.

Pioneering studies have been advanced in this group (S. J. Veenstra, 1983-1984) to resolve enantiomeric boranes by complexation with homochiral aminoalcohols thus producing diastereomeric mixture of aminoalcohol-boron complexes.[39,40] These complexes exhibit remarkable stabilities upon exposure to moisture and oxygen, to which most alkylboranes are extremely vulnerable. Additionally the fact that one diastereomer is thermodynamically more stable than the other allows for the separation of a single diastereomer from a mixture, thus renders a convenient solution to the preparation of homochiral borolanes. These accomplishments have facilitated our effort to prepare the homochiral borolane reagents (*R*,*R*)-1-1 and (*S*,*S*)-1-1

2.3.1. Preparation of B-Methoxy-2,5-dimethylborolane (2-51)

Depicted in Scheme 2.9 is the synthesis of *B*-methoxy-2,5-dimethylborolane. (2-51)

Scheme 2.9



Dibromohexanes 2-53 were prepared in 90% yield from 2,5-hexanediols 2-52 with 1.1 equiv of PBr3 (two equivalents used in the literature procedure).[41] Although it is possible to separate meso- and *dl*-2,5-dibromohexanes,[41] no such attempt was made, since the subsequent Grignard formation step was expected to epimerize the stereogenic centers. Grignard reagent 2-54 was prepared in 60-70% yield according to the literature procedure[42] but with some modifications. 2,5-Dichlorohexane was also prepared from the diol on the basis of Whiteside's report[43] that α,ω-di-Grignard generation from dichlorides is generally superior to that from dibromides. However, over the course of several runs, yields comparable to those obtained from the dibromide were realized (Marvin Yu, 1986). Since the preparation of the dichloride is somewhat more tedious than that of the dibromide, the dibromide remains to be the starting material of choice. Both di-Grignard reagents give comparable yield of the N,N-diethylaminoborolane and have comparable solubilities in THF (ca. 0.5 M at 20°C). The low solubility of the di-Grignard reagent 2-54 is a limitation to this method of construction of 2,5-dimethylborolane ring system on a large scale.

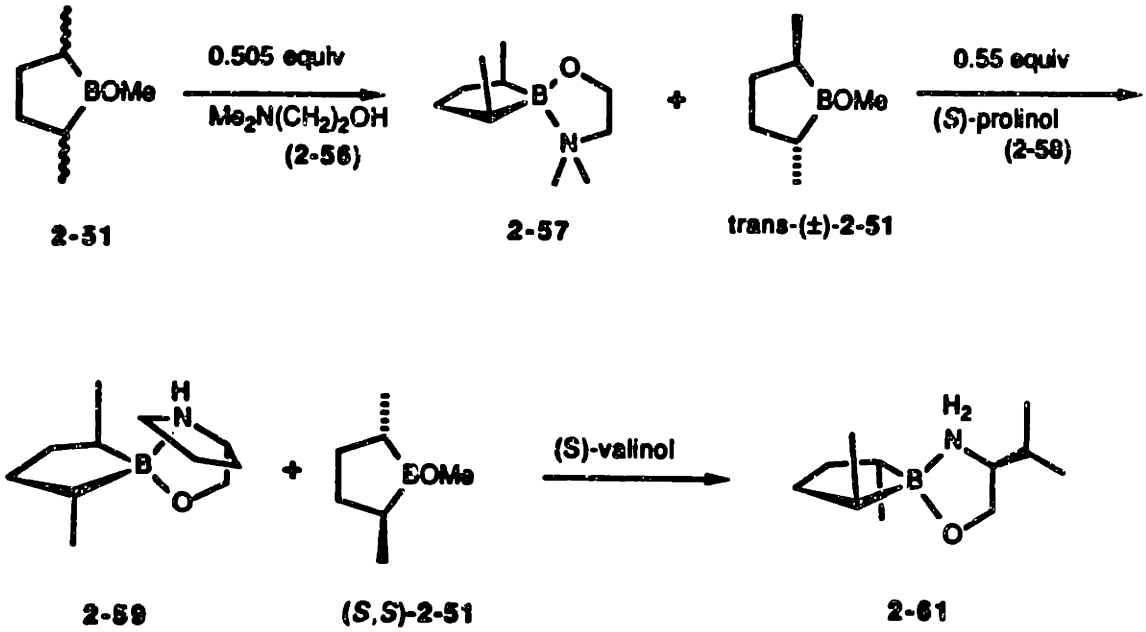
N,N-diethylaminodichloroborane (2-21) was prepared by addition of diethylamine to a solution of BCl_3 in benzene at an internal temperature of 3-5°C. The literature procedure[44] calls for a much lower temperature which leads to freezing of the benzene solution.

Construction of cyclic aminoborane was accomplished by adding Grignard reagent 2-54 to 2-21 at -78°C. The aminoborolane 2-55 was obtained in 56-70% yield depending upon the scale of reaction as a ~1:1 mixture of cis and trans isomers (^{1}H NMR: two methyl doublets at δ 0.93, d, *J*=7.2 Hz and 0.83, d, *J*=7.7 Hz). Treatment of the protonated amino group with methanol converted 2-55 to a mixture of *B*-methoxyborolanes 2-51 in good yield (85-90%) with cis/trans ratio of 47/53 as determined by the ^{1}H NMR analysis.

2.3.2. Separation of *cis/trans* Mixture and Resolution of *B*-methoxy-2,5-dimethylborolanes.

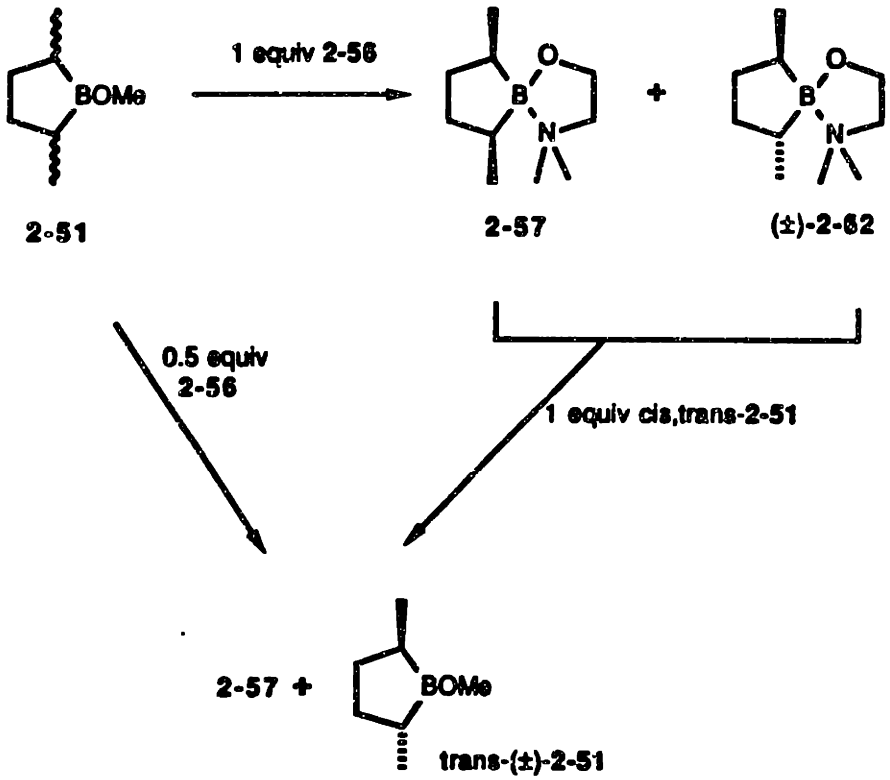
The birth of highly illusive homochiral 2,5-dimethylborolanes was facilitated by the resolution of racemic boron reagents as complexes with homochiral aminoalcohols, a technique developed in our laboratories. Separation of the cis and trans isomers was accomplished by taking advantage of the thermodynamic stability of the complex 2-57 (Scheme 2.10). The original procedure (T. Imai, 1985) involved treatment of the mixture of *B*-methoxyborolanes with 0.505 equiv of *N,N*-dimethylaminoethanol (2-56). Vacuum transfer of the volatile materials isolated (±)-trans-2-51 leaving solid complex 2-57 behind. The resulting (±)-2-51 was selectively complexed with 0.55 equiv of (*S*)-prolinol ((*S*)-2-58) to provide the (*R,R*)-complex 2-59. Another vacuum transfer then afforded (*S,S*)-2-51. (*S*)-Valinol was used to provide complex 2-61 for the purpose of purification and storage.

Scheme 2.10



However, examination of the resolution enhanced ^1H NMR (Gaussian-multiflied FID) indicated that the volatile product (±)-2-51 contained 5-10% of the undesired cis-bcrolane. Since the cis-isomer readily forms crystalline complexes with either (*S*)-, (*R*)-prolinol, or (*S*)-valinol, its presence complicated subsequent purification of the optically active complexes. This complication prompted us to further investigate the resolution process in the hope of obtaining more highly purified aminoalcohol complexes (J. S. Petersen, 1985).

Scheme 2.11

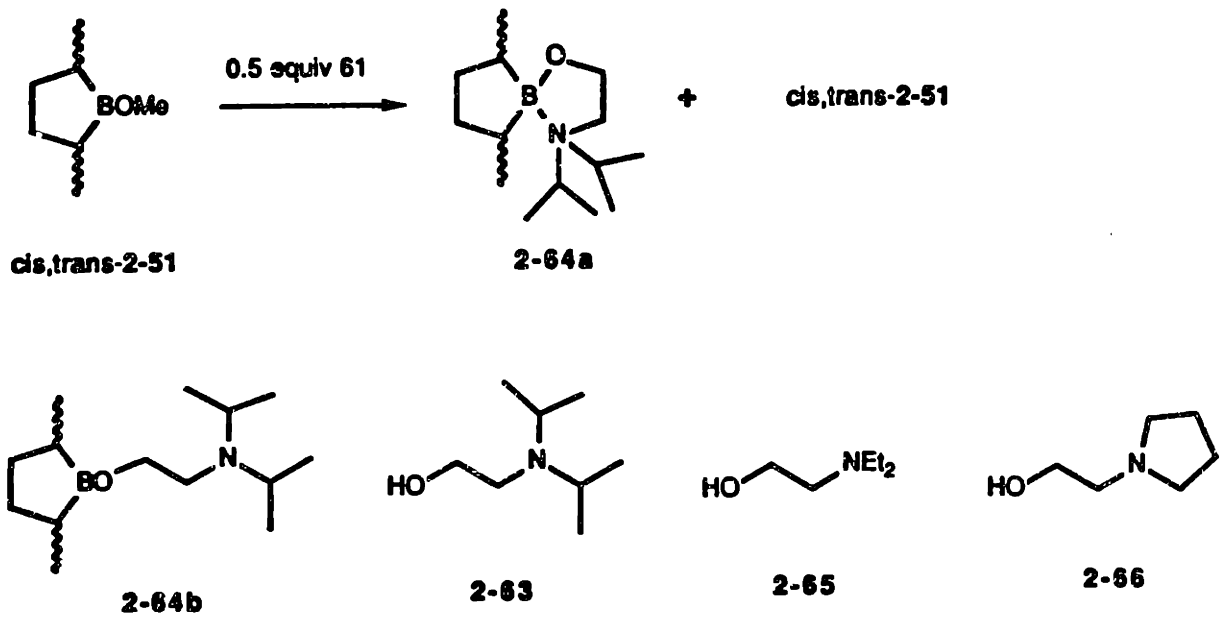


First it was established that the first resolution occurs under thermodynamic control (Scheme 2.11). Treatment of cis,trans-**2-51** with one equiv of *N,N*-dimethylaminoethanol rendered a complete conversion to cis-complex **2-57** and trans-complex (±)-**2-62** as evidenced by ^{11}B NMR (complete disappearance of 59 ppm peak and a new, broad peak around 12 ppm). These complexes were allowed to equilibrate with one equiv of *cis,trans*-**2-51** (pentane, 16 h, room temperature) and the resulting products were separated by vacuum transfer. The solid residue consisted primarily of *cis*-complex **2-57** and the volatile fraction was a 90:10 *trans/cis* mixture of methoxyborolanes **2-51**. Essentially the same result was obtained by treating the starting mixture with 0.5 equiv of aminoalcohol **2-56**. Thus, it was demonstrated that the complexes do equilibrate and this portion of the separation process occurrs under thermodynamic control.

Our first attempt to improve the resolution process involved modification of

the aminoalcohol (J. S. Petersen, 1985). We reasoned that larger alkyl groups would improve the trans/cis selectivity. However when N,N-diisopropylaminoethanol (2-63) was employed, the vacuum transferred product was a 1:1 cis/trans mixture (Scheme 2.12). Apparently the isopropyl groups are too large to allow complexation to occur and the open chain structure 2-64b most accurately depicts this compound.

Scheme 2.12



Substitution of *N,N*-diethylaminoethanolamine 2-65 again gave a 90:10 trans/cis mixture. The cis-complex was also less crystalline in this case. Although employment of (2-hydroxyethyl)pyrrolidine (2-66) afforded slightly better (but almost comparable) results (T. Imai, 1985), a new strategy was developed for improving the cis/trans separation. An obvious method for improving the tans/cis ratio is to increase the amount of aminoalcohol used. Of course this will lower the yield of the recovered trans-borolane. Since it was possible to analyze the cis/trans ratio of both complex and the methoxyborolane by ^{1}H NMR, we could determine the equilibrium

constant for the equation (J. S. Petersen, 1985):

$$tr^* + cis \rightleftharpoons tr + cis^* \quad (1)$$

$$K = [tr][cis^*]/[tr^*][cis] \quad (2)$$

where * designates complexed species.

Note that at low aminoalcohol concentrations the equation can be simplified to: $K = [cis^*]/[tr^*]$ and at high aminoalcohol concentration to: $K = [tr]/[cis]$. This allows K to be determined from a single measurement of either the complex ratio or the volatiles ratio depending upon the relative ease of the measurements. In the case at hand K was determined for aminoalcohol concentration of 0.5 equiv (both ratios measured) and was found to be approximately 100. With the knowledge of K and the assumption that all the aminoalcohol forms complexes, one can derive an equation relating the cis/trans ratio of the starting material to the amount of aminoalcohol added to the cis/trans ratio of the volatile product.

Initial conditions:

$$[tr] + [tr^*] = B$$

$$[cis] + [cis^*] = 1 - B$$

where B equals the % trans isomer in the original mixture times 1/100.

Substituting in the equilibrium equation:

$$K = \frac{[tr](1 - B - [cis])}{(B - [tr])[cis]} \quad (3)$$

Assuming that all the aminoalcohol forms complexes:

$$[aa] = [cis^*] + [tr^*]$$

or $1 - [aa] = [cis] + [tr]$

so $1 - [aa] - [cis] = [tr]$

where [aa] equals the concentration of aminoalcohol.

substituting:

$$K = \frac{(1 - [aa] - [cis])(1 - B - [cis])}{(B - 1 + [aa] + [cis])[cis]} \qquad (4)$$

Expanding this expression leads to:

$$(K - 1)[cis]^2 + \{(K - 1)B + 2 - K + (K - 1)[aa]\}[cis] + (1 - B)([aa] - 1) = 0$$

which is a quadratic equation where:

$a = K - 1$

$b = (K - 1)(B + [aa]) + 2 - K$

$c = (1 - B)([aa] - 1)$

$x = [cis]$

Thus $\frac{x}{(1 - [aa])}$ = % *cis* in vacuum transferred product.

In the case where K = 100 and B = 0.5, the effect of adding aminoalcohol on the % cis isomer remaining in the volatile fraction is shown in Fig. 2.1. Adding aminoalcohol rapidly reduces the concentration of the *cis* isomer up to about 0.5 equiv. Between 0.5 and 0.7 equivalents the concentration of the *cis* isomer decreases more slowly. Little further improvement of the *cis/trans* ratio occurs above 0.7 equiv of aminoalcohol. This behavior was rapidly exploited. If one adds 0.45 equiv of aminoalcohol, vacuum transfers, and then adds an additional 0.1 equiv of aminoalcohol (based on the starting methoxyborolane) the volatile product contains only 2% of the *cis* isomer. On the other hand if one simply adds 0.55 equiv of

aminoalcohol in one portion, the product contains 5.8% of the cis isomer -- nearly three times as much. Consequently the cis complex produced in the former process has a much higher *cis/trans* ratio.

In practice we effected the *cis/trans* separation by adding 0.45 equiv of aminoalcohol, vacuum transferring, and then adding 0.08-0.09 equiv of aminoalcohol (Scheme 2.13). In this fashion, product containing 2-4% of the cis isomer was obtained. It is important that the vacuum transfer be performed at *as low a pressure as possible* to permit most of the transfer to occur prior to substantial heating of the reaction mixture. At higher temperature the equilibrium constant is apparently not as great and a poor cis/trans ratio is observed in the volatile fraction.

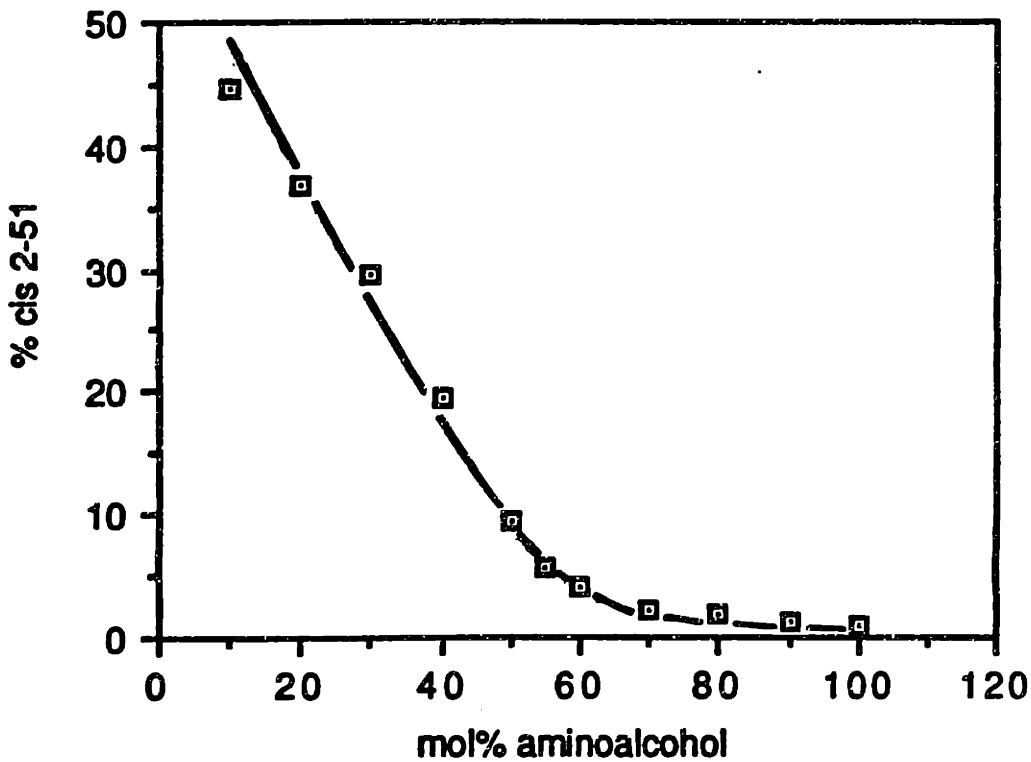
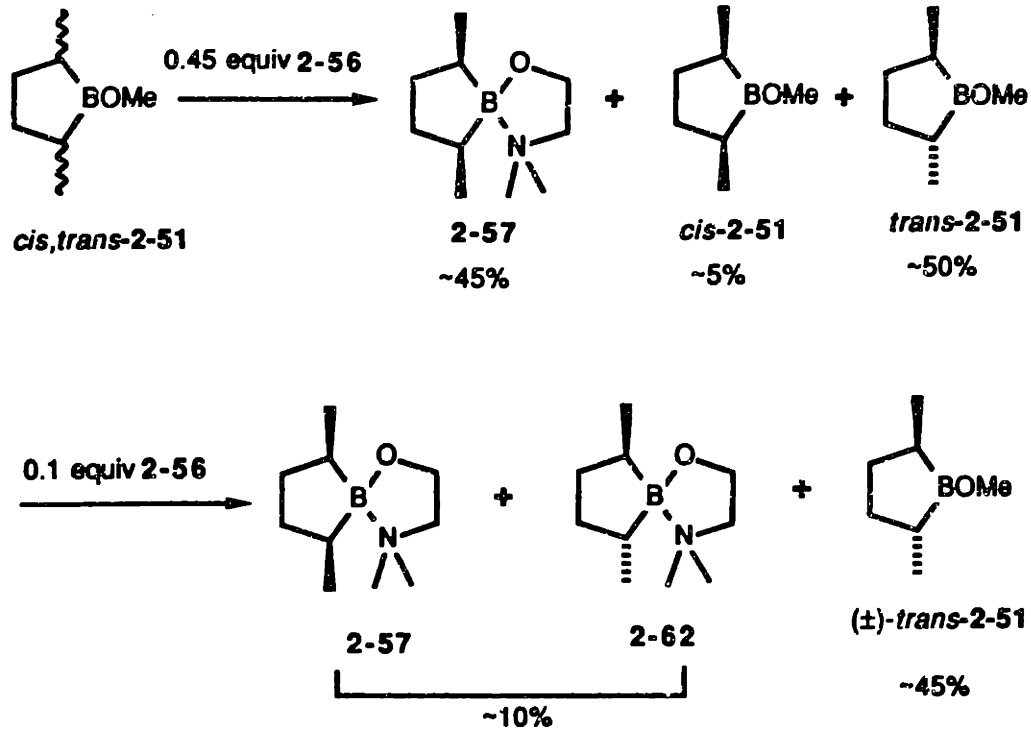


Fig. 2.1. The effect of adding aminoalcohol on the % *cis*-2-51 remaining in the volatile fraction when K = 100 and B = 0.5.

Scheme 2.13



We were still confronted with an additional issue of resolving trans-borolane 2-51 to obtain (*R,R*)-2-51 and (*S,S*)-2-51. To date it has not been established whether or not the reaction of prolinol (2-58) with trans-2-51 in pentane operates under kinetic or thermodynamic control. That a precipitate rapidly forms during the addition of prolinol to the solution of trans-2-51 in pentane strongly suggests a kinetic resolution. If the product ratio is a thermodynamic result, the analysis above is still applicable. If the product ratio is a kinetic one, the relevant equation is:[45]

$$k_{rel} = \ln\{(1 - c)(1 - ee)\}/\ln\{(1 - c)(1 + ee)\} \quad (5)$$

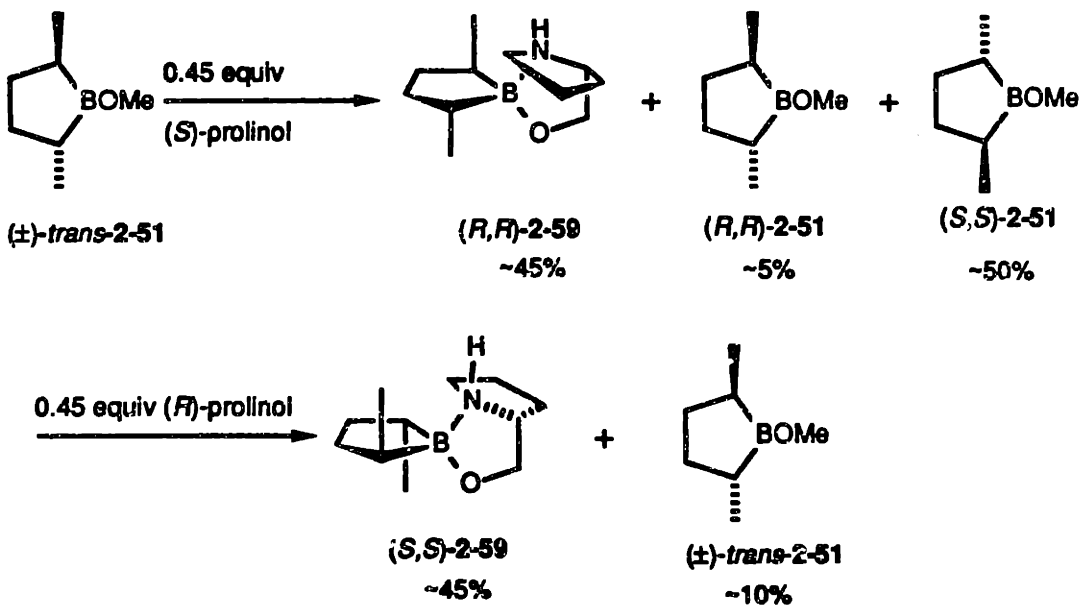
where c = equiv of aminoalcohol

and ee = %ee/100 of volatile product.

In either case, addition of 0.45 equiv of (*S*)-prolinol followed by vacuum transfer and addition of 0.45 equiv of (*R*)-prolinol was expected to provide highly pure complexes. In practice 0.45 equiv of (*S*)-prolinol (prepared from natural (*S*)-proline) was used to provide highly pure (*R,R*)-complex **2-59** as a mixture of (*R,R*)-, (*R,S*)-, and (*S,S*)-borolanes in a ratio of 97/2/1 on a 0.1 mole scale. Vacumm transfer of the volatile material and treatment with 0.45 equiv of (*R*)-prolinol provided (*S,S*)-complex with similar purity to that obtained for (*R,R*)-complex (Scheme 2.14). Final vacuum transfer of the volatile material provides ca. 0.1 equiv of (±)-**2-51**.

Recrystallization of the prolinol complexes in methylene chloride (45 mL/g, reflux, then cooling to 4°C) gave a 60% recovery of crystalline material of >99% ee. Concentration of the mother liquors and crystallization again gave a 60% recovery of 96-98% ee material. Additional crops of crystalline complex of lower % ee could be obtained. The prolinol complex is stable in refluxing methylene chloride (2 h, air, no decomposition by ^{1}H NMR) and the recrystallizations were performed without any

Scheme 2.14



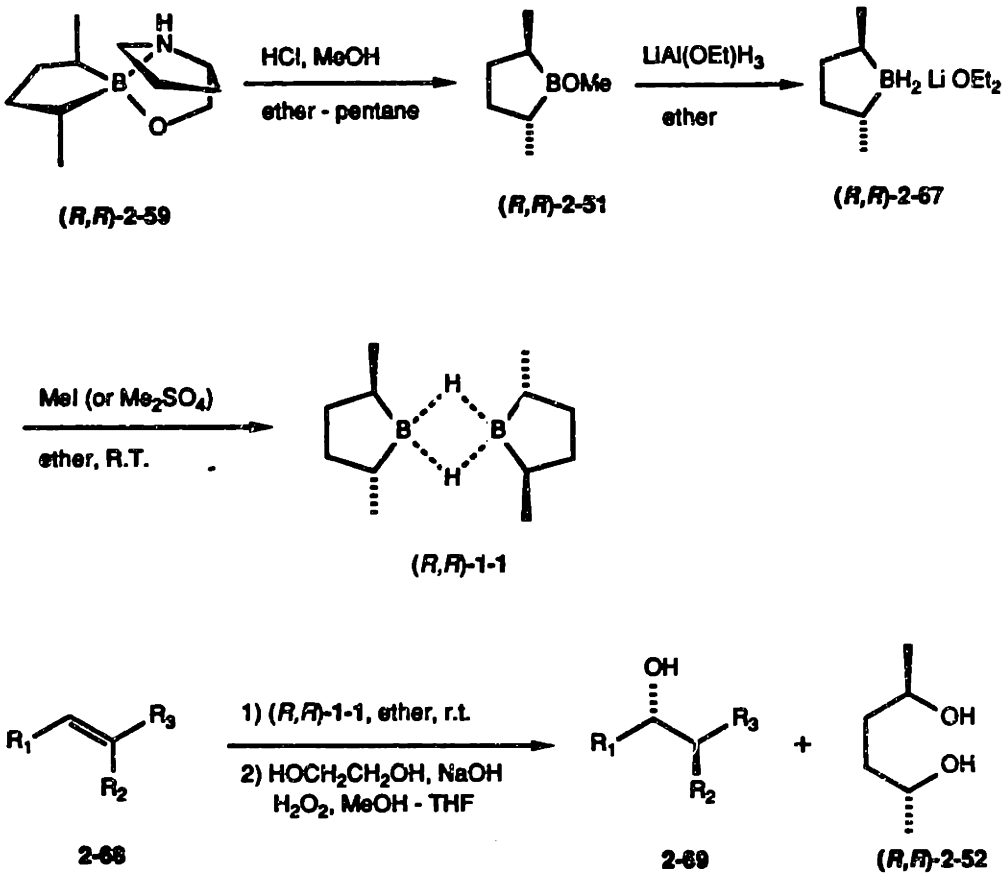
special precautions.

The per cent ee's of the complexes were determined by oxidation to diol and subsequent analysis of the corresponding bis(α-methoxy-α-trifluoromethylphenyl acetate) from the diol. It should be noted that the Mosher's acid available from Aldrich is of variable enantiomeric purity (typically 94-98% ee, J. S. Petersen, R. M. Kennedy, R. P. Short, and B. M. Kim, 1985). This ee was determined by the reaction of the acid with optically pure α-phenylethylamine (obtained from recrystallization of tartaric acid salt) and analysis of the diastereomeric amides by capillary GC or HPLC. Essentially pure (>99.8% ee) Mosher's acid can be obtained by one recrystallization of the corresponding amine salt in ethanol following the original literature.[46]

2.3.3. Asymmetric Hydroboration

Portrayed in Scheme 2.15 is the generation of the borolane (*R,R*)-1-1 from (*R,R*)-2-59 and subsequent use in asymmetric hydroboration.

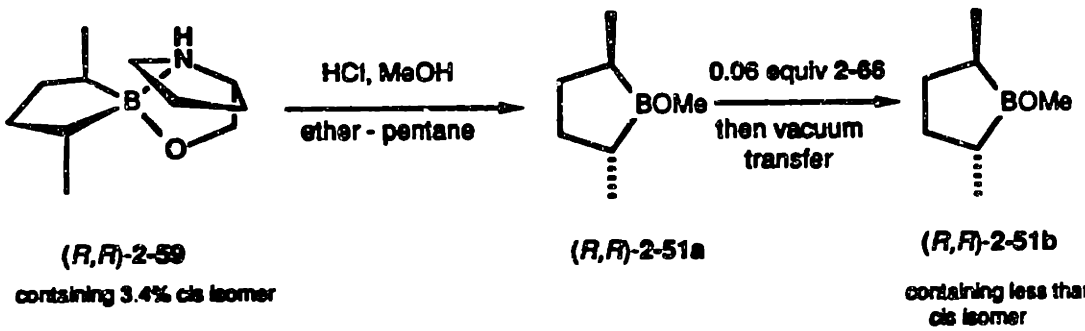
Scheme 2.15



The aminoalcohol complex (*R,R*)-2-59 can be directly converted to the dihydridoborate etherate (*R,R*)-2-67 with lithium aluminum hydride (T. Imai, 1985) or indirectly through (*R,R*)-2-51. The latter indirect route offers the advantage that (*R,R*)-2-67 is obtainable in high purity (see below). The generation of (*R,R*)-2-51 was effected by treating with methanol and ethereal HCl (see for example the conversions 2-22→2-

14, 2-47 → 2-48, and 2-55 → 2-51). Exemplified in Scheme 2.16 is a procedure for eliminating the undesired cis isomer from 2-59 at the stage of the methoxyborolane.(T. Imai, 1986). The aminoalcohol complex 2-59 which contained 3.4% of cis borolane

Scheme 2.16

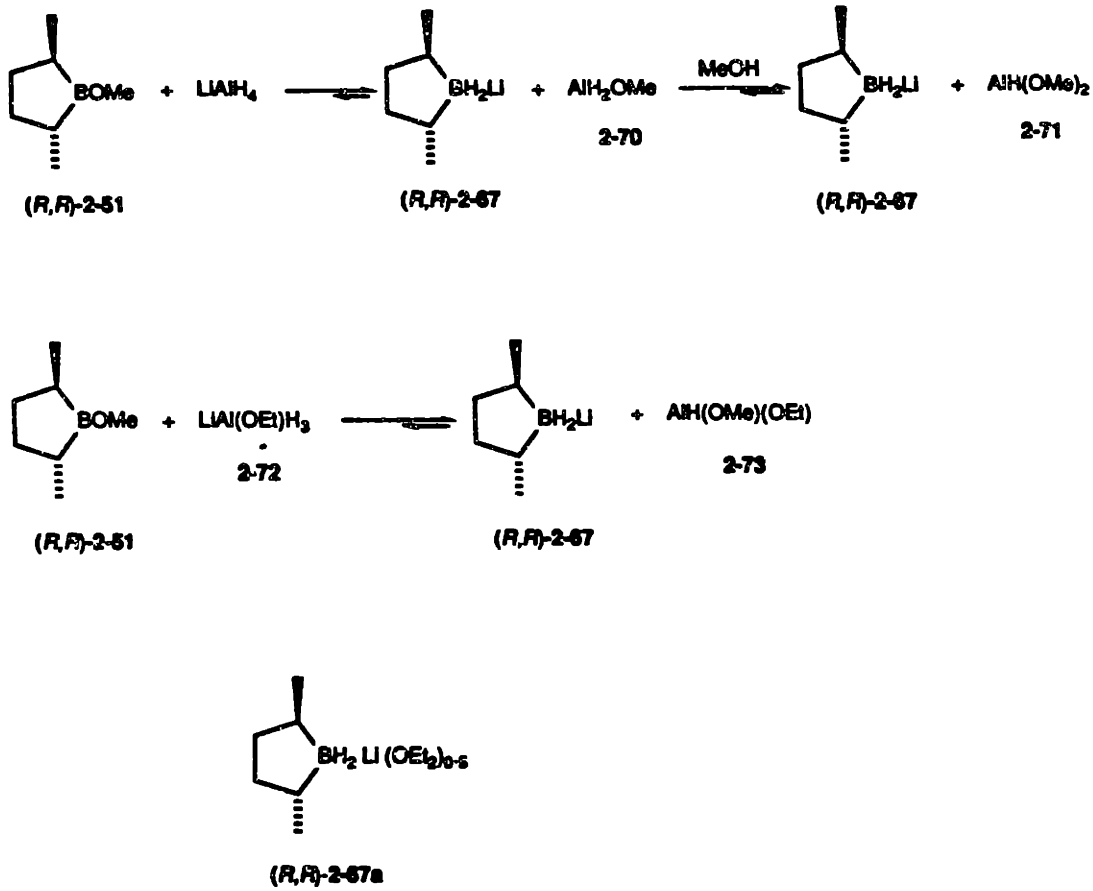


isomer was treated with HCl and methanol. The filtered and concentrated solution was treated with 0.06 equiv of *N*-(2-hydroxyethyl)pyrrolidine (2-66) and all volatile material was vacuum transferred. Analysis of the resulting methoxyborolane (*R,R*)-2-51b revealed that the content of the cis isomer was less than 1.0%. In the same manner enantiomeric impurities (e.g. (*S,S*)-isomer in (*R,R*)-complex) can also be removed by treating the methoxyborolane with antipodal prolinol (in this case (*R*)-prolinol) and then vacuum transferring.

The borate complex (*R,R*)-2-67 can be generated in two ways (Scheme 2.17):[47] (1) Treatment of (*R,R*)-2-51 with LAH produces (*R,R*)-2-67 together with soluble methoxyalane (2-70). Addition of methanol converts 2-70 to dimethoxyalane (2-71), which is insoluble in ether and can be removed by filtration. (2) 2-67 is generated with $LiAl(OEt)H_3$ (2-72, LAH + 0.5 EtOAc),[47] precipitating the methoxyethoxyalane (2-73). The latter route proved to be superior to the former one in terms of the yield and the

ease of manipulation.

Scheme 2.17



Thus the reduction of (*R*,*R*)-2-51 with LiAl(OEt)H3 generated crystalline dihydridoborate (*R*,*R*)-2-67 as an ether complex. Apparently the crystalline 2-67 or an ether solution of 2-67 can be stored at -78°C in an inert atmosphere over a year without any loss of chemical or stereochemical integrity. The amount of ether in the borohydride complex was found to be variable. Under normal condition removal of solvent (~0.1 mmHg, 2 h) from the complex 2-67 resulted in a monoetherate, whereas a half etherate (*R*,*R*)-2-67a was afforded by coevaporating the solvent with benzene under high vacuum (<0.01 mmHg) at elevated temperaure (ca. 60°C). Etherate equivalents between 0.5-1.0 were also found occasionally.

Therefore it was necessary to analyze carefully the ^1H NMR spectrum of 2-67 before proceeding to a subsequent reaction. Depicted in Fig. 2.2 is ^1H NMR spectrum of $-OCH_2CH_3$ region of (R,R)-2-67. The asymmetry of the borolane moiety is reflected in the ABX_3 pattern of the methylene proton resonances of the ether.

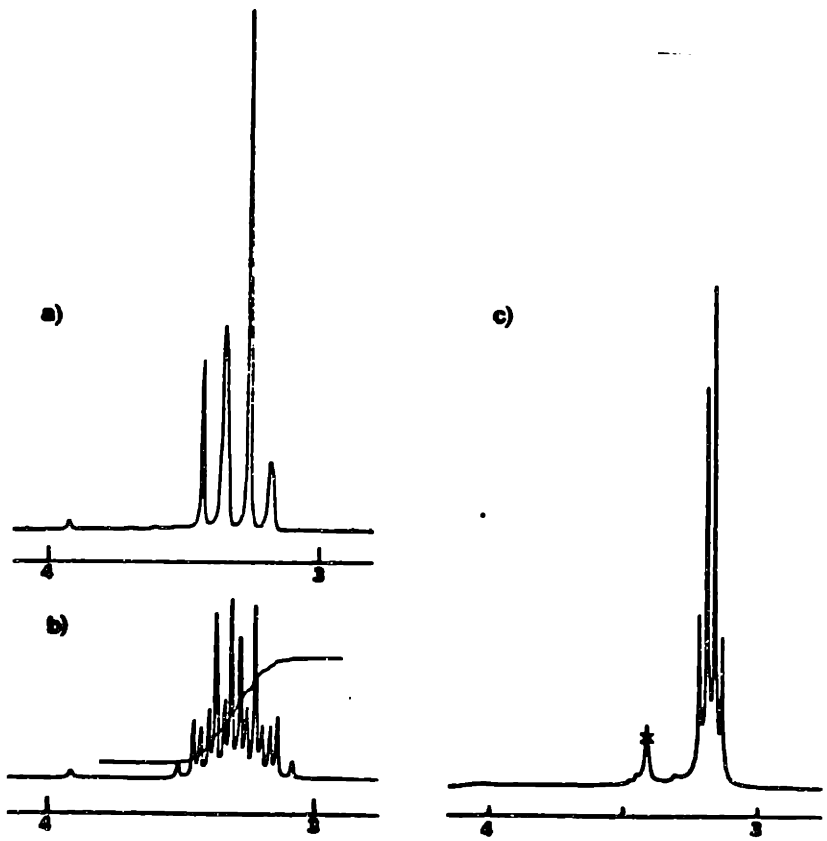


Fig 2.2. ^1H NMR spectra of OCH_2CH_3 region (3-4 ppm) of (a) (*R,R*)-2-67, irradiated at OCH_2CH_3, (b) (*R,R*)-2-67, and (c) (*R,S*)-2-67 (meso compound).

The borohydride 2-67 was dissolved in ether and used to generate *in situ* a known amount of the chiral borolane 1-1. As mentioned earlier in this chapter, the parent borolane isomerizes to 10-membered, 1,5-diboracyclodecane (2-32→2-33).[36] The borolane 1-1 was also found to undergo the same type of isomerization but with a half

life of 3-4 days at room temperature (0.5 M solution). Thus the hydroboration of even one of the most resistant olefins, 1-methylcyclohexene can be successfully executed to provide corresponding homochiral *trans*-2-methylcyclohexanol in a respectable yield (60%, entry 8 in Table 2.3). A variety of olefins smoothly reacted with **1-1** to provide trialkylboranes which were subjected to oxidation. The trialkylboranes obtained as above were rather resistant to the conventional oxidation conditions (aq $NaOH/H_2O_2$). However, use of ethylene glycol and methanolic NaOH (2 N or 6 N) smoothly furnished the corresponding alcohols in good to excellent yields. Summarized in Table 2.3 are the results of asymmetric hydroboration of achiral olefins with **1-1**,[20] together with the hydroboration results obtained from reagents **2-1** - **2-4** for a comparison.

Table 2.3[a] Asymmetric Hydroboration of Achiral Olefins with 1-1, 2-1, 2-2, 2-3, and 2-4.

entry	olefin	[b] reaction condtn time (h), temp (°C)	alcohol 2-69	[c] yield (%) of 2-69	[d] $[\alpha]^{27}_D$ of 2-69	% ee of 2-69 (absd)	% ee of 2-69 [e] 1-1	[f] Ipc_2BH (2-1)	[f] Lgf_2BH (2-2)	[f] $LienBH_2$ (2-3)	[f] $IpcBH_2$ (2-4)
1	[g]	1	HO, H	85	+0.25° (c 1.18, $CHCl_3$)[h]	[i] 1.4	1.5 (S)	32 (R)[j]			
2	[k]	36 (4°C) 2	OH	75	+13.3° (c 0.63, MeOH)[l]	[m] 95.2	97.6 (S)	99.1 (R)	78 (R)	55.0 (R)	24 (S)
3	[g]	6.5	OH	83	+8.86° (c 0.93, EtOH)[n]	[o] 96.4	99.9 (S)	94.1 (R)	71 (R)		
4	[k]	12 (-20°C) 48 (4°C) 6	OH	71	+13.4° (c 0.71, MeOH)[l]	[m] 97.0	99.5 (S)	14 (R)[j]	25 (S)	58.6 (R)	73 (S)
5	[g]	10	OH	83	+8.83° (c 1.05, EtOH)[n]	[o] 96.0	99.5 (S)				73 (S)
6	[g]	15	OH	90	+5.04° (c 1.13, EtOH)[p]	[m] 94.2	97.6 (S)	15 (R)[j]	70 (R)	66.5 (R)	53 (S)
7	[g]	9.5	HO	89	+46.6° (c 1.13, MeOH)[q]	[o] 97.0	100 (S,S)	24 (S,S)	63 (R,R)	45 (R,R)	66 (S,S)
8	[k]	96	HO	60(69)[r]	+37.8° (c 1.16, MeOH)[s]	[m] 93.2	95.6 (S,S)				71 (S,S)
9	[g]	12	HO	97	-10.6° (c 1.36, CCl_4)[t]	[n] 95.8	99.3 (S)		52 (R)		

a. Reaction in ethyl ether using 1.2 equiv of (*R,R*)-**1-1** and 2.4 equiv of CH_3I at room temperature (21-23 °C) unless otherwise noted.

b. Numbers in parenthesis designate reaction temperatures other than room temperature.

c. Determined by capillary GC analysis after acetylation (Ac_2O, pyr, and DMAP).

d. All optical rotations were measured at alcohol stage except entry 9 (acetate).

e. Numbers were corrected for the enantiomeric puritiy of each borane used.

f. Data from Brown's report (ref 24b and the following: Brown, H.C.; Ayyangar, N.R.; Zweifel, G. *J. Am. Chem. Soc.* **1964**, *86*, 1071.)

g. (*R,R*)-**1-1** of 96.5% ee was used for hydroboration.

h. Lit $[\alpha]^{28}_D$ -2.95° (*c* 60.521, $CHCl_3$) for *R* alcohol, Tsuda, K.; Kishida, Y.; Hayatsu, R. *J. Am. Chem. Soc.* **1960**, *82*, 3396.

i. Based on ^1H NMR analysis of the MTPA ester.

j. (+)-Ipc_2BH derived from (-)-α-pinene was used.

k. (*R,R*)-**1-1** of 97.5% ee was used.

l. $[\alpha]^{21}_D$ +12.0° (*c* 1.12, CH_3OH) for commercially available *S* alcohol (81.6% ee, HPLC analysis of MTPA ester, Aldrich Chemical Co.).

m. HPLC analysis of the derived MTPA esters.

n. Lit. $[\alpha]^{20}_D$ +8.0° (*c* 0.6, C_2H_5OH) for *S* alcohol, Davies, J.; Jones, J.B. *J. Am. Chem. Soc.* **1979**, *101*, 5405.

o. HPLC analysis of the Pirkle's carbamates: Pirkle, W.H.; Hoekstra, M.S. *J. Org. Chem.* **1974**, *39*, 3904.

p. Lit $[\alpha]^{25}_D$ +5.34° (*c* 5.0, C_2H_5OH) for *S* alcohol, Pickard, R.H.; Kenyon, J. *J. Chem. Soc.* **1913**, *103*, 1923.

q. Lit $[\alpha]^{25}_D$ +43.9° (*c* 1.00, CH_3OH) for 1*S*,2*S* alcohol, Partridge, J.J.; Chadha, N.K.; Uskokovic, M.R. *J. Am. Chem. Soc.*. **1973**, *95*, 532.

r. Yield in parenthesis is based on consumed starting material.

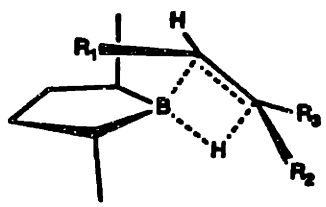
s. Lit $[\alpha]^{20}_D$ +42.9° (*c* 1, CH_3OH) for 1*S*,2*S* alcohol, Backstrom, R.; Sjoberg, B. *Ark. Kemi.* **1967**, *26*,

549.

t. Lit $[\alpha]^{25}_D$ -1.6° (*c* 1.1, CCl_4) for (*S*)-1-acetoxy-1-cyclohexylethane of 32±6% ee: This (-)-isomer was erroneously recorded as having an *R* configuration (personal communication from Professor Meyers): Meyers, A.I.; Ford, M.E. *J. Org. Chem.* 1976, *41*, 1735.

With the exception of the type I olefin (entry 1) all hydroborations proceeded with excellent enantioselectivities, clearly meeting the criteria set for double-asymmetric synthesis. Reagent **1-1** is sufficiently reactive to hydroborate even type IV olefins as reflected by high yields (entry 6-9) and remedies the deficiencey of some of the known chiral boranes, e.g. **2-1** .

The kinetic studies on the hydroboration with **1-1**, which will be discussed in the next section of this chapter, showed a best fit for 3/2 order rate kinetics---first order in substrate and a half order in the dialkylborane dimer. Thus the monomer is the reactive species responsible for asymmetric induction. Also Brown's kinetic studies[48,49] of hydroboration of dialkylboranes indicate that in general monomeric boranes rather than diboranes are the reacting species involved in the transition state. Coupled with the kinetic data, the extent and directionality of the observed asymmetric inductions lead to the proposal of the transition state model shown in **2-74** for the reaction of olefins with **1-1**.[50]



2-74 a R=H
b R=H

In the four center orientation invoked in **2-74** the distance between an olefinic carbon terminus and the boron atom must be quite short, and the distinction between

R and H of the carbon terminus by the 2-methyl group of the borolane moiety becomes obvious (**2-74a**). Thus a high degree of asymmetric induction with type II-IVolefins is afforded. The low per cent ee observed for the type I olefin is also understandable (transition state **2-74b**) and conforms to the uniformly marginal degree of asymmetric induction (4-23% ee) observed in the reactions of 3,4-disubstituted borolanes with the type II-IV olefins (see section 1 of this chapter). This result is again consistent with the view that the trajectory of the olefins toward the monomer of **2-8** or **2-9** is approximated by that shown in transition state **2-74**.

That the sp^3 hybridization of the boron atom has substantially developed in the transition state is also assisted by the computational study[51] on the hydroboration of cis-2-butene with **1-1** and 3,4-dimethylborolane (**2-75**).(see Fig 2.3-2.6). The calculated selectivities for 2,5-dimethylborolane (**1-1**) upon the reaction with cis-2-butene by MM2 models are indeed in good agreement with the experimental data.[51] The calculated selectivity for the reaction of (*R*,*R*)-**1-1** with cis-2-butene was 94.3% ee at 25°C, while 97.6% ee was observed experimentally with (*R*,*R*)-**1-1** at 0-25°C.

Fig. 2.3 Preferred transition state for reaction of (2*R*,5*R*)-dimethylborolane with *cis*-2-butene. $E_{rel} = 0$. Gives (*S*)-2-butanol. 35(*S*) : 1(*R*) ratio predicted at 25°C.

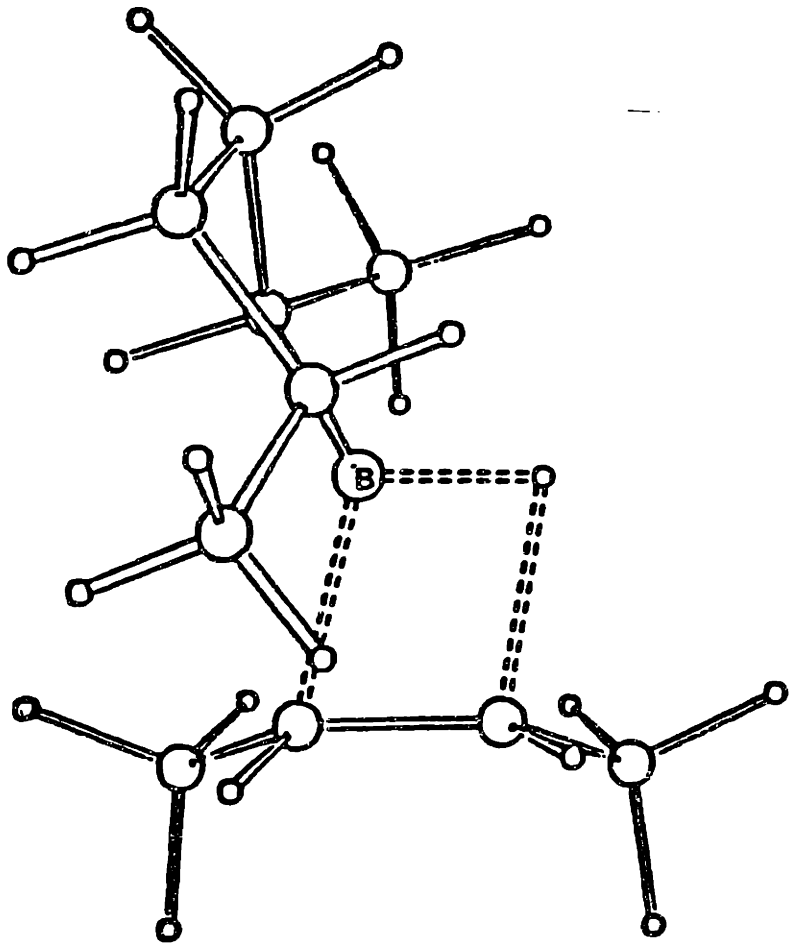


Fig. 2.4 Disfavored transition state for reaction of (2*R*,5*R*)-dimethylborolane with *cis*-2-butene. E_{rel} = 2.1 kcal/mol. Gives (*R*)-2-butanol. 35(*S*) : 1(*R*) ratio predicted at 25°C.

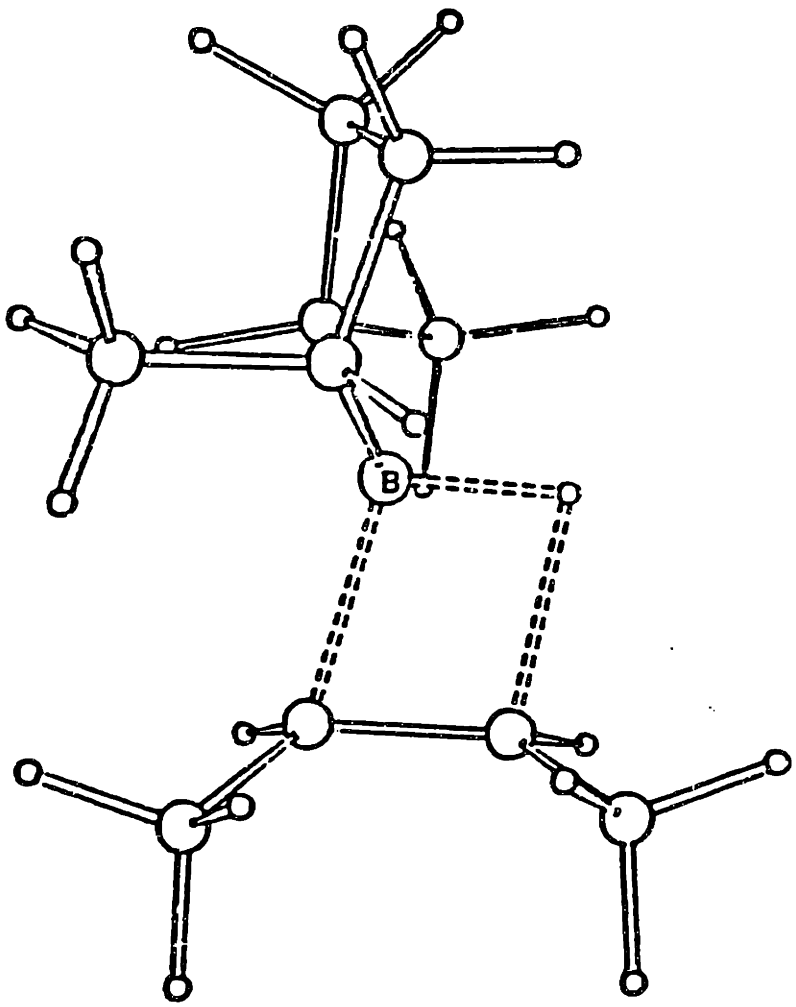


Fig. 2.5 Preferred transition state for reaction of (3*S*,4*S*)-dimethylborolane with *cis*-2-butene. $E_{rel} = 0$. Gives (R)-2-butanol. 1.2(*R*) : 1.0(*S*) ratio predicted at 25°C.

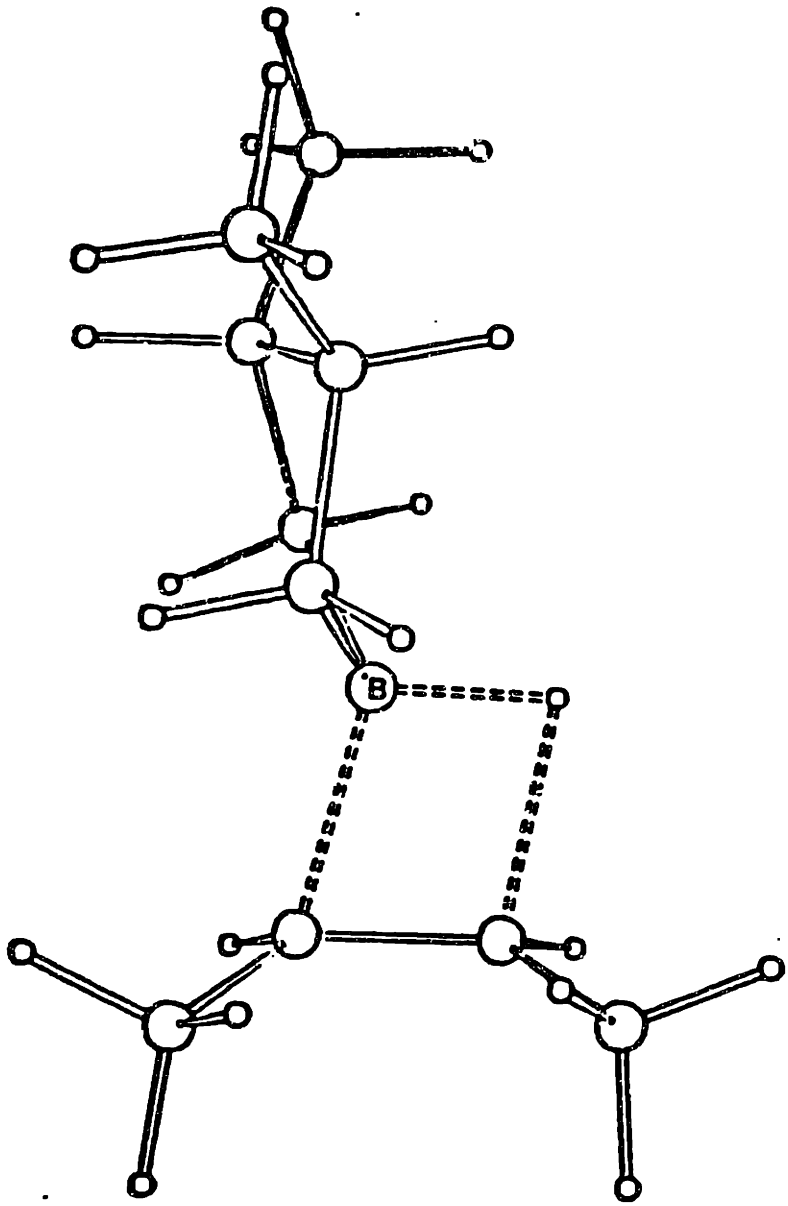
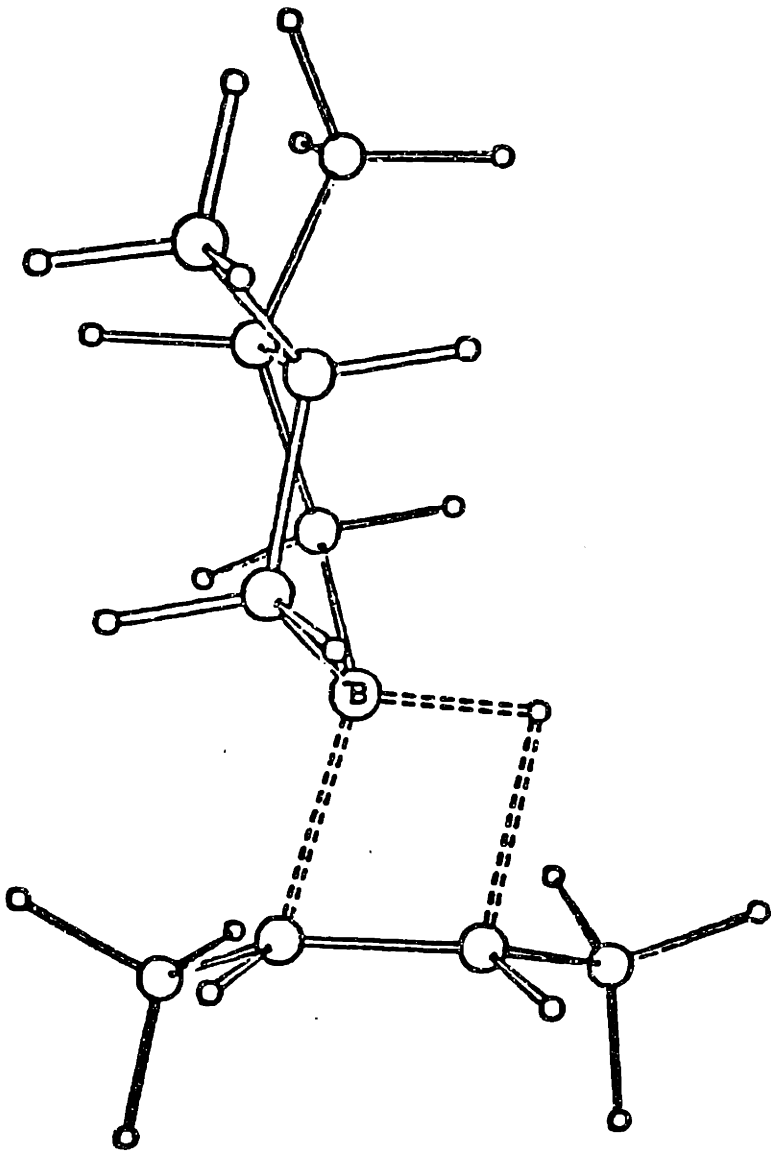


Fig. 2.6 Disfavored transition state for reaction of (3*S*,4*S*)-dimethylborolane with *cis*-2-butene. E_{rel} = +0.1 kcal/mol. Gives (*S*)-2-butanol. 1.2(*R*) : 1.0(*S*) ratio predicted at 25°C.



Concluding Remarks

The evolution of C_2 symmetric dialkylborolanes from 3,4-diethyl- and 3,4-dicyclohexylborolanes to 2,5-dimethylborolane was accompanied by the development of a new technique for resolving racemic boranes with homochiral aminoalcohols. The enantiomeric pair of borane reagents (*R,R*)- or (*S,S*)-**1-1** has simple structure of C_2 symmetry and meet the requirement of "98% ee" for the double-asymmetric synthesis in reactions with all types of representative achiral alkenes shown above except for type I.

The borolanes (*R,R*)- and (*S,S*)-**1-1** are superior to the existing chiral boranes such as **2-1**- **2-4** in terms of asymmetric induction and thus the stereoselective synthesis of numerous homochiral compounds is, in principle, possible through double-asymmetric synthesis and the major problems associated with hydroboration of type II-IV olefins are now essentially solved. Unlike conformationally flexible **2-1** , **2-2** and **2-4** , (*R,R*)- and (*S,S*)-**1-1** provide valuable information as to the transition state geometry of the reaction as its course is readily analyzed with conformationally rigid chiral reagents.

2.4 KINETIC STUDIES ON THE HYDROBORATION USING 2,5-DIMETHYLBOROLANE

The investigation of reaction mechanisms is heavily dependent on the study of reaction kinetics. In order to better understand the mechanism of asymmetric hydroboration with the 2,5-dimethylborolane (1-1), we embarked on the investigation of the kinetics of this process. Three methods for the determination of concentration vs. time for the reaction are: (1) aliquot quench and product determination by GC (used by Brown in his early studies), (2) quantitative IR spectrocopy of reaction mixture in a flow system (Brown's current method), or (3) ^{11}B NMR spectroscopy. Method one was rejected as being tedious and compromised by the uncertainties involved in any quenching procedure. Method two was judged undesirable because it required construction of an experimental apparatus, offers poor possibilities for variable temperature studies and could be somewhat inaccurate because of the difficulties in obtaining quantitative IR data. Although ^{1}H NMR has been widely employed for the kinetic studies, surprisingly no such studies based on ^{11}B NMR had been reported at the time this study was launched.[52] The successful use of ^{1}H NMR suggested the general feasibility of this approach. Also the accuracy and a wide variation of temperature control possible in NMR spectrometric method would allow the investigation of activation energies and entropies as well as permitting the determination of kinetic order. The first part of this section is focused on the feasibility of ^{11}B NMR for kinetic studies on the hydroboration using 9-BBN. Kinetic studies of hydroboration employing 1-1 by ^{11}B NMR is presented in the later part of this section. Most of the work presented in this section was carried out by Dr. J. S. Petersen in this research group and the following is a paraphrasing of his report.

2.4.1. Background

Many studies of the kinetics of hydroboration have been attempted. Unfortunately, the early studies are all focused on the reactions of BH_3 which as noted by Brown are very complicated.[53] The earliest work related to the current interest is Brown's study of the hydroboration reaction with disiamylborane.[54] However, the work on the kinetics with disiamylborane should be greeted with considerable scepticism† particularly in light of his more recent investigations with 9-BBN and borinane. Well aware of the uncertainties of his earlier work, Brown made good use of the availability and stability of 9-BBN to expand his kinetic studies.[57] In a series of reports the following has been conclusively established (see Scheme 2.18): (1) Substrates having low reactivity, i.e. cyclohexene react with 3/2 order kinetics -- first order in olefin and 1/2 order in 9-BBN dimer. (2) Moderately reactive substrates, 1-hexene, cyclohexanone, t-butanol react with first order kinetics -- first order in 9-BBN dimer. (3) Highly reactive substrates such as methanol and certain amines (reaction to form amine addition complexes) react with second order kinetics -- first order in substrate and first order in 9-BBN dimer. Cases of intermediate kinetics are also reported. However, as has been pointed out on numerous occasions, 9-BBN is an exceptionally stable dimer and thus may not show the same behavior as other dialkylboranes. Finally the hydroboration reactions of borinane dimer has been

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† In this work Brown determined that the reaction of disiamylborane with a variety of olefins in THF at 0°C proceeds with second order kinetics - first order in olefin and first order in the dialkylborane dimer. The determination that this dialkylborane exists as a dimer in THF rests on a molecular weight determination (note that the weight determined was somewhat lower) and the observation of the characteristic bridging hydride stretches in the IR.[55] Neither of these rules out the possibility of the presence of substantial amount of the monomer - THF complex. Additionally, since these studies were apparently carried out at higher concentrations than the usual kinetic studies they would tend to understate the importance of the presence of the monomer in the kinetic studies. In the case of 9-BBN, an exceptionally stable dimer, a substantial amount of monomer - THF complex is present as determined by ^{11}B NMR.[56] No ^{11}B NMR study of disiamylborane at varying concentrations has been reported.

examined in heptane at 0°C by Brown.[49a] In all cases where the kinetic order was determined the kinetics were found to be 3/2 order -- first order in olefin and 1/2 order in dimer. Note that in heptane the equilibrium should be heavily inclined to dimer. The dimethylborolane **1-1** should be more similar to borinane than 9-BBN.

Scheme 2.18.

$$[\text{9-BBN}_{\text{dimer}}] \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 2[\text{9-BBN}_{\text{monomer}}]$$

$$[\text{9-BBNmonomer}] + [\text{substrate}] \xrightarrow{k_2} \text{product}$$

$$[\text{9-BBNdimer}] + [\text{substrate}] \xrightarrow{k_3} \text{product}$$

if k_2[substrat] >> k_{-1}[9-BBN$_{\text{monomer}}$], then 1st order in 9-BBN dimer and 0th order in substrate,

if k_{-1}[9-BBNdimer] >> k_2[substrate], then 3/2 order; 1st order in substrate and 1/2 order in 9-BBN dimer.

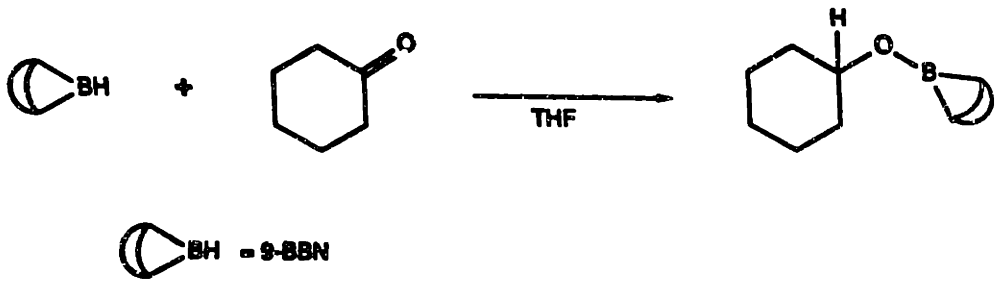
2.4.2. Application of ^{11}B NMR to the determination of hydroboration kinetics.

The purpose of this section is to show that ^{11}B NMR gives results identical to those obtained by Brown for some of the representative reactions such as the reduction of cyclohexanone and the hydroboration of cyclohexene by 9-BBN.

Typical of the results with cyclohexanone are the data of Experiments I and II (Scheme 2.19) (Table 2.4 and 2.5). As is readily seen from the graphs (Fig 2.7 and 2.8), plots of the natural logarithm of the integral of the peak area corresponding to 9-BBN

dimer (starting material) vs. time are very close to linear. The correlation coefficients, r's, are 0.9987 and 0.9994, respectively and the reactions were followed for 2.8 half lives.

Scheme 2.19



BH = 9-BBN

Table 2.4 Rate data measured by ^{11}B NMR for the reduction of cyclohexanone (0.50 M) with 9-BBN (0.50 M) in THF at 25°C (Exp I).

Spectrum No.	time (sec)	integral	ln([9-BBN$_{dimer}$])	
1	127	12.8	2.549	
2	187	11.5	2.442	
3	247	10.55	2.356	
4	307	9.25	2.225	
5	368	8.92	2.118	
6	428	8.11	2.093	
7	488	7.56	2.023	
8	548	6.83	1.921	
9	608	6.21	1.826	
10	728	5.26	1.660	
11	848	4.32	1.463	
12	969	3.60	1.281	
13	1089	2.88	1.058	
14	1209	2.41	0.880	>80% completion

Applying least square method,

intercept = 2.729

slope = -15.1×10^{-4}

correlation coefficient = -0.9987

$k_1 = 15.1 \times 10^{-4}$

Table 2.5 Rate data measured by ^{11}B NMR for the reduction of cyclohexanone (0.50 M) with 9-BBN (0.50 M) in THF at 25°C (Exp II)

Spectrum No	time (sec)	integral	ln([9-BBN$_{dimer}$])
1	120	13.36	2.592
2	180	12.45	2.522
3	240	11.06	2.403
4	659	6.02	1.795
5	719	5.57	1.717
6	780	5.07	1.623
7	840	4.62	1.530
8	900	4.32	1.463
9	1010	3.42	1.230
10	1140	2.81	1.033
11	1260	2.40	0.875

Applying least square method,

intercept = 2.787

slope = -15.1×10^{-4}

correlation coefficient = -0.9994

$k_1 = 15.1 \times 10^{-4}$

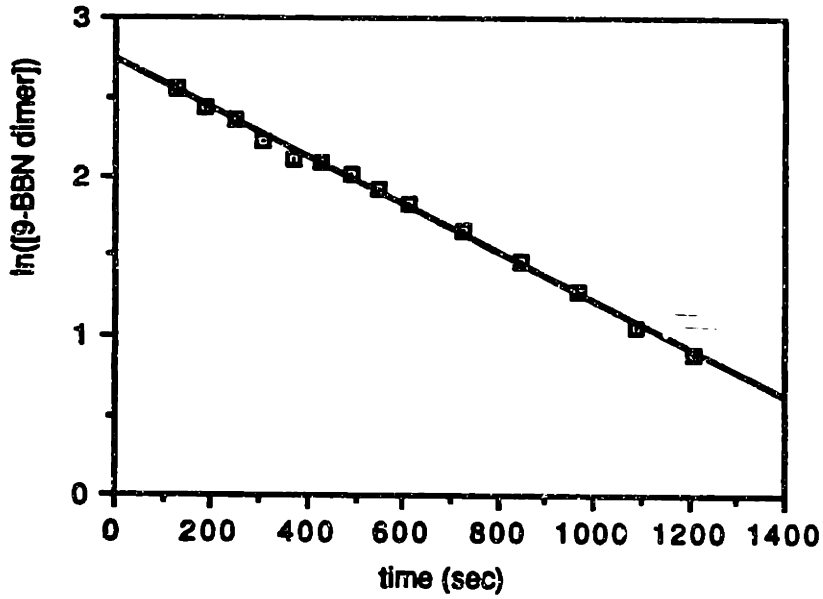


Fig. 2.7 Rate plot for the reduction of cyclohexanone (0.50 M) with 9-BBN (0.50 M) in THF at 25°C (Exp I).

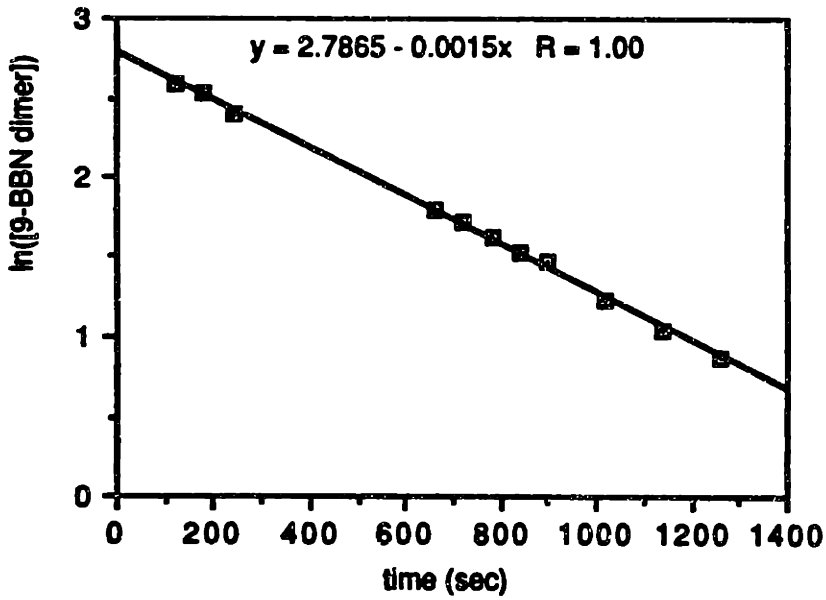
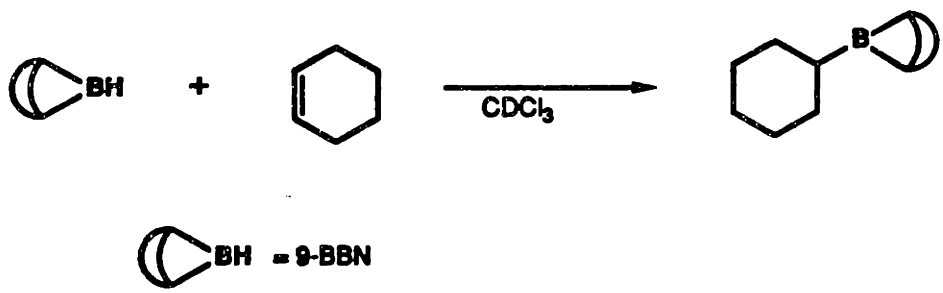


Fig. 2.8 Rate plot for the reduction of cyclohexanone (0.50 M) with 9-BBN (0.50 M) in THF at 25°C (Exp II).

Difficulties in obtaining accurate integrals precluded the use of data after the reaction was about 85% complete. The rate constant from duplicate runs (Exp I and II), 0.00151 sec^{-1} was very close to that of Brown's, 0.00144 sec^{-1}.[58] Having established that the results were reproducible and in good agreement with the literature value for this simple first order case, we went on to examine the 3/2 order reaction of cyclohexene with 9-BBN.

In Experiment III the reaction of 9-BBN dimer (0.2 M) with cyclohexene (0.4 M) was studies (Scheme 2.20). To allow the experiment to be run in locked mode and to allow homogeneity adjustments on the actual sample, this experiment was performed

Scheme 2.20



in $CDCl_3$ rather than CCl_4, the solvent used by Brown. As predicted by 3/2 order kinetics a plot of $1/\sqrt{[9\text{-}BBN_{dimer}]}$ is very close to linear as illustrated in Fig 2.9 (Table 2.6). Since this reaction was relatively slow ($k_{3/2} = 0.33 \times 10\text{-}4$), only the first 15% of the reaction was followed. Again the results were in good agreement with Brown's value, $k_{3/2} = 0.323 \times 10\text{-}4$.[51a]

An attempt to run the experiment under pseudo half order condition (excess olefin)(experiment IV) was unsuccessful because the kinetics changed from 3/2 order to first order rather than providing the 1/2 order kinetics predicted if the relationship

Table 2.6 Rate Data Measured by ^{11}B NMR for the hydroboration of cyclohexanone (0.41 M) with 9-BBN (0.21 M) in $CDCl_3$ at 25°C—three-halves order kinetics (Exp III).

Spectrum No.	time (sec)	integral of 9-BBN	[9-BBN]	$\frac{1}{\sqrt{\text{9-BBN}_{dimer}}}$
1	1506	12.46	0.1817	2.346
2	2106	12.14	0.1770	2.377
3	2706	11.94	0.1741	2.397
4	3306	11.84	0.1727	2.406
5	3907	11.56	0.1686	2.435
6	5258	11.14	0.1625	2.481
7	6032	10.97	0.1599	2.501
8	6632	10.78	0.1572	2.522
9	7233	10.62	0.1549	2.541
10	7833	10.47	0.1527	2.559

followed for >15% reaction.

Calculated for 3/2 order kinetics by least square method,

intercept = 2.303

slope = 0.330×10^{-4}

cor. coeff. = 0.9984

$k_{3/2} = 33.0 \times 10^{-4}$

Table 2.7 Rate data measured by ^{11}B NMR for the hydroboration of cyclohexanone (2.2 M) with 9-BBN (0.11M) in $CDCl_3$ at 25°C—pseudo first order kinetics (Exp IV).

Spectrum No.	time (sec)	9-BBN integral	[9-BBN$_{dimer}$]	ln([9-BBN$_{dimer}$])
1	625	17.10	0.1040	-2.263
2	945	16.28	0.0990	-2.312
3	1266	15.65	0.0952	-2.352
4	1587	14.92	0.0908	-2.400
5	1908	14.31	0.0870	-2.441
6	2229	13.63	0.0829	-2.490
7	2550	13.26	0.0807	-2.518
8	3167	12.05	0.0733	-2.613
9	3788	11.03	0.0671	-2.702
10	4408	10.21	0.0621	-2.779
11	4820	9.60	0.0584	-2.841
12	5420	8.75	0.0532	-2.933
13	6020	8.01	0.0487	-3.022
14	6620	7.55	0.0459	-3.081
15	7820	6.43	0.0391	-3.241
16	9019	5.11	0.0311	-3.471
17	10219	4.27	0.0260	-3.651

Reaction was followed to 75% completion.

Least squre results for pseudo first order kinetics,

intercept = -2.166 cor. coeff. = 0.9992

slope = -1.42×10^{-4} $k_1 = 1.42 \times 10^{-4}$

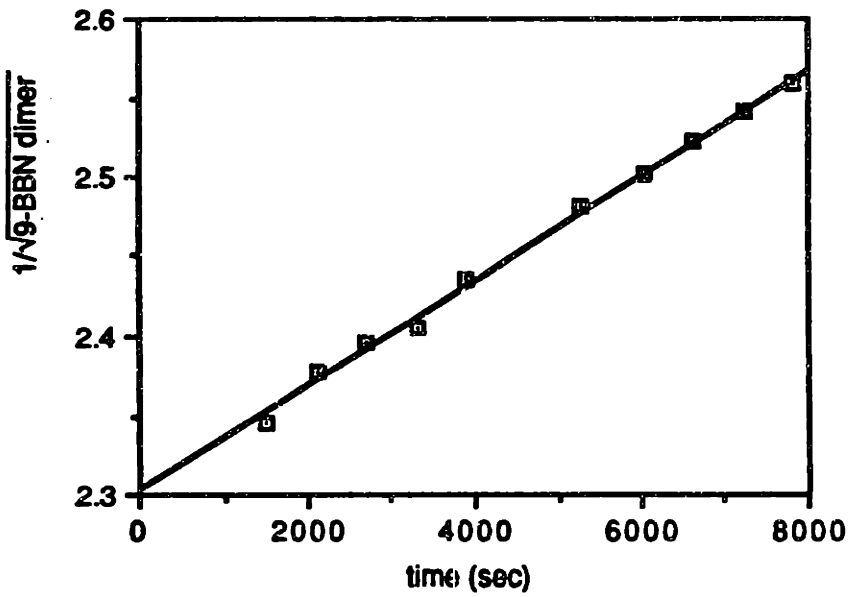


Fig. 2.9 Rate plot of 3/2 order kinetics measured by ^{11}B NMR for the hydroboration of cyclohexene (0.41 M) with 9-BBN (0.21 M) (Exp. III).

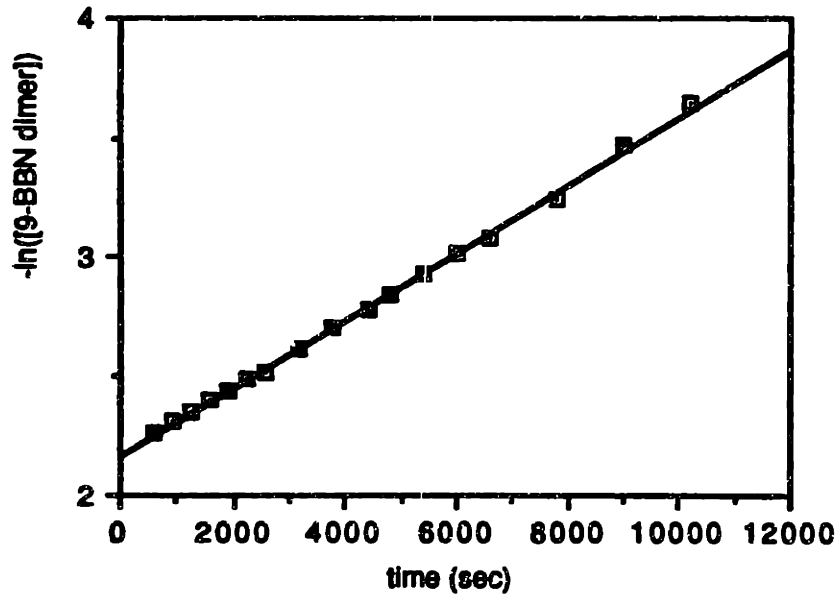


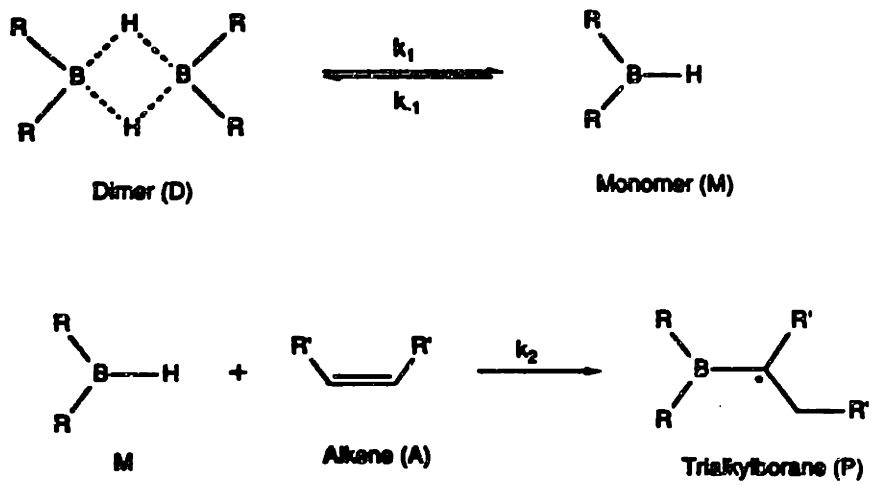
Fig 2.10 Rate plot of pseudo 1st order kinetics measured by ^{11}B NMR for the hydroboration of cyclohexene (2.2 M) with 9-BBN (0.11 M) (Exp IV).

k_{-1}[9-BBN] >> k_2[olefin] were still true under these conditions. The fit to first order kinetics was very good, however (Fig. 2.10), giving a rate of 1.54 x 10^{-4} sec^{-1} for the reaction of 9-BBN with 1-hexene in CCl_4 at 25°C (Table 2.7).[59] Thus a number of kinetic experiments have given the same results as those reported by Brown, establishing that ^{11}B NMR is a suitable tool for kinetic analysis.

2.4.3. Kinetics of Hydroboration with (*S,S*)-2,5-dimethylborolane {(S,S)-**1-1**}

A kinetic investigation of hydroboration with (*S,S*)-**1-1** has been undertaken to establish the nature of the reactive species in this reaction. In the previous section ^{11}B NMR was established as a suitable tool for the determination of the concentration of the dialkylborane. At the outset, we expected to find kinetic behavior similar to that reported by Brown for 9-BBN, borinane,[53] and more recently for disiamylborane.[49] This kinetic behavior is shown in Scheme 2.21 and the derivation of a general kinetic expression based on the scheme is listed below.

Scheme 2.21



$$\frac{d[P]}{dt} = -2d[D]/dt \quad (1)$$

$$\frac{d[P]}{dt} = k2[M][A] \quad (2)$$

Where [P] = concentration of product trialkylborane

[D] = concentration of dimer

[M] = concentration of monomer

[A] = concentration of alkene

From steady state assumption:

$$\frac{d[M]}{dt} = 2k_1[D] - 2k_{-1}[M]^2 - k_2[M][A] = 0 \quad (3)$$

From equation (3),

$$\frac{k_1[D]}{k_{-1}[M] + \frac{1}{2}k_2[A]} = [M] \quad (4)$$

Substituting (4) into (2),

$$\frac{d[P]}{dt} = \frac{k_1[D]k_2[A]}{k_{-1}[M] + \frac{1}{2}k_2[M]} \quad (5)$$

Substituting [D] into (5),

$$\frac{-d[D]}{dt} = \frac{k_1[D]\frac{1}{2}k_2[A]}{k_{-1}[M] + \frac{1}{2}k_2[A]} \quad (6)$$

If $k_{-1}[M] >> \frac{1}{2}k_2[A]$, then equation (6) becomes

$$\frac{-d[D]}{dt} = k_1[D]\frac{\frac{1}{2}k_2[A]}{k_{-1}[M]} \qquad (7)$$

Since $k_{-1}[M] >> \frac{1}{2}k_2[A]$ then equilibration is rapid relative to reaction and the following is true:

$$\frac{k_1}{k_{-1}} = \frac{[M]^2}{[D]} \quad \text{or} \quad \sqrt{\frac{k_1}{k_{-1}}[D]} = [M] \qquad (8)$$

Substituting in (7):

$$\frac{-d[D]}{dt} = \frac{k_1[D]\frac{1}{2}k_2[A]}{k_{-1}\sqrt{\frac{k_1[D]}{k_{-1}}}} \qquad (9)$$

and simplifying gives

$$\frac{-d[D]}{dt} = \frac{1}{2}\sqrt{\frac{k_1}{k_{-1}}[D]} \times k_2[A] \qquad (10)$$

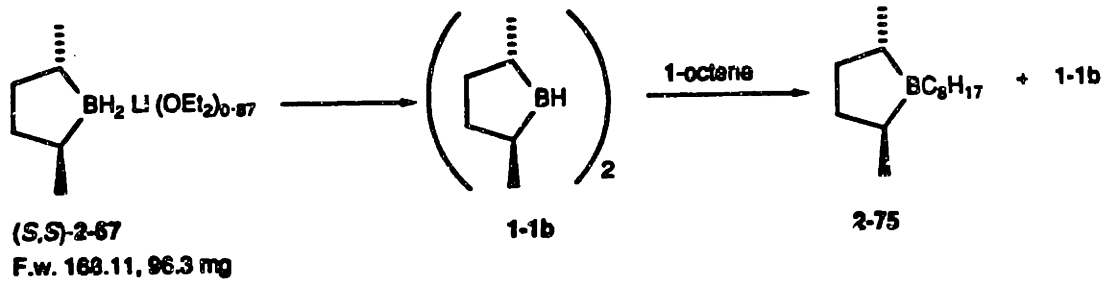
where $\frac{1}{2}\left(\frac{k_1}{k_{-1}}\right)^{1/2}k_2 = k_{3/2}$

For the purpose of the present discussion it is only important to recognize that if equilibrium is fast relative to the rection of the monomer with the alkene then the rate of reaction is proportional to the square root of the concentration of the dimer and proportional to the concentration of the alkene.

Unlike the case of simple first order kinetics, the first problem posed by 3/2

order kinetics is determining the initial concentration of the dimer. Our borohydride precursor (*S,S*)-**2-67**, a waxy white solid, can be weighed, and based on integration of the ethereal solvent peaks relative to the borohydride peaks (^{1}H NMR, see Section 2.3.3) and the assumption that the borohydride is converted to 100% of the theoretical amount of dimer, we can obtain a starting concentration. However when the graphs of 3/2 rate vs. time were examined, there was a pronounced tendency for the calculated rate to increase as time increased. Such a curvature could result from the presence of less than the calculated amount of borane dimer (*S,S*)-**1-1** Therefore an alternative method of determining the initial concentration was sought. It was tried to add known amounts of n-octyl-9-BBN to the borane dimer (*S,S*)-**1-1** (generated from the hydride *in situ*) and comparing the integrals of the trialkylborane to the dialkylborane. However, addition of the trialkylborane reproducibly caused a doubling of the peak corresponding the dimer. The calculated concentration of dimer was also inconsistent with other measurements and therefore this method of calibration was rejected. Next, use of trimesitylborane as an internal standard was attempted. It was expected that the steric bulk of this borane would prevent it from interacting with any of the boron species in solution. However, this highly crystalline compound (mp 194°C) was only sparingly soluble in the solvents of interest (hexane and ether). Finally, successful calibration was accomplished through the reaction of the borane dimer with a known amount of 1-octene. Typically the dimer was generated in the same manner as in the kinetic runs and allowed to react with 50% of the theoretical amount of olefin. From a spectrum at the beginning of the reaction and one at infinite time (for practical purposes 45 min to 1 h is sufficient in this case) one can calculate the amount of borane dimer originally present as shown in Scheme 2.22.

Scheme 2.22



(S,S)-2-67
F.w. 168.11, 96.3 mg

1-1b

2-75

From two such runs, the calculated amount of dimer present was 86% of that calculated based on integration of the ether solvate. The kinetics reported here are based on the octene calibration runs.

Once the initial concentration of the borolane dimer was determined, the rate calculations were relatively straightforward. Briefly, the calculation was performed as follows. First a response factor for the product peak relative to the dimer peak was determined. Next, based on the molecular weight of the borohydride 2-67, the octene correction factor, and the amount of solvent, an initial concentration is calculated. To calculate the concentration at t_0(t_0 is the first data point and corresponds to a time 2 to 4 min after the sample is transferred to the NMR probe) the integrals of the dimer peak and the response factor correlated product peak were compared and the % reaction prior to t_0 was determined. The dimer concentration at t_0 was calculated by multiplying the initial concentration times 1 - (1/100) x (% reaction at t_0). Next, the initial concentration of substrate was calculated and the substrate concentration at t_0 was calculated as above. Finally the concentration of the dimer at time t was calculated as the concentration at t_0 times the integral at t divided by the integral at t_0. These values are substituted into the desired integrated rate equation. The corresponding integrated rate equation is:

$$\frac{dx}{dt} = k(a - 2x)\sqrt{b - x}$$

$$= 2k(\frac{a}{2} - x)\sqrt{b - x}$$

where x = borolane dimer,

2x = alkene

$$\frac{dx}{(\frac{a}{2} - x)\sqrt{b - x}} = 2kdt$$

$$\text{if } \frac{a}{2} > b$$

$$\frac{1}{2}\left[\frac{2}{(\frac{a}{2} - b)^{1/2}} \left(\arctan(\frac{b - x}{\frac{a}{2} - b})^{1/2} - \arctan(\frac{b}{\frac{a}{2} - b})^{1/2}\right)\right] = kt$$

In Table 2.8, 2.9, and 2.10 are listed data obtained from the calculations according to the integrated rate equation from three different runs (Exp V-VII) and rate plots for each experiment are depicted in Fig. 2.11-2.13, respectively.

Table 2.8 Rate data for the hydroboration of *cis*-3-hexene (0.173 M) with (*S,S*)-1-1 dimer (0.0714 M) in ether at 11.0°C (Exp V).

spectrum No.	time (sec)	[dimer]	f(x)	
0	0	0.071363		
1	320	0.53674	-0.4605	
2	642	0.42695	-0.8585	
3	961	0.34848	-1.2305	
4	1281	0.027935	-1.6527	
5	1554	0.022324	-2.0954	
6	1875	0.018745	-2.4475	
7	2195	0.015370	-2.8514	
8	2516	0.012239	-3.3153	83% complete

$$8.157682 \times \left[\arctan\left(\frac{b-x}{0.015026^{a}}\right)^{1/2} - 1.140583 \right] = kt$$

$k_{3/2} = 13.1 \times 10^{-4}$

Table 2.9 Rate data for the hydroboration of *cis*-3-hexene (0.165 M) with (*S,S*)-1-1 dimer (0.070 M) in ether at 11.1°C (Exp VI).

spectrum No.	time (sec)	[dimer]	f (x)
0	0	0.069780	
1	193	0.059817	-0.2533
2	386	0.052908	-0.4645
3	699	0.040253	-0.9635
4	1013	0.032799	-1.3616
5	1326	0.024836	-1.9312
6	1640	0.019999	-2.3934
7	1953	0.016072	-2.8713
8	2267	0.012327	-3.4591
9	2580	0.010836	-3.7449

$$8.88071 \times \left[\arctan\left(\frac{b-x}{0.0126796}\right)^{1/2} - 1.16785 \right] = kt$$

$k_{3/2} = 14.8 \times 10_{-4}$

Table 2.10 Rate data for the hydroboration of *cis*-3-hexene (0.123 M) with (S,S)-1-1 dimer (0.0527 M) in ether at 11.1°C (Exp VII).

spectrum No.	time (sec)	[dimer]	f(x)
0	0	0.05274	
1	189	0.04566	-0.2768
2	378	0.03977	-0.5551
3	688	0.03276	-0.9671
4	997	0.02743	-1.3654
5	1306	0.02295	-1.7843
6	1616	0.01938	-2.1976
7	1925	0.01703	-2.5228
8	2210	0.01399	-3.0306
9	2519	0.01249	-3.3292
10	2829	0.01152	-3.5440
11	3138	0.00916	-4.1588
12	3448	0.00757	-4.6721
13	4057	0.00604	-5.2756

$$10.775 \times \left[\arctan\left(\frac{b - x}{0.0086135}\right)^{1/2} - 1.18674 \right] = kt$$

$$k_{3/2} = 13.0 \times 10^{-4}$$

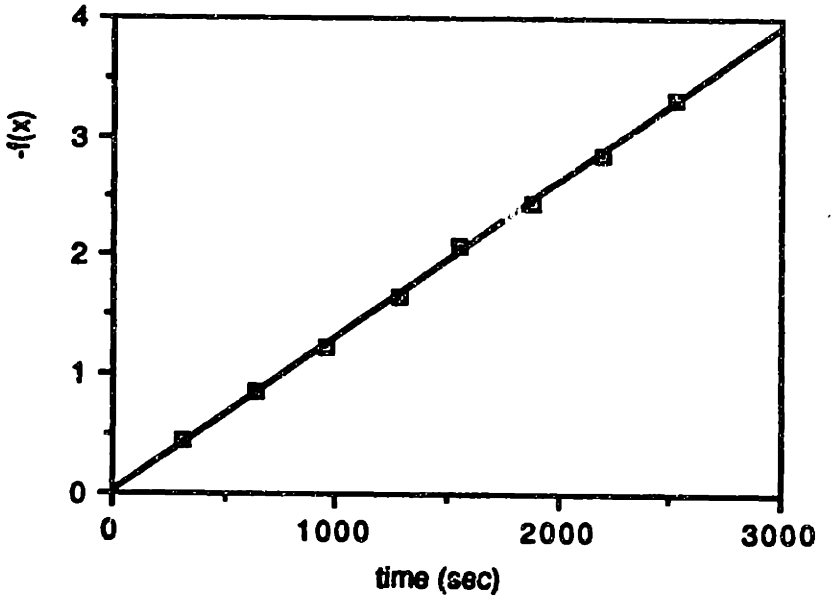


Fig. 2.11 Rate plot for the hydroboration of *cis*-3-hexene (0.173 M) with (*S,S*)-1-1 (0.071 M) in ether at 11.0℃ (Exp V).

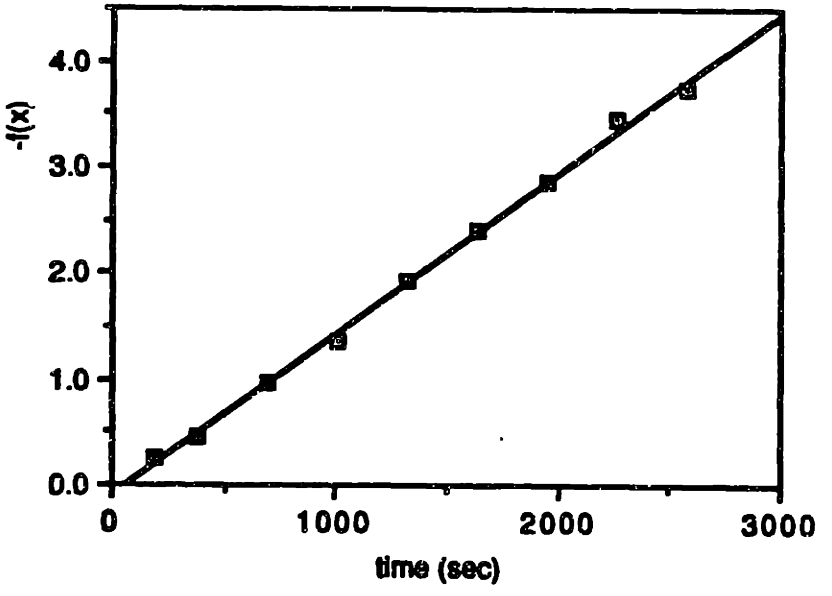


Fig. 2.12 Rate plot for the hydroboration of *cis*-3-hexene (0.165 M) with (*S,S*)-1-1 (0.070 M) in ether at 11.1℃ (Exp VI).

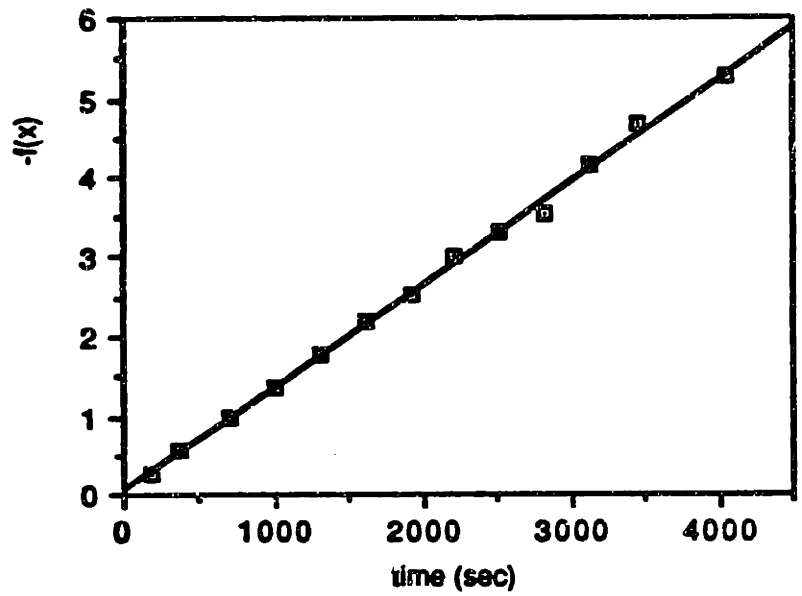


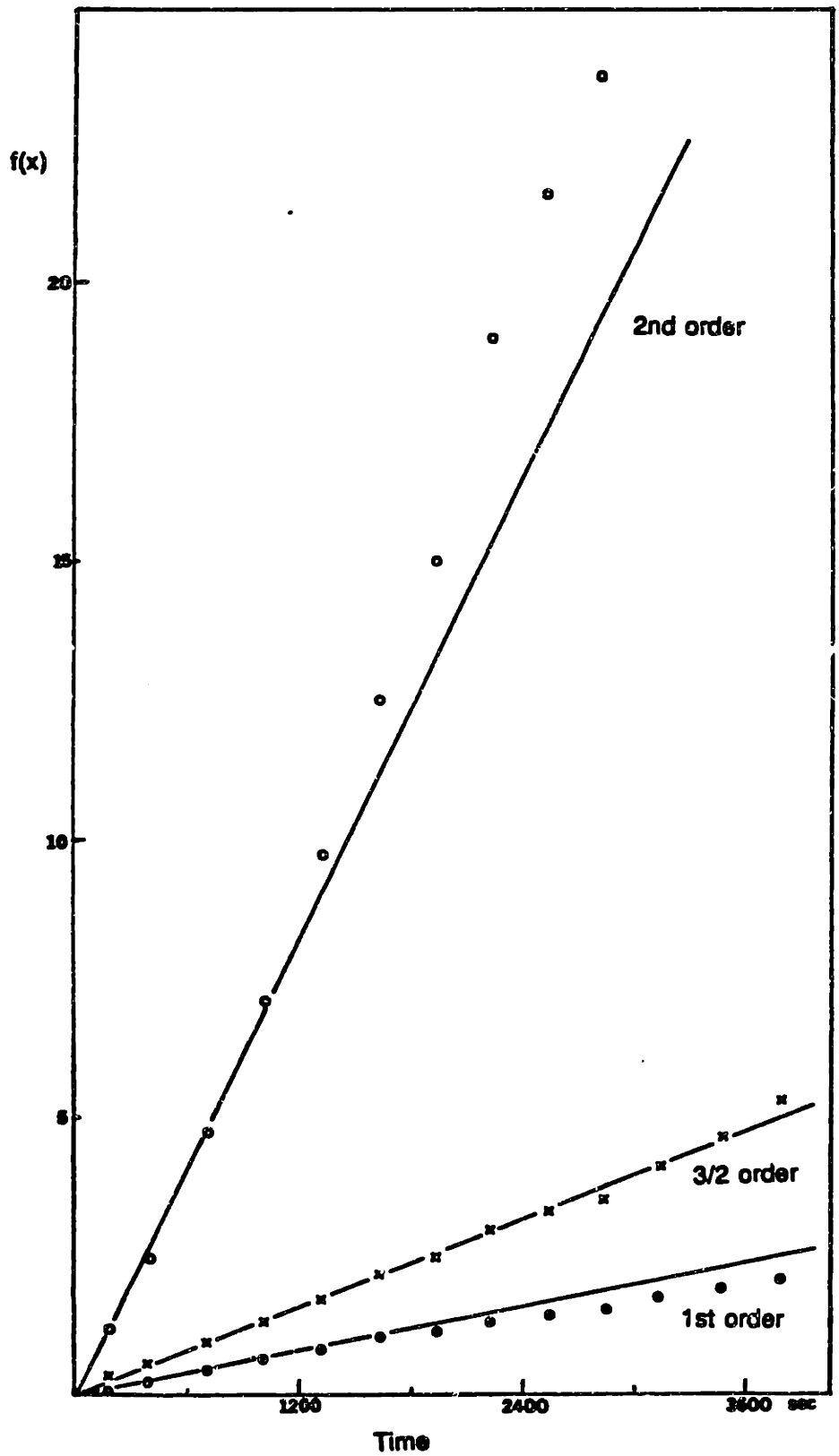
Fig. 2.13 Rate plot for the hydroboration of *cis*-3-hexene (0.123 M) with (*S,S*)-1-1 (0.053 M) in ether at 11.1℃.

Table 2.11. Three-halves order rate constants obtained for the hydroboration of cis-3-hexene with (*S,S*)-1-1 in ether at different concentrations.

Exp No.	[dimer]	[substrate]	3/2 rate x 10^4	temp
V	0.071	0.173	13.1	11.0
VI	0.070	0.165	14.8	11.1
VII	0.053	0.123	13.0	11.1

Results of the calculations from Exp V-VII are presented in Table 2.11 As can be seen in Table 2.11, the three-halves order rate constants derived from reactions starting at different initial concentrations are in good agreement. The rate data for Exp VII were evaluated to fit first, three-halves, and second order kinetics. While the first and second order rates show pronounced curvatures on the graphical treatment of the data, a straight line is observed for the 3/2 order calculations (Fig. 2.14).

Fig. 2.14 Evaluation of rate data from Exp VII to fit first, three-halves, and second order kinetics.



2.5 CONCLUSION

Two types of new homochiral borolanes were prepared. Although the preparation of 3,4-disubstituted borolanes **2-8** and **2-9** was straightforward, the degree of asymmetric induction was uniformly insignificant. The synthesis of air-stable 2,5-dimethylborolane prolinol complex **2-59** is more elaborate involving separation of the *trans* isomer from the *cis* and also resolution of the *trans*-racemate. The free borolane (*R,R*)- or (*S,S*)-**1-1** which are prepared in three steps from the corresponding complexes exhibited remarkable asymmetric induction with all olefins of type II-IV. Virtually no selectivity was observed in the reaction with type I olefins.

A mechanistic study on the hydroboration of **1-1** was carried out to clarify the transition state of this valuable reaction. ^{11}B NMR was utilized for the first time to quantify the boron species thereby allowing one to follow the kinetic behavior of the boranes. Three-halves order kinetics was observed for the hydroboration of **1-1** with *cis*-3-hexene; 1st order in the olefin and a half order in the borolane dimer. It is clear from this result that the monomer is the responsible species for the high enantioselection observed in the hydroboration.

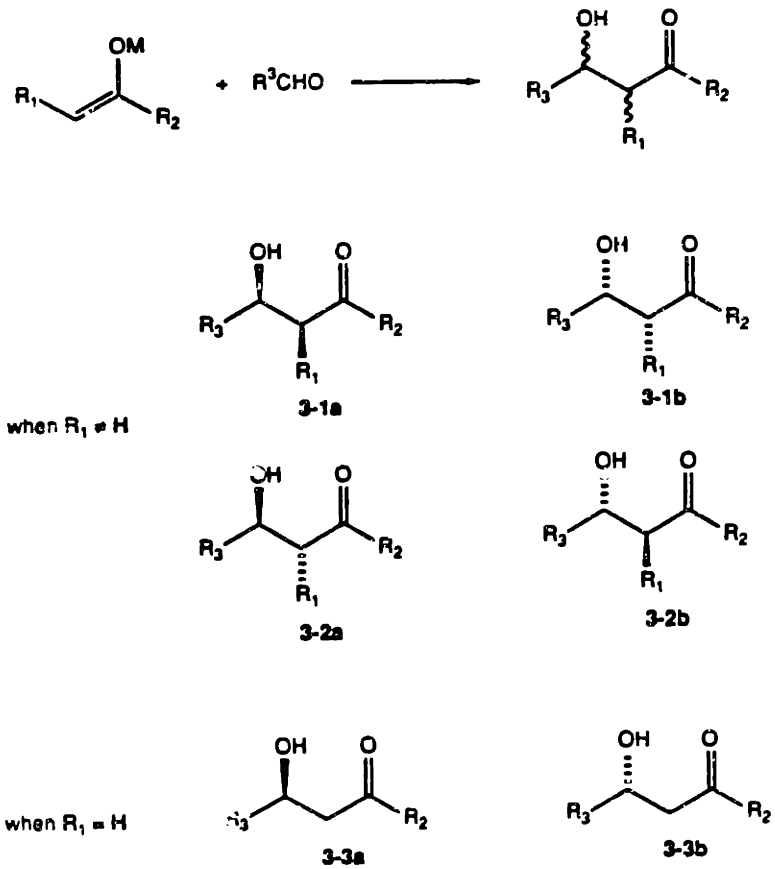
The kinetic results coupled with the experimental data obtained from the hydroboration using **1-1**, **2-8** and **2-9** provide a firm basis for proposing the transition state geometry of this reaction, which involves a fully developed sp^3-hybridized boron atom in a four center parallelogramic transition state, **2-74.**

Chapter 3. ALDOL REACTION

3.1 INTRODUCTION

Although the aldol reaction was first reported in the mid-nineteenth century,[60] it is only recently that intensive stereochemical investigations of this venerable reaction have been conducted,[61] mainly due to the delay of the development of reliable analytical methods for determining ratios of diastereomeric mixtures. Given the ubiquity of 1,3-diol and 1,3-ketol moieties in the natural products of acetate and propionate origin, such as macrolides and ionophores,[62] the stereoselective aldol reaction has received keen attention since late 1970's. Now the aldol reaction has become a very reliable method for the highly stereoselective carbon-carbon bond forming reaction, a process of paramount importance in organic synthesis.

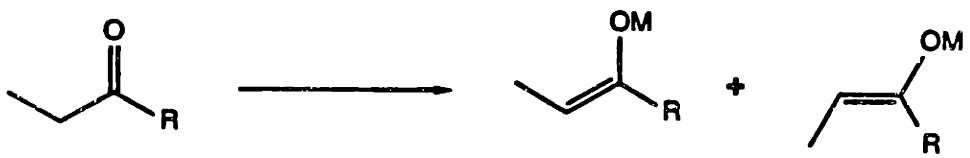
Scheme 3.1



In the aldol reaction between an enolate and an aldehyde, there are four possible product stereoisomers (Scheme 3.1). Consequently two stereochemical aspects are associated with the reaction. The first deals with two racemic diastereomers (3-1a and 3-1b vs. 3-2a and 3-2b, diastereoselection) and the second is related to absolute stereochemical configuration for a given diastereomer (enantioselection). Before we discuss stereochemical control of the aldol reaction, comments on the stereostructural notations are in order.

When the enolate of a carbonyl compound is generated, there is the possibility of generating two geometrically isomeric enolates. Of course, any sp^2 system can be described using the *Z/E* nomenclature system, however, the "*Z*(*O*)/*E*(*O*)" convention[63] will be used throughout the forthcoming discussion. Using this system, of the two substituents on C_1, the -OM substituent always takes highest priority regardless of what R is. Thus, 3-5 is the *Z*(*O*)- enolate and 3-6 is the *E*(*O*)-enolate (Scheme 3.2).

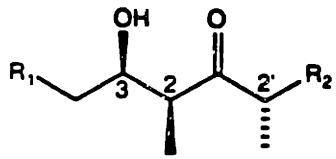
Scheme 3.2



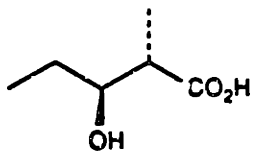
3-4 3-5 3-6

As for the stereochemical description for the aldol products, there are a handful of formalisms[64,65] including the traditional erythro-threo convention. However for purposes of general discussion it is convenient to have a simple convention for describing the relative configuration of two stereogenic carbons, such that the relationship between reaction topography and product stereostructure may be described without the confusion that often results from the use of stereostructural descriptions that change with trivial changes of structure.[64,65] For this purpose the "syn-anti"

description[66] proposed by this group is adopted in the present discussion. According to this convention, where the mainchain of a molecule is drawn in a zig-zag fashion, stereogenic centers on the mainchain are "syn" if they project on the same side of the chain and "anti" if they are on opposite sides. As depicted below, the two centers need not be contiguous. Of course when an absolute stereochemical description is required, Cahn-Ingold-Prelog system[63] can be conveniently used without any ambiguity as shown below.



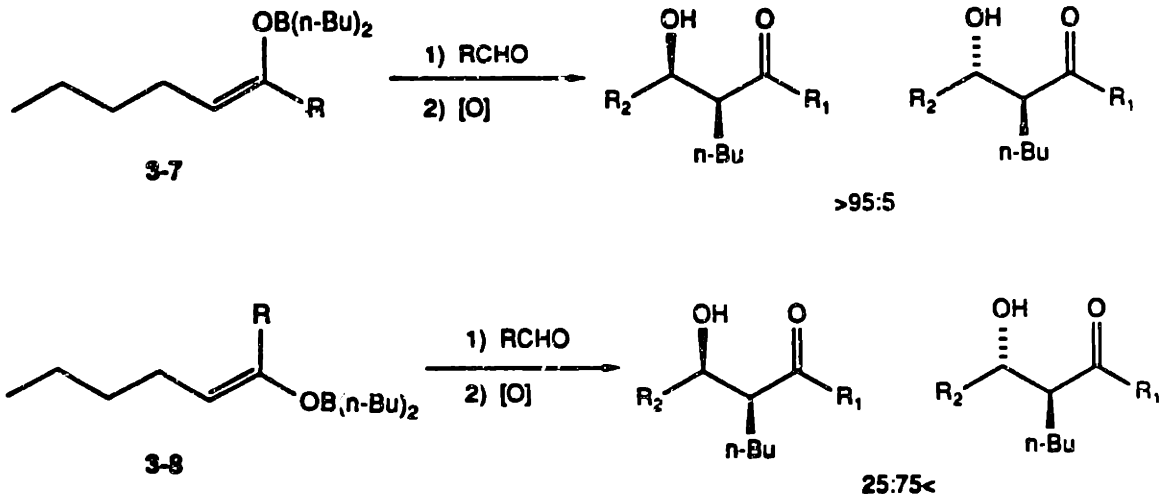
2,3-syn, 2,2'-anti, 2',3-anti



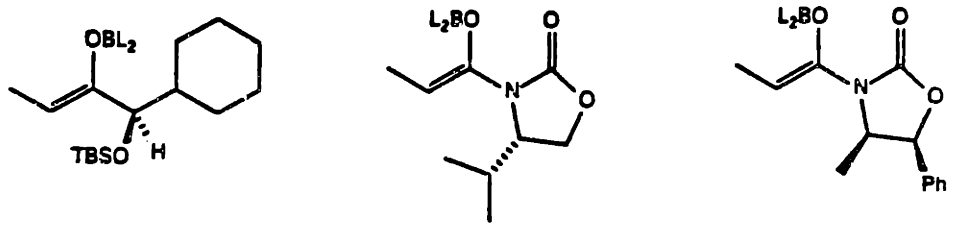
(2*S*,3*S*)-3-hydroxy-2-methylpentanoic acid

Fenzl and Köster, in their pioneering studies of the aldol reaction of *Z*(*O*)-diethylboron enolate with propiophenone, showed that a boron enolate is more stereoselective than other Group I, II, or III enolates.[68] A careful study on the stereodefined boron enolates was carried out by this research group.[69] The first reported study that employed both pure *Z* and *E* boron enolates illustrated that in reactions with various aldehydes the *Z* diethylboron enolates **3-7** showed uniformly high syn selectivity (syn/anti, >95:5), while the corresponding *E* enolates **3-8** were found to exhibit lower selectivity in favor of anti products (syn/anti, 25:75<) (Scheme 3.3).

Scheme 3.3



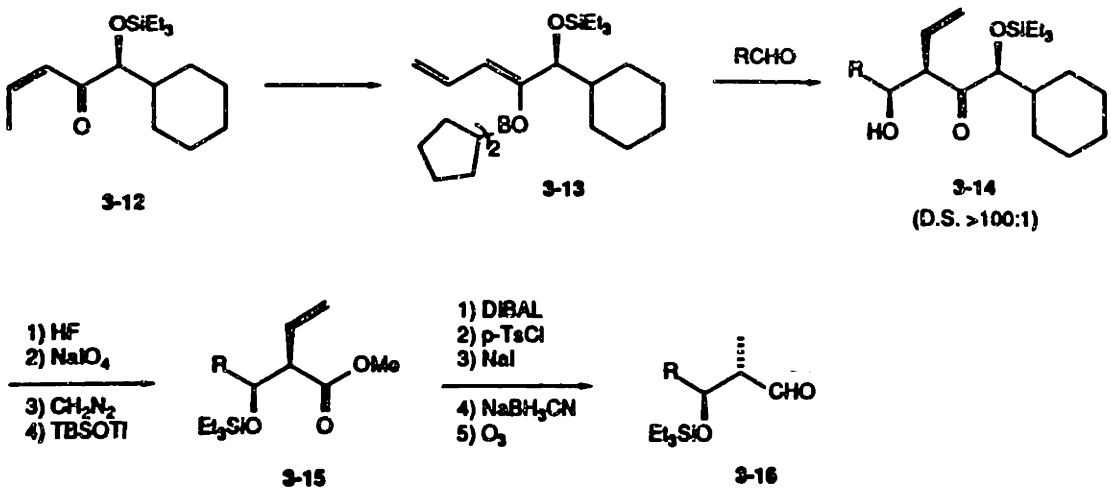
It was the advent of several chiral boron enolates in 1981 such as 3-9,[70] 3-10,[71] and 3-11,[71] derived from chiral mandelic acid, (*S*)-valine, and (1*R*,2*R*)-norephedrine, respectively, that facilitated the employment of the double-asymmetric synthesis methodology[2] in the synthesis of a number of natural products.[2,72,73]



3-9 3-10 3-11

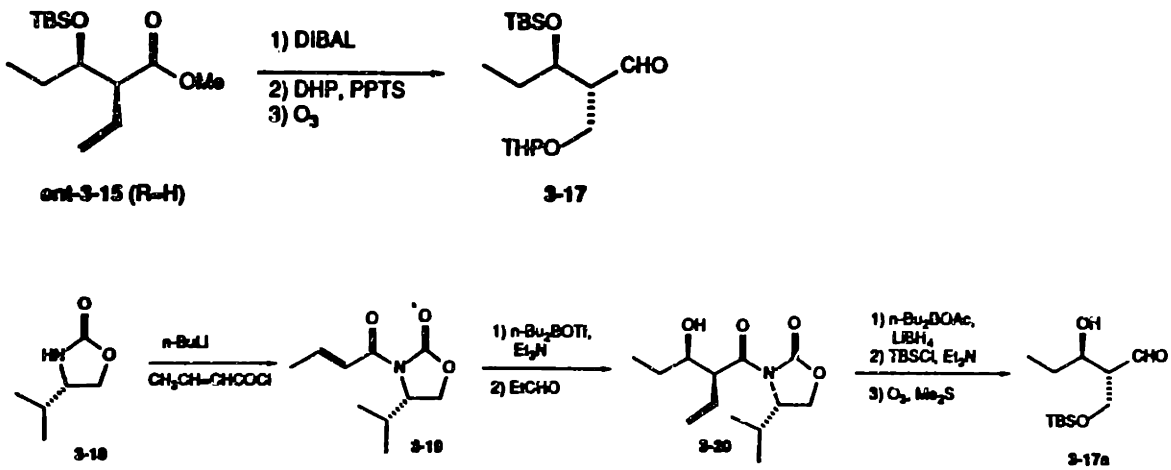
While the above reagents allowed for efficient construction of 2,3-syn unit (3-1a and 3-1b), the synthetic methodology for the 2,3-anti (3-2a and 3-2b) and simple 3-hydroxycarbonyl unit (3-3a and 3-3b) had yet to be explored.[74] To effect the construction of the unit 3-2a and 3-2b, one must often resort to the indirect, circuitous routes by modifying the enolates. Depicted in Scheme 3.4 is a typical example of such strategy.[63,75]

Scheme 3.4

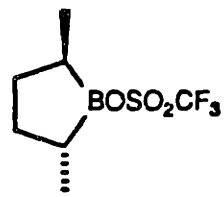


This methodology was applied to the construction of 3-hydroxy-2-(hydroxymethyl)carbonyl units **3-17** and **3-17a** in Masamune's[63b] and Evans'[61f,76] tylonolide syntheses, respectively (Scheme 3.5).

Scheme 3.5



Of particular cogency in the methodology involving reagents 3-9 - 3-11 is that the stereochemical control of the reaction is effected by the inherent chirality of the substrates and the chiral auxiliary remains in the product (internal reagent)†. In this regard, the employment of an external reagent such as 3-21 for the generation of the chiral boron enolates is attempted for reactions furnishing 2,3-anti aldol units. An



(*R,R*)-3-21

attractive aspect of aldol reaction with an external reagent is that it can also be used to couple large fragments which allows for a convergent synthesis of a large target molecule. The efficient use of aldol reactions for this purpose would require development of highly stereoselective reagents. Various boron reagents are tried in the aldol reaction of methyl ketones aiming at this goal.

As part of ongoing efforts in these laboratories to develop aldol methodology to allow for the construction of all possible aldol units (**3-1a, 3-1b, 3-2a, 3-2b,** and **3-3a, 3-3b**), the first half of this chapter is concerned with aldol reactions capable of constructing 2,3-anti- and 3-hydroxycarbonyl units and the other half is devoted to the problems of ketone aldol reactions focusing on the realization of triple asymmetric synthesis.

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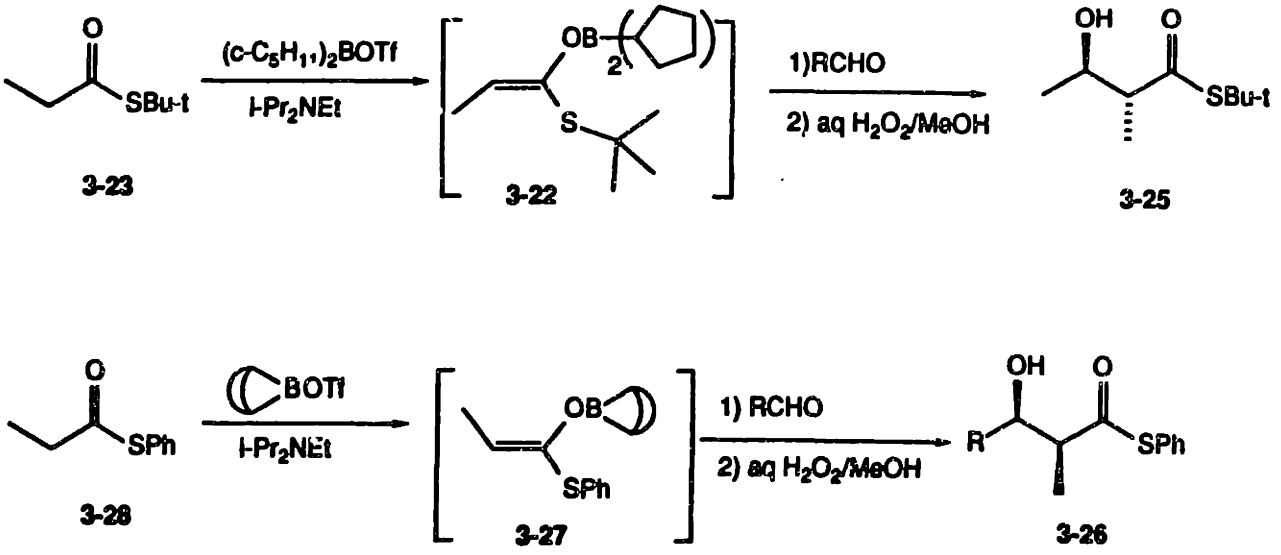
† For the definition of "internal" and "external" reagents, see Chapter 1.

3.2 ALDOL REACTIONS OF ENOLATES DERIVED FROM PROPANETHIOATES AND ETHANETHIOATES USING (*S,S*)-3-21.

3.2.1. 2,3-Anti Selective Aldol Reaction

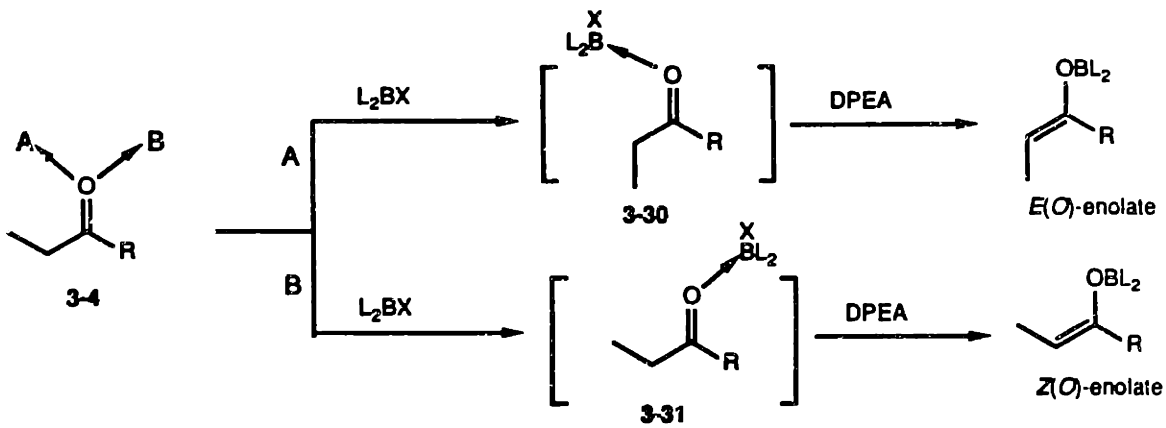
It has been known from the work in these laboratories that the *E*(*O*)- enolate 3-22 generated from *S*-tert-butyl propanethioate (3-23) with dicyclopentyl boron trifluoromethanesulfonate (3-24) and *N,N*-diisopropylethylamine (Hünig's base, DPEA) furnishes, upon reaction with aldehydes, anti- aldol products 3-25,[77] whereas syn- product 3-26 is obtained from the *Z*(*O*)- enolate 3-27 derived from the reaction of *S*-phenyl propanethioate (3-28) with 9-borabicyclo[3.3.1]-non-9-yl trifluoromethanesulfonate (9-BBN triflate, 3-29) under otherwise identical condition[78] (Scheme 3.6).

Scheme 3.6



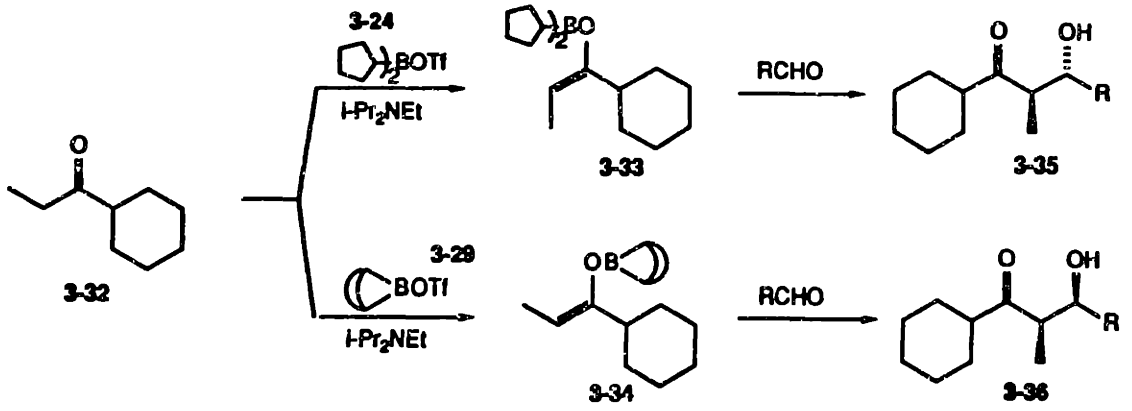
Several factors affecting the kinetic enolization are considered. At low temperature (-78---0°C) enolization is believed to be completely kinetically controlled.[79] A systematic study by this group[80] as well as by Evans *et al.*[79] revealed that the structural features of the carbonyl compound, tertiary amine, and boron triflate individually contribute to the observed enolate stereoselection. Recently both experimental and calculation studies by Reetz *et al.*[81] have shown that BF_3 forms an adduct with benzaldehyde in such an array that the Lewis acid BF_3 is complexed anti to the phenyl group in benzaldehyde and the B-O=C-C bonds lie essentially in a common plane. This behavior of Lewis acid complexation by carbonyl compound is rapidly extrapolated into the discussion of the kinetic enolization which utilizes a boryl triflate (a strong Lewis acid). It is reasoned that the position of initial complexation of a boryl triflate to the carbonyl oxygen is very much governed by steric or stereoelectronic interaction between the carbonyl compound and the boryl triflate. As shown in Scheme 3.7, a bulky boron moiety (e.g. **3-24**) may complex to the A side (anti to R) of

Scheme 3.7



the carbonyl oxygen (**3-30**), whereas a rather small boron moiety (e.g. **3-29**) may occupy the B side (syn to R) without causing steric congestion (**3-31**), thus giving rise to the predominant formation of E(O)- and Z(O)- enolates, respectively. A representative example is given in Scheme 3.8.[82]

Scheme 3.8



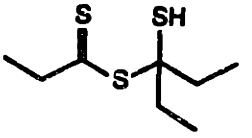
In the cases where thiol esters are employed, however, factors other than steric reasons are apparently involved and a more detailed discussion of these factors is forthcoming later in this section based on more experimental data.

That the *E*(*O*)/*Z*(*O*) ratio of the boron enolate is directly reflected in the syn/anti ratio of the aldol products had been amply demonstrated in earlier discussion. An initial set of experiments was aimed at the preparation of a highly *E*(*O*)- enriched boron enolate. In light of the aldol reaction with *S*-tert-butyl propanethioate (Scheme 3.7) reported earlier, a series of propanethioates were prepared and examined using the chiral boron reagent **3-21**.

The preparation of the thiol **3-37** according to the reported procedure[83] was, in our hands, found to be irreproducible (Scheme 3.9). With ambient reaction conditions a single product was obtained and identified as **3-38** by ^{1}H NMR and mass spectrometry.

Scheme 3.9

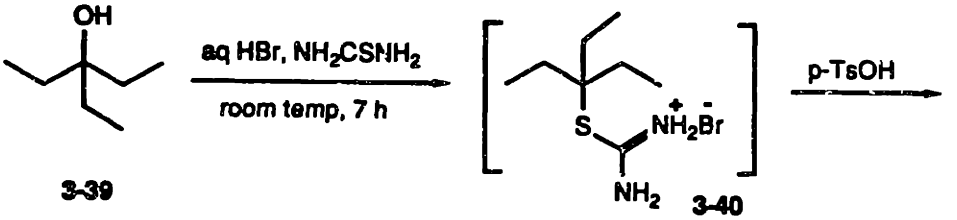
3-37



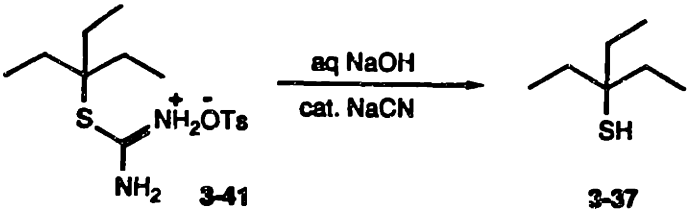
3-38

Treatment of 3-38 with Et_3Al even under vigorous condition (heptane, reflux, 12 h) did not provide the desired thiol 3-37 and instead, 3-38 was recovered unreacted. However, with minor modifications of the published procedure of Lee *et al.*[84] for similar tertiary thiols, thiol 3-37 could be furnished in quantity (Scheme 3.10).

Scheme 3.10



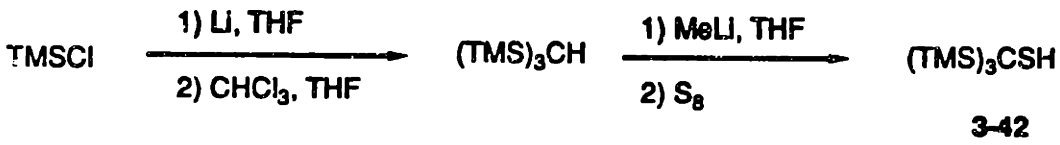
3-39 3-40



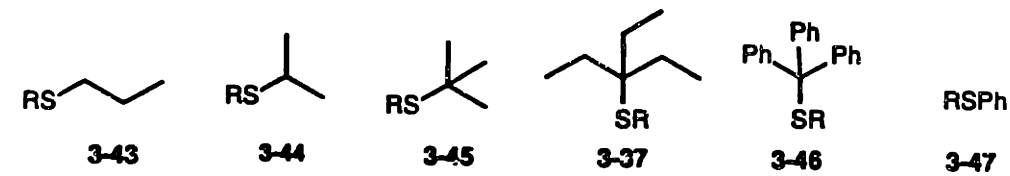
3-41 3-37

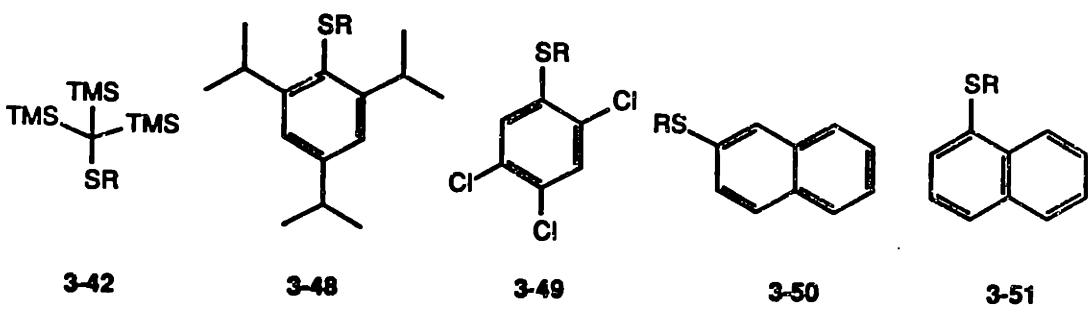
Stirring at room temperature, instead of literature-recommended refluxing, the mixture of the tertiary alcohol 3-39 and thiourea in 40% aq HBr solution smoothly furnished the thiouronium salt 3-40, which was converted to more crystalline salt 3-41 overall in 36-47% yield. Alkaline hydrolysis of 3-41 provided the thiol 3-37 as a colorless oil (30-40% from the alcohol). Tris(trimethylsilyl)methanethiol 3-42 was prepared essentially following the reported procedure[85,86] as depicted in Scheme 3.11.

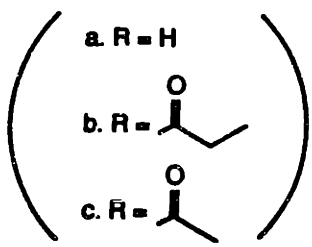
Scheme 3.11



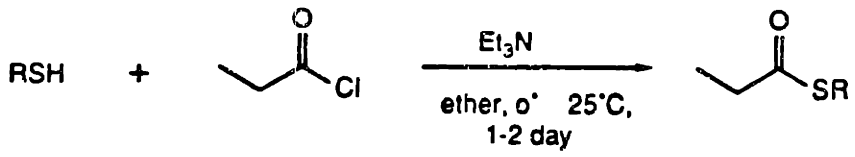
Since thiols 3-37 and 3-42 as well as commercially available thiols 3-43 - 3-51 were in our possession, a whole gamut of propanethioates were prepared by treating a mixture of a thiol and triethyl amine in ether with propionyl chloride as shown in Scheme 3.12





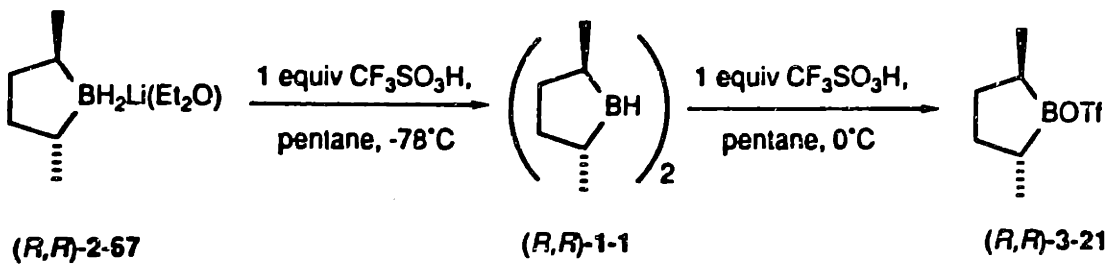


Scheme 3.12



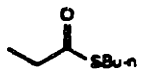
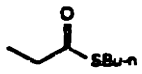
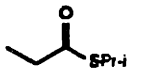
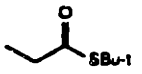
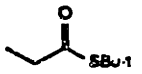
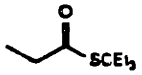
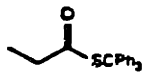
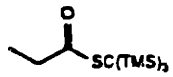
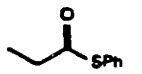
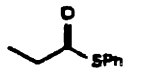
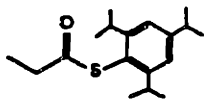
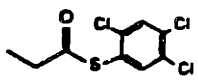
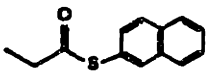
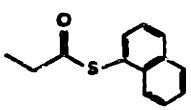
The boron triflate **3-21** was prepared from dihydridoborate complex **2-67** as depicted in Scheme 3.13. Free borolane **1-1** was formed by adding 1 equiv trifluoromethanesulfonic acid. Another equiv of the triflic acid was added into the filtered solution of borolane (*R,R*)-**1-1** to slowly generate the extremely air-sensitive triflate **3-21** (^{11}B NMR 64 ppm, C_6D_6).

Scheme 3.13



With various propanethioates in hand, the aldol reactions were carried out in a standard fashion using, in each case, a combination of propanethioate and (*R,R*)- or (*S,S*)-2,5-dimethylborolanyl triflate (**3-21**) in the presence of diisopropylethylamine to form an *E,Z*- mixture of the corresponding boron enolates. The mixture was then allowed to react with benzaldehyde. Table 3.1 summarizes the results of reactions with various propanethioates (T. Sato and B.M. Kim, 1985).

Table 3.1.[a] Anti/syn selectivity of aldol reactions with the enolate prepared from propanethioates and (*R*,*R*)-**3-21**

entry	propanethioates	solvent	yield of anti/syn combined (%)[b]	syn/anti ratio[c]	%ee of the major product[d]
1		ether	85	17:83	–
2		CH_2Cl_2	100	32:68	–
3		CH_2Cl_2	74	22:78	42
4		CH_2Cl_2	100	9:91	93
5		pentane	79	5:95	99
6		pentane	85	3:97	99.8
7		CH_2Cl_2	38	27:73	–
8		pentane	N.R.	–	–
9		CH_2Cl_2	91	93:7	11
10		ether	86	80:20	–
11		CH_2Cl_2	85	72:28	7
12		CH_2Cl_2	73	84:16	40
13		CH_2Cl_2	83	95:5	13
14		CH_2Cl_2	82	96:4	10

a. To a stirred solution of a propanethioate (0.17 M, 1 equiv) and DPEA (0.2 M, 1.2 equiv) in a given solvent was added (*R,R*)-3-21 (1.2 equiv) at -78°C. After stirring at 0°C for 1 h, the mixture was recooled to -78°C and benzaldehyde (1.5 equiv) was added. After 3-4 h, the reaction was complete and the mixture was worked up in the usual way. The yield was based on the amount of the propanethioate used.

b. Isolated yields unless otherwise noted.

c. Determined by ^{1}H NMR analysis of the crude product.

d. Determined by ^{1}H NMR analysis of the corresponding acetates in the presence of Eu(hfc)$_3$ as a chiral shift reagent. Values were corrected for the purity of (*R,R*)-**3-21**.

e. Determined by ^{1}H NMR in the presence of an internal standard.

The trend is clearly seen. The *E*(*O*)/*Z*(*O*) ratio which is equated to anti/syn ratio of the aldol products increases with the bulk of the alkanethiol moiety (entries 1-8). This confirms the argument addressed earlier that the bigger steric interaction between boron ligand and carbonyl attachment (in this case the thiol moiety) is, the higher the *E*(*O*)/*Z*(*O*) ratio. Since we have a fixed boron ligand, increasing the bulkiness of the thiol moiety helps increase the interaction.† However, with tris(trimethylsilyl)-methanethiol moiety (entry 8), the interaction is certainly too big to allow the reaction to occur.

As for the solvent effect, pentane proved to be the best solvent for higher anti-selectivity presumably due to the compression of the diastereomeric transition sates[79] (**3-52** and **3-53**) which elevates the enolization selectivity. In a similar vein, the enantioselection was also found to be best in pentane.

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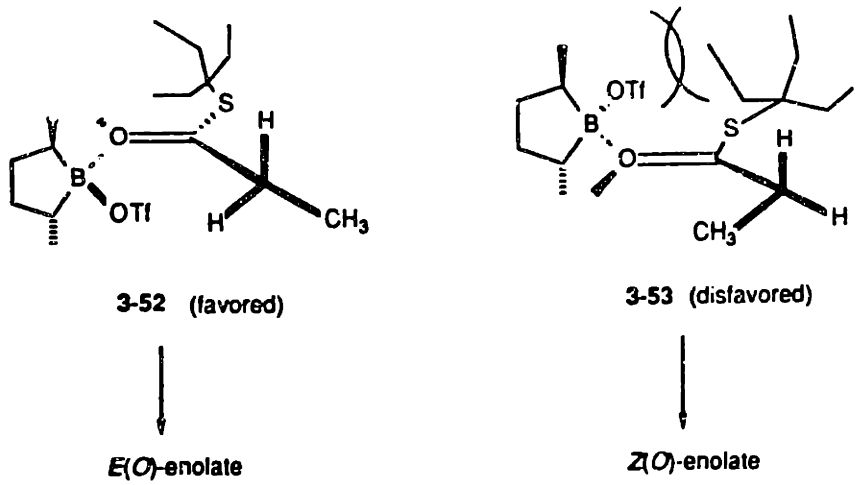
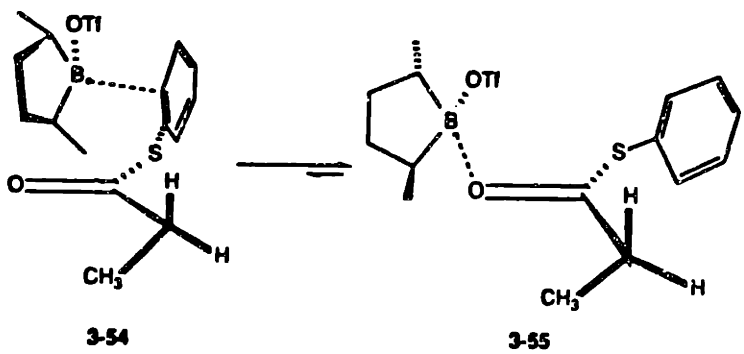
† This is also along the line of the argument for the stable configuration of isomeric dioxolenium ions[87] and protonated thioesters.[86]



Conversely, when arylthiol esters were employed, selective formatoion of *Z*(*O*) enolate (or syn- selectivity) prevailed (Table 3.1, entries 9-14). In this case, factors governing the degree of selectivity are not as clear as those for the alkanethiol esters. Neither the enolate geometry nor the enantiomeric excesses of the products appear to be under direct influence of the steric interaction between the borolane moiety and thiol group. Perhaps stereoelectronic effects may account for this anomaly. One explanation can be made for the selective formation of *Z*(*O*)- enolate based on the favorable interaction[89] between the aryl group of the thiol and the electrophilic boron atom as shown below, which is similar to the interaction often encountered in the electron-transfer complexes of aromatic compounds and Lewis acids including boron.[89]



This interaction would bring the borolane moiety close to the thiol side of the substrate (3-54), thus facilitating the kinetic *Z*(*O*)- enolate formation. The highest *Z*(*O*)-selectivities observed in the reactions involving *S*-naphthyl propanethioates (entries 13 and 14 in Table 3.1) can be explained by the stronger complexation of the aryl group to the boron, while poor *Z*(*O*)- selectivities in entries 11 and 12 may be due to poor complexation because of electronically weak (entry 12) or sterically hindered (entry 11) interaction. In this connection it is also not surprising to note the exceptionally low *E*(*O*)- selectivity with regard to the reaction involving *S*-triphenylmethyl propanethioate (entry 7) in light of the aforementioned tendency of favorable phenyl-boron interaction. Although this argument is self-consistent, it requires further experimental supports in order to be valid.

It became evident from Table 3.1 that the *E*(*O*)- enolate 3-55 is formed almost exclusively from *S*-3-(3-ethyl)pentyl propanethioate (3-37b) with 3-21 as shown in Scheme 3.14. Despite its apparent steric demand, 3-55 still retains a high degree of reactivity toward aldehydes.

Scheme 3.14

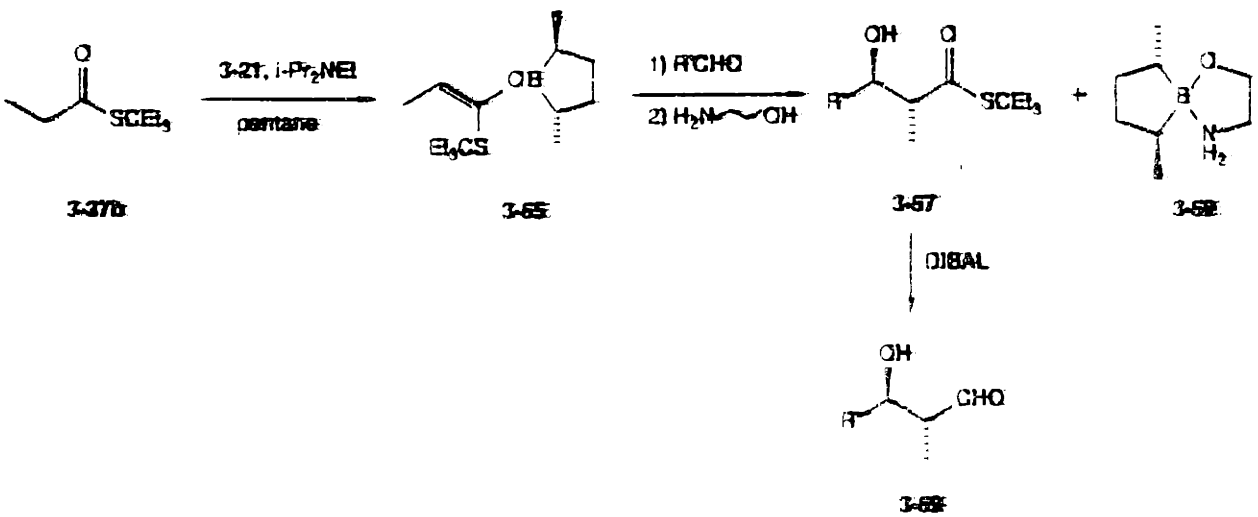


Table 3.2 summarizes the results obtained from the aldol reactions of representative aldehydes with **3-56**.[21] All reactions proceeded smoothly at -78°C and consistently furnished aldol products of 2,3-anti stereochemistry (anti/syn, >30:1) with all aldehydes examined.

Table 2. Aldol reactions of representative aldehydes with **3-55**.[a]

entry	aldehyde	reaction time (h)	isolated yield[b]	anti/syn ratio[c]	abs config	%ee obsd[d]	%ee corrected for the ee of **3-21** used[e]
1	n-BuCHO	12	91 (96)	33:1	2*R*,3*R*	93.0	97.9
2	i-PrCHO	18	85	30:1	2*R*,3*R*	95.4	99.5
3	t-BuCHO	36	95	30:1	2*R*,3*S*	95.8	99.9
4	c-C_6H_{11}CHO	21	82 (87)	32:1	2*R*,3*R*	93.1	98.0
5	PhCHO	3	(71)	33:1	2*R*,3*S*	95.7	99.8
6	BnO$(CH_2)_2$CHO	9	93	>30:1	2*R*,3*R*	92.2	97.1

a. Carried out in the same manner as described in footnote a of Table 3.1 except for the duration of the reaction.

b. Numbers in parentheses are estimated by ^{1}H NMR analysis using an internal standard.

c. Determined by ^{1}H NMR analysis.

d. Product **3-57** was converted to its acetate, the % ee of which was determined by ^{1}H NMR analysis with the aid of Eu(hfc)$_3$.

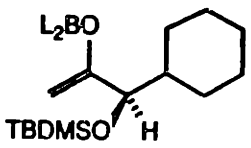
e. Enantiomeric purity of **3-21** was 95.0% ee for entries 1,4 and 6, and 95.9 for 2,3 and 5.

With (*S*,*S*)-**3-21** the aldehydes examined provided (2*R*)-aldol products **3-57** in generally >98% ee (>100:1). It is also of note that the chiral auxiliary of reagent **3-55** can be recovered as its 2-amino-2-methylpropanol complex **3-58** and the products **3-57** are equipped with a thioate functionality which can be readily converted to various functional groups, e.g. aldehyde **3-59**, carboxylic acid, or alcohol in one step.

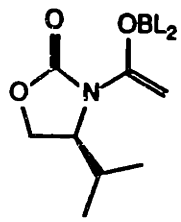
3.2.2. Aldol Reactions of Ethanethioates

Since the problems concerning the construction of 2,3-anti aldol units (**3-2a** and **3-2b**) were essentially solved, we turned our focus on whether equally high enantioselection could be obtained in the aldol reaction of ethanethioates using the same external boron reagent **3-21.**

It is of particular note that none of the "internal" reagents (e.g. **3-9b** and **3-10b**) provided significant selectivities on acetate (or methyl ketone) aldol reactions with



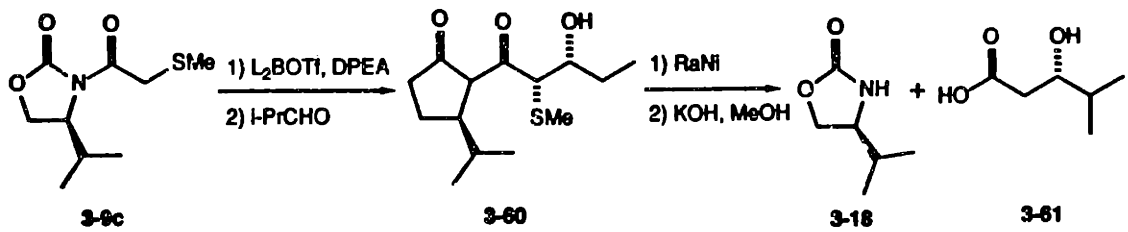
3-9b



3-10b

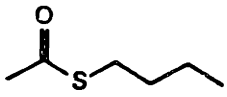
aldehydes. In fact a circuitous route had to be introduced in order to prepare homochiral carbonyl units having no substituent at α-position (e.g. **3-61**)[71] (Scheme 3.15).

Scheme 3.15

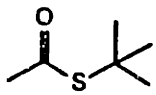


3-9c **3-60** **3-18** **3-61**

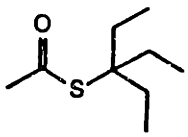
Ethanethioates having various steric demands were prepared and aldol reaction with these thiolesters were carried out as depicted in Scheme 3.16.



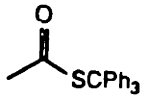
3-43c



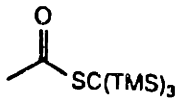
3-45c



3-37c

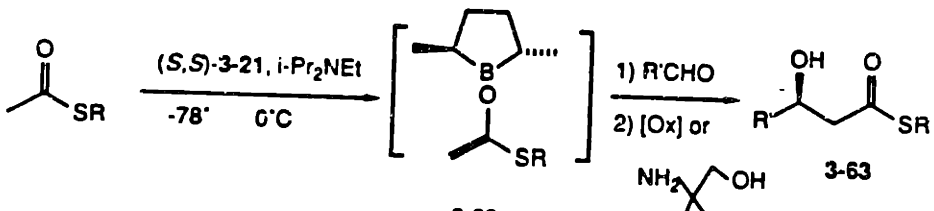


3-46c



3-42c

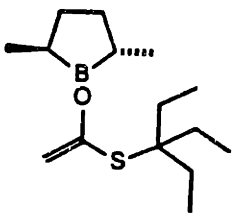
Scheme 3.16



3-62

3-56

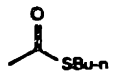
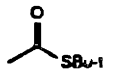
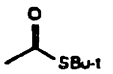
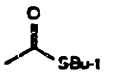
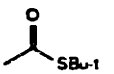
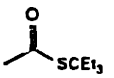
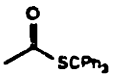
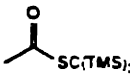
3-63



3-64

The triflate **3-21** was added to a mixture of an ethanethioate and diisopropylethylamine at -78°C and the mixture was warmed to 0°C. The formation of enolates was evidenced by the prepicitation of white solids (diisopropyl-ethylammonium triflate) between -78° and 0°C depending on the ethanethioates utilized. The solution of respective enolates **3-62** was recooled (see Table 3.3) and allowed to react with benzaldehyde. Collected in Table 3.3 are the data acquired from such aldol reactions (B.M. Kim and T. Sato, 1985).

Table 3.3. Aldol reaction of the enolate prepared from various ethanethioates and (S,S)-3-21 with benzaldehyde.

entry	ethanethioates	solvent	reaction condn	isolated yield	abs[a] config	% ee[b]
1		CH_2Cl_2	-78°C, 2 h	95	*S*	2
2		ether	-78°C, 3 h	94	*S*	73
3		CH_2Cl_2	-78°C, 3 h	100	*S*	72
4		toluene	-78°C, 3 h	100	*S*	71
5		pentane	-78°C, 3 h	100	*S*	83
6		pentane	-80~-85°C, 3 h	78	*S*	92.2
7		toluene	-78°C, 4 h	99	*S*	87
8		pentane	-65°C, 18 h	19	–	–

a. For the determination of the absolute configuration of aldol products, see text.

b. Values were determined by ^1H NMR analysis of the corresponding acetate with the aid of Eu(hfc)3 as a chiral shift reagent.

The data in Table 3.3 revealed a few significant trends. First, as noted in the case of propanethioate aldol reactions, the thiolesters exhibit an increase in enantioselectivity with increased steric requirements (entries 1-6). Again 3-ethyl-3-pentanethiol proved to be the best thiol moiety in terms of enantioselectivity. Next the solvent effect on the enantiomeric excesses was examined with *S*-tert-butyl ethanethioate (**3-45c**) as illustrated in entries 2-5. While aldol selections in ether, methylene chloride , and toluene all fell into a narrow range of 71-73% ee, the highest selectivity (83% ee, entry 5) was observed with pentane. Note that the same trend was encountered in the aldol reaction of propanethioates (see Table 3.1). These observations parallel those noted by Evans and coworkers.[79] The enantiomeric excess obtained for *S*-triphenylmethyl ethanethioate (**3-46c**) was slightly inferior to that for **3-37c**, presumably because of the employment of rather polar solvent (toluene). The thiolester **3-46c** was not soluble in hydrocarbon solvents such as pentane at low temperature. In the reaction with *S*-tris(trimethylsilyl)methyl ethanethioate (**3-42c**) the reactivity is sacrificed because of the excessive steric congestion (entry 8).

Since the chiral boron enolate **3-64** prepared from 3-ethyl-3-pentanethiol (**3-37**) has displayed the highest selectivity in aldol reactions with benzaldehyde, various aldehydes were examined with this ethanethioate. The results are shown in Table 3.4.

Table 3.4.[a] Aldol reactions of representative aldehydes with 3-64.

entry	aldehyde	reaction time (h)	reaction temp (°C)	isolated yield	abs config	% ee[b] obsd	% ee corrected[c] for the purity of 3-21
1	n-PrCHO	6	-78	82	*R*	86.6	91.2
2	i-PrCHO	10	-78	91	*S*	86.9	91.5
3	t-BuCHO	6	-78	71	*S*	94.4	98.4
4	c-C_6H_{11}CHO	9	-78	95	*S*	85.6	90.1
5	PhCHO	3	-82~-85	78	*S*	88.4	92.2
6	PhCHO	4	-100~-105	78	*S*	89.0	92.8
7	$PhCH_2O(CH_2)_2CHO$	7	-78	93	*R*	84.9	89.4

a. Carried out in the same manner as described in Table 3.1 except for the reaction time and temperature.

b. Determined by ^1H NMR analysis of the corresponding acetyl derivatives with the aid of Eu(hfc)3.

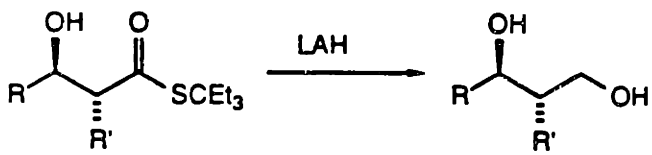
c. The enantiomeric excesses of 3-21 for entries 1,2, 4, and 7 were 95.0% and 95.9 for entries 3,5, and 6.

As outlined in Table 3.4, the ee's of the aldol products obtained from primary and secondary alkylcarboxaldehydes and aromatic aldehydes are found in a narrow range of 89-93% (entries 1, 2, and 4-7). Although there is still room for further improvement, these values are among the best obtained for aldol reactions of acetyl derivatives.[74] It is noted, however, that very high enantioselection is obtained with pivalaldehyde.

3.2.3. Determination of Absolute Configuration of Aldol Products

The assignment of the abolute configuration of the aldol products was made as follows: The aldol products **3-57** and **3-63** were converted to diols by reduction with LAH (Scheme 3.17). These diols **3-65a** and **3-66a** were compared with those independently prepared from the epoxyalcohols **3-69** with established absolute configuration as described in Scheme 3.18.

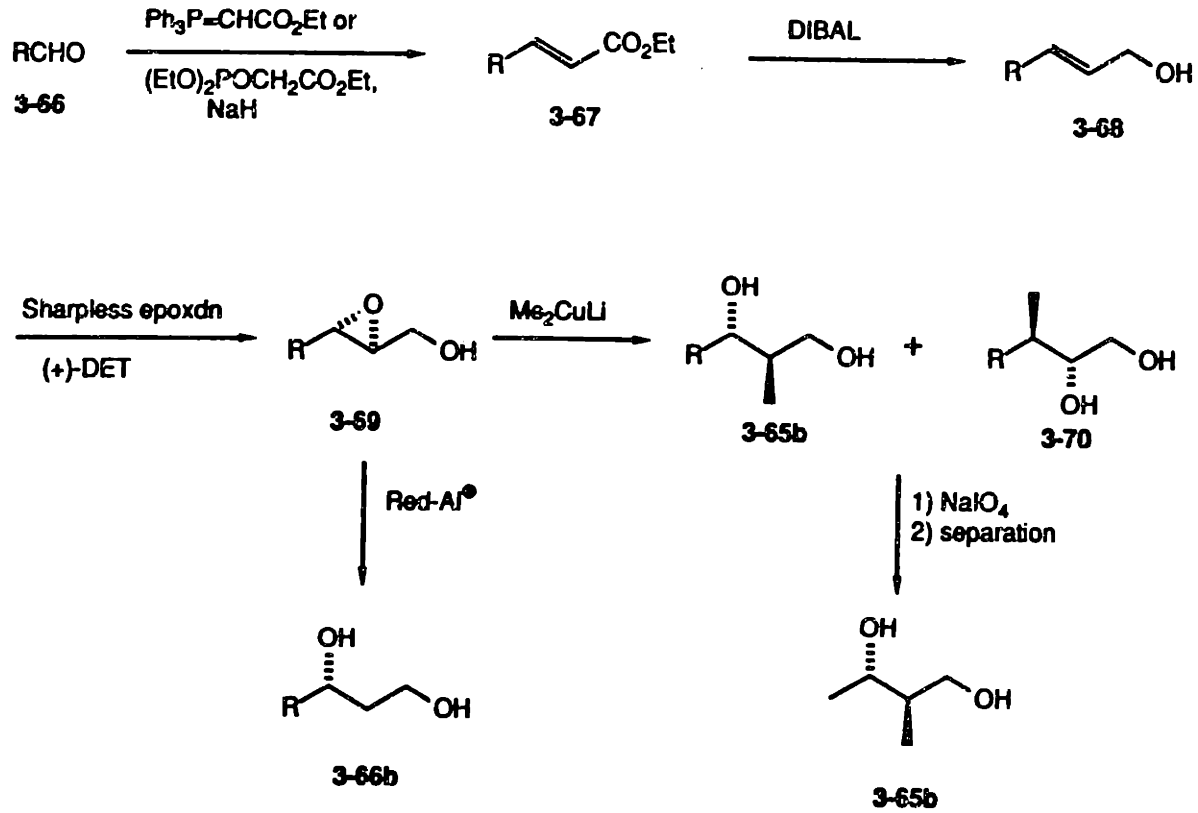
Scheme 3.17



R' = Me, **3-57**
R' = H, **3-63**

R' = Me, **3-65a**
R' = H, **3-66a**

Scheme 3.18



Allylic alcohols were prepared from aldehydes by Wittig ($PH_3P{=}CHCO_2Et$) or Wittig-Horner {$(EtO)_2POCH_2CO_2Et$/NaH} reaction followed by reduction with DIBAL. Sharpless epoxidation[90] of allylic alcohol **3-68** employing (+)-diethyl tartrate provided (2*S*,3*S*)-epoxyalcohols **3-69**. The enantiomeric purity of the epoxyalcohol was determined by capillary GC analysis of the corresponding MTPA ester. Opening of the epoxide with dimethylcuprate[91] afforded 2-methyl-1,3-diol **3-65b** together with 1,2-diols **3-70** as minor products. Removal of the undesired 1,2-diol **3-70** was accomplished by treatment of the diol mixture with sodium periodate followed by chromatographic separation. The 1,3-diol **3-66b** was obtained by opening of the epoxyalcohol **3-69** with

sodium bis(methoxyethoxy)aluminum hydride (Red-Al®).[92] Again 1,2-diols were removed by selective oxidation ($NaIO_4$) followed by chromatography. The diols from the aldol products **3-65a** and **3-66a** were identical to diols **3-65b** and **3-66b**, respectively, in all aspects except for the sign of optical rotations. The optical rotation values of the diols are tabulated in Table 3.5 (**3-65a** and **3-65b**) and Table 3.6 (**3-66a** and **3-66b**).

Table 3.5 Rotation Values for the Diols **3-65a** and **3-65b**.

		3-65a			3-65b			
entry	R	$[\alpha]^{22}_D$	$[\alpha]^{22}_{365}$	conc in $CHCl_3$	$[\alpha]^{23}_D$	$[\alpha]^{23}_{365}$	conc in $CHCl_3$	% ee
1	n-Pr	+33.6°	+97.4°	(1.04)	-34.1°	-98.9°	(0.95)	93
2	i-Pr	+19.6°	+56.3°	(0.750)	-20.2°	-60.1°	(1.04)	94
3	t-Bu	-11.1°	-32.4°	(0.605)	+8.8°	+27.1°	(1.13)	96
4	c-Hex	+24.9°	+73.6°	(1.38)	-25.1°	-74.8°	(0.995)	94
5	Ph	-46.8°	-158.8°	(0.340)				
6	$BnO(CH_2)_2$-	-3.13°	-11.2°	(0.735)	+1.3°	+7.7°	(1.025)	>90

Table 3.6 Rotation Values for the Diols **3-66a** and **3-66b**.

		3-66a			3-66b [a]		
entry	R	$[\alpha]^{22.5}_D$	$[\alpha]^{22.5}_{365}$	conc in $CHCl_3$	$[\alpha]^{23.5}_D$	$[\alpha]^{23.5}_{365}$	conc in $CHCl_3$
1	n-Pr	_	-6.22°	(0.402)	+11.2° [b] (c 1.33)	+4.9°	(1.15)
2	i-Pr	-13.8°	-43.1°	(0.448)	+13.8° [c]	+42.3°	(0.985)
3	t-Bu	-15.2°	-48.5°	(0.830)	+15.6°	+49.8°	(0.985)
4	c-Hex	-8.0°	-24.0°	(0.588)	+9.0°	+26.2°	(1.15)
5	Ph	-63.0°	-212.6°	(0.958)	+69.0°	+233°	(1.515)
6	$BnO(CH_2)_2$-	-11.6°	-36.7°	(0.735)	+12.4°	+36.7°	(0.995)

Captions for Table 3.6

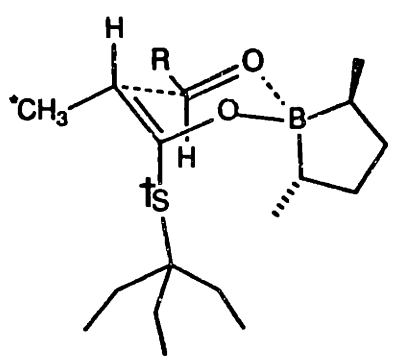
a. For the %ee's of the diols **3-72b**, see Table 3.5.

b. Measured in EtOH. Lit $[\alpha]^{20}_D$ -10.5° (*c* 1.45, EtOH) for the 90% ee (3*R*)-diol (Crump, D.R. *Aust. J. Chem.* **1982**, *35*, 945.)

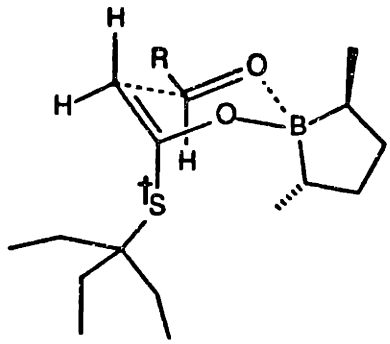
c. Lit $[\alpha]^{21}_D$ -2.97° (neat) for the 7.7% (3*S*)-diol (Vigneron, J.P.; Dhaenens, M.; Horeau, A. *Tetrahedron*, **1977**, *33*, 507). $[\alpha]^{22}_D$ +6.67° (*c* 1.29, $CHCl_3$) for the 27% ee (3*S*)-diol (Rossiter, B.E.; Sharpless, K.B. *J. Org. Chem.* **1984**, *49*, 3711).

3.2.4. Discussion on the Transition States of the Aldol Reactions

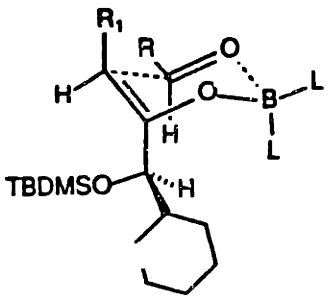
As has often been the case for many aldol reactions, a Zimmerman-Traxler model[93] is most conveniently adopted to rationalize the enantioselectivity observed in the aldol reactions involving **3-55** and **3-62**. Among four possible diastereomeric transition states for the reaction of **3-55** and an aldehyde, the lowest energy pathway (I) is best fit to avoid the interaction of the bulky thiol group and the methyl substituent of the borolane moiety.



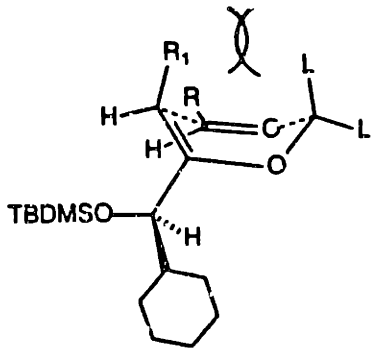
I



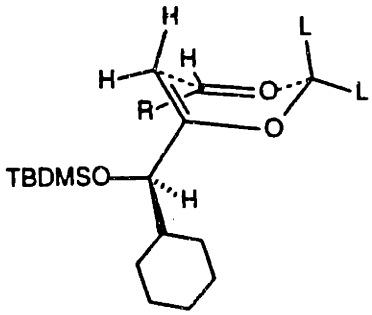
II



III



IV



V

The higher enantioselectivity exhibited by **3-55** than that by **3-62** is also easily rationalized in this context. In the transition state I, the asterisked methyl group steers the 3-ethyl-3-pentanethiol group toward the borolane moiety, the chirality of which is thus transferred effectively. In the absence of this "steering effect", as may be the case for the transition state II of the reaction with reagent **3-62**, the enantioselection of the reaction decreases. Of particular interest is that both reactions proceed through a chair-form transition state because neither **3-55** nor **3-62** have a *Z*(*O*)-methyl substituent (see below). As pointed out earlier in this chapter, it has been known for some time that the reaction involving **3-9a** (or **3-10a**) proceeds with near-perfect enantioselection but that with **3-9b** (or **3-10b**) provides a mixture of diastereomeric aldols with negligible selectivities, a puzzling observation for which no reasonable explanation has yet been offered.

While the reaction with **3-9a** proceeds via the preferred chair-like transition state III rather than IV where the steric hindrance between the Z(*O*)-methyl group (R') and the ligand (L) attached to the boron atom is prohibitably severe, the reaction with **3-9b** may proceed through the boat-like transition state IV (R' = H) or V, where the interaction between chiral auxiliary of the ketone and ligand attached to the boron is diminished. Both transition states IV and V would then be of approximately equal energy, differing only in the orientation of the reacting aldehyde with respect to **3-9b** as shown and the reaction would then proceed stereorandomly. Thus the presence of the methyl group (R_1 = Me) is essential for reagent **3-9a** to be enantioselective and for that matter, reagents of the same or a similar type having a group other than hydrogen for R_1 (e.g. **3-9c**, R_1 = -SMe) exhibit excellent selectivity.[61f,63,71,75,76,94] In contrast to the reagents **3-9b** or **3-10b**, the triethylcarbinyl group in I and II, despite its large steric bulk, apparently can be accomodated within the chair-form framework as the conformation of the group is flexible with its rotation along the axis of the sulfur and carbon atoms indicated by the dagger in I and II.

3.3 ALDOL REACTIONS OF METHYL KETONES

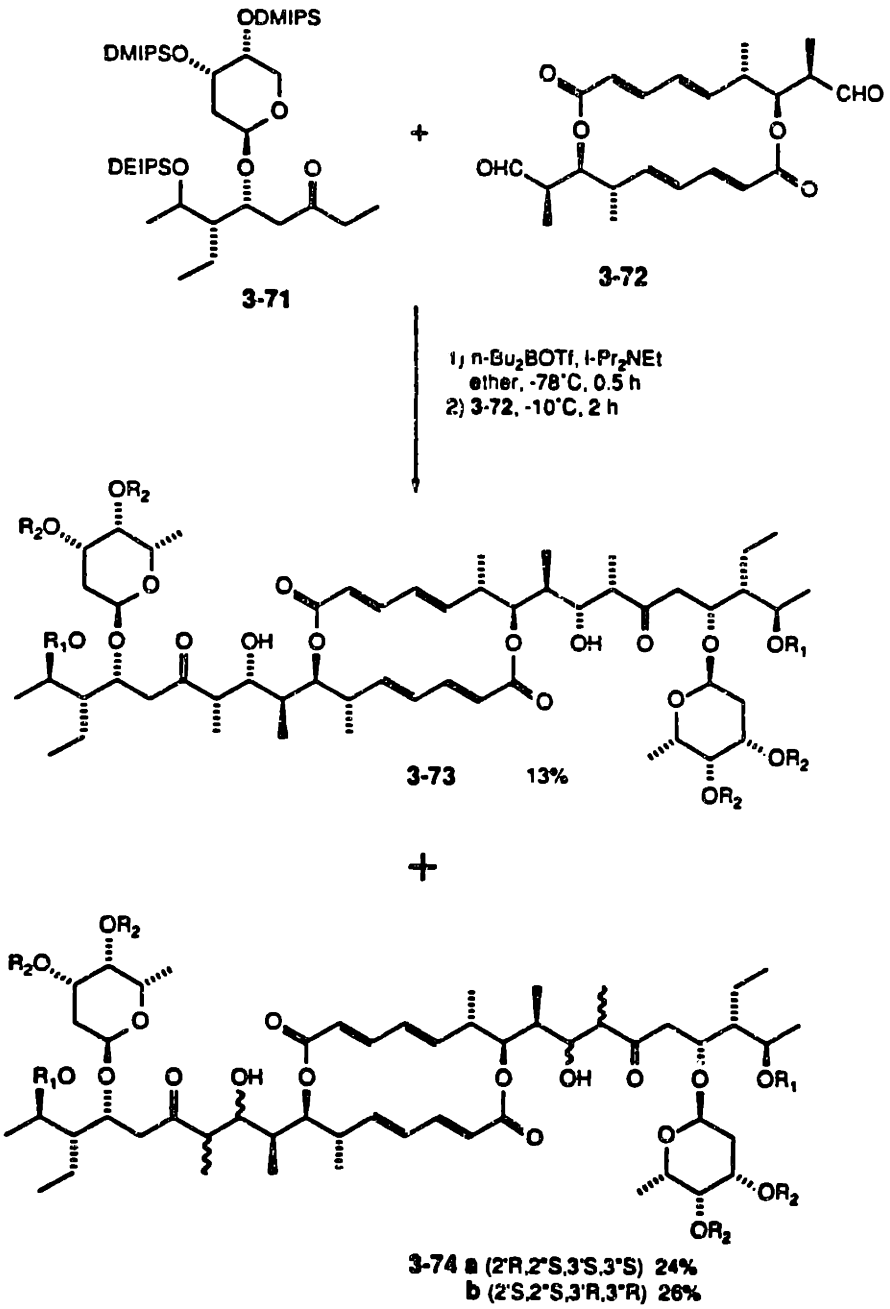
3.3.1. Background

The importance of convergence for the overall efficiency of synthesis of a large molecule has been well recognized, however no general methods yet exist for coupling reactions based on triple asymmetric synthesis (i.e. coupling of two homochiral fragments such that new chiral centers are stereoselsectively constructed in a controlled manner). One of the most frequently used reactions for effecting a stereoselective coupling is the aldol reaction. Indeed many of the examples of the syntheses of ionophore[95] and macrolide[72a,96] antibiotics and other natural products[97] utilized stereoselective aldol reactions for the crucial coupling steps.

Since the coupling reaction has to deal with predetermined chiralities of the target molecule, one had to heavily depend upon the diastereofacial selectivities of the two reactants (an enolate and an aldehyde). Therefore unless the diastereoselectivities of the coupling reactants fall into a matched case, the selectivity of the coupling reaction is capricious and unpredictable and it often remains as the least stereoselective step in the corresponding total synthesis. Depicted in Scheme 3.19 is a demonstrative example of such "mismatched", otherwise highly convergent, coupling reactions by Kinoshita *et al.*[96f], in their synthesis of elaiophylin (azalomycin B, **3-73** with R_1=R_2=H), a C_2-symmetrical 16-membered macrolide.

When the aldehyde **3-72** was treated with a boron enolate of **3-71** which was generated in a standard fashion, the desired diastereomer **3-73** was obtained only in 13% yield. This crucial closing stage of the total synthesis was enfeebled by the 2:1 preponderance of the unwanted "Cram" product **3-74b** over the desired "anti-Cram" product **3-73** which upon desilylation converts to the azalomycin B.

Scheme 3.19

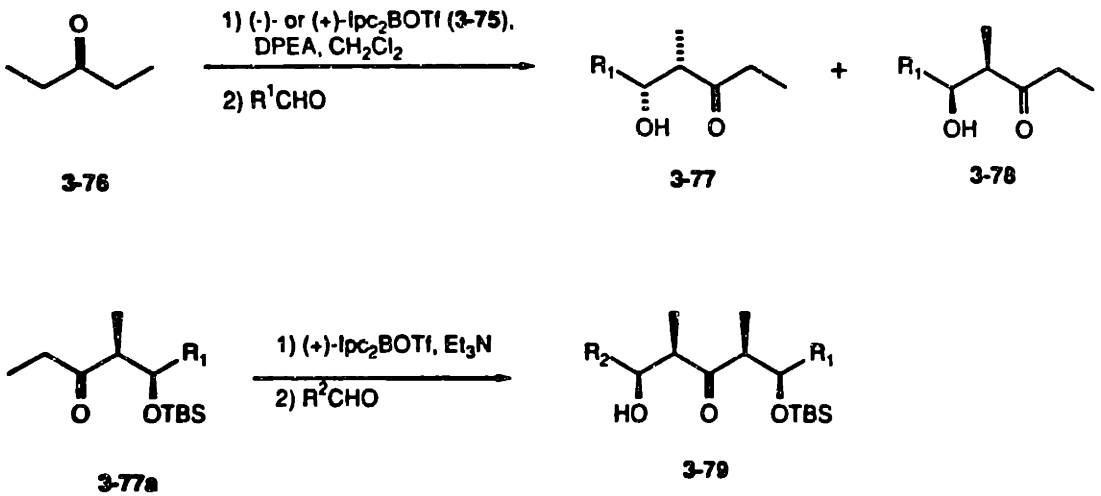


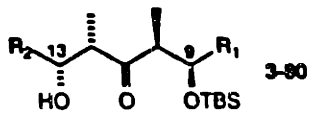
R1 = DEIPS, diethyl isopropylsilyl
R2 = DMIPS, dimethylisopropyl

The above result is sufficient to demonstrate that the present methodology is incapable of controlling a stereoselctive coupling and also to warrant a shfit of attention to a new strategy for the stereoselective coupling reactions. In this connection, the employment of ketone aldol reaction which is controlled by an "external reagent" is of particular attraction. However, powerful control of the stereochemistry in the desired direction is essential for this strategy to be useful.

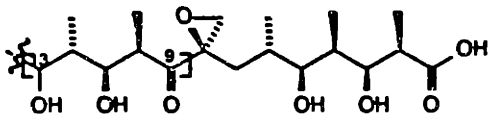
Recent progress by Paterson and coworkers[98] in the aldol reaction of ethyl ketones by utilizing boron enolates prepared with (+)- or (-)-diisopinocampheylboron triflate (IPC_2BOTf, **3-75**) bodes well for the significance of the "external reagent" strategy in the ketone aldol reaction. High diastereoselectivities (>90:10) with respectable enantiomeric excesses (66-90%) were observed in the aldol reaction of 3-pentanone with various aldehydes (Scheme 3.20). Double-asymmetric synthesis using the silylated aldol product **3-77a** also proceeded favorably with the aid of (+)-Ipc_2BOTf to afford **3-79**, a potential fragment of the ansa chain (**3-82**) of rifamycin S.

Scheme 3.20

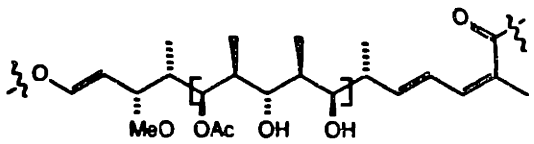




3-80



3-81



3-82

That the high selectivity encountered in the construction of **3-79** (30:1-47:1, **3-79/3-80**) was mainly due to the facial selectivities of the enolate itself (matched case) was clearly demonstrated when attempts to override it with antipodal boron reagent {(-)-**3-75**} (mismatched case) in order to secure the fragment **3-80** for the preparation of secoacid structure (**3-81**) of oleandomycin ended in failure. Undesired **3-79** was still favored in a ~3:1 ratio.

As part of continuing efforts in our laboratories to address these important synthetic problems, we sought to employ the strategy of the "external reagent" in ketone aldol reactions by making use of various homochiral boron reagents developed in our laboratories. This section is divided into two areas: (1) preparation and application of *B*-chloroboron reagents to the aldol reactions, and (2) asymmetric ketone aldol reactions using various chiral boron reagents.

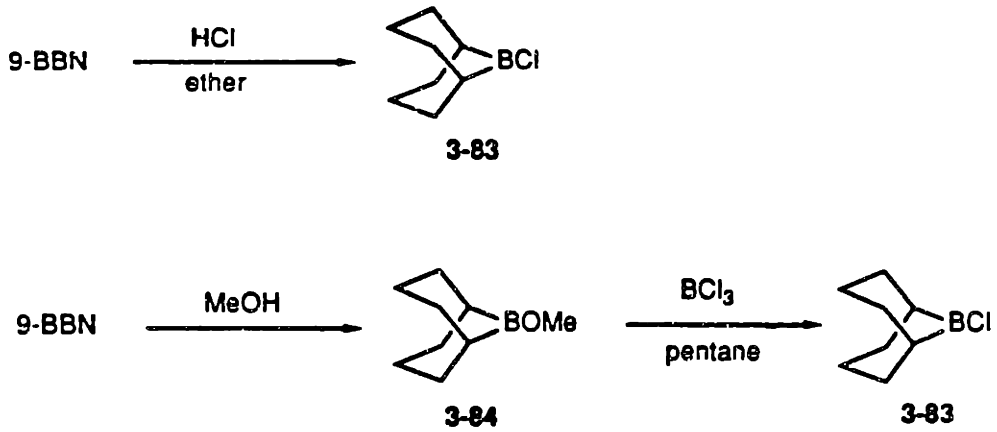
3.3.2. Preparation of Various Boron Reagents and Application to the Aldol Reactions

Although it has been well established that boron triflate is the best boron reagent to facilitate the formation of boron enolate,[99] we tried to find an alternative to this reagent since the preparation of the boron triflate from our boron reagents (aminoalcohol complexes) is still cumbersome: (1) it requires several steps from the aminoalcohol complexes to prepare (overall yield 50-70%) and (2) in some cases the free borolane generated in the course of the manipulation suffers thermodynamic instability under the reaction conditions (see below). In order to find a remedy for these problems, we looked into the possibility of the employment of different boron reagents, *B*-chloroboranes.

Boron trichloride and alkoxydichloroboranes were used by Seebach and Chow in their study of diastereoselective aldol reactions.[100] However, employment of dialkylchloroboranes to the aldol reaction has not been reported to date. In this section are addressed the preparation of such boron reagents and the examination in detail of the applicability of them to the aldol reactions.

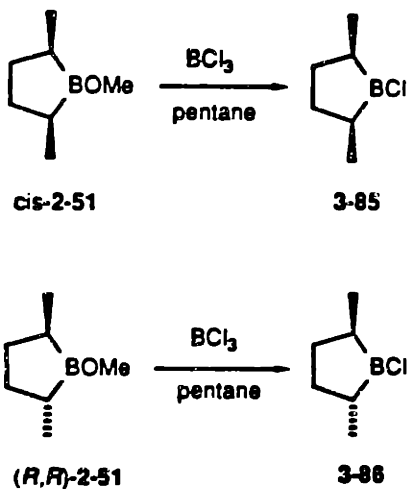
B-Chloro-9-BBN (**3-83**) could be prepared in two ways: (1) treatment of 9-BBN with an ethereal HCl solution[101] or (2) treatment of *B*-methoxy-9-BBN (**3-84**) with BCl_3 in pentane (Scheme 3.21). The latter method was preferred since it avoids the use of ether, the cleavage of which by *B*-chloro-9-BBN causes the formation of a side product.[101]

Scheme 3.21



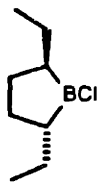
Likewise, *cis*- and *trans*-*B*-chloro-2,5-dimethylborolanes (3-85 and 3-86) were prepared from the corresponding *B*-methoxyborolanes (cis-2-51 and (*R*,*R*)-2-51) as shown below (Scheme 3.22).

Scheme 3.22

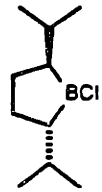


It was found that the enantiomeric purities of 3-85 and 3-86 are the same as those of the starting methoxyborolanes. A variety of *B*-chloroboranes (3-87 - 3-89) were prepared using the above method starting from various aminoalcohol complexes (3-90

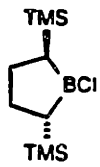
- 3-92), which had been prepared in these laboratories (3-90; T. Imai, 1986, 3-91; R.M. Kennedy and T. Imai, 1985, 3-92; R.P. Short and R.M. Kennedy, 1986) according to the method similar to that for (*S*)-prolinol complex of (*R*,*R*)-2,5-dimethylbrolane (2-59).



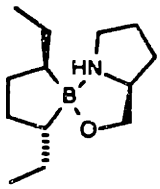
3-87



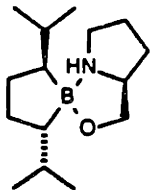
3-88



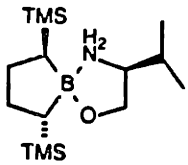
3-89



3-90



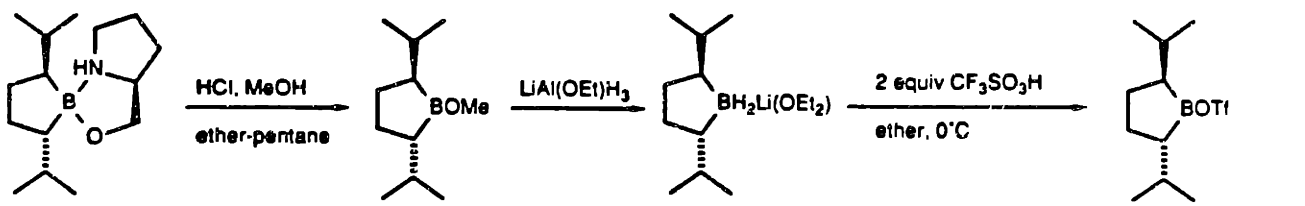
3-91



3-92

Particularly pertinent to the employment of the *B*-chloro-2,5-diisopropylborolane 3-88 is that it offers a remedy for the problems associated with the preparation of corresponding triflate 3-95a in that the synthesis of the triflate suffers severe epimerization (R.M. Kennedy and B.M. Kim, 1986) (Scheme 3.23).

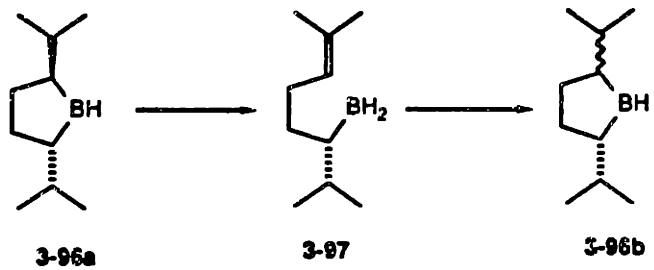
Scheme 3.23



3-91 → 3-93 → 3-94 (trans/cis = 98.4/1.6) → 3-95a (trans/cis = 85.6/14.4)

It was found that the free borolane **3-96a** generated from the dihydridoborate **3-94** undergoes facile dehydroboration - rehydroboration at room temperature as

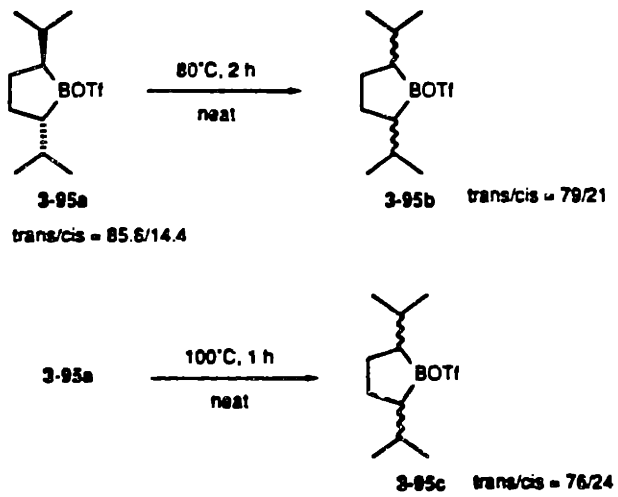
Scheme 3.24



3-96a **3-97** **3-96b**

depicted in Scheme 3.24 (R.M. Kennedy, 1986). In addition, the boron triflate **3-95a** also undergoes facile isomerization. Thus in a control experiment, the isomeric purity of the triflate **3-95a** notably decreased after thermal treatments as shown in Scheme 3.25.

Scheme 3.25

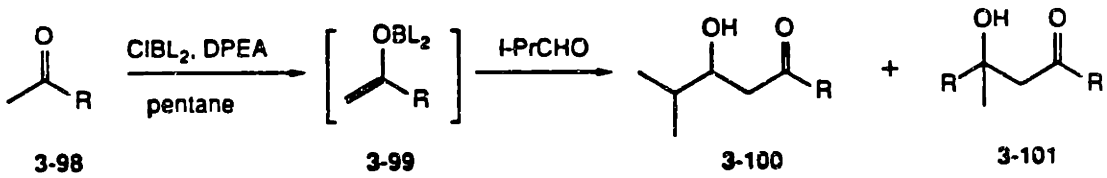


From these experiments it is very likely that deterioration of the isomeric purity of **3-95a** ocurred during distillation. Conversely, the chloroborolane **3-88**,

prepared from *B*-methoxyborolane as above (Scheme 3.21), could be obtained with essentially the same purity as that of **3-91**.

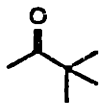
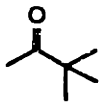
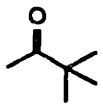
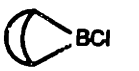
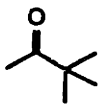
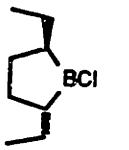
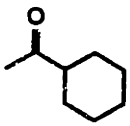
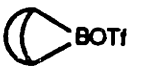
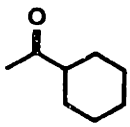
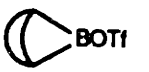
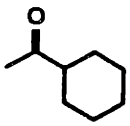
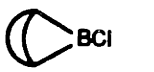
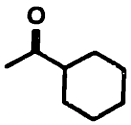
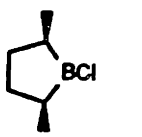
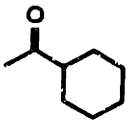
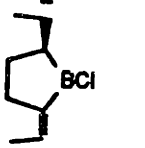
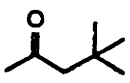
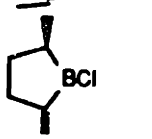
An initial set of experiments were carried out to examine whether the chloroboron reagents, compared to the corresponding boryl triflates, could be successfully employed in the aldol reaction of methyl ketones (Scheme 3.26). The results are collected in Table 3.7 (J. Garcia and B.M. Kim, 1987).

Scheme 3.26



3-98 **3-99** **3-100** **3-101**

Table 3.7.[a] Aldol reaction of enolates prepared from ketones and various boron reagents with isobutyraldehyde.

entries	ketone	boron reagents	enolate formation condn	aldol reaction condn	isolated yield (%) 3-100	3-101
1			0°C, 1.75 h	0°C, 4.75 h	83	trace[c]
2			0°C, 2.5 h	0°C, 4 h	53	21
3[d]			0°C, 2.5 h	0°C, 4 h	42	21
4			-78° 0°C, 10 min room temp, 30 min	-78°C, 4.5 h	91	trace[c]
5			0°C, 1.25 h	0°C, 4 h	73	10
6			-78°C, 3 h	0°C, 4 h	67	12
7			0°C, 2.5 h	0°C, 4 h	58	20
8			0°C, 2.5 h	0°C, 4 h	66	12
9			-78° 0°C, 10 min	-78°C, 4.5 h	72	6
10			0°C, 1.75 h	-78°C, 3 h	86	trace[c]

a. Unless otherwise noted, 1.0 equiv boron reagent was added to a mixture of ketone (0.15 M) and DPEA (1.2 equiv) then after a designated period was added isobutyraldehyde.

b. Yield was expressed in mol% of **3-101.**

c. Less than 3%.

d. DPEA was added to a mixture of ketone and the boron reagent.

As presented in Table 3.7, the reaction involving chloroboron regents presented complication due to the formation of side products **3-101** from the self-condensation of the boron enolate **3-99** with the starting ketone **3-98** (entries 2, 3, 7, and 8). It is suggested from these results that the formation of the boron enolate with chloroboron reagents is considerably slower than that with boron triflates. (compare the results in entries 1 vs 2, and 5, 6 vs 7). Of particular note is that while the reactions involving *B*-chloro-9-BBN (**3-89**)(entries 2, 3 and 7) suffers severe formation of **3-101** much less self-condensation is observed with sterically more demanding boron reagents (entries 4, 8, 9 and 10). 9-BBN, a peculiar cyclic boron reagent with the two C-B bonds tied back in a bicyclic ring, is regarded as a sterically unhindered moiety. That the self-condensation with smaller ligands on boron is better facilitated than that with large ligands on boron during enolate formation is revalidated by the fact that the reaction involving *B*-chloro-trans-2,5-dimethylborolane (**3-86**) gave much less of the self-condensed side product **3-101** than that with cis-*B*-chloro-2,5-dimethylborolane (**3-85**) (entries 10 and 8, respectively). An attempt to complex the ketone with the chloroborane prior to deprotonation (entry 3) did not improve the reaction yield. It is gratifying , however, that the chiral chloroboranes **3-86** and **3-87** provide an attractive alternative to the corresponding borolanyl triflates , and give respectable yields of aldol products (entries 4, 9 and 10).

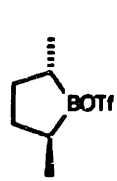
3.3.3. Asymmetric Aldol Reactions of Methyl Ketones with Various Homochiral Boron Reagents

With various homochiral *B*-chloroboranes (3-86 - 3-89) together with *B*-chlorodiisopinocampheylborane (Ipc_2BCl, 3-102, commercially available) and Ipc_2BOTf (3-75) in hand, we undertook the aldol reactions of three representative methyl ketones with isobutyraldehyde and the results are summarized in Table 3.8 (J. Garcia and B.M. Kim, 1987).

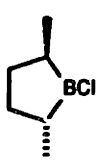
The data in Table 3.8 reveal a number of significant trends in yields and enantiomeric excesses of the aldol reactions with various boron reagents. First, all of the aldol reactions involving chloroboron reagents (entries 2, 3, 8, 9. 13, and 14) proceeded smoothly to afford good yields of aldol products except in the case where *B*-chlorodiisopinocampheylborane was employed (entry 9). As anticipated, almost all the reactions employing diisopinocampheylborane moieties (entries 4, 5, 10, 11, 12, and 15) suffered poor reactivities under the standard reaction conditions (see entry 9) and the reactions with these reagents must be carried out at elevated temperature (0°C instead of -78°C) to provide reasonable yields of aldol products. This illustrates that the isopinocampheyl ligand exhibits severe steric hindrance toward the incoming aldehyde in the respective transition state. The poorest reactivity observed with 2,5-bis(trimethylsilyl)borolane (3-89) (entry 6) may be due to excessive steric interaction and/or decreased reactivity due to the stereoelectronic stabilization of boron by silicone. Relative to the steric hindrance between the boron ligand and the ketone, not only the reactivities but the enantioselectivities of the aldol reactions showed informative correlations. Although no significant differences in enantioselections were noted between the 2,5-dimethyl- and 2,5-diethylborolane moieties 3-86 (or 3-21) and 3-87, respectively, a significantly lower enantioselectivities were observed in the reactions employing 2,5-diisopropylborolane moiety 3-88 (entries 2 and 8). In a similar

Table 3.8[a] Asymmetric aldol reaction of ketones with various boron reagents.

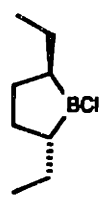
entry	ketone	boron reagent	solvent	reaction condn	isolated yield(%)	abs config	corrected[b] % ee
1		(*S,S*)-3-21	pentane	-78°C, 2 h	68	*S*	50
2	"	(*R,R*)-3-88	"	-78—65°C, 7 h	76	*R*	56
3	"	(*R,R*)-3-87	"	-78°C, 4.5 h	72	*R*	61
4	"	3-75[c]	"	0°C, 2 h	54	*R*	77
5	"	3-75[c]	CH_2Cl_2	0°C, 2 h	77	*R*	65
6	"	(±)-3-89	CH_2Cl_2	r. t., 24 h	trace[d]		
7		(*S,S*)-3-21	pentane	-78°C, 4 h	91	*S*	50
8	"	(*R,R*)-3-88	"	-78—65°C, 7 h	86	*R*	39
9	"	(*R,R*)-3-87	"	-78°C, 4.5 h	91	*R*	56
10	"	3-102	"	0°C, 2 h	7		28
11	"	3-75[c]	CH_2Cl_2	0°C, 2 h	66	*R*	23
12	"	3-75[c]	pentane	0°C, 2 h	29	*R*	24
13		(*R,R*)-3-86	"	-78°C, 3 h	86	*R*	64
14	"	(*R,R*)-3-87	"	-78°C, 7 h	80	*R*	55
15	"	3-75[c]	"	0°C, 2.5 h	85	*R*	52



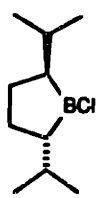
(*S,S*)-3-21



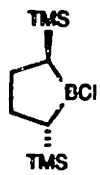
(*R,R*)-3-88



(*R,R*)-3-87



(*R,R*)-3-86



3-89

3-75

3-102

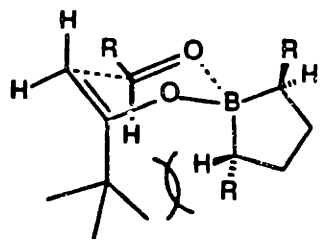
a. Unless otherwise noted, the enolate was prepared by adding the boron reagent (1.2 equiv) to a mixture of the ketone (1.0 equiv, 0.15-0.20 M) and DPEA (1.2 equiv) and then isobutyraldehyde (1.5 equiv) was added to the enolate.

b. Values were determined by HPLC (entries 1-6 and 13-15) or ^{1}H NMR analysis (entries 7-12) of the corresponding MTPA esters, and corrected for the enantiomeric purity of each boron reagents.

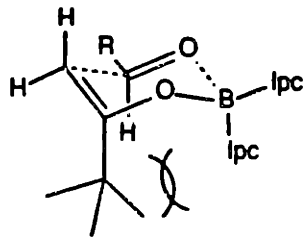
c. Prepared from (α)-(+)-pinene.

d. Less than 5% of the aldol products were obtained in repeated experiments.

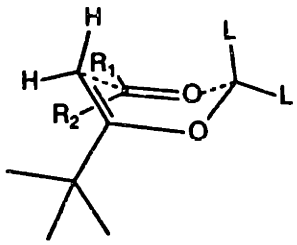
vein, with a given boron reagent the more hindered ketone (methyl t-butyl ketone) exhibits lower asymmetric induction (entries 7-12). This is not surprising when the corresponding trasnsition states of these reactions are considered.



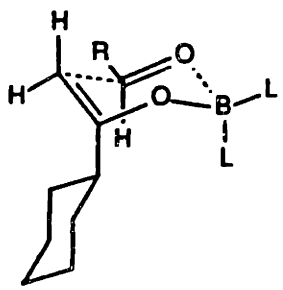
VI



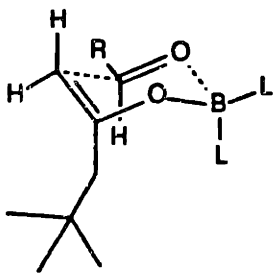
VII



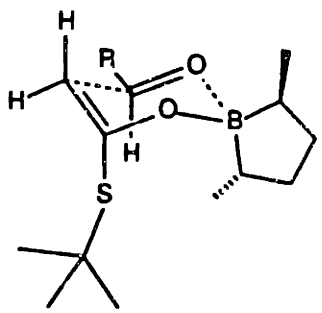
VIII



IX



X



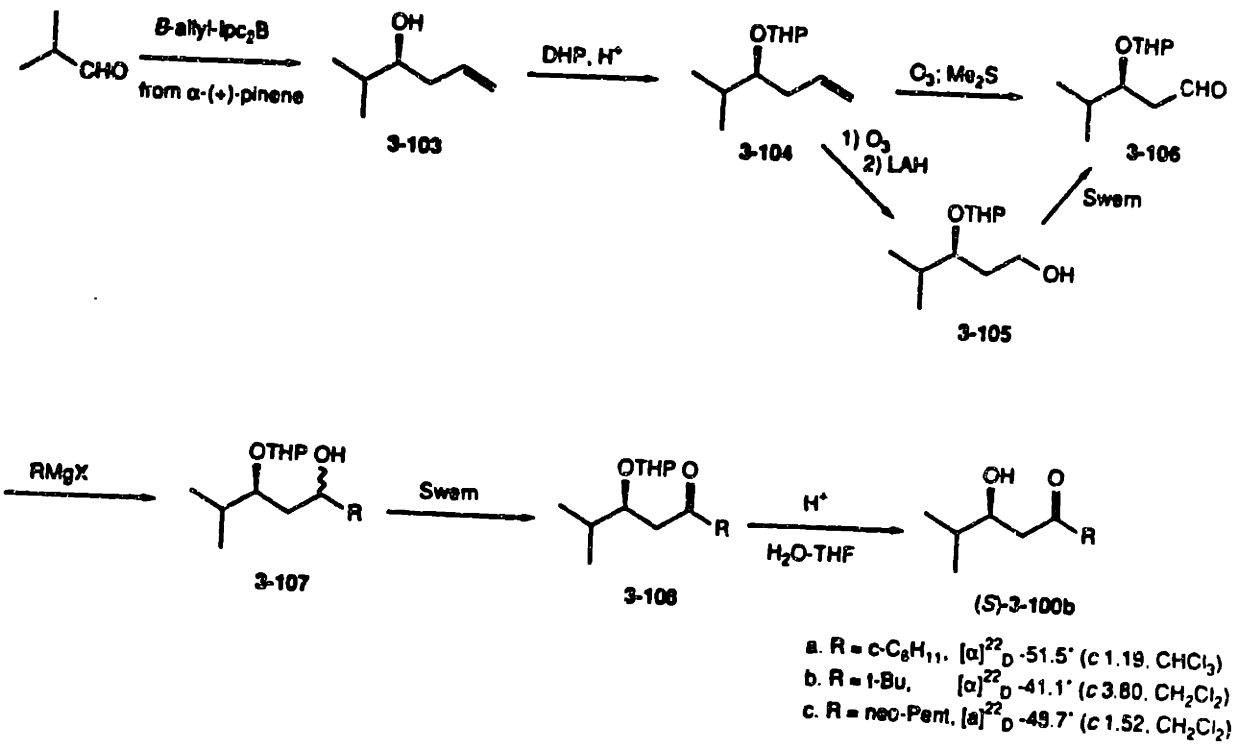
XI

As was mentioned earlier in this chapter (section 3.2.4.), the interaction between C_1 substituent of the enolate and the boron ligand plays a crucial role in determining the least energy pathway of several diastereomeric transition states. The lower enantioselectivities observed in the aldol reactions of methyl t-butyl ketone with any of the boron reagents can be easily understood by the unfavorable interaction of the boron ligand and t-Bu group of the enolate (VI and VII). With the above interaction being too strong, the boat-like transition state VIII may intervene as a competitive route for the aldol reactions and thus allow for two possible aldol products due to two similar energy pathways with regard to the orientation of R_1 and R_2 (R_1 = H, $R_2 \neq$ H or $R_1 \neq$ H, R_2 = H). This explanation is in accord with the observation of higher enantioselectivities for the aldol reactions of methyl cyclohexyl ketone (IX, entries 1-5) than those for the methyl t-butyl ketone. The highest enantioselectivity was recorded with $(Ipc)_2BOTf$ (entry 4). Encouraged by the high enantiomeric excesses observed in the aldol reactions involving *S*-t-butyl ethanethioate (~85% ee) and *S*-3-(3-ethyl)pentyl ethanethioate (90-98% ee) (see XI), the aldol reaction of methyl neopentyl ketone, a methylene analogue of the *S*-t-butyl ethanethioate was tried (entries 13-15). A marginal degree of enhancement in ee values for the 2,5-dimethylborolanyl case (64% ee vs 60 and 50% ee, entries 13, 1, and 7, respectively) was observed, however the selectivities still had room for further improvement. In cases where other boron reagents were employed, ee's between those obtained for methyl cyclohexyl ketone and methyl t-butyl ketone were obtained, which suggests that the interaction between the C_1-substituent of the enolate and the boron ligand in transition state X is still larger than that in transition state XI.

Of particular note is that all the aldol reactions examined in Table 8 afforded products possessing consistent absolute configuration with regard to the boron reagents. The assignment of the absolute configuration of the aldol products was accomplished by comparison with authentic aldol products prepared from compounds

of established stereochemistry. Thus, portrayed in Scheme 3.27 is the synthesis of authentic aldols starting from a homochiral compound.

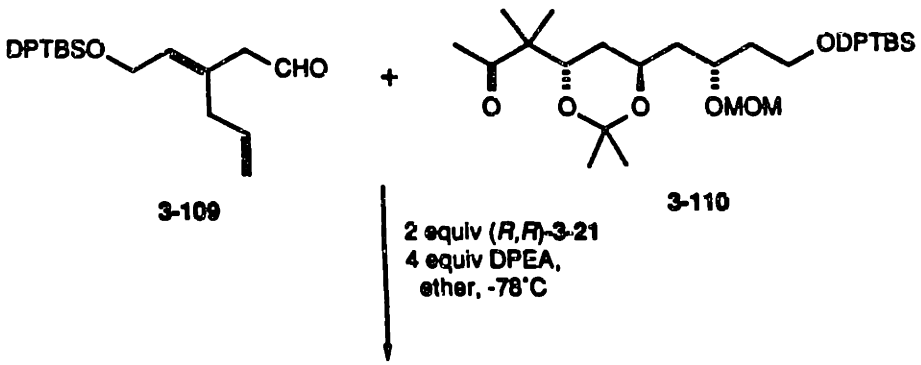
Scheme 3.27



The (*S*)-configuration of homoallylic alcohol 3-103 ($[\alpha]^{22}_D$ -1.63° (*c* 8.245, C_6H_6), 81.6% ee) was secured by using *B*-allyldiisopinocampheylborane[102] derived from α-(+)-pinene. After the alcohol was protected the terminal olefin was cleaved to the corresponding aldehyde 3-106 by ozonolysis. Grignard addition to aldehyde 3-106 followed by oxidation afforded the protected hydroxyketone 3-108 Removal of the THP ether by hydrolysis converted 3-108 to (*S*)-3-100b, (*S*)-MTPA derivative of the aldol products were compared with that of (*S*)-3-100b by ^1H NMR and HPLC analysis to unambiguously verify the absolute configuration as depicted in Table 3.8.

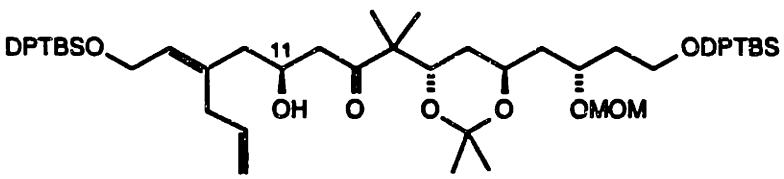
Although there is still room for further improvement in ketone aldol reactions, we sought to apply this methodology to a convergent coupling reaction of two fragments towards the total synthesis of bryostatin 1 (3-108) as shown in Scheme 3.28.

Scheme 3.28



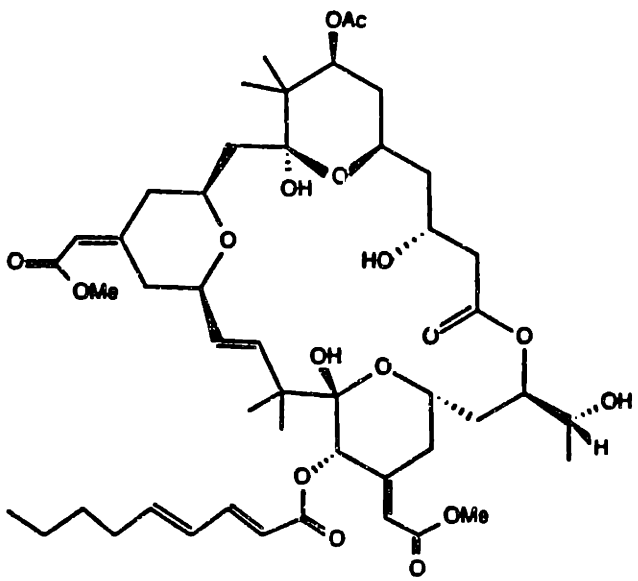
3-109

3-110



3-111

6:1 at C(11)



3-108 (bryostatin 1)

The boron enolate derived from **3-110** with the aid of (*R,R*)-**3-21** underwent an aldol reaction with aldehyde **3-109** with a 6:1 stereoselection at C(11). This is heartening since no appreciable selectivities are observed when achiral boron enolate of **3-110** was employed in the aldol reaction.

In summary of this section, asymmetric aldol reactions of methyl ketones were examined using various homochiral boron reagents with the aim of developing a methodology to selectively couple two hommochiral fragments to afford a convergent synthesis of complex natural products. *B*-Chlorodialkylborane reagents have emerged as practical alternatives to the boron triflates in the formation of boron enolate. A partial success has been recorded with regard to the enantioselectivities of the aldol reactions involving methyl ketones and various boron reagents, thus a further improvement is anticipated for this methodology to be useful for the double- or triple asymmetric synthesis.

3.4 Summary

The problems associated with the construction of 2,3-anti-3-hydroxy-2-methyl- and 3-hydroxycarbonyl units, which were addressed at the outset of this chapter, have been essentially solved through the efficient exploitation of the external chiral boron reagent **3-21**. Enantiomeric excesses higher than 98% have been achieved in the aldol reactions of *S*-3-(3-ethyl)pentyl propanethioate involving **3-21** and representative aldehydes thus allowing for double asymmetric synthesis to be serviceable.[103] In the aldol reactions involving ethanethioate 89-98% ee's were obtained for the products and there is still room for further improvement, although the enantioselectivities are among the highest to date.[74]

Rationales are provided for the high anti-selectivity of *S*-3-(3-ethyl)pentyl propanethioate as well as enantioselectivities obtained for both propanethioates and ethanethioate aldol reactions. An explanation is given for the low selectivities obtained with reagents **3-9b** and **3-10b**.

Partial success has been recorded in attempts to achieve triple asymmetric synthesis through the efficient use of ketone aldol reaction. Moderate to good enantiomeric excesses were obtained in the aldol reactions of ketones with isobutyraldehyde involving various homochiral 2,5-disubstituted borolanes as well as Ipc_2BOTf. That *B*-chloroboron reagents can be utilized as practical alternatives to the boron triflates was also proved in the aldol reactions of ketones. Rational explanations for the selectivities obtained in the ketone aldol reactions, which are similar to those offered in the thioate aldol reactions, are given.

CHAPTER 4. ALLYL- AND CROTYLBORATION OF ALDEHYDES

4.1. INTRODUCTION

3-Hydroxycarbonyl and 3-hydroxy-2-methylcarbonyl units are characteristic structural elements of polyketide-type natural products such as macrolides and polyether antibiotics.[62] For the stereoselective construction of the above units, the aldol methodology has been considered perhaps the most direct approach toward this synthetic objective.[61] Since the development of stereoregulated aldol condensation reactions (see chapter 3), a number of related reactions, such as the reactions of allylic organometallic reagents with aldehydes have recently emerged as effective and practical alternatives.[104]

Among various allyl metal reagents, allylboranes have been the focus of keen attention due to the feasible employment of chiral borane ragents. Reactions of several chiral allyl- and crotyl boron compounds with aldehydes have recently been reported to proceed with high stereoselection to provide the corresponding homoallylic alcohols, which are synthetic equivalents of the structural units referred to above.

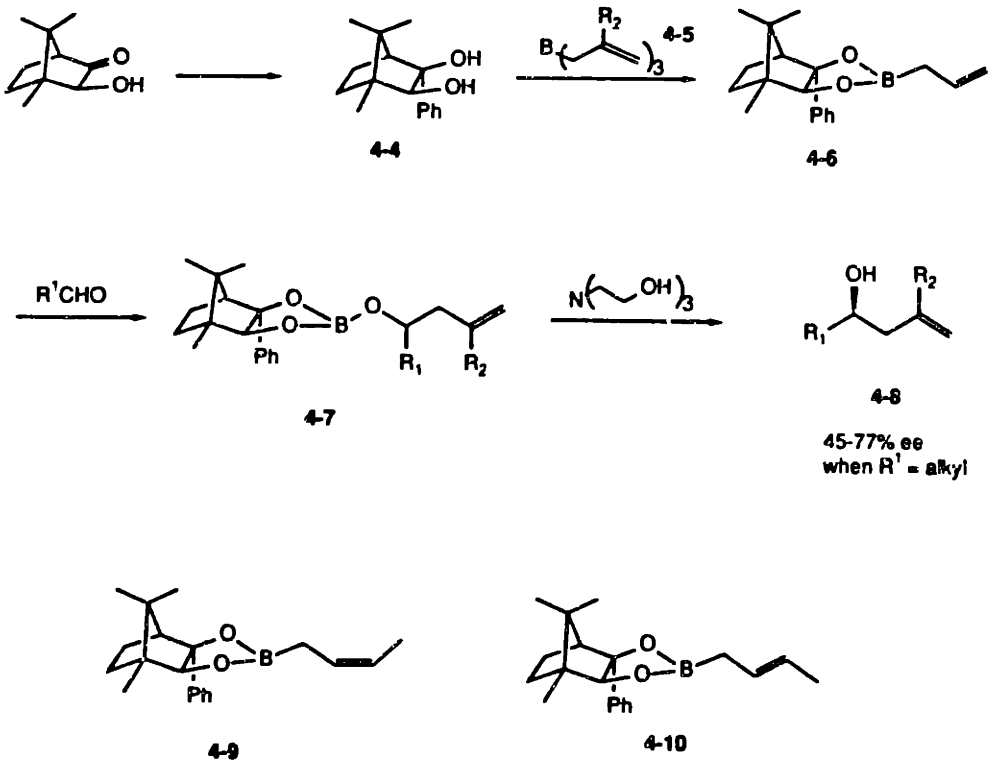
This chapter is focused on the reaction of the titled allyl- and crotyl-boron reagents with various achiral and chiral aldehydes yielding homoallylic alcohols of exceptionally high enantiomeric purity.

4.2. BACKGROUND

Allylboranes were first advanced by Mikhailov[105] and hence several achiral allyl- and crotylboron reagents have been developed and applied to the stereoselective addition to aldehydes or imines by several groups.[106-113]

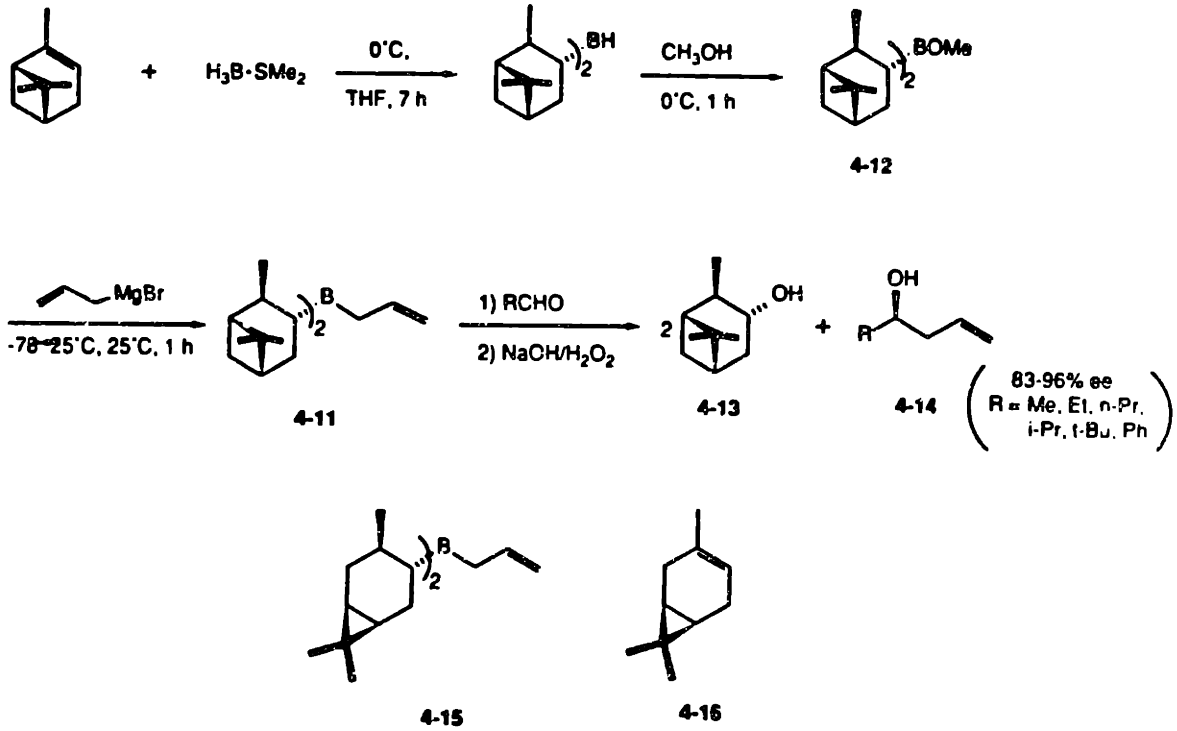
The first chiral *B*-allylboronate **4-6** was prepared from (+)-camphor derivative **4-4** by Hoffmann *et al.*[114] and upon reaction with aldehyde afforded homoallylic alcohols in excellent yields with enatiomeric excesses ranging between 45-77% with aliphatic aldehydes (Scheme 4.1). When the reaction was carried out with aromatic aldehydes and other π-conjugated aldehydes, the selectivities were inferior (24-54% ee). Employment of (*Z*)- and (*E*)-crotyl derivative of the chiral boronates (**4-9** or **4-10**) to the reaction with achiral[115] or chiral[116] aldehydes were also first examined by Hoffmann and results conforming to the rule of double-asymmetric synthesis[2] were obtained. However, the enantioselectivity of the reagents did not meet the criteria set for the double-asymmetric synthesis (98% ee); a careful selection of "matched" pairs was necessary for predominant formation of the desired isomer.

Scheme 4.1



Another type of allylboron reagent, *B*-allyldiisopinocampheylborane ($Ipc_2BCH_2CH{=}CH_2$, **4-11**) has been prepared from naturally occuring α-(-)- or (+)-pinene and successfully utilized by Brown *et al.*[102,117] for the synthesis of chiral homoallylic alcohols with substantially higher enantioselectivities than those obtained by Hoffmann[114] (Scheme 4.2).

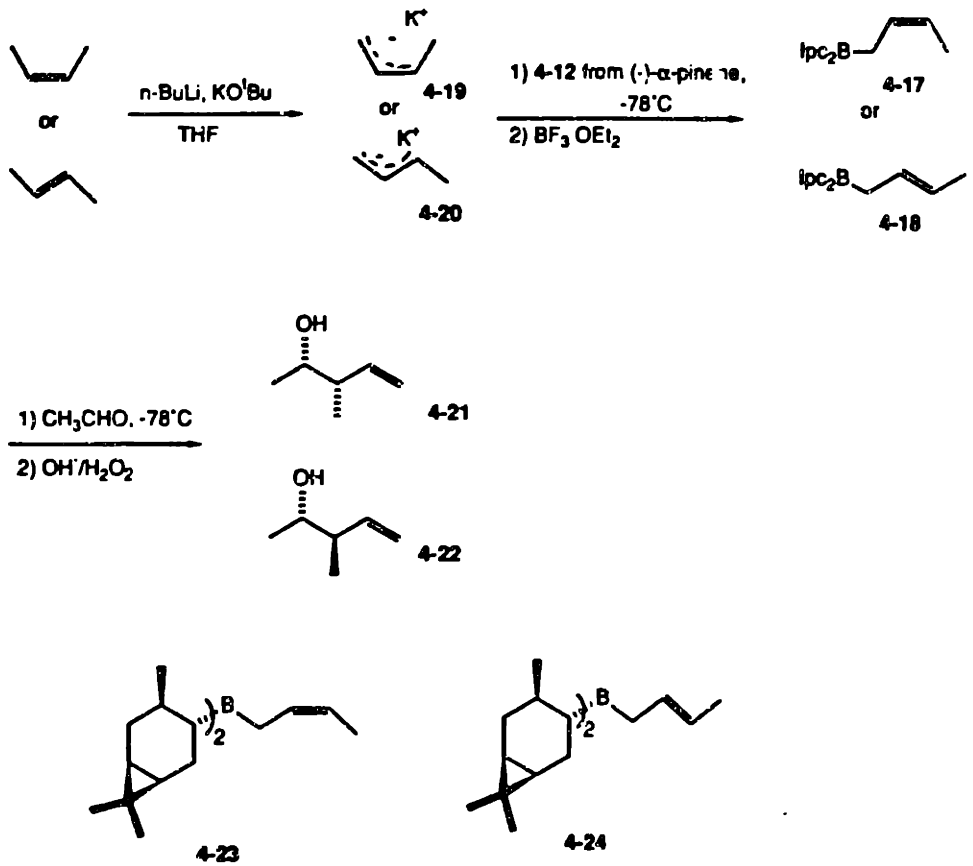
Scheme 4.2



Later Brown introduced an improved allylboron reagent, *B*-allyldiisocaranylborane (**4-15**),[117c,118] derived from readily available monoterpene (+)-Δ^3-carene (**4-16**). The reagent **4-15** furnished upon reaction with various aldehydes products **4-14** exhibiting 86-99% ee, which are higher than those obtained with **4-11**. It should be noted however that only one enantiomer of the terpene **4-16** is available in nature.

Owing to the preparation of isomerically pure (Z)- and (E)-crotyl metal reagents developed by Schlosser,[119] Brown adroitly prepared optically active (Z)- and (E)-crotyldiisopinocampheylboranes (4-17 and 4-18).[120] The diastereoselectivities obtained for the reaction of 4-17 (syn/anti) and 4-18 (anti/syn) with acetaldehyde were 99% in both cases and the enantioselectivities fell in a narrow region of 90-92% ee. (Scheme 4.3).

Scheme 4.3

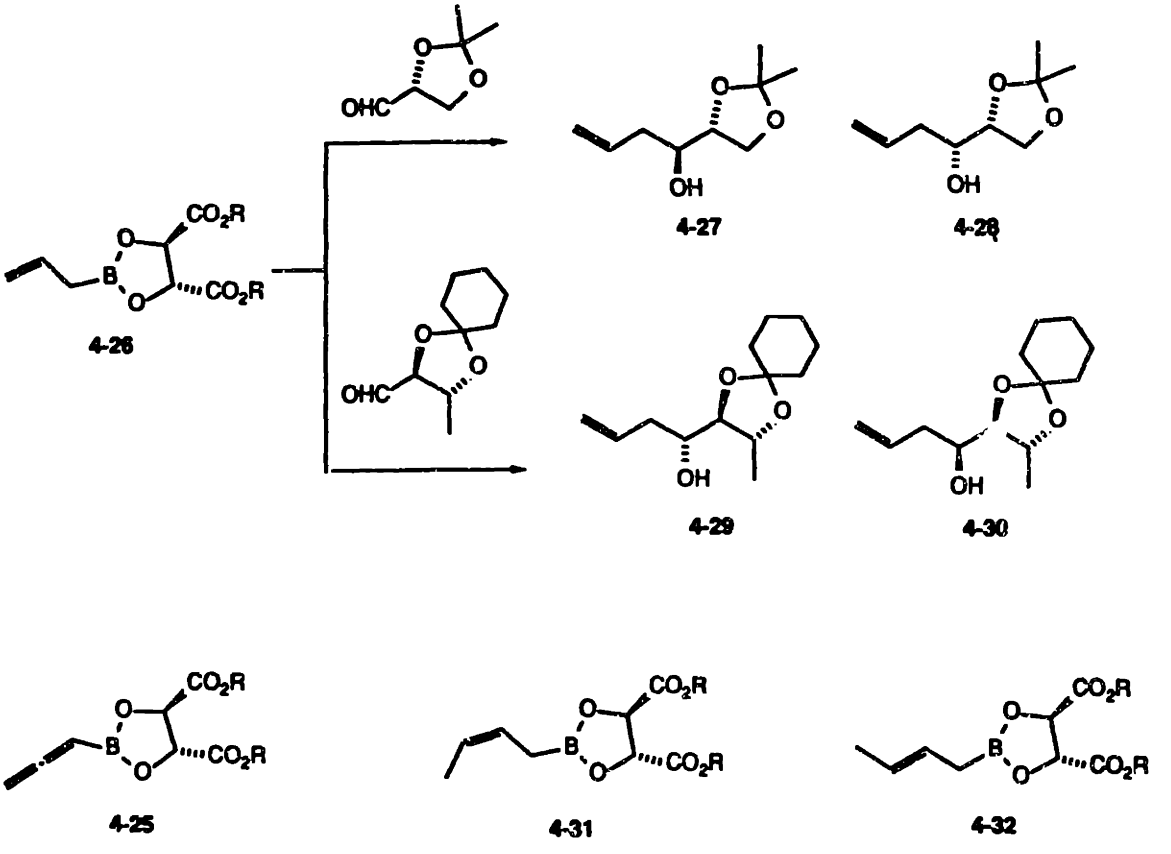


(Z)- and (E)-Crotyldiisocaranylboranes (4-23 and 4-24)[120b] also showed similar diastereoselectivities and slightly enhanced enantioselections (94% ee) upon reaction with n-propanal. Reactions of 4-11, 4-17, and 4-18 with homochiral aldehydes were also

carried out by Brown and the results conforming to the rule of double-asymmetric synthesis were reported.[121]

Yamamoto *et al.*[122] prepared chiral allenylboronate **4-25** which was shown to exhibit excellent (>90% ee) asymmetric induction upon reaction with various aldehydes. A similar class of chiral allylboron reagent was made use of by Roush *et al.*[123] *B*-Allylboronate derivatives of tartrate ester, **4-26** was prepared and utilized for asymmetric allylation reactions with chiral aldehydes (Scheme 4.4). Again a "matched" pair of the reagent and the substrate in the reaction with chiral aldehydes was carefully selected to predominantly furnish the desired isomer.

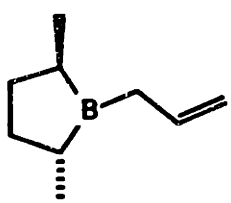
Scheme 4.4



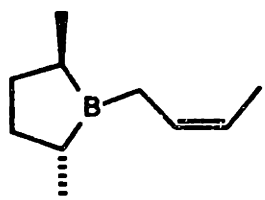
The crotylboronate reagent **4-31** and **4-32** were also employed in the reactions with chiral aldehydes yielding homoallylic alcohols with three contiguous chiral centers.[124] By successfully utilizing a combination of these reagents a short synthesis of a key intermediate toward the total synthesis of rifamycin S was accomplished, "testimonying the efficiency and brevity of this methodology."[125]

A few other reagents utilizing efficient chirality transfer were also reported by several groups,[126,127] and the discussion of these reagents is excluded in this account since the methodology is rather unrelated to the work presented here.

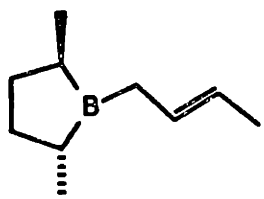
This section has been concerned with the known allyl- and crotylboron reagents in the reaction with chiral or achiral aldehydes to afford homoallylic alcohols in diastereo- and/or enantioselective fashion. We were somewhat curious whether the 2,5-dimethylborolane system, which induced remarkable stereoselection in the aldol reaction,[21] could also be utilized as the allyl- and crotylboron reagent with the same selectivity. The next two sections deal with the addition of the allyl- and crotyl moiety from our reagents and the final section addresses reasonable rationalizatior of the high selectivities observed with the reagents **4-1**, **4-2**, and **4-3**.



(R,R)-**4-1**



(R,R)-**4-2**

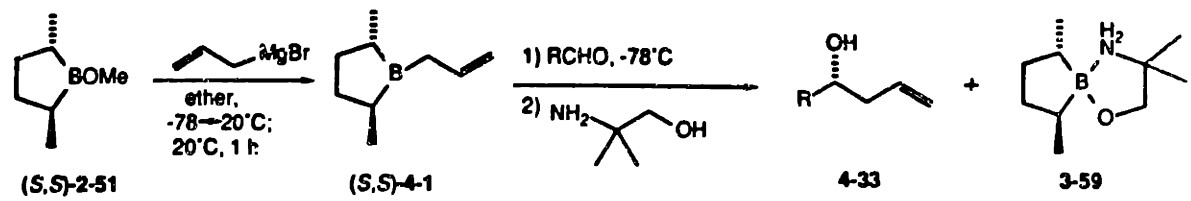


(R,R)-**4-3**

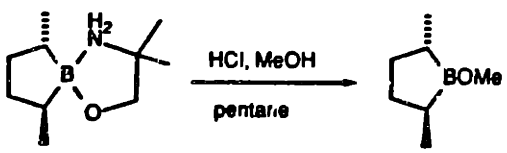
4.3. ALLYLBORATION USING *B*-ALLYL-2,5-DIMETHYLBOROLANE (4-1)

The preparation of **4-1** (^{11}B NMR δ 86 ppm) followed that reported for **4-11** by Brown[102] starting from the *B*-methoxy-2,5-dimethylborolane (Scheme 4.5). After addition of an aldehyde (0.9 equiv) to a 0.5 M solution of **4-1** in ether at -78°C, the solution was stirred 1 h and then warmed to 25°C over a period of 1 h. The ^{11}B NMR (δ 56) confirmed that transfer of the allyl group to the aldehyde had been completed at this stage. Addition of 2-amino-2-methylpropanol (1.2 equiv) to the rection mixture liberated homoalylic alcohol **4-33** precipitating the borolane moiety as an aminoalcohol complex **3-59**. The recovered aminoalcohol complex **3-59** retained full stereochemical integrity and could be reused by generating the methoxyborolane as shown in Scheme 4.5. Table 4.1 summarizes the results of allylboration with representative chiral aldehydes. The ee's of the products range between 85 and 93%. Stirring the reaction mixture longer at -78°C did not improve the enantiomeric excesses of the products. The finding that the highest enantioselection was obtained in the case where the least hindered aldehyde was employed parallels Brown's observation with his reagent **4-11**.

Scheme 4.5



(*S,S*)-2-51 (*S,S*)-4-1 4-33 3-59



3-59 (*S,S*)-2-51

Table 4.1. Reaction of 4-1 with representative achiral aldehydes.

entry	aldehyde	yield [a]	abs config of alcohol	%ee [b] obsd	%ee [b] corrected for the ee of 4-1 [c]
1	EtCHO	86	S [d]	86 [e]	93
2	i-PrCHO	72	R [f]	79	85
3	c-C_6H_{11}CHO	88 [g]	R [h]	82	88
4	t-BuCHO	91	S [i]	80	86

a. Yields were calculated by capillary GC analysis (methyl silicone, 0.20 mm x 12 m) using an internal standard unless otherwise noted.

b. Values were determined by HPLC analysis (chemcosorb Si60, 3m, 4.6 x 250 mm) of the corresponding (S)-MTPA esters of the product alcohol s unless otherwise noted.

c. (*S,S*)-2-51 of 92.8% ee was used.

d. $[\alpha]^{22.2}_D$ +5.25° (*c* 3.05, benzene); lit. $[\alpha]^{20}_D$ +4.74° (*c* 10.76, benzene) for 77% ee (*R*)-alcohol[114c]; $[\alpha]^{23}_D$ +5.30° (*c* 10.76, benzene) for 86% ee (*R*)-alcohol.[102]

e. %Ee's were calculated from ^{1}H NMR analysis (CH_3CH_2-) of the corresponding (*S*)-MTPA derivative.

f. $[\alpha]^{21.5}_D$ -1.74° (*c* 3.86, benzene); lit $[\alpha]^{20}_D$ -2.62° (*c* 11.82, benzene) for 70% ee (*S*)-alcohol[114c]; $[\alpha]^{23}_D$ -3.36° (*c* 11.82, benzene) for 90% ee (*S*)-alcohol.[102]

g. Isolated yield.

h. Absolute configuration was assumed on the basis of predicted ^{1}H NMR and HPLC behavior of the corresponding Mosher's ester compared with those of similar alcohols. See Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

i. $[\alpha]^{22.2}_D$ +10.17 (*c* 1.29, benzene); lit $[\alpha]^{20}_D$ -5.32 (*c* 10.90, benzene) for 45% ee (*S*)-alcohol.[114c]

4.4. CROTYLBORATION

4.4.1. Reaction of *B*-(*Z*)- and (*E*)-Crotyl-(*R*,*R*)-2,5-Dimethylborolanes {(*R*,*R*)-4-2 and (*R*,*R*)-4-3} with Achiral Aldehydes.

The preparation of the crotylborolanes (*R*,*R*)-4-2 and (*R*,*R*)-4-3 adopted the Schlosser procedure[119] modified by Brown[120] as shown in Scheme 4.6. Thus, the methoxyborolane upon reaction with (*Z*)- or (*E*)-crotylpotassium (4-19 or 4-20, respectively) provided, with the aid of $BF_3{\cdot}OEt_2$, (*R*,*R*)-4-2 and 4-3, respectively. Reactions of each crotylborolane with aldehydes were carried out in a manner similar to that described for 4-1 to provide selectively anti- or syn-homoallylic alcohols (4-34 - 4-37) as summarized in Table 4.2 (J. Garcia, 1987). As expected, (*R*,*R*)-4-2 and 4-3 lead to the predominat formation of the syn (4-34) and anti (4-36) products, respectively, with an average selectivity of 20:1. The high diastereoselectivities (99:1) reported by Brown was not observed with our borolane system. However, % ee's of the major product range between 95-97 for the (*R*,*R*)-4-3 series and between 86-97 for (*R*,*R*)-4-2. Thus, with the exception of entry 1 these crotylboron reagents exhibit exceedingly high enantioselectivities among those reported to date with achiral aldehydes.

Scheme 4.6

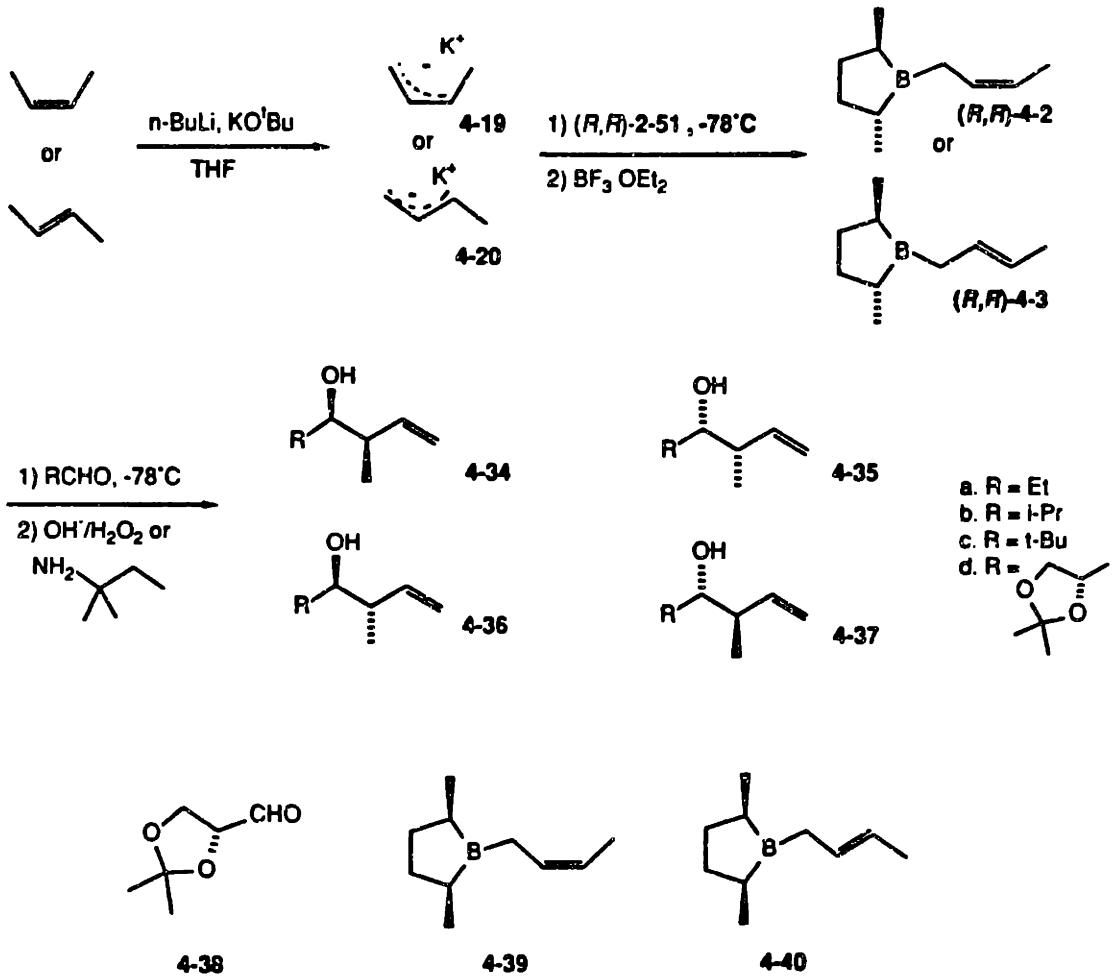

or
n-BuLi, KO'Bu
THF
K+
4-19
or
K+
4-20
1) (R,R)-2-51 , -78°C
2) BF3 OEt2
B
(R,R)-4-2
or
B
(R,R)-4-3
1) RCHO, -78°C
2) OH-/H2O2 or
NH2
OH
R
4-34
OH
R
4-35
OH
R
4-36
OH
R
4-37
a. R = Et
b. R = i-Pr
c. R = t-Bu
d. R =
O
O
CHO
O
O
4-38
B
4-39
B
4-40

Table 4.2. Reaction of crotylborolanes (*R,R*)-4-2 and (*R,R*)-4-3 with representative achiral aldehydes.

entry	crotyl-borolane	aldehyde	yield [a]	anti-/syn-[b] ratio	major product	% ee of the major product
1	(*R,R*)-4-2	EtCHO	73	7/93	4-34a [d]	86
2	(*R,R*)-4-2	i-PrCHO	70	4/96	4-34b [e]	93
3	(*R,R*)-4-2	t-BuCHO	75 [f]	5/95	4-34c [g]	97
4	(*R,R*)-4-3	EtCHO	81	93/7	4-36a [d]	96
5	(*R,R*)-4-3	i-PrCHO	76	96/4	4-36b [h]	97
6	(*R,R*)-4-3	t-BuCHO	72	96/4	4-36c [h]	95

a. Combined yield for syn- and anti- products. Unless otherwise noted yields were based on the amount of borolane reagent used and calculated by capillary GC analysis (5% phenyl methyl silicone, 0.20 mm x 12 m) of the alcohols using an internal standard.

b. Determined by capillary GC analysis (see footnote a).

c. Determined by HPLC analysis (chemcosorb Si60 3m, 4.6 x 250 mm) of bis-(*R*)-MTPA esters of the corresponding 1,3-diols obtained from ozonolysis of and followed by reductive workup. Values are corrected for the purity of (*R,R*)-2-51 (97.9% ee).

d. Bis-(*R*)-MTPA esters of the corresponding 1,3-diols (see footnote c) from the products were compared with authentic samples obtained from the crotyl derivative of (-)-Ipc_2BH.[120]

e. $[\alpha]^{25}_D$ -7.54° (*c* 0.83, $CHCl_3$) for the corresponding 1,3-diol: lit $[\alpha]^{25}_D$ +10.29° (*c* 0.91, $CHCl_3$) for the antipode.[70]

f. Yield was based on the amount of the aldehyde used.

g. The absolute configuration was assumed and in accordance with predicted ^1H NMR and HPLC behavior of the bis-(*R*)-MTPA derivative of the corresponding 1,3-diol. See reference in footnote h of Table 4.1.

h. The absolute configuration of the product was determined by the comparison of bis-(*R*)-MTPA derivatives of the corresponding 1,3-diols (see footnote c) with those of authentic diols provided from our previous work.[21]

4.4.2. Reaction of (*R,R*)- or (*S,S*)-**4-2** and **4-3** with chiral aldehydes: Double Asymmetric Synthesis

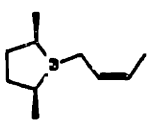
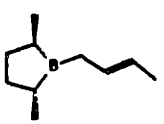
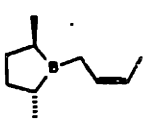
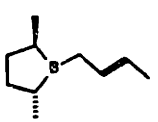
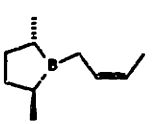
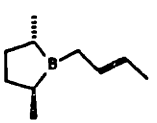
Encouraged by the above results we have carried out several double-asymmetric synthesis using **4-2** and **4-3** and (*R*)-2,3-*O*-isopropylidenglyceraldehyde (**4-38**) (J. Garcia, 1987).

A set of experiments were conductd in order to determine the D.S. of the aldehyde toward the reaction with the crotylborolanes. With the aid of achiral reagents **4-39** and **4-40** (see Scheme 4.6 for the structures), the D.S. of aldehyde is estimated to be 4.2/1 for the reaction with (*Z*)-crotylborolane (entry 1, Table 4.3) and 2.1/1 for that with (*E*)-crotylborolane (entry 2). The D.S.'s of the reagents **4-2** and **4-3** are approximately 25:1 and 50:1, respectively (Table 4.2).

Entries 3-6 summarize the results of a series of double-asymmetric syntheses using (*R,R*)- or (*S,S*)-**4-2** and **4-3**. Reaction of aldehyde with (*R,R*)-**4-2** and (*S,S*)-**4-2** provided mostly syn-alcohols with a diastereomeric ratio of 99:1 (matched, entry 3) and 5.7:1 (mismatched, entry 5), respectively, whereas formation of anti alcohols prevailed

with a diastereomeric ratio of 48:1 (matched, entry 4) and 7.6:1 (mismatched, entry 6), respectively, when (*R*,*R*)-**4-3** and (*S*,*S*)-**4-3** were emlpoyed. The well-established rule of double-asymmetric synthesis is once again clearly validated and the diastereoselectivities of the major syn- or anti-products in the matched cases are among the highest obtained with the known crotylboron reagents.

Table 4.3 Reaction of Crotylboranes (*R,R*)-4-2 and (*R,R*)-4-3 with aldehyde 4-38 .

entry	crotylborolane		yield [a]	product ratio (%)[b] 4-34d	4-35d	4-36d	4-37d	syn/anti ratio	ratio of 4-34d/4-35d or 4-36d/4-37d obsd	corrected[c]
1		4-39	57 [d]	77.5	18.3	2.4	1.8	95.8:4.2	4.2/1	
2		4-40	62 [d]	9.2	1.3	60.6	28.8	10.5:89.4	2.1/1	
3		(*R,R*)-4-2	66	91.6 [e]	1.6	4.5	2.3	93.2:6.8	57.3/1	99/1
4		(*R,R*)-4-3	71	0.9	0.2	96.1 [f]	2.8	1.1:98.9	34.3/1	48/1
5		(*S,S*)-4-2	65	15.4	81.7 [g]	0.5	2.4	97.1:2.9	1/5.3	1/5.7
6		(*S,S*)-4-3	74	0.4	1.6	12.4	85.6 [h]	2.0:98.0	1/6.9	1/7.6

Captions for Table 4.3

a. Combined yield of all four possible isomers. Yields were determined by capillary GC analysis (5% phenyl methyl silicone, 0.20 mm x 12 m) using an internal standard.

b. Values were determined by capillary GC analysis (5% phenyl methyl silicone, 0.20 mm x 12 m) of crude products.

c. Corrected values for the composition of the reagents and the diastereofacial selectivity of the aldehyde **4-38**: 97.9% ee for (*R,R*)-**2-51** (*R,R* 98.4%, *R,S* 1.11%, and *S,S* 0.49%) and 96.1% ee for (*S,S*)-**2-51** (*R,R* 1.2%, *R,S* 1.5%, and *S,S* 97.3%).

d. Yields were not optimized.

e. $[\alpha]^{25}_D$ +6.2° (*c* 0.7, CH_2Cl_2); lit $[\alpha]^{22}_D$ +6.3° (*c* 1.25, CH_2Cl_2), ref 110d.

f. $[\alpha]^{25}_D$ +45.5° (*c* 1.72, CH_2Cl2); lit $[\alpha]^{23}_D$ +47.6° (*c* 2.1, CH_2Cl_2), ref 110d.

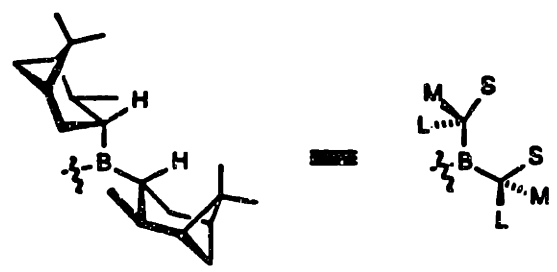
g. $[\alpha]^{25}_D$ +16.5° (*c* 0.52, CH_2Cl_2); lit $[\alpha]^{23}_D$ +14.5° (*c* 0.95, CH_2Cl_2), ref 110d.

h. $[\alpha]^{25}_D$ -11.5° (*c* 0.9, $CHCl_3$); lit $[\alpha]^{22}_D$ -11.4° (*c* 0.9, $CHCl_3$), ref 110d.

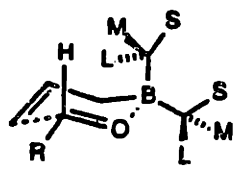
4.5. DISCUSSION ON THE TRANSITION STATES OF THE ALLYL- AND CROTYLBORATION USING 4-1, 4-2, AND 4-3.

It is believed that allyl- or crotylboration proceeds 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. The origin of asymmetric induction observed in the allyl- or crotylborations using chiral boron reagents has been attributed to several factors: (1) steric interactions, (2) either favorable or repulsive stereoelectronic interactions, or (3) crucial bond rotation after the formation of a complex between a reagent and an aldehyde.

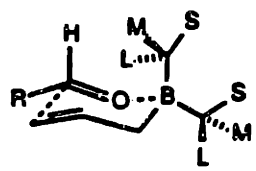
Brown apparently invoked steric interaction in his *B*-allyldiisopinocampheylborane case. He made use of an empirical model which is based on a three-dimensional representation of a presumed lowest energy conformation for Ipc_2BH, where the borane group and the *trans*-methyl on the pinane moiety have a diequatorial arrangement as shown in **4-41**. Two diastereomeric transition states **4-42** and **4-43** are offered as possible candidates. However, no precise distinction as to the origin of asymmetric induction between these two has been provided.[116,120b]



4-41

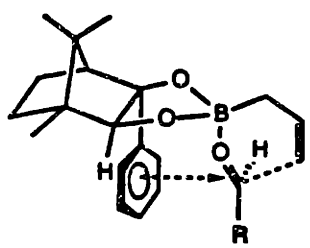


4-42

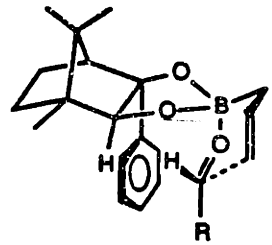


4-43

Stereoelectronic interactions were invoked in the Hoffmann's allyl- and crotyl boronate (e.g. **4-6**).[114b] A favorable interaction of phenyl group in the boronate moiety and carbonyl group of an aldehyde is assumed as in **4-44**, which is more favored than **4-45**.

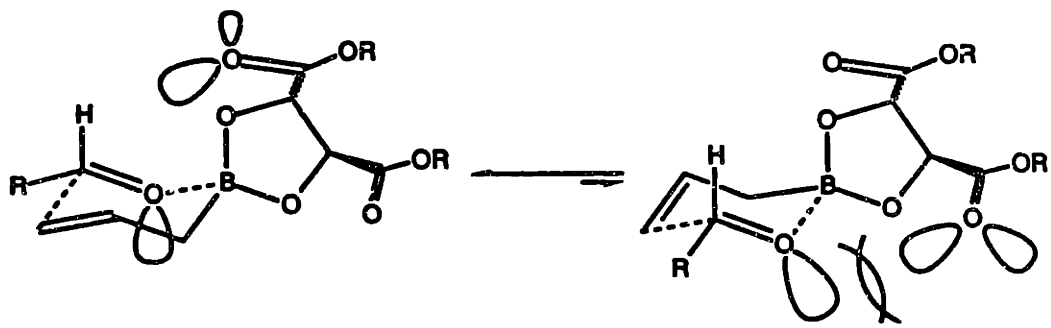


4-44



4-45

Another stereoelectronic arguement was addressed by Roush *et al.*[122a,123a] with the tartrate derived boronate. As shown below, transition state **4-46** is favored as a consequence of lone pair electronic repulsive interactions involving the aldehydic oxygen and the ester carbonyl oxygen that destabilize **4-47** relative to **4-46**.

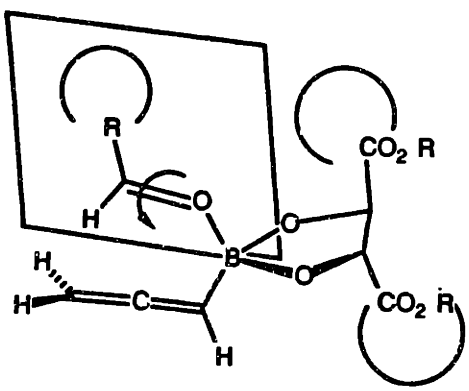


4-46 (favored)

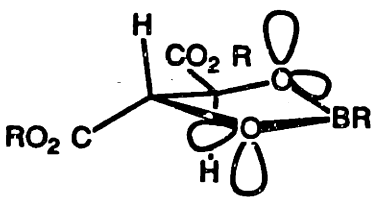
4-47 (disfavored)

Yamamoto[12b] advanced an intriguing postulate that employed rotation of the plane containing O=C bond prior to C-C bond forming reaction as shown in **4-48** based on the anti-coplanar structure of carbonyl-boron complex[81] to explain the asymmetry induced in the reaction of allenylboronate **4-25** derived from tartrate and an aldehyde.

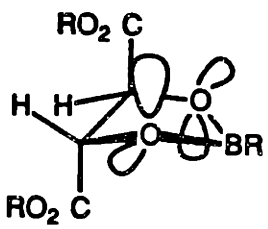
When this arguement is extrapolated, Roush's rationale is greeted with an alternative explanation as follows. When an aldehyde is complexed to the boronate, it may have two options to rotate (whether the rotation is incurred on the plane involving O=C as in Yamamoto's postulation, thus breaking the coplanarity of the B-O=C bonds, or B-O=C bond with preservation of the coplanarity has not been established), and the direction of this rotation may as well be governed by the interaction of aldehydic oxygen and the lone pair electrons of the dialkoxy oxygens, the conformation of which is chirally distorted as shown below (**4-49** or **4-50**). However, it should be noted that the absolute configurations of Yamamoto's product alcohols are opposite to those obtained by Roush when the boronates from tartrates of the same absolute configuration were employed.



4-48

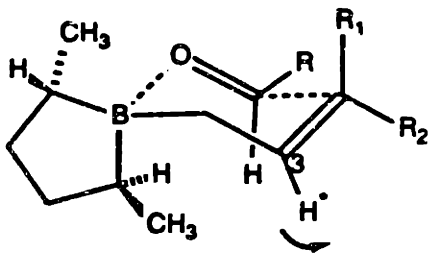


4-49

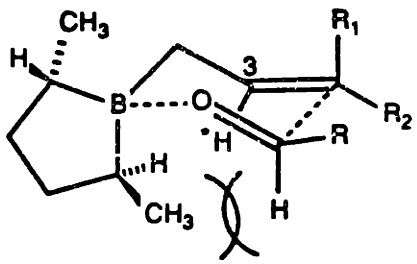


4-50

We reasoned that the asymmetric induction observed with our 2,5-dimethylborolane system can be explained in steric terms. The distinction between two diastereomeric transition states **4-51** and **4-52** relies upon the key interaction (**4-52**) of the aldehydic proton with the methyl group of the borolane moiety†, which is absent in transition state **4-51**. In **4-51** the olefinic carbon (C_3) retains sp^2 hybridization throughout the reaction pathway so that the vinyl proton (H*) swings out of the pseudo axial position bringing about much less interaction with the methyl group. We believe that the same argument applies to the transition states of the allylboration with **4-11**, although conformationally flexible dipinane ligands render the precise picture of the transition states less tangible. The possibility of crucial rotation[12b] through the B-O bonds of aldehyde-boron complex[81] directed by the symmetry element of the borolane system in an early transition state is not ruled out at this point.



4-51



4-52

† This transition state based on the notion that the vinylic carbon preserves the sp^2 hybridization was suggested by Dr. R.M. Kennedy in this research group.

4.6 SUMMARY

This chapter has dealt with the question of whether the 2,5-dimethylborolane system can be employed in the allyl- and crotyl addition reaction[22] to carbonyl compounds to furnish equally high selectivities to those found in aldol reactions.[21] After various known asymmetric allyl- and crotylboron reagents were briefly reviewed, the allyl- and crotylboration employing **4-1**, **4-2**, and **4-3** were examined. Reaction of **4-1** with various achiral aldehydes provided homoallylic alcohols in high enantioselectivities (85-93% ee) and even higher ee's (86-97%) were observed for the reactions of crotylborolanes **4-2** and **4-3** with achiral aldehydes. A chiral aldehyde **4-38** was examined with crotylborolanes to provide highly diastereo- and enantioselective syn and anti homoallylic units, respectively, confirming the rule of double asymmetric synthesis.

In an effort to identify the transition states to match the observed selectivities and the absolute sense of chiral induction with **4-1**, **4-2**, and **4-3**, various transition state models proposed previously with reagents **4-6**, **4-11**, **4-26**, and **4-25** were examined in detail. The new transition state model **4-51** which avoids the steric interaction between the aldehydic proton and the chiral borolane methyl group is suggested to explain the observed experimental data.

CHAPTER 5. EXPERIMENTAL

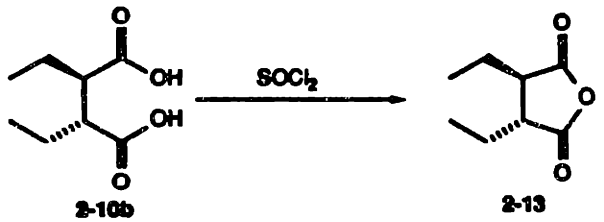
5.1 GENERAL METHODS

All manipulations of boron compounds were performed under an argon atmosphere using syringe or modified Schlenk techniques. Solvents were distilled under argon from the indicated reagents - Tetrahydrofuran (THF) and ether {sodium-benzophenone ketyl}, olefin free pentane, hexane, heptane, triethylamine, diisopropylamine, toluene, and CH_2Cl_2 {CaH_2}, methanol {$Mg(OMe)_2$}, and chloroform, deuterochloroform, and ethyl acetate {P_2O_5}. All the reagents were purified and dried before use according to normal procedure unless otherwise noted. Olefins were distilled from LAH. Aldehydes were distilled from anhyd Na_2SO_4. 3-Benzyloxypropanal was used immediately after distillation. Trifluoromethanesulfonic acid (TfOH) was distilled under argon. LAH in ether (1.0 M solution, Aldrich), MoO_5.pyr.HMPA (MoOPH), ethereal solutions of ethyl magnesium bromide and allyl magnesium bromide, triphenythiocarbinol, 1- and 2-naphthylthiol, and thiourea (all from Aldrich) were used without further purification. Eu(hfc)3 was dried *in vacuo* (P_2O_5, 0.1 mmHg, 24 h) before use. Boiling points and melting points (argon sealed capillary) were uncorrected. NMR spectra were recorded on the following spectrometers: Bruker WH250 (^1H, 250 MHz, Me_4Si, internal standard), Bruker WH270 (^{13}C, 67.9 MHz, Me_4Si, internal standard), JEOL FX90 (^{11}B, 28.7 MHz, $BF_3{\cdot}OEt_2$, external standard), and Varian XL-300 (^1H, ^{13}C, and ^{11}B) and Varian XL-400 (^1H and ^{13}C); they are reported in ppm (δ) downfield from the indicated standards and were recorded in $CDCl_3$ unless otherwise noted. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter in 1-dm cells. HPLC analyses were performed on a Waters 6000A instrument with a Chemcosorb Si60 column (3μ, 4.6x250 mm) and UV detection (254 nm). IR spectrum was recorded on Perkin-Elmer 283B Infrared Spectrophotometer and reported in cm^{-1}. Analytical gas chromatography was

performed on a Hewlett Packard 5880A Gas Chromatograph using a 9 m OV-101, 12 m methyl silicone, or 12 m 5% phenyl methyl silicone column.

5.2. HYDROBORATION (CHAPTER 2)

dl-2,3-Diethylsuccinic anhydride (2-13)

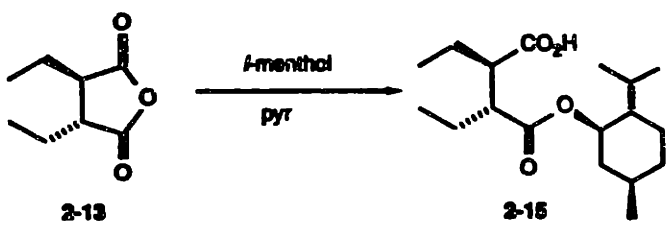


A solution of *dl-threo*-2,3-diethylsuccinic acid (2-10b) (31.13 g, mmol) in freshly distilled thionyl chloride (140 mL) was heated to reflux for 1 h. After the mixture was cooled to room temperature excess thionyl chloride was evaporated under reduced pressure. Trace of thionyl chloride was removed by co-evaporation with benzene three times. The residue was then distilled *in vacuo* (bp 72~73°C/0.19 mmHg) to give 27.30 g (97.8%) of *dl-threo*-2,3-diethylsuccinic anhydride as a colorless oil. The trans/cis ratio of 79:21 was obatined by capillary GC analysis.

^{1}H NMR (250 MHz) δ 1.07 (6H, t, *J*=7.4Hz), 1.87 (4H, m), 2.78 (2H, m) for *dl* compound.

IR(film) 2970,2940, 2880, 1865, 1785, 1460, 1210, 1110, 1005, 920.

l-Menthyl 2,3-diethylsuccinate (2-15)



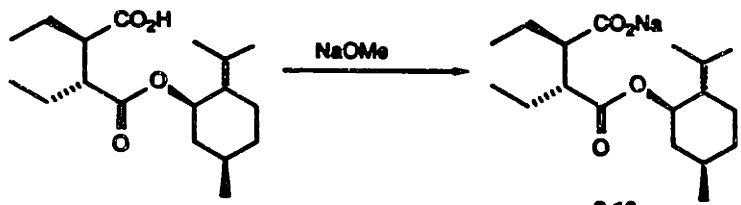
A solution of the anhydride 2-13 (27.27 g, 0.175 mol) and *l*-menthol (54.57 g, 0.349 mol) in dry pyridine (70.6 mL, 0.873 mol) was heated at 100°C for 18 h. Cooled (20°C) reaction mixture was diluted with ether (600 mL) and washed with cold aq. 3N

HCl solution (400 mL, 200 mL, and 200 mL) and sat aq NaCl solution (50 mL x2). The ethereal solution was dried over anhyd Mg_2SO_4. Removal of solvent under reduced pressure gave 82.18 g of residue. *l*-Menthol was removed by bulb-to-bulb distilatilation. Flash chromatography (silica gel, $CHCl_3/CH_3OH$ = 9/1) of the remaining oil gave pure *l*-menthyl 2,3-diethylsuccinate (51.1 g, 94%) as a colorless oil.

^1H NMR (250 MHz) 0.73 (3H, d, *J*=6.9Hz), 0.8~1.0 (15H, m), 1.3~1.7 (8H, m), 2.67 (2H, m), 4.69 (1H, m), 10.0 (1H, br s).

IR (film) 3500~2300 (br), 2960, 2940, 2880, 1730, 1710, 1460, 1390, 1370, 1265, 1240, 1180, 980, 960, 750.

Sodium *l*-menthyl *dl*-2,3-diethylsuccinate (2-16)



2-15 2-16

To a mechanically stirred solution of the half acid **2-15** (51 g, 0.163 mol) in methanol (250 mL) containing phenolphthalein (6 mg) as an indicator, was added a solution of sodium methoxide (9.68 g, 0.179 mol) in methanol (250 mL) dropwise at 0°C over a period of 1 h until the solution became pink. A small amount of the half acid was added to quench the excess base. Solvent was removed under reduced pressure. Upon standing, an amorphous solid precipitated among oily residue (67.68 g). Ether (400 mL) was added and the suspension was stirred vigorously while refluxing for 1h. Cooled suspension was filtered and washed with ether (300 mL) to give 11.3 g (20.7%) of (2*R*, 3*R*)-**2-16a**. mp>270°C, $[\alpha]^{20}_D$ -54.05° (*c* 1.31, CH_3OH).

Solvent from the mother liquor was evaporated. Ether (300 mL) was added to the residue and the solution was allowed to stand for 12 h. The solution was filtered

and washed with ether (600 mL) to give 10.91 g (20%) of (2RS, 3RS) isomer free from meso compound. mp 242~249°C, $[\alpha]^{20}_D$ -52.3° (c 0.53, CH_3OH).

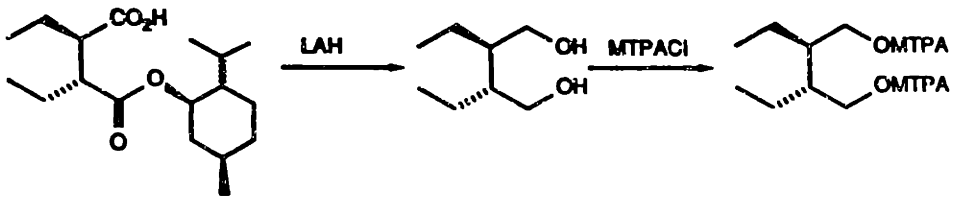
^1H NMR (CD_3OD, 250 MHz) δ 0.76 (2H, d, *J*=7.0 Hz), 0.8~1.0 (15H, m), 1.3~1.8 (8H, m), 1.9~2.1 (2H, m), 3.45 (1H, q, *J*=7.0 Hz), 3.62 (1H, dt, *J*=3.5, 8.8 Hz), 5.65 (1H, dt, *J*=3.9, 10.6 Hz).

IR (Nujol) 1700, 1575, 1275, 1330.

Resolution of sodium *l*-menthyl *dl*-2,3-diethylsuccinate **2-16a**

To a magnetically stirred solution of *l*-menthyl hydrogen *dl*-2,3-diethylsuccinate (2.5 g, 8.0 mmol) in methanol (50 mL) containing phenolphthalein (1.4 mg) as an indicator was added sodium methoxide (0.43 g, 8.0 mmol) in methanol (50 mL) dropwise at 0°C over a period of 20 min until the solution became pink. A small amount of the half acid was added to neutralize the base. Solvent was removed under reduced pressure to afford 3.11 g of residue. Ether (100 mL) was added and the suspension was stirred for 3 h. Filtration followed by washing with ether (100 mL) gave a white crystal (1.70 g). Recrystallization from methanol (2 mL) and ether (50 mL) afforded 0.73 g of sodium *l*-menthyl *d*-2,3-diethylsuccinate, mp > 270°C, $[\alpha]^{23}_D$ -55.2° (*c* 0.52, CH_3OH), which, upon further crystalization, provided 0.60 g of **2-16a**. mp > 270°C, $[\alpha]^{20}_D$ -56.6° (*c* 0.505, CH_3OH).

Preparation of diol 2-17 and determination of the enantiomeric purity



2-16 2-17

To a magnetically stirred suspension of LAH (105 mg, 2.69 mmol) in THF (20 mL) was added the *d*-half acid sodium salt (300 mg, 0.897 mmol) in portions over 2.5 min at room temperature. The mixture was refluxed for 15 h. A THF solution of water (3%, 7 mL) was slowly added to quench excess LAH and the mixture was stirred vigorously for 30 min. A drop of water was introduced to check the existence of the hydride. Celite 545 (2.0 g) was added and the mixture was stirred vigorously for 30 min. Filtration through a celite bed (~1 cm) and evaporation of the solvent from the filtrate gave a crude product. Purification by flash chromatography (silica gel, $CHCl_3$---$CHCl_3/CH_3OH$ = 97/3) provided pure *d*-trans-2,3-diethylbutanediol (116 mg, 88.5%). $[\alpha]^{20}_D$ +1.76° (*c* 1.02, EtOH), $[\alpha]^{20}_D$ +10.3° (*c* 0.525, $CHCl_3$).

To a stirred solution of the diol 2-17 (23.6 mg, 0.61 mmol), (-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (75.6 mg, 0.323 mmol), and DMAP (93.9 mg, 0.0323mmol) in CH_2Cl_2 (1mL) was added N,N'-dicyclohexylcarbodiimide (DCC) (86.6 mg, 0.42 mmol) at once at room temperature. Soon a white precipitate appeared in the reaction mixture. After 12 h, it was filtered and washed with ether. The combined solution of the filtrate and the washing was washed with 0.5 N aq HCl solution, sat aq $NaHCO_3$ solution, and brine. The organic layer was dried over anhyd $MgSO_4$. Evaporation of the solvent followed by flash chromatography (silica gel, n-hexane/ether=9/1) provided 76.5 mg (81.9%) of a viscous oil. ^1H nmr spectral analysis indicated 90~95% ee for the diol (2*R*, 3*R*)-2-17.

^1H NMR (250 MHz) of bis-(-)-MTPA ester of (2*R*,3*R*)-2-17: δ 0.84 (6H, t, *J*=7.4 Hz), 1.1~1.45

(4H, m), 1.65~1.75 (2H, m), 3.52 (6H, s), 4.11 (2H, dd, *J*=4.6, 11.4 Hz), 4.24 (2H, dd, *J*=5.3, 11.4 Hz), 7.35~7.50 (10H, m).

^{1}H NMR (250 MHz) of bis-(-)-MTPA ester of (2*S*, 3*S*)-2-17: δ 0.83 (6H, t, *J*=7.4 Hz), 1.1~1.45 (4H, m), 1.65~1.75 (2H, m), 3.50 (6H, s), 4.09 (2H, dd, *J*=4.8, 11.3 Hz), 4.30 (2H, dd, *J*=5.8, 11.3 Hz), 7.35~7.50 (10H, m).

Racemic 2,3-diethylbutanediol ((±)-2-17)

To a magnetically stirred suspension of LAH (3.61 g, 95.08 mmol) in THF (500 mL) in a 1 L three-neck round bottom flask equipped with a thermometer and a reflux condenser, was added a sodium salt of the half acid 2-16 (10.60 g, 31.69 mmol) in portions over 15 min at room temperature. The mixture was heated to reflux for 18 h. The reaction was followed by TLC. When the reaction was complete, the flask was cooled to room temperature and 3% water solution in THF (240 mL) was added dropwise over 1 h. Stirring was continued for 30 min. One drop of water was added to check the existence of the hydride and Celite 545 was added. The mixture was stirred vigorously for 30 min and filtered through a Celite bed (~1 cm). After washing the residue with ether, the combined solution of the filtrate and the washings were condensed by rotary evaporation. Flash column chromaography (silica gel 200 g, $CHCl_3$ — $CHCl_3/CH_3OH$ = 9/1) followed by distillation under reduced pressure afforded 4.13 g (89.2%) of the racemic diol as a colorless oil. bp 87-88°C/0.04 mmHg, $[\alpha]^{20}_D$ -1.6° (*c* 1.000, EtOH), $[\alpha]^{20}_D$ -2.7° (*c* 0.52, $CHCl_3$).

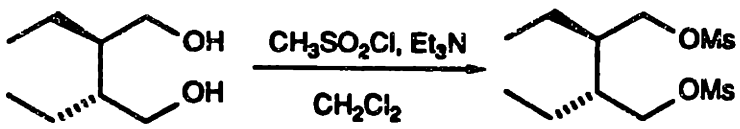
IR (film) 3300 (br), 2960, 2930, 2880, 1465, 1380, 1170, 1035, 1000.

^{1}H NMR (250 MHz) ∂ 0.93 (6H, t, *J*=7.0 Hz), 1.3~1.6 (6H, m), 3.56 (2H, dd, *J*=3.2, 11.3 Hz), 3.70 (2H, d, *J*=11.3 Hz), 4.32 (2H, br s).

(2*R*,3*R*)-2,3-Diethylbutanediol ((2*R*,3*R*)-2-17)

bp 86℃/0.03 mmHg, $[\alpha]^{20}_D$ +1.58° (*c* 1.01, EtOH), $[\alpha]^{20}_D$ +9.4° (*c* 0.50, $CHCl_3$) for 72.8% ee (determined by ^1H NMR analysis of the corresponding bis-MTPA esters).

(2*R*,3*R*)-2,3-diethylbutane-1,4-diyl bismethanesulfonate (2-18)



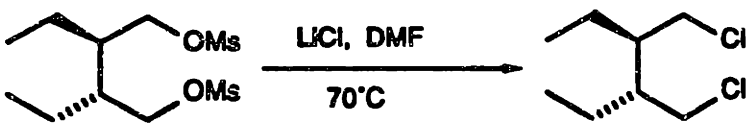
2-17 2-18

To a stirred solution of the diol 2-17 (4.0 g, 27.4 mmol) and triethylamine (11.07 g, 109.4 mmol) in CH_2Cl_2 (150 mL) at -10℃ was added methanesulfonyl chloride (5.29 mL, 68.4 mmol) dropwise while maintaining the reaction temperature below -10℃. Stirring was continued for 1 h at -10℃. The mixture was poured into ice-water (170 mL) and extracted with CH_2Cl_2 (150 mL x 2). The organic layer was washed with cold 0.1 N aq HCl (200 mL), sat aq $NaHCO_3$ (200 mL), and sat brine (200 mL) and dried over anhyd $MgSO_4$. Filtration followed by removal of solvent furnished crystalline bis-mesylate 2-18 (8.30 g, quantitative). mp 62-64℃; $[\alpha]^{20}_D$ +1.68° (*c* 1.01, $CHCl_3$).

IR (film) 3020, 2970, 2940, 2880, 1465, 1410, 1345, 1170, 970, 935, 820, 730.

^1H NMR δ 0.94 (6H, t, *J*=7.4 Hz), 1.3~1.6 (4H, m), 1.76~1.88 (2H, m), 3.00 (6H, s), 4.20 (4H, d, *J*=4.9 Hz).

(2*R*,3*R*)-3,4-bis(chloromethyl)hexane (2-19)



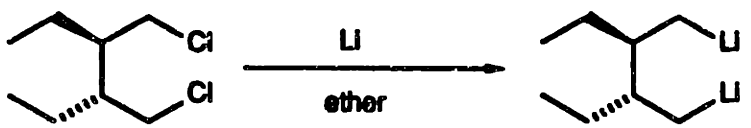
2-18 2-19

To a magnetically stirred solution of the bis-mesylate 2-18 (8.17 g, 27.0 mmol) in DMF (33 mL) was added dry lithium chloride (6.91 g, 162.9 mmol) at room temperature. The reaction mixture was heated to 70°C for 16 h. After cooling the slurry-like reaction mixture was poured into brine (110 mL) and extracted with ether (110 mL x 3). The ethereal solution was washed twice with brine and dried over anhyd $MgSO_4$. Filtartion followed by removal of solvent afforded 5.20 g of a yellowish residue. Flash chromatography (silica gel, petroleum ether) of the crude product and subsequent distillation under reduced pressure provided 4.50 g (91.0%) of pure 2-19. bp 84-85°C/8 mmHg; $[\alpha]^{20}_D$ +5.87° (*c* 1.005, $CHCl_3$).

IR (film) 2970, 2940, 2880, 1460, 1380, 1290, 970, 770, 720, 680.

^1H NMR 0.95 (6H, t, *J*=7.4 Hz), 1.34~1.65 (4H, m), 1.80 (2H, m), 3.67 (4H, m).

(2*R*,3*R*)-2,3-diethyl-1,4-dilithiobutane (2-20)

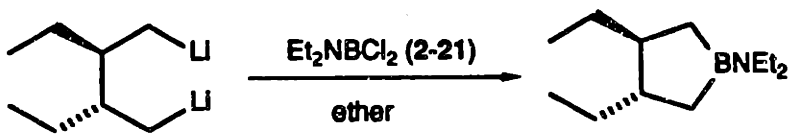


2-19 2-20

To a magnetically stirred suspension of lithium (1% Na, 0.90 g, 130 mmol) in dry ether (30 mL) in a pre-dried, argon flushed 200 mL three-neck round bottom flask equipped with a septum, a pressure-equalizing droppping funnel, and a thermometer, was added a solution of the dichloride 2-19 (4.36 g, 23.8 mmol) in ether (30 mL) at 0°C

over a period of 5 h. Stirring was continued for 15 h. The reaction was checked intermittantly with GC. The solution was filtered through a Celite 545 bed into a 100 mL graduated cylinder and the residue was washed with ether (7 mL x 3). Total volume of the pale yellow solution was 82 mL. The concentration determined by titration with sec-BuOH in toluene using bipyridyl as an indicator was 0.245 M (20.1 mmol, 84.4%).

(3*R*,4*R*)-*B*-(diethylamino)-3,4-diethylborolane (2-22)



2-20 **2-22**

To a cooled (-78°C), magnetically stirred solution of **2-20** (80 mL, 0.245 M, 19.6 mmol) in a 200 mL three-neck round bottom flask equipped with an addition funnel and a thermometer, was added a solution of dichloro(diethylamino)borane **2-21** (3.65 g, 23.73 mmol) in ether (30 mL) dropwise for 25 min. A white precipitate appeared upon the addition of the borane reagent. The reaction mixture was stirred for 30 min at -78°C, allowed to warm to room temperature, and stirred at the temperature for 1 day. The mixture was filtered through a celite bed (~1 cm) and the filtrate was concentrated by distillation at atmospheric pressure. The residual yellowish oil was distilled under reduced pressure to afford 3.62 g (94.5% yield) of the desired aminoborolane **2-22**. bp 83-84°C/1.7 mmHg.

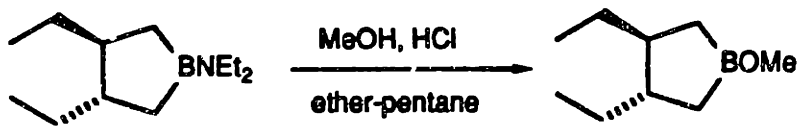
IR (film) 2960, 2920, 2870, 1520, 1500, 1460, 1395, 1375, 1340, 1285, 1235, 1205, 1140, 1060, 850, 775.

^{1}H NMR δ 0.31 (2H, m), 0.89 (6H, t, *J*=6.2 Hz), 1.04 (6H, t, *J*=7.0 Hz), 1.1~1.35 (6H, m), 1.64 (2H, m), 3.03 (4H, q, *J*=7.0 Hz); ^{11}B BNMR δ 50.4.

MS (EI) m/e (rel intensity) 195 (4.3), 111 (73), 69 (100).

HRMS m/e calcd for $C_{12}H_{26}BN$ 195.2158, found 195.2159.

(3*R*,4*R*)-3,4-diethyl-*B*-methoxyborolane (2-14)



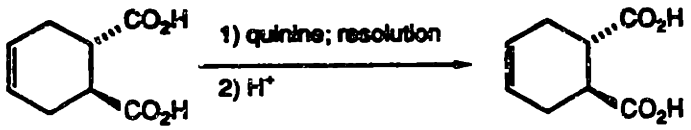
2-22 **2-14**

To a magnetically stirred solution of the aminoborolane **2-22** (1.36 g, 6.97 mmol) in ether (20 mL) in a double Schlenk tube, were added dry, degassed methanol (1.13 mL, 27.9 mmol) and an ethereal solution of dry HCl gas (1.67 N, 4.60 mL, 7.67mmol) at room temperature. A pale yellow precipitate came out of solution immediately upon addition of HCl solution. Stirring was continued for 36 h. Most of the solvent was removed under reduced pressure and pentane (30 mL) was added. The pentane solution was filtered and the residue was washed with pentane (5 mL x 3). Solvent from the combined solution was removed under reduced pressure at 0°C. Final vacuum distillation of the residue afforded 0.96 g (89.7% yield) of the desired *B*-methoxyborolane **2-14**. bp 71-72°C/15 mmHg

IR (film) 2960, 2930, 2870, 1490, 1470, 1370, 1350, 1240, 1215, 1070, 1000, 970, 935, 885, 850, 775.

^{1}H NMR δ 0.32 (2H, m), 0.89 (6H, t, *J*= 7.0Hz), 0.9~1.1 (2H, m), 3.72 (3H, s); ^{11}B NMR δ 59.3.

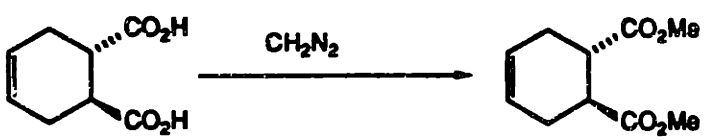
Resolution of (1*RS*,2*RS*)-4-cyclohexene-1,2-dicarboxylic acid (2-26)



2-25 (1*S*,2*S*)-(+)-2-26

To a boiling solution of the diacid (2-25) (1.00 g, 5.88 mmol) in 95% ethanol (10 mL) was added a hot solution of quinine (3.81 g, 11.7 mmol) in 95% ethanol (20 mL). The reaction mixture was filtered while hot and washed with hot 95% ethanol (5 mL). The filtrate was allowed to stand for 12 h at room temperature. Filtration yielded 2.24 g (46.6% recovery) of quinine salt. mp 185-198°C (dec.); $[\alpha]^{20}_D$ -124.3° (*c* 1.00, EtOH). Recrystallization from 95% ethanol afforded 1.35 g (60.3% recovery) of crystals. mp 179-197°C (dec.); $[\alpha]^{20}_D$ -113.0° (*c* 1.00, EtOH). 0.81 g (60.0% recovery) of crystals were obtained from the third crystallization. mp 181-198°C (dec.); $[\alpha]^{20}_D$ -108.8° (*c* 0.50, EtOH). It was dissolved in 2 N HCl (3.0 mL) and extracted with ether (3 x 10 mL) and the ethereal solution was washed with sat NaCl solution (1.5 mL). The solution was dried over anhyd Na_2SO_4 and concentrated *in vacuo* to afford 0.17 g (100% yield) of the free acid 2-26. Recrystallization from benzene/n-hexane gave (1*S*,2*S*)-4-cyclohexene-1,2-dicarboxylic acid (2-26) (0.12 g, 70.6% yield) as a powdery solid. mp 151-155°C; $[\alpha]^{20}_D$ +143.7°C (*c* 1.00, 95% EtOH); lit $[\alpha]^{26}_D$ -160.0 ±1.3° (*c* 2.7, 95% EtOH); Walbosky, H.M.; Barash, L.; Davis, T.C. *Tetrahedon*, **1963**, *19*, 2333.

Determination of the optical purity of 2-26



2-26

To a stirred solution of the diacid 2-26 (20 mg, 0.12 mmol) in methanol (3 mL) was added a freshly prepared solution of diazomethane in ether. When the reaction

was complete, the solvent was removed by rotary evaporation. The crude poduct was dissolved in ether (3 mL) and the ethereal solution was washed with sat $NaHCO_3$ (3 mL), 1 N HCl (2 mL), and sat NaCl (3 mL) solution. It was dried over anhyd Na_2SO_4 and concentrated to afford 16.5 mg (71% yield) of dimethyl (1*S*,2*S*)-4-cyclohexene-1,2-dicarboxylate. ^1H NMR amalysis of the dimethyl ester in the presence of $Eu(hfc)_3$ showed 92.9% ee.

Resolution of 2-25 on Large Scale

Two separate large scale preparations of the optically active diacid were carried out.

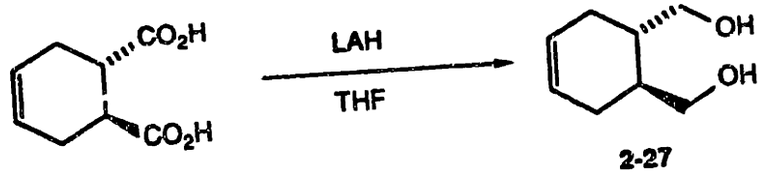
A. From diacid **2-25** (20.0 g, 0.118 mol) and quinine (76.2 g, 0.235 mol), 31.9 g (33.2% recovery) of the salt was obtained after first recrystallization. mp 178-198°C (dec.); $[\alpha]^{20}_D$ -117.0° (*c* 1.00, EtOH).

6.50 g of free diacid **2-26** (98.2%) was obtained from this salt. mp 154-162°C; $[\alpha]^{20}_D$ +135.8° (*c* 1.00, EtOH).

B. Similary, starting from diacid **2-25** (15.0 g, 88.5 mmol) 26.1 g (36.1% recovery) of the partially resolved salt was obtained after 1st recrystallization. mp 180-200°C (dec.); $[\alpha]^{20}_D$ -114.3° (*c* 1.00, EtOH). Upon subsequent extraction under acidic condition, 5.35 g (99%) of the free diacid **2-26** was afforded. mp 160-166°C; $[\alpha]^{20}_D$ +101.7° (*c* 1.00, EtOH). Diacids from paths A and B were combined together and recrystallized once more from acetone, benzene, and n-hexane to provide 11.26 g (95% recovery) of **2-26**. mp 152-163°C (dec.); $[\alpha]^{20}_D$ +109.9° (*c* 1.00, EtOH). ^1H NMR analysis of the corresponding dimethyl ester with the aid of $Eu(hfc)_3$ (0.3 equiv) indicated 71.5% ee.

^1H NMR of the dimethyl ester; δ 2.1~2.5 (4H, m), 2.75~3.0 (2H, m), 3.70 (6H, s), 5.79 (2H, s).

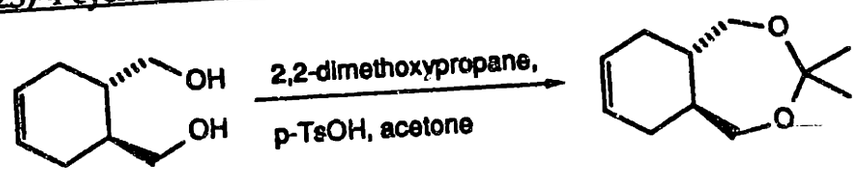
(1S,2S)-4-cyclohexene-1,2-dimethanol (2-27)



2-26 2-27

To a stirred suspension of LAH (3.35 g, 88.3 mmol) in THF (100 mL) in a 1 L three-neck flask equipped with a thermometer, and an addition funnel, was added a THF solution (50 mL) of **2-26** (5.0 g, 29.4 mmol, 71.2% ee) over a period of 1 h at room temperature. After addition of more THF (50 mL), the mixture was heated to reflux with vigorous stirring for 46 h. To the cooled (20℃) mixture was added a solution of water (6.7 mL) in THF (200 mL) and stirring was continued for 30 min. The existence of hydride was checked by a drop of water . Celite (10 g) was added to the mixture and it was stirred vigorously for 30 min. The gelatinous mixture was filtered through a Celite bed (~1cm) and the residue was washed with THF until no extraction of the diol was indicated by TLC. The combined filtrate was concentrated under reduced pressure to give crude diol. Distillation under reduced pressure afforded 3.65 g (87.3% yield) of the pure diol **2-27**. bp 100-104℃/0.05 mmHg; mp 50-51℃; $[\alpha]^{25}_D$ +48.3° (*c* 1.035, EtOH); IR (film) 3330 (br), 3020, 2900, 1660, 1475, 1440, 1065, 1020, 990, 955, 650; ^{1}H NMR δ 1.6~2.1 (6H, m), 3.50~3.75 (4H, m), 3.98 (2H, br s), 5.65 (2H, d, *J*=2.4 Hz).

(1S,2S)-4-cyclohexene-1,2-dimethanol acetionide (2-28)



2-27 2-28

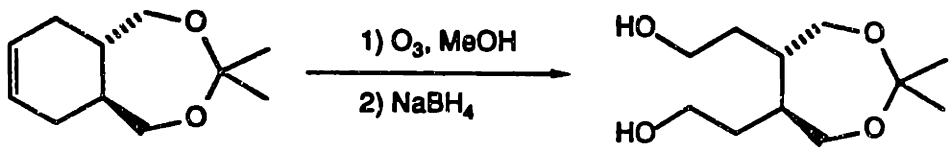
To a magnetically stirred solution of the diol **2-27** (4.12 g, 29.0 mmol) and 2,2-

dimethoxypropane (4.53 g, 43.5 mmol) in acetone (120 mL), was added p-toluenesulfonic acid (55 mg, 0.29 mmol) and stirring was continued for 18 h at room temperature. Solvent was removed by rotary evaporation and the residue was dissolved in ether (60 mL). The ethereal solution was washed with sat NaCl, sat $NaHCO_3$, and sat NaCl solution. Dried (anhyd $MgSO_4$) soltuion was concentrated to afford the acetonide **2-28** (4.67 g, 93.4% yield). bp 44°C/0.08mmHg.

IR (film) 3030, 2990, 2930, 2890, 2830, 1450, 1430, 1380, 1370, 1260, 1220, 1160, 1090, 1070, 1030, 980, 910, 930, 780, 650.

^1H NMR δ 1.35 (6H, s), 1.4~1.7 (4H, m), 1.90~2.05 (2H, m), 3.45~3.65 (4H, m), 5.68 (2H, d, *J*=3.2 Hz).

(2*S*,3*S*)-2,3-bis(hydoxyethyl)-1,4-butanediol acetonide (2-29)



2-28 **2-29**

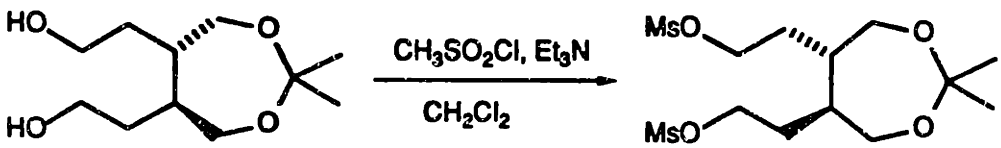
A solution of **2-28** (3.60 g, 19.8 mmol) in methanol (300mL) was placed in a 1 L three-neck flask equipped with a thermometer, a magnetic stirring bar, a gas inlet , and a gas outlet connected to a trap containing KI in acetic acid/water. Ozone (~0.9 mmol/min) was passed into the cooled (-78°C) solution for 10 min. The reaction was followed by TLC. Excess ozone was removed by bubbling nitrogen into the reaction mixture for 30 min. $NaBH_4$ (1.66 g, 43.9 mmol) was added at once and the mixture was warmed to 0°C. Stirring was continued for 3 h at 0°C and 4 days at room temperature. The solvent was co-evaporated three times with methanol and once with ether. Water (8 mL) was added and the product was extracted with ether (3 x 10 mL). Dried (anhyd Na_2SO_4) and concentrated material (1.06 g) was purified on a chromatographic column

(silica gel, $CHCl_3/CH_3OH$, 19/1) yielding 3.04 g (70.5% yield) of the desired product as a solid. mp 52-54℃; R_f 0.44 ($CHCl_3/CH_3OH$, 9/1).

IR (film) 3380 (br), 2990, 2940, 2880, 1450, 1375, 1290, 1220, 1160, 1050, 830.

^1H NMR δ 1.32 (6H, s), 1.55~1.75 (6H, m), 2.77 (2H, br s), 3.46 (2H, dd, *J*=12.5, 4.0 Hz), 3.71 (4H, t, *J*=6.1 Hz), 3.80 (2H, br d, *J*=12.5 Hz).

(2*S*,3*S*)-2,3-Bis(methanesulfonyloxyethyl)-1,4-butanediol acetonide (2-30)



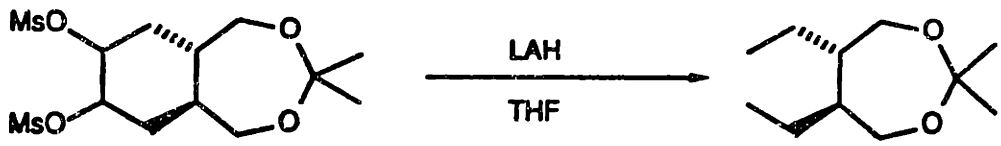
2-29 2-30

To a magnetically stirred solution of the diol 2-29 (3.00 g, 13.7 mmol) and triethylamine (7.66 mL, 55.0 mmol) in methylene chloride (80 mL) was added methanesulfonyl chloride (2.66 mL, 34.4 mmol) at once at -10°C. Stirring was continued for 1 h at the temperature. The reaction mixture was poured into ice - water (100 mL) and extracted with CH_2Cl_2 (2 x 50 mL). Combined solution was washed with cold 0.1 N HCl , sat $NaHCO_3$, and sat NaCl soltuion. Drying (anhyd Na_2SO_4) followed by solvent removal *in vacuo* afforded a crude bis-mesylate 2-30 (5.15 g, quantitative) as a yellow oil. The crude product was used for the subsequent resction. R_f 0.15 (n-hexane/EtOAc, 1/1), 0.8 ($CHCl_3/CH_3OH$, 9/1).

IR (film) 1990, 1940, 1455, 1315, 1165, 1055, 945, 810, 725.

^1H NMR δ 1.31 (6H, s), 1.4~1.7 (2H, m), 1.7~2.1 (4H, m), 3.02 (6H, s), 3.45 (2H, dd, *J*=14.5, 2.0 Hz), 3.81 (2H, d, *J*=14.5 Hz), 4.33 (4H, t, *J*=7.0 Hz).

(2S,3S)-2,3-diethyl-1,4-butanediol acetonide (2-31)



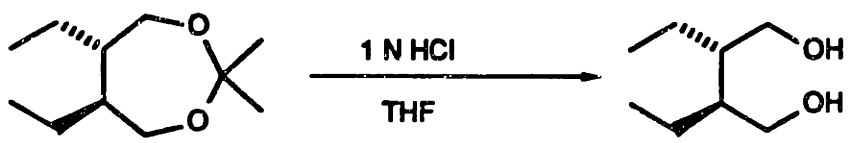
2-30 2-31

To a magnetically stirred suspension of LAH (1.09 g, 28.7 mmol) in THF (50 mL) was added a THF (50 mL) solution of the bis-mesylate **2-30** (5.12 g, 13.7 mmol) at 0°C. Stirring was continued for 18 h at room temperature. 3% Water in THF (81 mL) was added to quench the excess hydride and the mixture was stirred for 30 min. Celite 545 (10 g) was added and stirring was continued for 30 min. The gelatinous mixture was filtered through a Celite bed (~1cm) and the residue was washed with ether (30 mL). Solvent from the combined solution was removed *in vacuo* and the residue was purified by flash chromatography (silica gel, n-hexane/ether, 19/1). Distillatioin of the product under reduced pressure yielded 1.55 g (60.5% yield) of pure **2-31** as a colorless oil. R_f 0.46 (n-hexane/ether, 9/1); bp 33°C/0.08 mmHg.

IR (film) 2950, 2870, 1460, 1370, 1280, 1215, 1160, 1075, 1060, 1020, 930, 825.

^{1}H NMR δ 0.91 (6H, t, *J*=7.4 Hz), 1.21 (2H, m), 1.31 (6H, s), 1.39 (4H, m), 3.49 (2H, dd, *J*=12.3, 6.7 Hz), 3.70 (2H, dd, *J*=12.3, 1.9 Hz).

(2S,3S)-2,3-diethyl-1,4-butanediol (2-17a)



2-31 (2S,3S)-2-17a

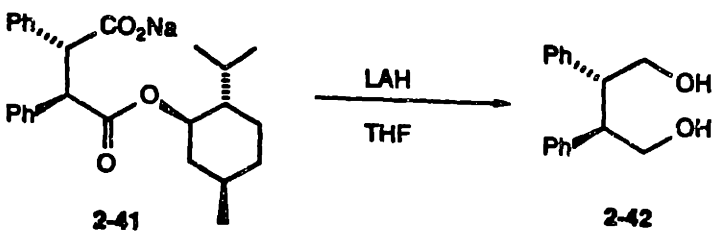
A solution of the acetonide **2-31** (1.50 g, 8.05 mmol) in 1 N HCl/ THF (1/1, 20 mL) was stirred for 12 h at room temperature. The raction mixture was carefully

neutralized with 1 N aq NaOH solution and extracted with ether continuously for 9 h. The crude diol after solvent removal was purified by flash chromatography (silica gel, $CHCl_3/CH_3OH$, 19/1) followed by vacuum distillation to give 1.12 g (95.0% yield) of diol **2-17a**. R_f 0.52 ($CHCl_3/CH_3OH$, 9/1); bp 93°C/0.1 mmHg; $[\alpha]^{25}_D$ -2.0° (*c* 1.115, EtOH), $[\alpha]^{20}_D$ -10.6° (*c* 0.52, $CHCl_3$).

The diol **2-17a** showed physical data identical to those obtained for diol **2-17** except for the sign of the optical rotation.

^1H NMR analysis of the corresponding MTPA ester of the diol **2-17** and **2-17a** (MTPACl, DMAP, pyr, 12 h room temp) provided unambiguous evidence for the assignment of the (2*R*,3*R*)- configuration of alcohol **2-17**

(2*R*, 3*R*)-2,3-diphenyl-1,4-butanediol (**2-42**)



2-41 **2-42**

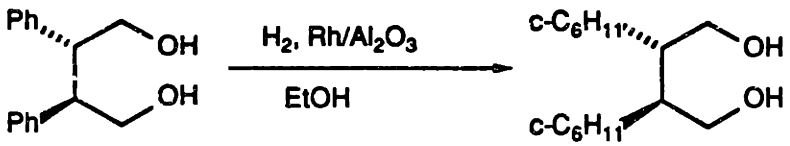
To a magnetically stirred solution of LAH (1.32 g, 34.8 mmol) in THF (400 mL) was added sodium menthyl (2*R*,3*R*)-2,3-diphenylsuccinate **2-41** (5.0 g, 11.6 mmol) in portions over 15 min at room temperature. The reaction mixture was heated to reflux for 12 h. The reaction was followed by TLC. A solution of water in THF (3%, 88 mL) was added dropwise to the cooled mixture (0°C) and the stirring was continued for 30 min at room temperature. One drop of water was added to check the existence of the hydride and Celite (23 g) was added. After vigorous stirring for 30 min the mixture was filtered through a Celite bed (~1 cm). Solvent from the filtrate was evaporated under reduced pressure and the residue was purified on a chromatographic column (silica gel, $CHCl_3$—$CHCl_3/CH_3OH$ = 97/1) to afford 2.5 g (89.0% yield) of the diol as a white

crystal (mp 99-100°C). $[\alpha]^{25}_D$ -46.9° (*c* 0.525, $CHCl_3$). Recrystallization from benzene/n-hexane gave 85% of a crystal with mp 99-100°C, $[\alpha]^{25}_D$ -47.6° (*c* 0.500, $CHCl_3$)

IR (KBr) 3290 (br), 2970, 2930, 2860, 1960, 1890, 1600, 1580, 1495, 1475, 1450, 1425, 1335, 1310, 1270, 1215, 1190, 1180, 1155, 1100, 1080, 1070, 1045, 1030, 1020, 910, 855, 840, 765, 715, 700, 645, 600, 555, 450.

^{1}H NMR (250 MHz) δ 2.24 (2H, s), 3.26 (2H, m), 3.96 (4H, m), 6.95~7.2 (10H, m).

(2*S*, 3*S*)-2,3-dicyclohexyl-1,4-butanediol (2-43)



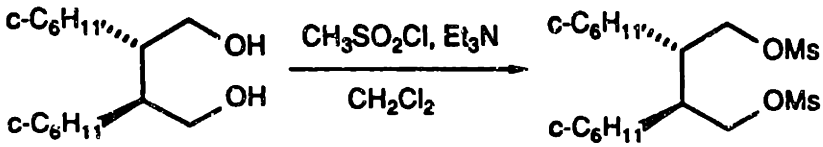
2-42 **2-43**

To a solution of **2-42** (9.7 g, 40.0 mmol) in anhydrous ethanol (60 mL) were added glacial acetic acid (0.7 mL) and 5% Rh/Al_2O_3 (5.6 g). The mixture was shaken in a Parr Hydrogenator under a hydrogen atmosphere (50 psi) for 45 h at room temperature. The mixture was filtered through a celite bed (~1 cm) and solvent from the filtrate was removed under reduced pressure. Crystallization of the crude product (10.06 g) from benzene/n-hexane afforded 6.21 g (61%) of a white crystal of the diol **2-43**. mp 109°C, $[\alpha]^{23}_D$ -2.3° (*c* 0.52, $CHCl_3$). Purification of the residue from the mother liquor on a flash column chromatography (silica gel 150 g, $CHCl_3/CH_3OH$ = 99/1) afforded another 3.23 g of crystalline diol (combined yield 92.7%). mp 109-109.5°C, $[\alpha]^{24}_D$ -2.4° (*c* 0.505, $CHCl_3$).

IR (KBr) 3320 (br), 2920, 2850, 1445, 1320, 1280, 1270, 1260, 1250, 1195, 1130, 1120, 1105, 1070, 1040, 1030, 1000, 980, 890, 840.

^{1}H NMR (250 MHz) δ 0.78~2.0 (24H, m), 3.66 (2H, d, *J*=11.7 Hz), 3.72 (2H, s), 3.77 (2H, dd, *J*=4.0, 11.7 Hz).

(2S,3S)-2,3-Dicyclohexyl-1,4-butanediyl bis-mesylate (2-44)



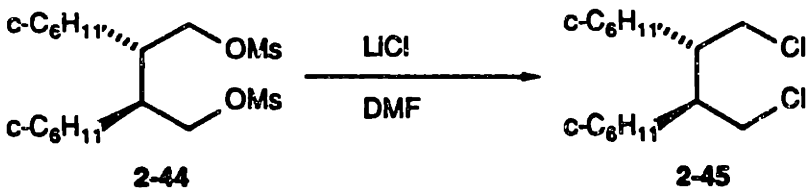
2-43 2-44

To a magnetically stirred solution of the diol **2-43** (3.5 g, 13.8 mmol) in THF (100 mL) at -78°C was added triethylamine (8.35 g, 82.5 mmol) and stirring was continued for 10 min. Methanesulfonyl chloride (6.32 g, 55.2 mmol) was added to the mixture over a period of 5 min. A white precipitate came out of solution upon the addition. The mixture was warmed to -23°C and stirred for 1 h. The yellow reaction mixture was washed with brine (50 mL) and the aqueous phase was extracted with ether (20 ml x2). Combined organic solution was washed with brine (3 x 40 mL) and dried over anhyd MgSO4. Solvent was removed in vacuo and the pale yellow paste was dissolved in abs EtOH (150 mL). Removal of solvent afforded 5.28 g (93% yield) of **2-44** as a white crystal. mp 83.5-84°C.

IR (film) 2940, 2860, 1480, 1450, 1358, 1335, 1175, 995, 970, 945, 840.

^{1}H NMR δ 0.10~1.80 (24H, m), 3.04 (6H, s), 4.24 (2H, dd, *J*=4.4, 10.3 Hz), 4.34 (2H, dd, *J*=4.5, 10.3 Hz).

(2S,3S)-2,3-Dicyclohexyl-1,4-dichlorobutane (2-45)



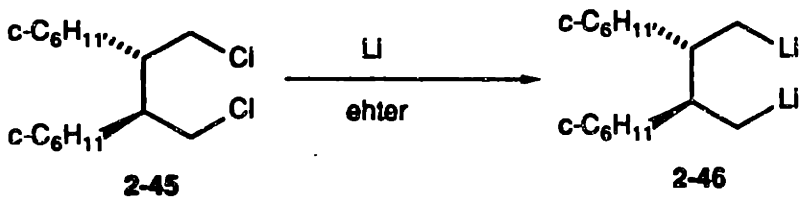
2-44 2-45

To a magnetically stirred solution of the bis-mesylate (5.0 g, 12.2 mmol) in DMF (15 mL) was added LiCl (3.1 g, 73.1 mmol) at room temperature. Mild exothermic reaction was observed. After 1 h, the mixture was heated to 50~60°C for 19 h. The cooled reaction mixture was poured into sat brine (50 mL) and the mixture was extracted with ether (3 x 20 mL). The ethereal solution was washed with sat brine (2 x 20 mL) and dried over anhyd MgSO4. Removal of solvent followed by a flash chromatogrphy (silica gel 200 g, pet. ether) afforded 3.32 g (93% yield) of a colorless oil, which showed positive result on Beilstein test. bp (T_b) 100-120°C (0.12 mmHg).

IR (film) 2925, 2850, 1445, 1280, 740.

^{1}H NMR δ 1.03~1.86 (24H, m), 3.55 (2H, dd, *J*=6.4, 11.3 Hz), 3.67 (2H, dd, *J*=3.5, 11.1 Hz).

Preparatipon of (2S,3S)-2,3-dicyclohexyl-1,4-dilithiobutane (2-46)

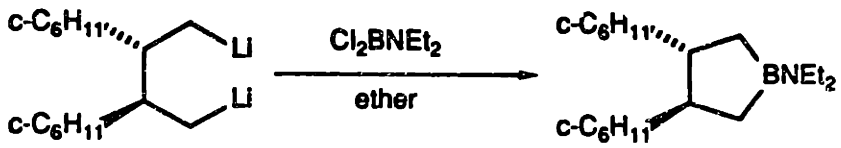


2-45 2-46

To a suspension of lithium (115 mg, 16.6 mmol, containing 5% Na) in freahly distilled ether (10 mL) in a cooled (-23°C) two-neck round bottom flask equipped with a condenser, a dropping funnel, and a magnetic stirr bar, was added dropwise an ethereal solution (5 mL) of the dichloride **2-45** (1.00 g, 3.43 mmol) over a period of 20 min. After 20 min stirring the mixture was warmed to 0°C and stirring was continued for 4.5 h.

The solution was filtered through a Celite 545 bed (~1 cm) and the residue was washed with ether (2 and 1 mL) to give 16 mL of a colorless solution. Titration with sec-BuOH indicated the concentration 0.32 N (0.16 M, 2.56 mmol, 75% yield).

(3*S*,4*S*)-*B*-(*N*,*N*-diethylamino)-3,4- dicyclohexylborolane (2-47)



2-46 **2-47**

An ether solution of the dilithium solution (0.16 M, 14 mL, 2.24 mmol) was added to a cooled (-78°C) solution of dichlorodiethylaminoborane (517 mg, 3.36 mmol) in ether (10 mL) over a period of 6 min. The mixture was stirred for 12 h while allowed to warm to room temperature. It was filtered through a Celite bed (~1 cm) and the residue was concentrated under reduced pressure. Distillation of the colorless residue under reduced pressure (T_b 150-170°C/0.27 mmHg) provided 607 mg (2.00 mmol, 89% yield) of a colorless crystal. mp 66-68°C.

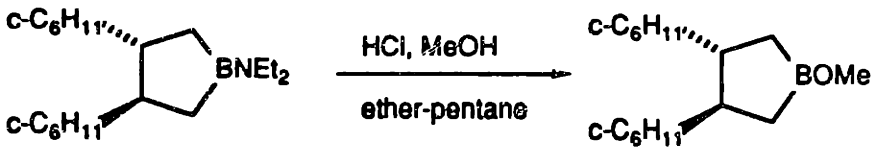
IR (KBr) 2960, 2920, 2850, 1528, 1500, 1462, 1448, 1400, 1370, 1340, 1285, 1238, 1200, 1095, 1060, 975, 885, 850.

^{1}H NMR (C_6D_6) δ 0.6~0.7 (2H, m), 0.95 (6H, t, *J*=7.0 Hz), 0.9~1.9 (26H, m), 2.86~3.02 (4H, m); ^{13}C NMR(C_6D_6) δ 15.7, 19.1 (br), 26.5, 27.2, 27.5, 27.7, 33.4, 39.0, 43.9, 47.2; ^{11}B NMR (C_6D_6) δ 50.4.

MS(EI) m/e (rel intensity) 303 (M^+, 34.5), 288 (22.9), 220 (100), 207 (20.6), 194 (33.4), 178 (35.3), 138 (24.4), 124 (68.6), 110 (83.5), 98 (53.9), 97 (62.3), 96 (68.8), 84 (65.9), 81 (84.4).

HRMS m/e calcd for $C_{20}H_{38}BN$ 303.3097, found 303.3098.

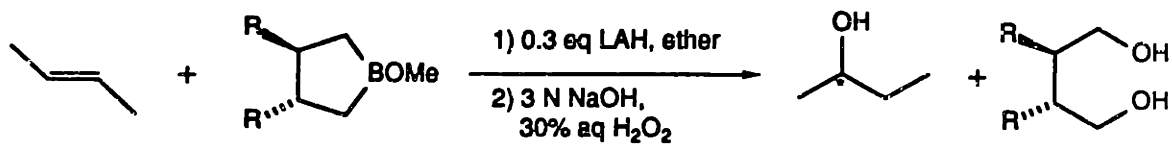
B-Methoxy-3,4-dicyclohexylborolane (2-48)



2-47 **2-48**

To a mixture of the aminoborolane (847 mg, 2.79 mmol) and methanol (1.00 mL, 24.7 mmol) at 0°C was added an ethereal solution of dry HCl (1.5 N, 1.86 mL, 2.79 mmol) and stirring was continued for 2 h at room temperature. All volatile materials were removed under reduced pressure (40 mmHg, room temperature) and pentane (5 mL) was added to the residue. The mixture was filtered and the filtrate was concentrated under reduced pressure. Final distillation under reduced pressure (T_b 85-90°C/0.01 mmHg) afforded 596 mg (2.27 mmol, 81% yield) of a colorless liquid.
IR (film) 2920, 2845, 1469, 1445, 1370, 1260, 1240, 1200, 1372, 1080, 978.

Representative Procedure for Asymmetric Hydroboration Using 2-8 or 2-9



2-8 or 2-9

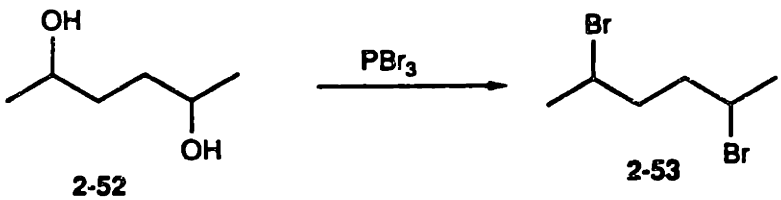
To a solution of *trans*-2-butene (37 mL gas, 1.5 mmol) in ether (2 mL) at 0°C, was added an ethereal solution of LAH (0.19 mL, 1.32 M, 0.25 mmol). The mixture was cooled to -40°C and methoxyborolane **2-14** or **2-48** (0.75 mmol) was added at once. The reaction mixture was warmed to -20°C (entries 1-3, Table 2.1, and entries 1,2, Table 2.2) or +4°C (entries 1,2, Table 2.1, and entries 3,4, Table 2.2) and stirred for 30 min. Then the reaction mixture was allowed to stand at -20°C or +4°C for a given period (see Table 2.1 and 2.2). Dodecane (52.8 mg) was added as an internal standard. Water (20

μL) was added to quench residual LAH and the mixture was treated with 3 N aq NaOH (0.3 mL) followed by 30% aq H_2O_2 (0.3 mL). After stirring vigorously for 2 h, K_2CO_3 (~1 g) was added and stirring was continued until two layers were formed. The organic layer was separated and the aqueous layer was extracted with ether (1 mL). Combined ether solution was dried over anhyd K_2CO_3.

To a portion (one third) of the ethereal solution were added pyridine (1 mL), DMAP (~5 mg), and 3,3-dimethylbutanoyl chloride (62 μL, 0.5 mmol). The mixture was stirred for 1 h. Formation of a white precipitate was observed immediately after the addition of acid chloride. The reaction mixture was diluted with ether (10 mL), washed with 1 N HCl (10 mL), sat aq $NaHCO_3$ (10 mL), and finally with water (10 mL). The ethereal solution was dried over anhyd $MgSO_4$. The solution was examined with capillary GC (OV-101, 9 m) to determine the yield.

The crude product was concentrated under reduced pressure and the product was purified on a preparative GC (10% SE-30, 1/4", 6 ft). Enantiomeric excesses were determined by ^1H NMR analysis of the pure ester in the presence of $Eu(hfc)_3$.

2,5-Dibromohexane (2-53)



2-52 2-53

2,5-Hexanediol **2-52** (37.1g, 0.314mmol) was placed in a 250 mL r.b. flask equipped with a thermometer, mechanical stirrer and a dropping funnel containing PBr3 (33 mL, 0.351mmol). PBr3 was added dropwise to the cooled (ice/MeOH) alcohol with stirring. Initially very strong exothermic reaction occurs (T_i 5-15°C). However after 20 min internal temperature 5°C was maintained with ice/MeOH cooling. The

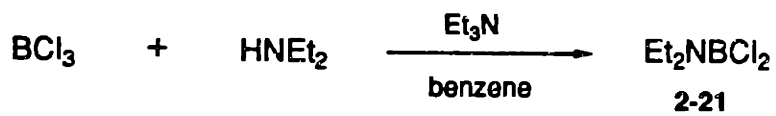
reaction mixture was stirred for 10 min after the addition of the PBr_3 (the addition took ~90min) and it was allowed to stand for 20 h at room temperature (Note 1.) The dropping funnel was replaced by a condenser and the reaction mixture was heated to 95-110°C for 1 h. After cooling it was poured into 500 mL water (with 200 g ice) (Note 2). The product was extracted with hexane (150 mL, and 50 mL) and the hexane solution was washed with conc H_2SO_4 (50 mL), water (100 mL), sat aq $NaHCO_3$ (100 mL) and sat aq NaCl (100 mL) solution. The organic layer was dried over anhyd Na_2SO_4. After filtration followed by solvent removal by rotary evaporation, the residue was distilled under reduced pressure (125-139°C/100 mmHg) to give 70.24g (0.29 mmol, 92.4%) of a colorless oil (Note 3).

Note 1. The initially very viscous solution became free flowing during the course of the addition.

Note 2. Little or no exothermic reaction was observed.

Note 3. The reaction can be scaled up to 5 mol yielding 90-95 % of products.

N,N-diethylaminodichloroborane (2-21)[40]



Dry benzene (200 mL) was placed in a 4 L three-neck round bottomed flask fitted with a mechanical stirrer, a dropping funnel and a thermometer. The flask was cooled to 5-10°C (Note 1) with ice-water bath. Boron trichloride (150 mL, 1.73 mol) (Note 2) was dissolved in the benzene with stirring by transfer via cannula. The flask was cooled with dry ice - methanol and a solution of freshly distilled diethylamine (197 mL, 1.71 mol) in benzene (300 mL) (Note 3) was added dropwise over a period of 2.5 h

resulting in the formation of a white precipitate of $BCl_3 \cdot HNEt_2$. The cooling bath was removed and the reaction mixture was warmed to room temperature while being continually stirred. The stirring was continued for 1 h. A solution of triethylamine (242 mL, 1.73 mol) in benzene (300 mL) was added to the suspension through the addition funnel with continued stirring. The addition funnel was replaced by a reflux condenser and the reaction mixture was heated to reflux for 3 h and then stirred at room temperature overnight (12 h). The solution was filtered through a filter chamber via cannula and the solid was washed with benzene (100 mL x 2). Solvent was removed from the combined solution of the filtrate and washings by fractional distillation. The residual dark brown fuming liquid was distilled through a fraction column affording 180 g (68 %)(Note 4) of **2-21** as a very air-sensitive oil (Note 5). bp 145-147°C.

Note 1. Internal temperature lower than 5°C results in freezing of the solvent.

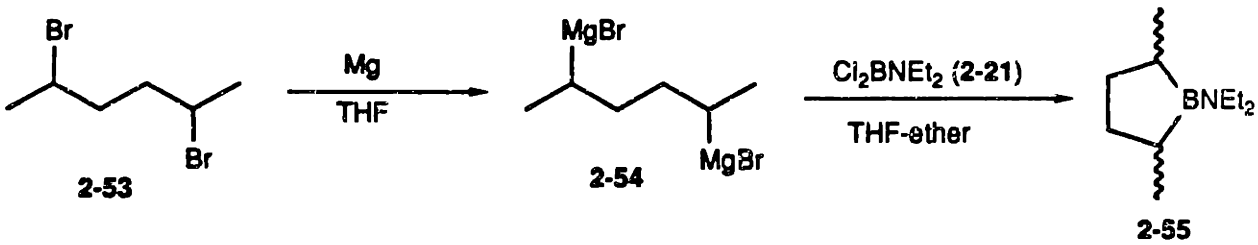
Note 2. Trichloroborane was condensed from a lecture bottle at -20°C to a graduated cylinder and was transferred via cannula into the benzene with the aid of a positive pressure of argon.

Note 3. Diethylamine should be added to the addition funnel after the addition of trichloroborane. Prior addition of diethylamine resulted in the formation of a severe fuming which caused clogging of the gas outlet.

Note 4. Yields of 60-70 % were obtained from various scales of reactions.

Note 5. The product should be kept under argon with a greased glass stopcock at 4°C to avoid decomposition.

B-(*N*,*N*-diethylamino)-2,5-dimethylborolane (2-55)

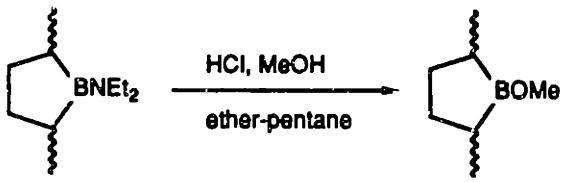


Dibromoethane (3.0 mL, 0.035mol) was added to a mechanically stirred suspension of Mg turnings (78 g, 3.21 g atom) in THF (160 mL). After 30 min most of THF was removed via cannula and fresh THF (270 mL) was added. Then a solution of 2,5-dibromohexane (299 g, 1.24 mol) in THF (650 mL) was added at a rate that maintained the internal temperature at 30-34°C. The resulting mixture was stirred overnight, filtered through glass wool and diluted with THF to a volume of 2 L. Hydrolysis of an aliquot and titration for total base showed the concentration of this solution to be 0.39 M (63% yield, typically 60-65%). The Grignard solution was added to a cooled, magnetically stirred (Note 1) solution of N,N-diethylaminodichloroborane (124 g, 0.80 mol) in ether (1.0 L) at a rate that allowed maintenance of an internal temperature of -70 to -65°C. The resulting suspension was allowed to warm to 20°C overnight. The solids were allowed to settle and the supernatant was removed via cannula. The solids were washed with pentane (four times x 250 mL) and the combined supernatants were concentrated by fractional distillation. The residue was vacuum-transfered to a cold (dry ice-acetone) receiver by heating the residue to 120°C at 0.1 torr. Distillation under reduced pressure gave the diethylaminoborolane **2-55** as a mixture of isomers (72.8 g, 0.44 mol) in 56% yield. On small scale reactions yields up to 70% were obtained.

bp 79-82°C (15 mmHg); ^{1}H NMR δ .83 (3H, d, *J*=7.7Hz), .93 (3H, d, *J*=7.2Hz), 1.04 (6H, d of t, *J*=1.0, 7.2Hz), 1.05-1.80 (6H, m), 3.9-3.2 (4H, m); ^{13}C NMR δ 15.4, 15.6, 15.7, 16.5, 22.8, 33.7, 34.2, 42.3, 42.6,; ^{11}B NMR δ 50.

Note 1. Use of mechanical stirrer is necessary with reactions of larger scale.

Cis- and *trans*-Bmethoxy-2,5-dimethylborolane (2-51)



2-55 2-51

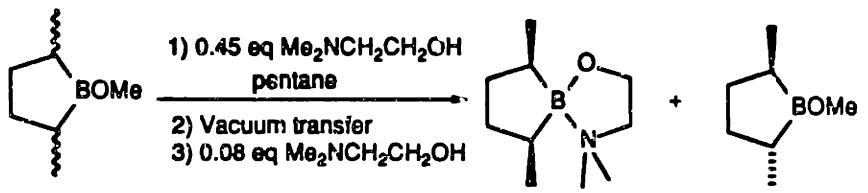
Methanol (41.3 mL, 1.02 mol) and *N,N*-diethylaminoborolane 2-55 (131 g, 0.18 mol) in pentane (1.3 L) was placed in a 3 L three-neck round bottom flask equipped with a thermometer, a mechanical stirrer and a dropping funnel. A solution of ethereal HCl (234 mL, 0.80 mol) was slowly added from the addition funnel to a cooled solution (ice - water bath). The internal temperature was maintained between 5-10°C. A white precipitate formed during the addition and the resulting suspension was stirred at 20°C for 12 h. The solution was filtered (Note 2), the precipitate washed with pentane (2 x 150 mL) and the solvent removed from the combined solution of the filtrate and washings by distillation at atmospheric pressure through a 50 cm Vigreux column. The residue was distilled under reduced pressure to give the methoxyborolanes as a colorless oil (85 g, 0.67 mol, 86% yield, cis:trans ratio 47:53) bp 49-52 °C (33 mmHg). For other physical data see characterization of pure isomers below.

Note 1. Dry HCl gas was bubbled into magnetically stirrered dry, oxygen-free ether cooled with ice-water bath and the resulting ethereal HCl solution was titrated with a standard solution of aq sodium hydroxide using THF as a solvent.

Note 2. The filtration was executed by using a large filter chamber or preferably using a

separatory funnel with glass wool and dry celite.

(*R,S*)-*B*-(2-*N,N*-dimethylaminoethoxy)-2,5-dimethylborolane (2-57) and trans-(±)-methoxyborolane (trans-2-51)



2-51 *cis*-2-51 *trans*-(±)-2-51

N,N-dimethylethanolamine (11.5 mL, 114 mol, 45 mol %) was added via a syringe to a magnetically stirred solution of cis- and trans-methoxyborolane (32.0 g, 0.254 mol) in pantane (220 mL) in a 500 mL round bottom flask fitted with a septum at room temperature. After 2 h the solution was vacuum transferred (Note 1) to a receiver cooled to -78°C in dry ice - acetone. The trnsfer was completed by reducing the pressure to 0.1 torr and heating (Note 2) the reaction flask to 70-80°C. The white crystalline residue was essentially pure cis complex (21.0 g, 114 mol, 100%, cis:trans ratio >98:2 by ^{1}H NMR). Recrystallization from pentane gave pure cis complex 2-57. The vacuum transferred material was treated with a second portion of dimethylaminoethanol (2.1 mL, 21 mmol, 8 mol %). Vacuum transfer as above gave a solid residue (4.2 g, 23 mmol, 109%, cis:trans ratio 1:2). The vacuum transferred material was concentrated by distillation at atmospheric pressure. The residue was distilled at reduced pressure to give trans-methoxyborolane as a colorless oil (12.9 g, 103 mmol, 86%, cis:trans ratio 2:98).

Data for complex 2-57: mp 59-60°C; ^{1}H NMR δ 0.55 (2H, m). 0.82 (6H, d, *J*=7.3 Hz), 1.1-1.6 (4H, m), 2.49 (6H, s), 2.85 (2H, t, *J*=7 Hz), 3.89 (2H, t, *J*=7 Hz); ^{13}C NMR δ 17.0,23.4,34.9, 44.6, 59.1, 59.5; ^{11}B NMR δ 12.8; MS(EI) m/e (relative intensity) 183 (7), 182 (M^+, 2.4),

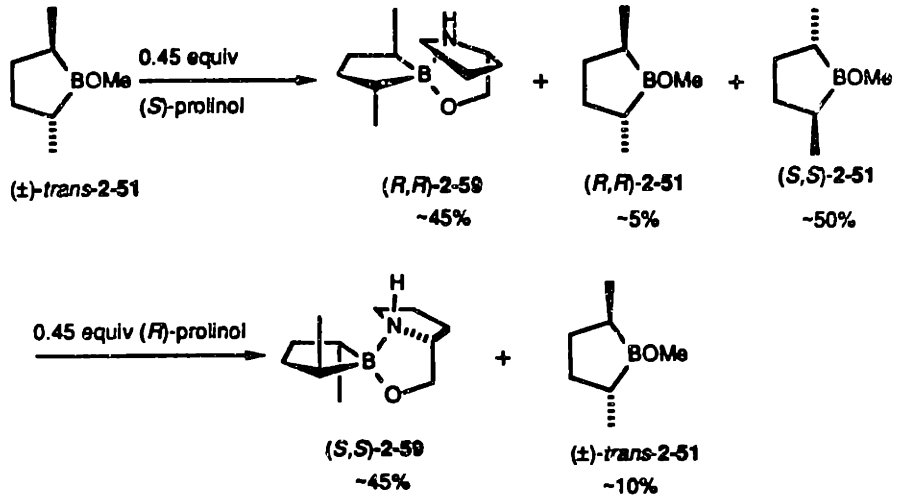
140 (29), 72 (44), 58 (100); HRMS m/e calcd for $C_{10}H_{22}BNO$ 183.1794, found 183.1794.

Data for trans-methoxyborolane trans-2-51: bp 51-54°C (34 mmHg); ^{1}H NMR δ 0.95 (6H, br s), 1.05-1.2 (2H, m), 1.8-2.0 (4H, m), 3.80 (3H, s); ^{13}C δ 14.0, 24.5, 33.5, 55.1; ^{11}B NMR δ 57.

Note 1. The reaction flask was connected to a receiver flask with a stillhead (or a V-shaped joint) and an adaptor which was connected to a vacuum source (see Fig.) and it was cooled to -78° C with dry ice-acetone bath. Then high vacuum (0.1 mmHg) was applied to the system. With the stopcock closed, the reaction flask was allowed to slowly warm up to room temperature while the receiver flask was cooled (-78°C).

Note 2. Heat should not be applied until most of the volatile materails are transferred to the receiver flask, since at higher temperature the equilibrium constant of cis/trans complex is not high.

(S)-prolinol complex of (R,R)-2,5-dimethylborolane and (R)-prolnol complex of (S,S)-2,5-dimethylborolane [(R,R)-2-59 and (S,S)-2-59]



(S)-(+)-Prolinol (4.66 g, 46.1 mmol, 45 mol %) in ether (5 mL) was added dropwise to a magnetically stirred solution of trans-borolane (12.9 g, 102 mmol) in pentane (100 mL) in a 250 mL round bottom flask at 0°C. A white precipitate formed during the addition. The suspension was stirred 30 min at 0°C and 1.5 h at 20°C. The volatile materials were vacuum-transferred to a receiver cooled with dry ice-acetone. The transfer was complete by reducing the pressure to 0.1 mmHg and raising the temperature to 70-80°C. The white crystalline residue was nearly pure (R,R)-complex (8.81 g, 45.2 mmol, 98%, 96.2% ee, *RR/RS/SS*=97.7/0.77/1.50). Crystallization from CH_2Cl_2 gave the pure complex (1st crop; 6.48 g, 72%, 99.0% ee, 2nd crop; 1.35 g, 15%, 94.8% ee) (Note 1).

The volatile material was treated with (R)-(-)-prolinol (4.66 g, 46.1 mmol, 45 mol %) in ether (5 mL) as above. Vacuum transfer gave nearly pure (S,S)-complex (7.92 g, 40.6 mmol, 88.0%, 97.2% ee). Recrystallization from CH_2Cl_2 gave the pure complex (6.48 g, 33.2 mmol, 72.0%, >98% ee) (Note 2). Final vacuum transfer of the volatile material gave racemic trans-borolane which was reserved for the combination of the

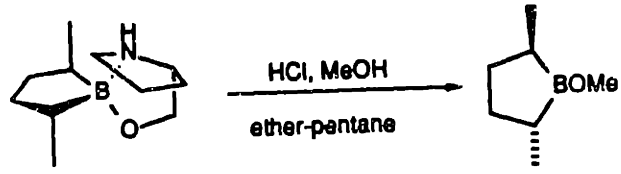
material from several batches of reactions.

Physical data for complex **2-59**:

mp 225-226℃; $[\alpha]^{21}_D$ +23.2° (*c* 1.28, $CHCl_3$) for (*R,R*)-**2-59**; ^1H NMR δ 0.50~0.70 (2H, m), 0.89 (6H, d, *J*=7.2 Hz), 1.7~1.85 (4H, m), 2.0~2.2 (2H, m), 2.85~3.2 (2H, m), 3.56 (1H, dd, *J*=3.2, 9.2 Hz), 3.60~3.75 (1H, m), 3.91 (1H, dd, *J*=6.2, 9.1 Hz), 4.1~4.25 (1H, br s); ^{13}C NMR δ 18.0, 26.0, 27.2, 31.2, 36.6, 48.6, 61.5, 67.4; ^{11}B NMR δ 11; MS(EI) m/e (rel intensity), 195 (M^+, 10.4), 194 (6.6), 152 (73), 139 (64), 138 (58), 84 (50), 70 (100); HRMS m/e calcd for $C_{11}H_{22}BNO$ 195.1794, found 195.1783.

Note 2. For determination of the purity of the complexes, see below.

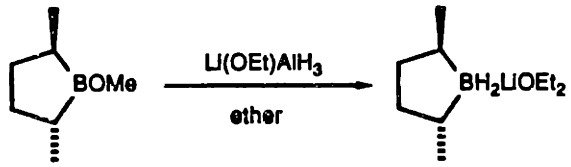
Preparation of (*R,R*)-methoxyborolane (*R,R*)-**2-51** from aminoalcohol complex (*R,R*)-**2-59**



(*R,R*)-**2-59** (*R,R*)-**2-51**

A solution of ethereal HCl (15.4 mL, 18.8 mmol) was added dropwise to a magnetically stirred solution of methanol (0.95 mL, 23 mmol) and the complex (*R,R*)-**2-59** (3.50 g, 17.9 mmol) in pentane (50 mL) at 0℃. After 6 h the solution was filtered. The filtrate was concentrated by distillation through a Vigreux column at atmospheric pressure and the residue was distilled at reduced pressure (60-61℃, 61-63 mmHg) to give (*R,R*)-**2-51** (1.83 g, 81% yeld). Yields vary from 80-95%.

Synthesis of (*S,S*)- or (*R,R*)-dihydro-2,5-dimethylboratacyclopentane etherate (2-67)



(*R,R*)-2-51 (*R,R*)-2-67

Ethyl actate (1.17 mL) was added to a magnetically stirred solution of $LiAlH_4$ in ether (24 mL, 1.0 M solution from Aldrich) in a double-Schlenk tube at 0°C. After stirring for 30 min. *B*-methoxy-2,5-dimethylborolane **2-51** (3.02 g, 24.0 mmol) in ether was added via cannula with stirring. White suspension formed upon the addition of the methoxyborolane. The reaction mixture was stirred for 0.5 h at 0°C and 18 h at room temperature. The solution was filtered through the glass fritt by tilting the receiver flask and cooling with dry ice-acetone drenched cotton. Ether from the filtrate was vacuum-transferred to the residue and the residue was stirrred with ether and the solution was filtered again. This procedure was repeated three times. Final filtrate was then transferred to a pre-weighed flask capped with a septum. Solvent was removed under reduced pressure (first under aspirator pressure (Note 1) then under vacuum (0.1 mmHg, 20°C) and the residue was dissolved in pentane. Removal of solvent from clear pentane solution (Note 2) gave borohydride as a solid monoetherate (3.57 g, 88%)(Note 3).

^1H NMR (C_6D_6) δ 0.98 (6H, t, *J*=7.2 Hz), 1.26 (2H, m), 1.42 (6H, d, *J*=6.8 Hz), 1.55 (2H, m), 2.28 (4H, m), 3.11 (2H, dq, *J*=6.9, 10.1 Hz), 3.18 (2H, dq, *J*=7.2, 10.1 Hz); ^{13}C NMR (C_6D_6) δ 14.4, 22.3, 24.1, 38.9, 66.3; ^{11}B NMR (C_6D_6) δ -11.6 (*J*=70 Hz)

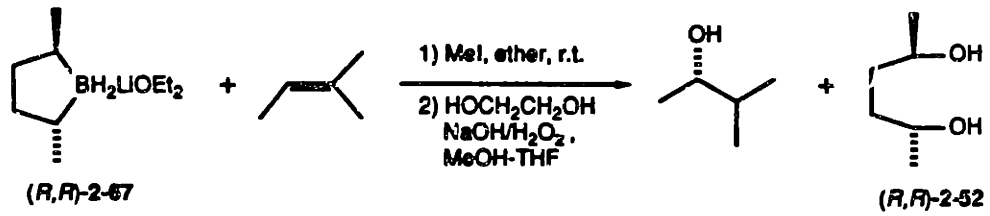
Note 1. The suction line should have a dry ice-acetone trap in order to keep moisture from deteriorating the product.

Note 2. If the pentane solution is not clear, the remaining suspension is again filtered through a

filter chamber.

Note 3. Yields vary from 85 to 95%.

Typical procedure for asymmetric hydroboration of olefins using (*R,R*)-1-1



(*R,R*)-2-67 (*R,R*)-2-52

Borohydride (*R,R*)-**2-67** (3.6 mL, 1.8 mmol, 0.50 M solution in ether) was added to a solution of 2-methyl-2-butene (0.159 mL, 1.5 mmol) in ether (2 mL) at 4°C. Then iodomethane (0.224 mL, 3.6 mmol) was added. The solution was stirred at 22°C for 15 h. The solvent was removed in vacuo (50 torr) and the residue was dissolved in THF (1.3 mL). Ethylene glycol (0.2 mL, 3.6 mmol, degassed), methanolic NaOH (2.7 mL, 10.8 mmol, degassed) and 30% H_2O_2 (0.9 mL, 9 mmol) were added at 4°C. The solution was heated to 40-50°C for 2 h. Continuous extraction with pentane (25 mL) gave a soltuion containing primarily 3-methyl-2-butanol. Continuous extraction with ether (20 mL) gave a solution of 2,5-hexanediol. The pentane solution was concentrated by distillation at atmospheric pressure. The residue (ca. 1.5 mL) was diluted with pentane (2.5 mL) and decane (100μL) was added as an internal standard for GC analysis. A portion (0.4 mL) of the pentane solution was acetylated with acetic anhydride (0.5 mL), pyridine (0.5 mL), and DMAP (3 mg). After the usual workup GC analysis showed that the overall yield of 2-acetoxy-3-methylbutane and 2,5-diaceoxyhexane were 90 and 26%, respectively. Chromatography of the remaining pentane solution (ether/pentane, 1/4), concentration at atmospheric pressure and bulb to bulb distillation (T_b 80-100°C, 320 mmHg) gave 3-methyl-2-butanol (105 mg). The MTPA ester of this alcohol was prepared as follows: A solution of the alcohol (10 mg), DMAP (2 mg), pyridine (0.1 mL)

and (*R*)-MTPA chloride (30 μL) in CH_2Cl_2 (1 mL) was stirred at 20°C for 12 h. After usual workup HPLC analysis of this oil (0.3 % ether/hexane, 2 mL/min) showed two peaks in a ratio of 97.1 (t_R 34.5 min) to 2.9 (t_R 32.3 min).

The ether solution from continuous extraction was dried ($MgSO_4$), evaporated and distilled (bulb-to bulb, T_b 120-130°C/30 mmHg) to give 2,5-hexanediol (161 mg, 76%). The bis-MTPA ester was prepard as above. HPLC analysis (7% ether/hexane, 2mL/min) showed 95.7% of the bis-MTPA ester of *R,R*-diol (t_R 18.4 min), 4.3% of the bis-MTPA ester of the *R,S*-diol (t_R 22.1 min) and <0.1% of the bis-MTPA ester of the *S,S*-diol (t_R 25.7 min). Thus the ee of (*R,R*)-**2-67** used to correct the optical purity of the butanol was 95.7.

Analysis of optical purity of complexe **2-59**, methoxyborolane **2-51**, and borohydride **2-67**

The optical purities of the above compounds were determined as follows: A solution of the appropriate borolane (0.1 mmol) in THF (2 mL) was oxidized by the addition of ethylene glycol (0.012 mL), 2 M methanolic NaOH (0.3 mL, 0.6 mmol) and 30% H_2O_2 (0.05 mL) followed by heating to 40-50°C for 2 h. The solution was cooled, diluted with ether (5 mL) and saturated with anhydrous K_2CO_3. The solution was filtered and the filtrate dried over K_2CO_3. Filtration and removal of solvents *in vacuo* (20°C, 0.1 mmHg) gave crude 2,5-hexanediol. Treatment with (*R*)-MTPA chloride (3 equiv) as above gave the bis-MTPA diesters which were analyzed by HPLC. When samples were analyzed at each stage, the effective enatiomeric excesses so determined were in agreement within ±0.5%.

Our use of the term enantiomeric excess is not, strictly speaking, proper because our calculations include a correction for the presence of the cis isomer. The cis isomer

is treated as though it were a 1/1 mixture of the (*R*,*R*) and (*S*,*S*) compounds. Thus an HPLC analysis showing the presence of 95% (*R*,*R*), 4% (*R*,*S*), and 1% (*R*,*S*) diesters provides an effective ee of (95 + 2)- (1 + 2) or 94% ee.

Determination of absolute configuration of complexes **2-57**, (*R*,*R*)-**2-59** , and (*S*,*S*)-**2-59**

A solution of (*R*,*R*)-prolinol complex (*R*,*R*)-**2-59** (779 mg 4.0 mmol) in THF (20 mL) was oxidized as above with ethylene glycol (0.44 mL, 7.9 mmol), 2 M methanolic NaOH (12 mL, 24 mmol), and 30% H_2O_2 (2 mL, 20 mmol). Ether (50 mL) was added and the solution was washed with brine (2 x 10 mL). The aqueous phase was extracted with ether (2 x 10 mL). The combimed organic layers were dried (K_2CO_3) and evaporated. Chromatography (ethyl acetate) of the residue afforded (*R*,*R*)-2,5-dihydroxyhexane (356 mg, 75% yield). The diol was acetylated with acetic anhydride (1.5 mL), pyridine (1.5 mL), and DMAP (30 mg) at 20°C for 12 h. Standard workup followed by chromatography (ethyl acetate/hexane, 1/9) gave (*R*,*R*)-2,5-diacetoxyhexane (482 mg, 80% yield). Bulb to bulb distillation gave pure diacetate.

bp 80-90°C/4 mmHg; $[\alpha]^{21}_D$ +3.00 (*c* 8.32, $CHCl_3$); ^1H NMR δ 1.18 (6H, d, *J*=6.2 Hz), 1.55 (4H, m), 2.00 (6H, s), 4.86 (2H, m); ^{13}C NMR δ 19.8, 21.1, 31.5, 70.4, 170.4.

A solution of this acetate (349 mg, 1.73 mmol) in THF was added to a suspension of LAH (131 mg, 3.45 mmol) in THF (10 mL) at 4°C and stirred for 1 h. Ether (15 mL) was added followed by 1 M aq NaOH (0.5 mL) and the insoluble material was removed by filtration. Evaporation gave (*R*,*R*)-2,5-dihydroxyhexane (217 mg, 100%). Bulb to bulb distillation afforded pure diol.

bp 90-100°C/4 mmHg; mp 51-53°C; ^1H NMR δ 1.18 (6H, d *J*=6.1 Hz), 1.54 (4H, m), 2.06 (2H, s), 3.84 (2H, m); ^{13}C NMR δ 23.6, 36.0, 68.2; $[\alpha]^{21}_D$ -31.9° (*c* 7.38, $CHCl_3$). Lit $[\alpha]^{23}_D$ -35.6° (*c* 8.29, $CHCl_3$) Serck-Hannsen, K.; Stallberg-Stenhangen, S.; Stenhangen, E. *Ark.*

Kemi. **1953**, *5*, 203. The bis-MTPA of this diol was prepared as above and shown to be a 92% *R,R*, 4% *R,S*, and 4% *S,S* mixture of diesters.

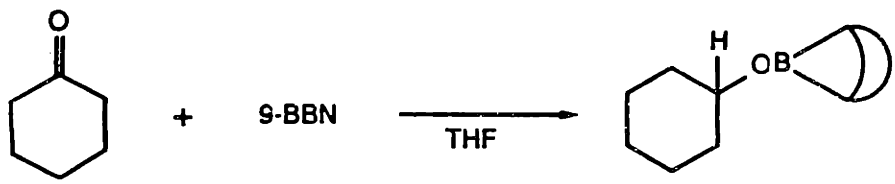
Oxidation and acetylation of the (*S,S*)-prolinol complex (*S,S*)-**2-59** gave (*S,S*)-2,5-diacetoxyhexane identical with the (*R,R*)-diacetate except for rotaiton. $[\alpha]^{21}_{D}$ -3.27 (c 7.98, $CHCl_3$). Reduction with LAH gave (*S,S*)-2,5-dihydroxyhexane identical with (*R,R*)-diol except for rotaiton. $[\alpha]^{21}_{D}$ +34.2° (*c* 6.82, $CHCl_3$). Lit $[\alpha]^{25}_{D}$ +35.1° (*c* 9.49, $CHCl_3$) Serck-Hanssen et al. The bis-MTPA ester was 1% *R,R*, 3% *R,S*, and 96% *S,S*.

Oxidation and acetylation of the cis complex **2-57** gave (*R,S*)-2,5-diacetoxyhexane (70% yield). bp 80-90°C/4 mmHg; ^{1}H NMR δ 1.21 (6H, δ, *J*=6.2 Hz), 1.56 (4H, m), 2.03 (6H, s), 4.87 (2H, m); ^{13}C NMR δ 19.8, 21.1, 31.7, 70.5, 170.4; $[\alpha]^{21}_{D}$ -0.027° (*c* 7.53, $CHCl_3$). Reduction with LAH gave (*R,S*)-2,5-dihydroxyhexane. bp 90-110°C/4 mmHg; ^{1}H NMR δ 1.18 (6H, d, *J*=6.1 Hz), 1.55 (4H, m), 2.03 (2H, s), 3.84 (2H, m); ^{13}C NMR δ 25.2, 34.8, 67.6; $[\alpha]^{21}_{D}$ 0° (c 8.06, $CHCl_3$). The bis-MTPA ester was 4% *R,R*, 92% *R,S*, and 4% *S,S*.

Kinetic Studies of Hydroboration using ^{11}B NMR spectroscopy

The data presented below were obtained with a pulse width of 45° (PW 90° = 10.5 μsec) and a delay between pulses of one second (typical T1's for ^{11}B are 25-100 mili sec) using the Varian XL-300 multinuclear NMR. Each data point is the summation of 16 pulses acquired over 20 seconds. The variable temperature air flow was 9-10 L/min as recommended by Varian to obtain homogeneous temperature in the sample probe. Temperatures were determined through the use of methanol calibration standard and the data were corrected to temperatures using the equation of Raiford.[130] Sample volumes were 0.4 mL. All the ^{11}B NMR experiments were performed with decoupler off since up to ~50% difference was obtained due to sample heating from the decoupler.

Experiment I and II



Cyclohexanone (26μL, 0.25 mmol) was added to a THF solution of 9-BBN (0.5 M, 0.50 mL, 0.25 mmol) in an nmr tube. The nmr tube was inserted into the probe and data acquisition was obtained.

NMR parameters:

VT temperature displayed 23.9-24.0°C.

VT air flow 9.5L/min.

Decoupler off. Gain 24 dB

Spin 22-24. Unlocked

Temperature Calibration for Exp I and Exp II.

SF = 299.958

Flow = 9-10 L/min

VT off Spin 22 Gain 04

PW = 2 NT = 1 Unlocked

Table 5.1 Temperature Calibration for Exp I and II.

run	1	2	3	4	5
-OH	1719.77	1719.77	1719.28	1720.26	1719.28
CH_3-	1249.99	1249.99	1249.50	1250.96	1250.96
$\Delta\nu$	469.78	469.78	469.78	469.30	468.32

Average $\Delta\nu$ = 469.39 (344.27 for 220 MHz)

Using Raiford's Equation:

$T(K) = 429.2 - 0.283\,(\Delta\nu) - 2.862 \times (\Delta\nu)^2$ at 220 MHz.

Calculated temperature = 24.9°C

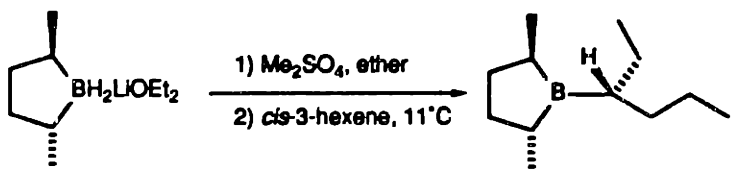
Experiment III

9-BBN (84.6 mg, 0.3496 mmol) in $CDCl_3$ (1.70 mL) was stirred under argon for 10 min. Cyclohexene (70μL, 0.6911 mmol) was added to the solution and the mixture was transferred to an NMR tube. The final concentration of 9-BBN was 0.2056 M. The sample tube was inserted in the NMR probe at 24.0°C (VT display). The reaction was followed for >15%.

Experiment IV

9-BBN (42.4 mg, 0.175 mmol) in $CDCl_3$ (1.20 mL) was stirred for 10 min and cyclohexene (0.35 mL, 3.46 mmol) was added. The mixture was ransferred to an NMR tube and kinetic measurement was abtained. Reaction was followed to 75% completion.

Representative Preocedure for Kinetics Experiment with (*S,S*)-**1**-**1** (Exp V, VI, and VII)



(*R,R*)-**2-67**

The borate complex (*S,S*)-**2-67** (82.2 mg, 0.489 mmol) was placed in a 10 mL round bottomed flask contaning a magnetic stir bar in a glove bag and it was weighed. The flask was purged with argon two times. Then ether (2.45 mL, freshly distilled) was

added and the solution was stirred for 10 min. Dimethyl sulfate (49μL, 0.518 mmol) was added to the ccoled (0°C, ice-water bath) solution. Immediate gas evolution was observed. The mixture was stirred for 20 min and cooled to -78°C (dry ice - acetone bath). cis-3-Hexene (61 μL, 0.492 mmol) was added and the mixture was filtered into an NMR tube using a syringe fitted with a glass fritt. Sample height was ~6 cm.

NMR parameters:

VT air 10 L/min

VT display 9.0-8.9°C

spin 25, unlocked, RG 26.

Temperature Calibration

Table 5.2 Temperature calibration with MeOH for Exp V.

-OH	1818.88	1818.88	1818.88	1819.37
CH_3-	1311.00	1311.00	1310.52	1311.00
Δν	507.88	507.88	508.36	508.37

Av 508.37

Using Raiford's equation, calibrated temperature is 283.98°K = 11.0°C.

Evaluation of 2nd order fit for Exp VII

The integrated rate equation is:

$$\frac{dx}{dt} = k(a - x)(b - x)$$

a = initial concentration of substrate

b = initial concentration of dimer

our equation becomes:

$$\frac{dx}{dt} = k(a - 2x)(b - x)$$

$$\frac{dx}{dt} = 2k\left(\frac{a}{2} - x\right)(b - x)$$

Thus $$\frac{1}{2\left(\frac{a}{2} - b\right)} \ln \frac{b\left(\frac{a}{2} - x\right)}{\frac{a}{2}(b - x)} = kt$$

In case of Exp VII,

b = 0.05274

a = 0.06135

Thus $$58.07 \ln \frac{0.0032356 - 0.05274x}{0.0032356 - 0.06135x} = kt$$

Table 5.3 Rate Data to Fit 2nd Order Kinetics for the Hydroboration of cis-3-Hexene with (S,S)-**1-1** (Exp VII).

Spectrum No.	time (sec)	[dimer]	$(\frac{a}{2}-x)$	f(x)
1	189	0.04566	0.05427	1.2502
2	378	0.03977	0.04838	2.5990
3	688	0.03276	0.04137	4.7691
4	997	0.02743	0.03601	7.0229
5	1306	0.02295	0.03156	9.7181
6	1616	0.01938	0.02799	12.566
7	1925	0.01703	0.02564	14.9795
8	2210	0.01399	0.02260	19.0694
9	2519	0.01249	0.02110	21.6673
10	2829	0.01152	0.02013	23.6290
11	3138	0.00916	0.01777	29.6700
12	3448	0.00757	0.01618	35.3276
13	4057	0.00604	0.01465	42.6707

Evaluation of 1st Order Fit for Exp VII.

The integrated rate equation is:

$$\frac{dx}{dt} = a - x$$

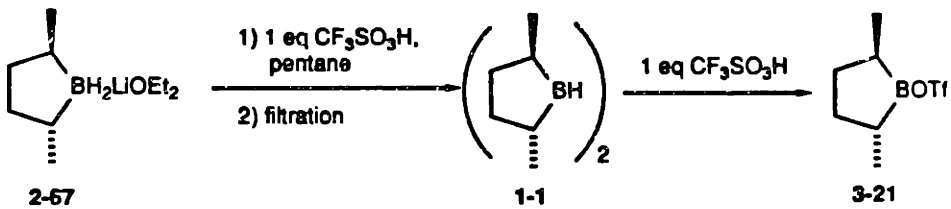
$$\ln(a - x) - \ln a = kt$$

where a = initial concentration of dimer.

Table 5.4 Rata Data to fit 1st Order Kinetics for the Hydroboration of cis-3-Hexene with (*S,S*)-1-1 (Exp VII).

Spectrum No.	time	[dimer]	ln([dimer])	ln(a - x) - lna	m x 10^4
0	0	0.05274	-2.942	0	
1	189	0.04566	-3.087	-0.145	7.67
2	378	0.03977	-3.225	-0.283	7.49
3	688	0.03276	-3.419	-0.477	6.93
4	997	0.02743	-3.596	-0.654	6.56
5	1306	0.02295	-3.774	-0.832	6.37
6	1616	0.01938	-3.944	-1.002	6.20
7	1925	0.01703	-4.073	-1.132	5.88
8	2210	0.01399	-4.269	-1.327	6.00
9	2519	0.01249	-4.383	-1.441	5.72
10	2829	0.01152	-4.464	-1.522	5.40
11	3138	0.00916	-4.693	-1.751	5.58
12	3448	0.00757	-4.884	-1.942	5.63
13	4057	0.00604	-5.109	-2.167	5.34

Preparation of 2,5-Dimethylborolanyl Trifluoromethanesulfonate (3-21)



2-67 1-1 3-21

To a magnetically stirred solution of the borohydride **2-67** (3.35g, 18.8mmol) in pentane(50mL) in a double-Schlenk tube (Note 1.) was added trifluoromethanesulfonic acid (1.66 mL, 18.8 mmol) at -78°C over a period of 5 min. Hydrogen gas evolution was observed during the addition. The flask was warmed to 0°C and stirring was continued for 20 min. The solution was filtered through a glass fritt and the remaining solid was washed with pentane (10 mL) and the solution filtered. To the stirred filtrate was added another equivalent of trifluoromethanesulfonic acid (1.66 mL, 18.8 mmol) at 0°C. The gas evolution has ceased after 1 h. Stirring was continued for 2 h allowing the solution to warm to room temperature. The solution was transferred via a cannnula to a 100 mL round bottm flask and most of the solvent was removed by fractional distillation through a 30 cm vigreux column at atmospheric pressure. The residue was transferred via a cannula to a 10 mL round bottom flask and final distillation under reduced pressure (bp 40-45°C, 5mmHg) gave 3.23g (13.2 mmol, 70.2%) (Note 2.) of **3-21** as an extremely air sensitive, colorless oil.

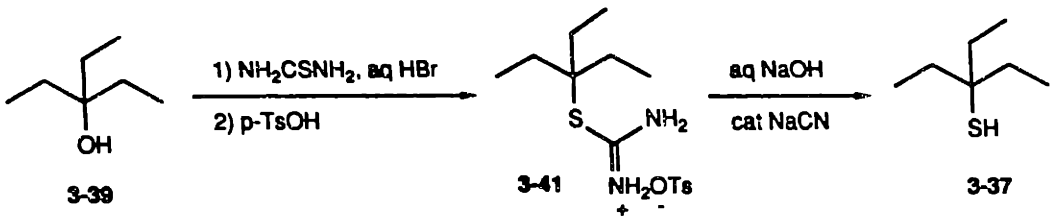
^{1}H NMR(C_6D_6) δ 0.72-1.10 (10H, m), 1.81 (2H, m); ^{13}C NMR (C_6D_6) d 13.2, 28.3, 33.1, 126.4; ^{11}B NMR (C_6D_6) δ 63.3.

Note 1. Any modified technique using one Schlenk filter chamber will be appropriate for this

manipulation.

Note 2. Yieids vary from 70 to 80%.

Preparation of 3-Ethyl-3-pentanethiol (3-37)



A mixture of 3-ethyl-3-pentanol **3-39** (24.17 g, 0.208 mol), thiourea (17.43 g, 0.229 mmol), and 48% aq HBr solution (38.56 mL, 0.229 mol) in a 250 mL two-neck flask was stirred at room temperature. The reaction was followed by GC with the disappearance of the alcohol and the appearance of 3-ethyl-2-pentene, a side product presumably from the elimination through the carbocation. After 7 h stirring, the aqueous phase was separated and treated with 20% aq p-toluenesulfonic acid (99 mL, 0.104 mol) to give a white precipitate at once. The mixture was cooled to 4°C, kept for 12 h and filtered. Drying (P_2O_5, <50°C, 0.1 mmHg, 24 h) the wet solids afforded 29.58 g (36% yield) of **3-41** as white flakes.

mp 186-189°C; IR ($CHCl_3$) 3700-2800 (br), 2960, 1645; ^1H NMR δ 0.89 (9H, t, *J*=7.3 Hz), 1.69 (6H, q, *J*=7.3 Hz), 2.34 (3H, s), 7.15 (2H, d, *J*=8.0 Hz), 7.49 (2H, br s), 7.71 (2H, d, *J*=8 Hz), 9.21 (2H, br s); ^{13}C NMR δ 8.3, 21.3, 29.1, 65.7, 126.0, 129.0, 140.1, 141.0, 169.2.

The thiouronium salt **3-41** (29.5 g, 85.4 mmol) was pulverized to fine powder and added in portions to a solution of NaOH (5.12 g) in 60 mL H_2O containing a catalytic amount of NaCN (5 mg). The reaction mixture was stirred for 2 h under argon at room temperature and then distilled into a separatory funnel (bp 95-100°C, azeotrope with water). The organic phase from the distillate was washed with water (10 mL), dried (anhyd $MgSO_4$), and distilled to afford 10.11 g (90% yield) of a colorless

oil with peculiar odor. bp (T_b) 71-75°C (41 mmHg); IR ($CHCl_3$) 3350, 2963; 1H NMR δ 0.91 (9H, t, *J*=7.4 Hz), 1.30 (1H, s), 1.58 (6H, q, *J*=7.4 Hz); ^{13}C NMR δ 8.54, 32.81, 52.73; MS (EI) m/e (rel intensity) 132 (M^+, 10.8), 103 (19.4), 99 (31.3), 69 (39.2), 61 (37.7), 57 (100).

Synthesis of Tris(trimethylsilyl)methane[85]

$$TMSCl \xrightarrow[2)\ CHCl_3,\ THF]{1)\ Li,\ THF} (TMS)_3CH$$

A mixture of chlorotrimethylsilane (67.9 g, 0.625 mol) and lithium dispersion (3.6 g, 0.519 mol, 1% Na) in THF (250 mL) was placed in a 1 L three-neck round bottom flask equipped with an efficient condenser, a dropping funnel and an overhead stirrer. The mixture was heated to reflux and a soluiton of chloroform (10.3 g, 0.0863 mol) in THF (50 mL) was added dropwise. Vigorously exothermic reaction was observed. After the addition the reaction mixture was refluxed for 1 h then the temperature was held at 20°C for 2 days with stirring. The soluiton was decanted via cannula, dried (anhyd $MgSO_4$), and distilled under reduced pressure (70-72°C, 5mmHg) to afford 12.2 g (61% yield) of a colorless oil.

^1H NMR δ -0.02 (1H, s), 0.11 (27H, s); ^{13}C NMR δ 3.27, 4.16

Synthesis of tris(trimethylsilyl)methanethiol (3-42)[86]

$$(TMS)_3CH \xrightarrow[2)\ S_8]{1)\ MeLi,\ THF} (TMS)_3CSH$$

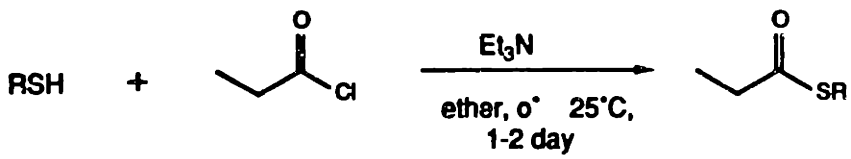
3-42

A mechanically stirred solution of tris(trimethylsilyl)methane (17.67 g, 76.0

mmol) and an ethereal soluiton of methyl lithium (2.37 M, 38.5 mL, 91.25 mmol) in THF (150 mL) was heated to reflux for 22 h. After the flask was cooled to 20°C, sulfur (2.92 g, 91.2 mmol) was added. Stirring was continued for 10 h at the temperature and the solution was diluted with an equal volume of brine. The organic layer was extracted with hexane (100 mL), concentrated to a minimum volume, and extracted with 3 N KOH/MeOH solution (10 x 20 mL). The alkaline phase was diluted with water (150 mL), acidified with cold 2 N aq HCl soluiton (300 mL) and the organic compounds were extracted with hexane (100 mL, then 30 mL). The hexane solution was washed with water (100 mL), dried (anhyd MgSO4), and concentrated in vacuo. Flash chromatography (silica gel, hexane/ether , 50/1) afforded 8.56 g (43% yield) of the thiol **3-42** as a white solid.

^{1}H NMR δ 0.18 (27H, s), 1.05 (1H, s); ^{13}C NMR δ 1.32, 2.90; MS (EI) m/e (rel intensity) 264 (M^+ 8.4), 249 (8.9), 233 (11.0), 201 (6.1), 161 (15.0), 159 (8.5), 73 (100), 59 (42.5).

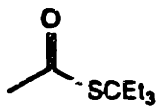
Typical procedure for the Preparation of a Thioate



To a magnetically stirred solution of 3-ethyl-3-pentanethiol (**3-37**) (5.30 g, 40.1 mmol) and triethylamine (4.06 g, 40.1 mmol) in ether (100 mL) was added propionyl chloride (3.71 g, 40.1 mmol) in ether (10 mL) at 0°C over a period of 20 min. After 48 h stirring, the reaction mixture was washed with water (50 mL), 0.5 N aq. NaOH solution (30 mL), water, (50 mL) and brine (50 mL). Dried (anhyd $MgSO_4$) product was concentrated under reduced pressure. Bulb-to-bulb distillation of the crude product afforded 5.33 g (71% yield) of a colorless oil. bp T_b 101-109°C (29 mmHg); IR (film) 2968,

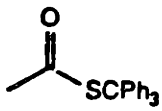
1688, 1455, 925; ^{1}H NMR δ 0.87 (9H, t, *J*=7.4 Hz), 1.12 (3H, t, *J*=7.6 Hz), 1.77 (6H, q, *J*=7.4 Hz), 2.47 (2H, q, *J*=7.5 Hz).

Physical Data for Other Ethane- and Propanethioates



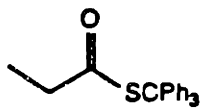
3-37c

^{1}H NMR δ 0.84 (9H, t, *J*=7.4 Hz), 1.74 (6H, q, *J*=7.4 Hz), 2.20 (3H, s).



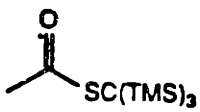
3-46c

IR (CCl_4) 3050, 1695; ^{1}H NMR δ 2.27 (3H, s), 7.20~7.35 (15H, m).



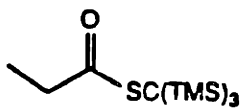
3-46b

mp 119.5-122℃; IR (CCl_4) 3055, 3020, 1698; ^{1}H NMR δ 1.09 (3H, t, *J*=7.4 Hz), 2.52 (2H, q, *J*=7.4 Hz), 7.19~7.31 (15H, m).



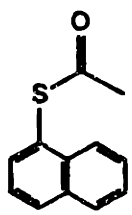
3-42c

IR ($CHCl_3$) 1690; ^{1}H NMR δ 0.20 (27H, s), 2.25 (3H, s); ^{13}C NMR δ 2.6, 16.1, 29.4, 197.8.



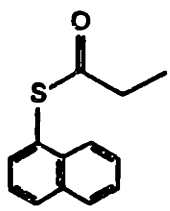
3-42b

IR ($CHCl_3$) 1692; ^{1}H NMR δ 0.20 (27H, s), 1.14 (3H, t, *J*=7.4 Hz), 2.52 (2H, q, *J*=7.4 Hz).



3-51c

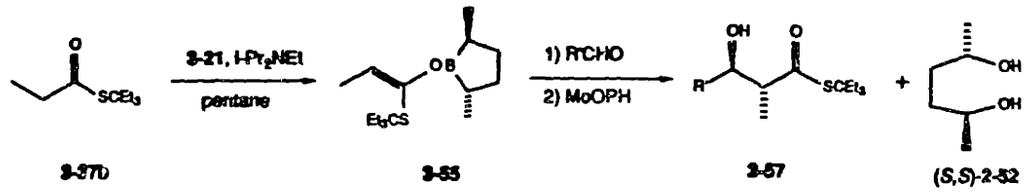
bp (T_b) 115-120℃/0.15 mmHg; ^{1}H NMR δ 2.47 (3H, s), 7.46~7.59 (3H, m), 7.70 (1H, dd, *J*=7.2, 1.0 Hz), 7.88 (1H, dd, *J*=7.1, 2.2 Hz), 7.95 (1H, d, *J*=8.2 Hz), 8.19 (1H, dd, *J*=8.8, 1.8 Hz).



3-51b

bp (T_b) 130-135℃/ 0.19 mmHg; ^{1}H NMR δ 1.25 (3H, t, *J*=7.4 Hz), 2.76 (2H, q, *J*=7.4 Hz), 7.46~7.58 (3H, m), 7.70 (1H, dd, *J*=7.2, 1.9 Hz), 7.88 (1H, dd, *J*=7.1, 2.2 Hz), 7.94 (1H, d, *J*=8.1 Hz), 8.18 (1H, dd, *J*=7.2, 1.9 Hz).

Typical Procedure for Aldol Reactions of a Propanethioate Using (*S,S*)-3-21



To a magnetically stirred solution of propanethioate **3-37b** (94 mg, 0.5 mmol) and diisopropylethylamine (105 mL, 0.6 mmol) in pentane (3 mL) was added the triflate **3-21** (146 mg, 0.6 mmol) at -78°C. After stirring at 0°C for 1 h, the mixture was recooled to -78°C and n-butanal (68 mL, 0.75 mmol) was added. Stirring was continued for 12 h. MoOPH (326 mg, 0.75 mmol) was added at -78°C and the mixture was stirred for 0.5 h at 0°C and for 45 min at room temperature. The reaction mixture was poured into 1 N aq. NaOH solution (5 mL) and the organic material was extracted with ether, washed with cold 1 n aq HCl solution (3 mL), sat aq $NaHCO_3$ solution (3 mL) and finally with brine (5 mL). The organic layer was dried over anhyd $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure. The crude product was directly analyzed by ^1H NMR spectroscopy in the presence of $Cl_2CHCHCl_2$ (10 mL) as an internal standard indicating a 96% yield of the aldol products with an anti/syn ratio of 33/1. The two isomers were separated by preparative TLC (hexane/ether, 10/1) to give 118.1 and 3.7 mg of anti and syn aldol products, respectively. The pure anti isomer was converted to acetyl derivative (Ac_2O, pyridine and DMAP, 4°C, 12 h) and the corresponding acetate was analyzed by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$. 93.0% ee (97.9% ee, corrected for 95.6% ee of (*S,S*)-**3-21**) was obtained.

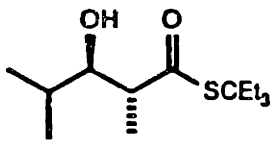
Alcohol: R_f 0.69 (pentane/ether, 4/1); IR ($CHCl_3$) 3490 (br), 2958, 1653, 1451; ^1H NMR δ 0.85 (9H, t, *J*=7.4 Hz), 0.90 (3H, t, *J*=6.8 Hz), 1.29~1.50 (4H, m), 1.76 (6H, q, *J*=7.4 Hz), 2.54 (1H, of ABX, *J*=8.5, 15.7 Hz), 2.64 (1H, ABX, *J*=3.6, 15.8 Hz), 2.75 (1H, br s), 3.98 (1H, m): MS (EI) m/e (rel intensity), 242 (M^+ - H2O), 227 (4.9), 163 (73.8), 144 (24.9), 129 (76.1), 111

(79.3), 99 (100), 98 (100), 57 (100); HRMS m/e calcd for $C_{14}H_{28}O_2S$ 260.1810, found 260.1810.

Acetate: ^{1}H NMR δ 0.84 (9H, t, *J*=7.4 Hz), 0.89 (3H, t, *J*=7.3 Hz), 1.25~1.41 (1H, m), 1.52~1.60 (1H, m), 1.74 (6H, q, *J*=7.5 Hz), 2.01 (3H, s), 2.63 (1H, ABX, *J*=5.5, a4.6 Hz), 2.71 (1H, ABX, *J*=7.3, 14.7 Hz), 5.19 (1H, m).

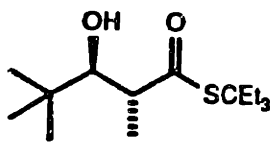
Spectral Data for Other Propanethioate aldol Products

S-3-(3-Ethyl)pentyl (2*R*,3*R*)-2,4-dimethyl-3-hydroxypentanethioate



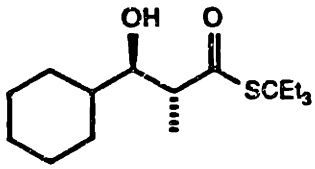
IR ($CHCl_3$) 3520 (br), 2965, 1650, 1452; ^{1}H NMR δ 0.85 (9H, t, *J*=7.4 Hz), 0.92 (3H, d, *J*=7.1 Hz), 0.94 (3H, d, *J*=7.0 Hz), 1.21 (3H, d, *J*=7.2 Hz), 1.71 (1H, m), 1.75 (6H, q, *J*=7.4 Hz), 2.46 (1H, d, *J*=8.3 Hz), 2.77 (1H, dq, *J*=7.0, 7.2 Hz), 3.26 (1H, m).

S-3-(3-Ethyl)pentyl (2*R*,3*S*)-2,4,4-trimethyl-3-hydroxypentanethioate



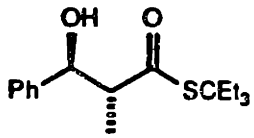
IR ($CHCl_3$) 3485 (br), 2963, 1648, 1450; ^{1}H NMR δ 0.85 (9H, t, *J*=7.5 Hz), 0.92 (9H, s), 1.37 (3H, d, *J*=7.3 Hz), 1.74 (6H, q, *J*=7.6 Hz), 2.82 (1H, dq, *J*=1.1, 7.2 Hz), 3.13 (1H, d, *J*=1.1 Hz).

S-3-(3-Ethyl)pentyl (2*R*,3*R*)-2-methyl-3-cyclohexyl-3-hydroxypropanethioate



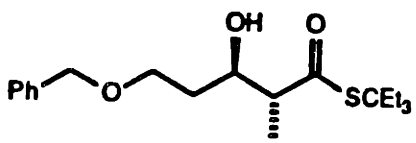
IR ($CHCl_3$) 3480 (br), 2965, 1648, 1445; ^{1}H NMR δ 0.86 (9H, t, *J*=7.6 Hz), 0.96~1.86 (11H, m), 1.23 (3H, d, *J*=7.3 Hz), 1.75 (6H, q, *J*=7.5 Hz), 2.48 (1H, d, *J*=9.0 Hz), 2.80 (1H, dq, *J*=5.0, 7.1 Hz), 3.24 (1H, ddd, *J*=5.0, 6.6, 8.7 Hz).

S-3-(3-Ethyl)pentyl (2*R*,3*S*)-2-methyl-3-hydroxy-3-phenylpropanethioate



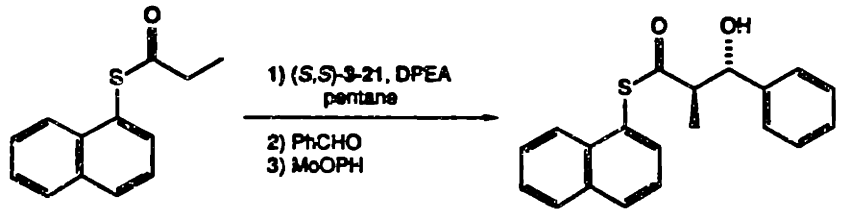
^{1}H NMR δ 0.82 (9H, t, *J*=7.5 Hz), 1.03 (3H, d, *J*=7.0 Hz), 1.75 (6H, q, *J*=7.5 Hz), 2.78 (1H, d, *J*=5.0 Hz), 2.90 (1H, m), 4.72 (1H, dd, *J*=5.2, 7.7 Hz), 7.25~7.36 (5H, m).

S-3-(3-Ethyl)pentyl (2*R*,3*R*)-2-methyl-3-hydroxy-5-benzyloxypentanethioate



^{1}H NMR δ 0.85 (9H, t, *J*=7.4 Hz), 1.16 (3H, d, *J*=7.2 Hz), 1.76 (6H, q, *J*=7.4 Hz), 1.69~1.81 (2H, m), 2.66 (1H, dq, *J*=6.7, 6.8 Hz), 3.11 (1H, d, *J*=5.3 Hz), 3.60~3.70 (2H, m), 3.84~3.94 (1H, m), 4.49 (2H, s), 7.25~7.33 (5H, m).

Aldol Reaction with 1-Naphthylthiol propanethioate (3-51b)

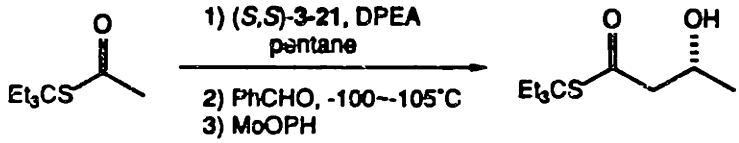


3-51b

To a magnetically stirred solution of thiol ester **3-51b** (108 mg, 0.5 mmol) and DPEA (105 mL, 0.6 mmol) in dichloromethane (3 mL) was added boron triflate **3-21** (124 mL, 0.6 mmol) at -78°C. The mixture was stirred for 10 min at -78°C and 1.5 h at 0°C. Benzaldehyde (76 mL, 0.75 mmol) was added to the cooled (-78°C) mixture and stirring was continued for 4.5 h. After usual workup with MoOPH, solvent-free crude product was analyzed with ^{1}H NMR in the presence of $ClCH_2CH_2Cl$ (10 mL) as an intenal standard to give 82% yield of aldol products with anti/syn ratio of 4/96. Separation of the major syn isomer on the prep TLC (hexane - ether, 4/1) followed by ^{1}H NMR analysis of the corresponding acetate (Ac_2O, DMAP and pyridine, 4°C, 12 h) indicated 9.6% ee of 2*R*,3*R* aldol product (10% ee, corrected for the purity of the triflate, 95.9% ee).

^{1}H NMR of the alcohol, δ 1.34 (3H, d, *J*=7.2 Hz), 2.65 (1H, d, *J*=2.9 Hz), 3.20 (1H, dq, *J*=7.2, 4.9 Hz), 5.11 (1H, dd, *J*=4.8, 2.6 Hz), 7.36~7.95 (12H, m); ^{1}H NMR of acetate δ 1.38 (3H, d, *J*=6.9 Hz), 2.09 (3H, s), 3.39 (1H, dd, *J*=8.4, 6.9 Hz), 6.1 (1H, d, *J*=8.1 Hz), 7.33~7.90 (12H, m).

Typical Procedure for Ethanethioate Aldol Reactions using (*S,S*)-3-21

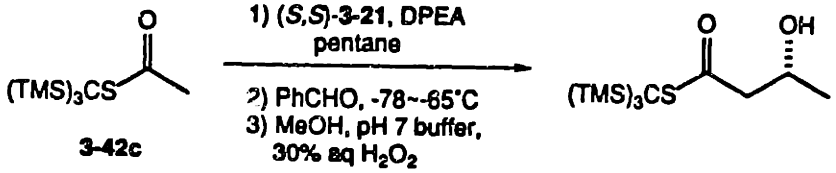


To a magnetically stirred solution of **3-37c** (87 mg, 0.5 mmol) and diisopropylethylamine (105 mL, 0.6 mmol) in pentane (3 mL) was added the borolanyl triflate 3-21 (146 mg, 0.6 mmol) at -78°C. Stirring was continued for 30 min at -78°C and 1 h at 0°C. The mixture was cooled (-100~-105°C, EtOH/liq N_2) and benzaldehyde (80 mg, 0.75 mmol) was added. The mixture was stirred for 4 h at the temperature. The usual workup with MoOPH followed by purification on a preparative TLC (hexane/ether, 4/1, R_f 0.44) afforded 109.4 mg (78% yield) of product as a colorless oil. ^1H NMR analysis of the corrsponding acetyl derivative (Ac_2O, DMAP, and pyridine, 4°C, 12 h) in the presence of Eu(hfc)3 (0.4 equiv) indicated 89.0% ee (92.8% ee, corrected for 95.9% ee of) of (3*S*)-hydroxy ester.

Alcohol: R_f 0.44, pentane/ether (4/1); IR (film) 3440 (br), 3065,3030, 2865, 1673, 1452; ^1H NMR δ 0.84 (9H, t, *J*=7.4 Hz), 1.76 (6H, q, *J*=7.4 Hz), 2.81 (1H, ABX, *J*=4.3, 15.4 Hz), 2.89(1H, ABX, *J*=8.0, 15.8 Hz), 3.13 (1H, d, *J*=3.1 Hz), 5.10 (1H, m), 7.25~7.34 (5H, m); MS (EI, 40 eV) m/e (rel intensity), 280 (M^+, 1.2), 252 ($M^+ - H_2O$), 0.73), 181 (6.7), 165 (3.6), 105 (40.0), 77 (34.6), 69 (27.6), 57 (100); HRMS m/e calcd for $C_{16}H_{24}O_2S$ 280.1497, found 280.1497.

Acetate: ^1H NMR δ 0.80 (9H, t, *J*=7.4 Hz), 1.73 (6H, q, *J*=7.4 Hz), 2.03 (3H, s), 2.81 (1H, ABX, *J*=5.3, 15.1 Hz), 3.08 (1H, ABX, *J*=9.1, 14.7 Hz), 6.13 (1H, dd, *J*=5.2, 9.1 Hz), 7.27~7.33 (5H, m).

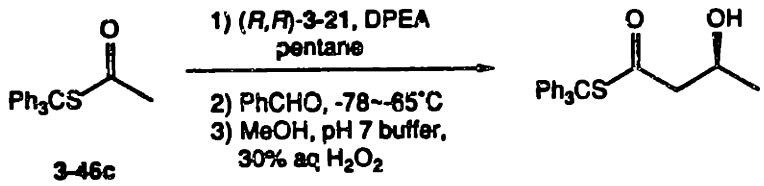
Aldol Reaction of S-Tris(trimethylsilyl)methyl Ethanethioate (3-42c) with 3-21



To a magnetically stirred solution of the ethanethioate **3-42c** (74 mg, 0.241 mmol) and diisopropylethylamine (46 mL, 0.265 mmol) in pentane (3 mL) was added (*S,S*)-**3-21** (65 mg, 0.265 mmol) at -78°C. Stirring was continued for 10 min and the mixture was warmed to 0°C and stirred for 1 h. To the recooled reaction mixture (-78°C) benzaldehyde (37 mL, 0.362 mmol) was added and stirring was continued for 18 h at -78~-65°C. Then the reaction was quenched with MeOH (0.8 mL) and pH 7 phosphate buffer (0.8 mL). The mixture was warmed to room temperature and 30% aq H_2O_2 (0.4 mL) was added. After 2 h vigorous stirring, the mixture was extracted with ether (2 x 5 mL) and the ethereal layer was dried ove anhyd MgSO4. Concentrated crude product was purified on a preparative TLC (1000μ, 20 x 20 cm, hexane/ether, 7/1, two times developing) to afford 17 mg (17% yield) of a white needle. ^1H NMR spectrum of the (*R*)-MTPA ester of the product alcohol prepared in the usual manner exhibited 62% ee.

^1H NMR of alcohol; δ 0.22 (9H, s), 2.92 (1H, AB**X**, *J*=15.6, 4.4 Hz), 3.02 (1H, A**B**X, *J*=15.6, 8.2 Hz), 3.15 (1H, d, *J*=2.8 Hz, -OH), 5.11 (1H, m), 7.25~7.42 (5H, m); MS (EI, 40 eV) m/e (rel intensity), 397.5 ($M^+ - CH_3$), 379.6 (4.3), 292.3 (49.6), 264.3 (19.9), 233.3 (53.4), 221.3 (51.0), 175.2 (71.1), 161.2 (90.4), 105 (92.6), 73 (100); HRMS m/e calcd for ($M^+ - CH_3$) 397.1509, found 397.1509.

Aldol Reaction of *S*-Triphenylmethyl ethanethioate using 3-21



To a magnetically stirred soltuion of *S*-triphenylmethyl ethanethioate **3-46c** (159 mg, 0.5 mmol) and the diisopropylethylamine (105 mL, 0.6 mL) in toluene (3 mL) was added (*R,R*)-3-21 (183 mg, 0.6 mL) at -78°C. Then the mixture was stirred for 30 min at 0°C. To the recooled flask was added benzaldehyde (76 mL, 0.75 mmol) and stirring was continued for 4 h. After usual oxidatve workup (pH 7 buffer, MeOH, and H_2O_2), the crude product was purified on a prparative TLC (silica gel, 1000μ, 20 x 20 cm, hexane/ether, 1/1) to afford 210 mg (99% yield) of a white solid.

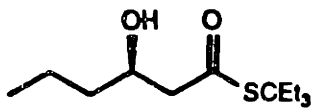
^{1}H NMR δ 2.89 (1H, d, *J*=4.0 Hz, -OH), 2.97 (1H, A**B**X, *J*=15.6, 3.9 Hz), 3.05 (1H, A**B**X, *J*=15.6, 8.0 Hz), 5.13 (1H, ddd, *J*=8.0, 4.0, 3.9 Hz), 7.24~7.45 (20H, m); MS (EI, 38 eV) m/e (rel intensity) 243 (Ph_3C^+, 84.5), 165 (100), 105 (24.9); HRMS m/e calcd for Ph_3C^+ 243.1174, found 243.1174.

A fraction of the alcohol was derivatized with (*S*)-MTPACl (DMAP, pyridine) and ^{1}H NMR analysis of the corresponding MTPA ester showed 87.4% ee (89.0% ee, corrected for the purity of the triflate, 98.2% ee).

^{1}H NMR of the MTPA ester, δ 2.99 (1H, A**B**X, *J*=15.6, 6.5 Hz), 3.23 (1H, A**B**X, *J*=15.5, 7.7 Hz), (3H, s), 6.30 (1H, dd, *J*=7.7, 6.6 Hz), 7.10~7.39 (25H, m).

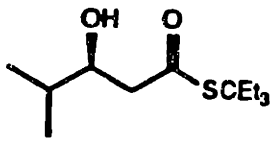
Spectral Data for Other Ethanethioate Aldol Products

S-3-(3-Ethyl)pentyl (3*R*)-3-hydroxyhexanethioate



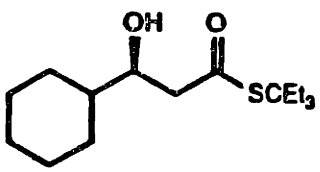
IR ($CHCl_3$) 3540 (br), 3010, 2860, 1658; ^1H NMR δ 0.85 (9H, t, *J*=7.4 Hz), 0.90 (3H, t, *J*=6.8 Hz), 1.29~1.50 (4H, m), 1.76 (6H, q, *J*=7.5 Hz), 2.54 (1H, ABX, *J*=8.5, 15.7 Hz), 2.64 (1H, ABX, *J*=3.6, 15.8 Hz), 2.75 (1H br s), 3.98 (1H, m).

S-3-(3-Ethyl)pentyl (3*R*)-3-hydroxy-4-methylpentanethioate



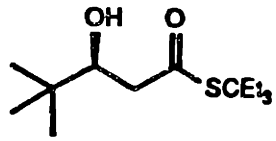
IR ($CHCl_3$) 3515 (br), 2962, 1660; ^1H NMR δ 0.85 (9H, t, *J*=7.4 Hz), 0.89 (3H, d, *J*=6.3 Hz), 0.91 (3H, d, *J*=6.7 Hz), 1.71 (1H, m), 1.76 (6H, q, *J*=7.5 Hz), 2.53 (1H ABX, *J*=9.1, 15.7 Hz), 2.63 (1H, ABX, *J*=3.0, 15.3 Hz), 2.72 (1H br s), 3.74 (1H, m)

S-3-(3-Ethyl)pentyl (3*R*)-3-hydroxy-3-cyclohexylpropanethioate



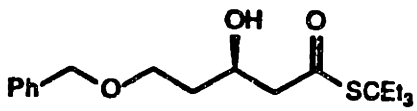
IR ($CHCl_3$) 3500 (br), 2918, 1655; ^1H NMR δ 0.85 (9H, t, *J*=7.4 Hz), 0.94~1.83 (11H, m), 1.75 (6H, q, *J*=7.2 Hz), 2.54 (1H, ABX, *J*=8.7Hz, 15.8 Hz), 2.65 (1H, ABX, *J*=2.9, 15.9 Hz), 2.69 (1H, d, *J*=4.6 Hz), 3.73 (1H, m).

S-3-(3-Ethyl)pentyl (3*R*)-3-hydroxy-1,4-dimethylpentanethioate



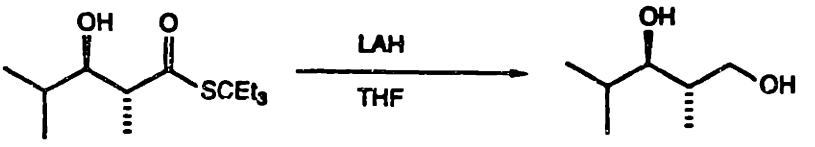
^{1}H NMR δ 0.82 (9H, t, *J*=7.4 Hz), 0.89 (9H, s), 1.77 (6H, q, *J*=7.4 Hz), 2.45 (1H, ABX, *J*=11.3, 15.8 Hz), 2.67 (1H, ABX, *J*=1.1, 15.7 Hz), 2.70 (1H, d, *J*=2.8 Hz), 3.67 (1H, m).

S-3-(3-Ethyl)pentyl (3*R*)-3-hydroxy-5-benzyloxypentanethioate



^{1}H NMR δ 0.85 (9H, t, *J*=7.4 Hz), 1.68~1.86 (2H, m), 1.75 (6H, q, *J*=7.4 Hz), 2.63 (2H, m), 3.24 (1H br s), 3.59~3.68 (2H, m), 4.21 (1H, m), 4.49 (2H, s), 7.24~7.33 (5H, m).

Representative Procedure for Reduction of Aldol Products to Diols

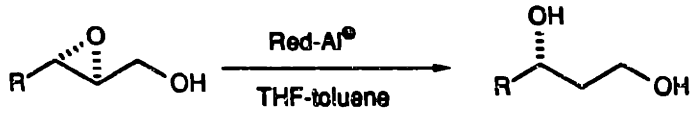


3-57 3-65a

To the aldol product 3-57 (R = i-Pr) (102 mg, 0.392 mmol) in THF (10 mL) was added an LAH solution in ether (1.15 M, 1.02 mL) at 0°C with stirring. After 2 h, excess LAH was decomposed by dropwise addition of 3% H_2O in THF with vigorous stirring. After 30 min one drop of water was added to the mixture to ensure that no trace of hydride existed. Celite (1.5 g) was added to the gelatinous suspension and stirring ws continued for another 30 min. Then the mixture was filtered through a Celite bed (~2 cm) and the filtered material was washed with THF (3 x 20 mL). Removal of solvent followed by flash chromatography (silica gel, hexane/ether, 1/2) and bulb-to-bulb distillation provided 42 mg (81% yield) of a colorless oil.

bp (T_b) 100-105°C/0.5 mmHg; $[\alpha]^{22}_D$ +19.6°, $[\alpha]^{22}_D$ +56.3° (*c* 0.750, $CHCl_3$); Rf 0.48, ether; IR ($CHCl_3$) 3608, 3490 (br), 2955; ^1H NMR δ 0.84 (3H, d, *J*=6.8 Hz), 0.87 (3H, d, *J*=6.6 Hz), 0.93 (3H, d, *J*=7.1 Hz), 1.81 (1H, m), 2.95 (2H, br s), 3.32 (1H, dd, *J*=3.9, 7.8 Hz), 3.60 (1H, ABX, *J*=7.0, 10.7 Hz), 3.73 (1H, ABX, *J*=3.7, 10.7 Hz); MS (EI, 22 eV) m/e (rel intensity), 115 (M^+ - OH), 91 (3.7), 83 (7.1), 69 (6.8), 57 (9.5), 43 (100); HRMS m/e calcd for (M^+ - H_2O) 114.1045, found 114.1045.

Synthesis of Diols by Red-Al® Reductions of 2,3-epoxyalcohols 3-69



3-69 3-66b

To a solution of an epoxide **3-69** (1.5 mmol) in THF (20 mL) at 0°C was added 1.1 mL (3.75 mmol) of a solution of Red-Al (3.4 M) in toluene. The solution was allowed to warm to 25°C and then stirred for 18 h. To the mixture was added methanol (2 mL) and water (1 mL) and stirring was continued for 30 min. The mixture was diluted with ether (30 mL) and anhyd magnesium sulfate was added with vigorous stirring. Filtration and concentration *in vacuo* afforded an oil which was purified by flash column chromatography (silica gel, hexane/ethyl acetate, 2/1--1/1).

Table 5.5 Synthesis of Diols **3-65b**.

Entry [a,b]	R	Yield[c,d]
1	n-Pr-	84%
2	i-Pr-	96%
3	t-Bu-	87%[e]
4	c-C6H11-	79%
5	Ph-	77%[f]
6	$PhCH_2OCH_2CH_2$-	81%

a. For the preparation of 2,3-epoxyalcohols, see ref 101.

b. For the Red-Al reduction of 2,3-epoxyalcohols, see ref 103.

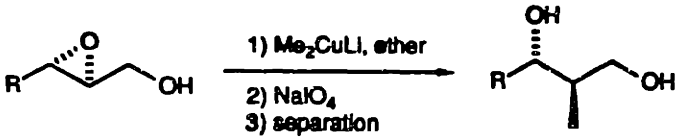
c. For specific rotation values, see Table 3.6 in the text.

d. Spectroscopic data were identical with those obtained from the aldol reactions.

e. mp 48°C.

f. The crude product contained ~10% of the 1,2-diol by ^1H NMR and the mixture was treated with $NaIO_4$ as described for diols **3-65b** and **3-70**.

Synthesis of Diols **3-65b** by Addition of $LiCuMe_2$ to 2,3-Epoxyalcohols **3-69**



3-69 **3-65b**

To a solution of the epoxide **3-69** (2 mmol) in ether (15 mL) was added at -20°C a soluiton of $LiCuMe_2$ (2.5 mmol) in ether (20 mL). The reaction ws followed by TLC (hexane/ethyl acetate, 1/1). When the reaction was complete (see below for reaction conditions), 10% NH_3 in sat aq NH_4Cl (20 mL) was added and stirring was continued for 2 h in the presence of oxygen. The colorless organic layer was separatd and the dark blue aqueous phase was extracted with three portions of ether (25 mL). The combined organic layer was washed with brine, dried over anhyd Na_2SO_4 and concentrated *in vacuo*. The 1,2-diol present in the product mixture was removed by treating with $NaIO_4$ (426 mg, 2 mmol) in aqueous THF (20 mL, 1/1) for 2 h. The aqueous phase was saturated with sodium chloride and the mixture was extracted with ether. The combined organic layer was dried over sodium sulfate, concentrated under reduced pressure, and purified on a chromatographic column (silica gel, hexane/ethyl acetate, 5/1–1/1).

Table 5.6 Synthesis of Diols **3-65b**.

Entry[a,b]	R	Reaction Condition	Yield[c,d]
1	$CH_3CH_2CH_2$-	-20℃, 0.5 h	37%
2	$(CH_3)_2CH$-	-20℃ to 0℃, 8 h	75%[e]
3	$(CH_3)_3CH$-	20℃, 18 h	92%[f]
4	c-C_6H_{11}-	-20℃ to 20℃, 18 h	52%[g]
5	$PhCH_2OCH_2CH_2$-	-20℃, 1.5 h	58%

a. For the cuprate opening of 2,3-epoxyalcohols, see ref 102.

b. Only 1,2-diol was obtained from 3-phenylglycidol.

c. For specific rotations, see Table 3.5 in the text.

d. Spectroscopic data are identical with those obtained for **3-65a**.

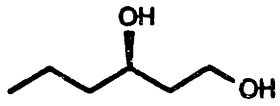
e. mp 42℃.

f. mp 39℃.

g. mp 58℃.

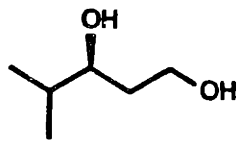
Physical data for 1,3-diols

(3*R*)-1,3-Hexanediol



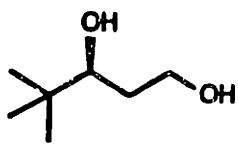
R_f 0.26 (ether); bp (Tb) 89-95°C (0.5 mmHg); $[a]^{21.5}_{365}$ -6.22° (*c* 0.402, $CHCl_3$); IR ($CHCl_3$) 3610, 3510 (br), 2950, 2928; ^1H NMR d 0.91 (3H, t, *J*=7.0 Hz), 1.30~1.49 (4H, m), 1.60~1.72 (2H, m), 2.43 (2H, br s), 3.79~3.91 (3H, m).

(3*S*)-4-Methyl-1,3-pentanediol



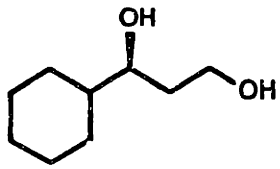
R_f 0.28 (ether); bp (T_b) 90-100°C (0.5 mmHg); $[\alpha]^{21.5}_D$ -13.8°, $[\alpha]^{21.5}_{365}$ -43.1° (*c* 0.448, $CHCl_3$); IR ($CHCl_3$) 3720, 3495 (br), 2960; ^1H NMR δ 0.91 (3H, d, *J*=6.8 Hz), 0.93 (3H, d, *J*=5.9 Hz), 1.62~1.71 (3H, m), 2.23 (2H, br s), 3.61 (1H, m), 3.79~3.93 (2H, m); MS (EI, 38 eV) m/e (rel intensity), 101 (M^+-OH, 11.5), 100 (M^+-H_2O, 4.6), 85 (9.2), 83 (21.1), 75 (85.1), 59 (41.0), 57 (83.7), 42 (100); HRMS m/e calcd for (M^+ - H_2O) 100.0888, found 100.0888.

(3*S*)-4,4-Dimethyl-1,3-pentanediol



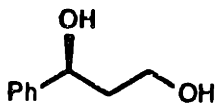
R_f 0.37 (ether); bp (T_b) 95-100°C (0.6 mmHg); $[\alpha]^{21.5}_D$ -15.2°, $[\alpha]^{21.5}_{365}$ -48.5° (*c* 0.830, $CHCl_3$); IR ($CHCl_3$) 3730, 3492 (br), 2948; ^1H NMR δ 0.88 (9H, s), 1.54~1.68 (2H, m), 2.74 (2H, br s), 3.46 (1H, dd, *J*=2.2, 10.6 Hz), 3.82 (2H, m); MS (EI, 26 eV) m/e (rel intensity), 115 (M^+ - OH, 3.7), 83 (17), 75 (33.7), 57 (72.3), 40 (100); HRMS m/e calcd for $C_7H_{16}O_2$ 132.1150, found 132.1150.

(3*S*)-3-Cyclohexyl-1,3-propanediol



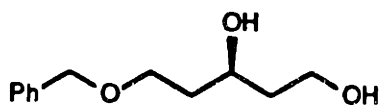
R_f 0.33 (ether); bp (T_b) 98-103°C (0.4 mmHg); $[\alpha]^{21.5}_D$ -8.0°, $[\alpha]^{21.5}_{365}$ -24.0° (*c* 0.588, $CHCl_3$), IR (film) 3340, 2920, 2850, 1445, 1040; ^1H NMR δ 0.93~1.83 (13H, m), 2.43 (2H, br s). 3.59 (1H, ddd, *J*=6.1, 8.8, 10.3 Hz), 3.76~3.90 (2H, m); MS (EI, 26 eV) m/e (rel intensity), 158 (M^+, 0.6), 141 (M^+ - OH, 6.7), 140 (M^+ - H_2O, 8.8), 122 (7.8), 113 (18.7), 112 (17.2), 111 (14.2), 95 (25.3), 81 (35.6), 75 (100); HRMS m/e calcd for $C_9H_{18}O_2$ 158.1307, found 158.1308.

(3*S*)-3-Phenyl-1,3-propanediol



R_f 0.32 (ether); bp (T_b) 110-114°C; $[\alpha]^{21.5}_D$ -63.0°, $[\alpha]^{21.5}_{365}$ -212.6° (*c* 0.958, $CHCl_3$); IR (film) 3380, 3020, 2940, 1600, 1450, 1040, 745, 690; ^1H NMR δ 1.24~2.10 (2H, m), 2.31 (2H, br s), 3.86 (2H, dd, *J*=5.2, 5.8 Hz), 4.96 (1H, dd, *J*=3.9, 8.5 Hz), 7.25~7.36 (5H, m); MS (EI, 38 eV) m/e (rel intensity), 152 (M^+, 14.7), 134 (7.7), 107 (100), 105 (24.8), 79 (45.6); HRMS m/e calcd for $C_9H_{12}O_2$ 152.0837, found 152.0837.

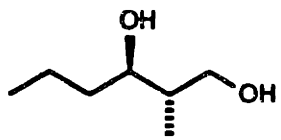
(3*S*)-5-Benzyloxy-1,3-pentanediol



R_f 0.18 (ether); $[\alpha]^{21.5}_D$ -11.6°, $[\alpha]^{21.5}_{365}$ -36.7° (*c* 0.735, $CHCl_3$); IR (film) 3400, 3030, 2890, 1450, 1360, 1020; ^1H NMR δ 1.66~1.95 (6H, m), 3.63~3.78 (2H, m), 3.83 (2H, dd, *J*=5.0, 6.2 Hz), 4.09 (1H, m), 4.51 (2H, s), 7.27~7.35 (5H, m); ^{13}C NMR δ 36.64, 38.50, 61.25, 68.87, 71.20, 73.34, 127.69, 128.48, 137.84; MS (EI, 38 eV) m/e (rel intensity), 192 (M^+-H_2O, 3.8),

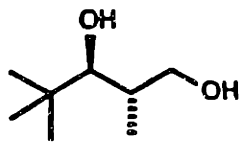
164 (4.1), 146 (9.5), 107 (32.4), 91 (100), 86 (24.5); HRMS m/e calcd for $M^+ - H_2O$ 192.1150, found 192.1150.

(2*S*,3*R*)-2-Methyl-1,3-hexanediol



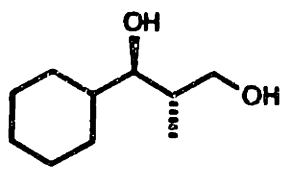
R_f 0.40 (ether); bp (T_b) 78-84°C (0.4 mmHg); $[\alpha]^{22.5}_D$ +33.6°, $[\alpha]^{22.5}_{365}$ +97.4° (*c* 1.04, $CHCl_3$); IR ($CHCl_3$) 3610, 3488 (br), 2965, 2938; ^1H NMR δ 0.91 (3H, d, *J*=7.2 Hz), 0.96 (3H, t, *J*=7.1 Hz), 1.34~1.76 (5H, m), 2.46 (1H (br s), 2.71 (1H, br s), 3.57 (1H, t, *J*=7.5 Hz), 3.64 (1H, dd, *J*=7.5, 10.7 Hz), 3.79 (1H, br d, *J*=10.3 Hz); MS (EI, 40eV) m/e (rel intensity), 115 (M^+-OH, 1.8), 97 (10.0), 89 (17.9), 73 (51.0), 71 (40.9), 55.0 (100); HRMS m/e calcd for M^+ - OH 115.1123, found 115.1123.

(2*S*,3*S*)-2,4,4-Trimethyl-1,3-pentanediol



R_f 0.61 (ether); bp (T_b) 101-105°C (0.5 mmHg); $[\alpha]^{22.0}_D$ -11.1°, $[\alpha]^{22.0}_{365}$ -32.4° (*c* 0.605, $CHCl_3$); IR ($CHCl_3$) 3680, 3500 (br), 2958; ^1H NMR δ 0.93 (9H, s), 1.03 (3H, d, *J*=7.1 Hz), 1.90 (1H, m), 2.92 (1H br s), 3.23 (1H, d, *J*=4.7 Hz), 3.62 (1H, dd, *J*=6.1, 11.0 Hz), 3.79 (1H, dd, *J*=3.1, 10.6 Hz); MS (EI, 25 eV) m/e (rel intensity), 129 (M^+ - OH), 113 (9.2), 89 (79.9), 87 (50.3), 71 (100); HRMS m/e calcd for ($M^+ - CH_3$ - OH) 113.0966, found 113.0967.

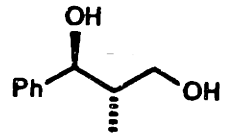
(2*S*,3*R*)-2-Methyl-3-cyclohexyl-1,3-pentanediol



R_f 0.49 (ether); bp (T_b) 98-104°C (0.4 mmHg); $[\alpha]^{22.5}_D$ +24.9°, $[\alpha]^{22.5}_{365}$ +73.6° (*c* 1.38,

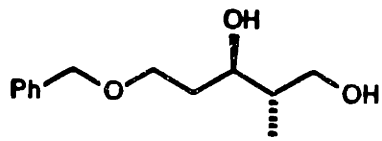
$CHCl_3$); IR ($CHCl_3$) 3720, 3500 (br), 2928, 2850; ^1H NMR δ 0.90 (3H, d, *J*=6.7 Hz), 1.08~1.91 (11H, m), 2.32 (1H, br s), 2.78 (1H, br s), 3.34 (1H, dd, *J*=3.6, 6.5 Hz), 3.64 (1H, dd, *J*=7.1, 10.0 Hz), 3.77 (1H, br d, *J*=10.5 Hz); MS (EI, 40 eV) m/e (rel intensity), 172 (M^+, 0.23), 154 (M^+-H_2O, 3.37), 113 (63.2), 95 (100), 89 (74.9), 83 (63.9), 71 (30.2), 55 (35.5); HRMS m/e calcd for $C_{11}H_{22}O_2$ 172.1463, found 172.1462.

(2*S*,3*R*)-2-Methyl-3-phenyl-1,3-propanediol



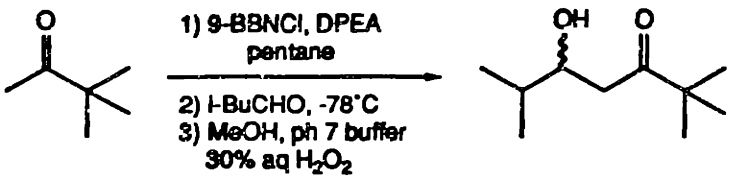
R_f 0.47 (ether); bp (T_b) 114-118°C (0.4 mmHg); $[\alpha]^{21.0}_D$ -46.8°, $[\alpha]^{21.0}_{365}$ -158.8° (*c* 0.34, $CHCl_3$); IR ($CHCl_3$) 3600, 3495 (br), 3000, 2960; ^1H NMR δ 0.68 (3H, d, *J*=7.0 Hz0, 1.96~2.09 (1H, m), 2.93 (2H, br s), 3.65~3.77 (2H, m), 4.52 (1H, d, *J*=8.4 Hz), 7.25~7.38 (5H, m); MS (EI, 38 eV) m/e (rel intensity), 166 (M^+, 3.0), 148 (14.6), 107 (100), 105 (44.6), 79 (33); HRMS m/e calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0995.

(2*S*,3*R*)-2-Methyl-5-hydroxy-1,3-pentanediol



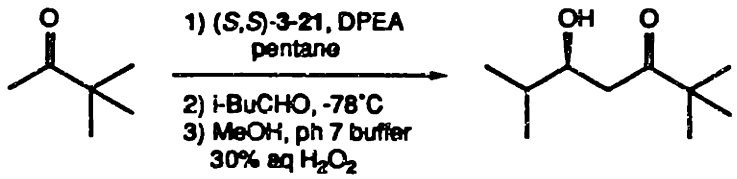
R_f 0.36 (ether); $[a]^{21.5}_D$ -3.13°, $[\alpha]^{21.5}_{365}$ -11.2° (*c* 0.735, $CHCl_3$); IR (film) 3400 (br), 3040, 2880, 1450, 1080, 1020, 730, 690; ^1H NMR δ 0.84 (3H, d, *J*=7.1 Hz), 1.67~1.86 (5H, m), 3.58~3.79 (5H, m), 4.51 (2H, s), 7.25~7.35 (5H, m); MS (EI, 40 eV) m/e (rel intensity), 206 (M^+-H_2O, 1.03), 165 (2.56), 147 (6.2), 146 (4.8), 118 (11.4), 107 (48.3). 91 (100); HRMS m/e calcd for (M^+ - H_2O) 206.1307, found 206.1306.

Representative procedure for the aldol reation using *B*-Chloro-9-BBN (3-83)



To a magnetically stirred solution of methyl t-Butyl ketone (66mL, 0.5 mmol) and diisopropylethylamine (100 mL, 0.58 mmol) in pentane (4 mL) at -78°C, was added a pentane solution of *B*-chloro-9-BBN (1.75 M, 350 mL, 0.613 mmol). The solution was allowed to warm to 0°C and stirring was continued for 2.5 h. To the recooled (-78°C) reaction mixture was added isobutyraldehyde (60 µL, 0.661 mmol) and it was stirred for 4 h at the temperature. MeOH (1.5 mL) and pH 7 phosphate buffer solution (1.5 mL) were added to the cold mixture and it was warmed to room temperature. 30% aq H_2O_2 (0.75 mL) was added and the mixture was stirred for 12 h. The organic material was extracted with ether (2 x 5 mL) and the ethereal solution was dried over anhyd MgSO4. Filtered solution was concentrated under reduced pressure and the resulting crude product was purified on a chromatographic column (silica gel, pentane/ether, 2/1) to afford 45.8 mg (53% yield) of the desired aldol product along with 43.3 mg (21%) of self-condensed product.

Representative Procedure for the Asymmetric Ketone Aldol Reaction using 2,5 dimethylborolanyl triflate (3-21)



To a magnetically stirred solution of methyl t-butyl ketone (37.5mL, 0.30mmol) and diisopropylethylamine (58 μL, 0.33 mmol) in pentane (3 mL) was added the triflate 3-21 (80 μL,0.36 mmol) at - 78°C. The mixture was warmed up to 0°C to give white precipitates and the stirring was continued for 2 h. The flask was cooled to -78°C and benzaldehyde (40 μL, 0.39 mmol) (Note 1.) was added. The mixture was stirred for 6 h at -78°C. Methanol (1 mL) and pH 7 phosphate buffer solution (1 mL) were added to the solution and the reaction mixture was warmed up to room temperature. 30% Aq hydrogen peroxide (0.5mL) was added and the reaction mixure was stirred vigorously for 1.5 h. The organic layer was extracted with ether (2 x 5 mL) and the combined ether solution was dried over anhyd $MgSO_4$.(Note 2.) Purification on a preparative TLC (silica gel, 20x20x0.1cm) gave 48 mg (78% yield) of a colorless oil. Rf 0.20 (hexane/ether = 4/1)

^{1}H NMR δ 1.11 (9H, s), 2.86 (2H, d, *J*=5.8Hz), 3.56 (1H, d, *J*=3.0Hz), 5.11 (1H, dt, *J*=3.0, 6.0Hz), 7.25-7.37 (5H, m).

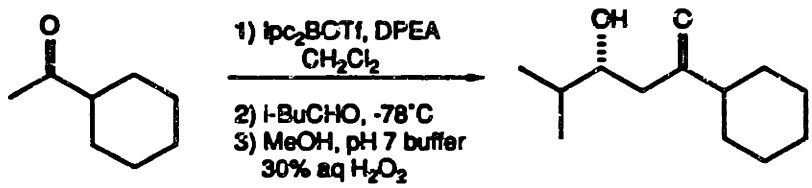
(*S*)-MTPA ester of the alcohol {(*R*)-MTPACl, DMAP, pyridine, room temperature, 24h} showed 26% ee (28% ee, corrected for the purity of 3-21, 94.1% ee) from the analysis of ^{1}H NMR.

Note 1. The use of an excess aldehyde is not necessary to complete the reaction.

Note 2. Alternative workup prosedures; (1) MoOPH (195mg, 1.5eq) was added to the cold (-78°C)

reaction mixture and it was stirred for 10 min at the temperature, 30 min at 0°C and 45 min at room temperature. Then the reaction mixture was poured into aq 1 N NaOH solution (3mL) and the organic phase was extracted with ether (5 mL), washed with cold 1 N HCl solution (3 mL), sat aq $NaHCO_3$ solution, and finally with brine. (2) The mixture was filtered through a filter chamber and to the filtrate was added 2-amino-2-methyl-1-propanol (57 µl., 2equiv). After stirring 30 min, the mixture was filtered (sometimes through silica gel bed) to afford a solution free from the aminoalcohol complex 3-58.

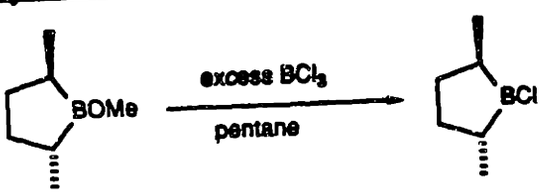
Representative Procedure of Ketone Aldol Reaction Using $(Ipc)_2BOTf$ (3-75)



To a magnetically stirred suspension of $(Ipc)_2BH$ (153 mg, 0.536 mmol) in CH_2Cl_2 (1 mL) was added TfOH (52 mL, 0.59 mmol) at 0°C. The solution was stirred at 0°C for 2.5 h and then the solvent was removed *in vacuo*. After adding pentane (1 mL) the mixture was cooled to -78°C and diisopropylethylamine (144 mL, 0.83 mmol) was added. Stirring was continued for 5 min and cyclohexyl methyl ketone (59 mL, 0.413 mmol) was added. The suspension was warmed to 0°C and stirred at the temperature for 4 h. Isobutyraldehyde (80 mL, 0.89 mmoL) was added and stirring was continued for 2 h. The reaction was quenched by adding MeOH (1.5 mL) and pH 7 phosphate buffer (1.5 mL), and 30% aq H_2O_2 (0.75 ml) and the mixture was stirred for 12 h at room temperature. The organic compounds were exracted with ether (2 x 5 mL) and the ethereal solution was dried over anhyd $MgCO_4$. Filtered solution was concentrated under reduced pressure and purification of the residue on a chromatographic column (silica gel, pentane/ether, 4/1, R_f=0.28) afforded 44 mg (54% yield) of the desired aldol

product as a colorless oil. HPLC analysis (5% ether/hexane, 2.0 mL/min) of the corresponding MTPA derivative of the alcohol indicated 77% ee.

Representative Procedure for the Preparation of Chloroborolanes: *B*-Chloro-2,5-dimethylborolane (3-86)



(*R,R*)-2-51 (*R,R*)-3-86

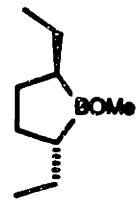
Trichloroborane (4 mL) was condensed into a graduated cylinder at -78°C. The cold bath was removed and trichloroborane was transferred to a 50 mL round-bottomed flask containing pentane (20 mL) cooled to -78°C. (*R,R*)-*B*-Methoxy-2,5-dimethylborolane (1.72 g, 13.65 mmol) was added via cannula with stirring and the raction mixture was allowed to warm to room temperature. Stirring was continued for 30 min. All the volatile material was removed by fractional distillation at atmospheric pressure and the residue was distilled under reduced pressure to furnish 1.51 g (85% yield) of a colorless oil.

bp 55-57°C/55 mmHg.

^{1}H NMR δ 1.06 (6H, br s), 0.95~1.28 (4H, m), 2.06 (2H, m); ^{13}C NMR δ 13.6, 33.5, 36.6 (br); ^{11}B NMR δ 81.1.

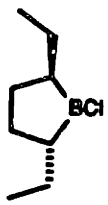
Physical Properties of Various Borolane Reagents

(*R,R*)-*B*-Methoxy-2,5-diethylborolane



1H NMR (C_6D_6) δ 0.8~0.9 (2H, m), 0.97 (6H, t, *J*=7.3 Hz), 1.18 (2H, m), 1.35 (2H, m), 1.64 (2H, m), 3.46 (3H, s); ^{13}C NMR (C_6D_6) δ 14.1, 22.9, 30.4, 34.0 (br), 54.7; ^{11}B NMR (C_6D_6) δ 57.4.

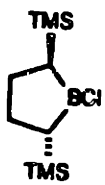
(*R,R*)-*B*-Chloro-2,5-diethylborolane (3-87)



(*R,R*)-3-87

bp (T_b) 63-65℃/20 mmHg; ^1H NMR δ 0.75~0.85 (2H, m), 0.95 (6H, t, *J*=7.2 Hz), 1.25 (2H, m), 1.42 (2H, m), 1.74 (2H, m), 2.10 (2H, m); ^{11}B NMR δ 81.2.

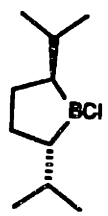
(±)-*B*-Chloro-2,5-bistrimethylsilylborolane



(±)-3-89

^1H NMR (C_6D_6) δ 0.09 (18 H, m), 1.05 (2H, m), 1.84 (4H, m); ^{13}C NMR (C_6D_6) δ -0.5, 29.4, 34.4 (br); ^{11}B NMR (C_6D_6) δ 77.2.

(*R,R*)-*B*-Chloro-2,5-diisopropylborolane ()

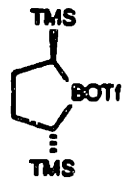


(*R,R*)-3-88

^1H NMR δ 0.85 (3H, d, *J*=6.8 Hz), 0.96 (3H, d, *J*=6.8 Hz), 0.88~0.97 (2H, m), 1.30~1.37 (2H, m), 1.91~1.96 (2H, m), 2.11~2.17 (2H, m); ^{13}C NMR δ 20.98 (-CH_3), 22.33 (-CH_3), 25.03 (-

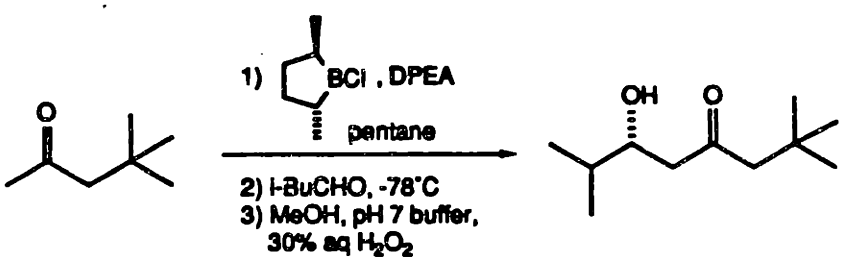
CH_2-), 27.30 (-CH-), 50.80 (-HC-B); ^{11}B NMR δ 80.7.

(±)-2,5-bis-Trimethylsilylborolanyl trifluormethanesulfonate



70% yield from *B*-methoxy-2,5-bistrimethylsilylborolane; bp (T_b) 75-80°C/0.2 mmHg; ^1H NMR (C_6D_6) δ 0.06 (18H, m), 1.01 (2H, m), 1.7 (4H, m); ^{13}C NMR (C_6D_6) δ -0.3, 26.1 (br), 28.0; ^{11}B NMR (C_6D_6) δ 64.5.

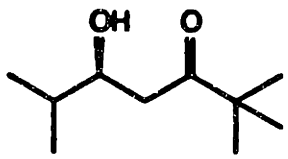
Ketone Aldol Reaction Using *B*-Chloro-trans-2,5-dimethylborolane (3-86)



To a magnetically stirred soltuion of 4,4-dimethyl-2-pentanone (70.5 μL, 0.5 mmol) and disiopropylethylamine (105 μL, 0.6 mmol) in pentane (2 mL), was added the chloroborolane **3-86** (100 μL, 0.7 mmol) at -78°C. Then the mixture was warmed to 0°C and stirring was continued for 100 min. To the recooled (-78°C) reaction mixture was added isobutyraldehyde (92 mL, 1.02 mmol) and the mixture was stirred for 3 h. An oxidative workup as above followed by column chromatography (silica gel, pentane/ether, 2/1) afforded 80 mg (86% yield) of the desired aldol product. HPLC analysis of the corresponding MTPA ester showed 60.0% ee (63.9% ee, corrected for the purity of the chloroborolane) of the product alcohol.

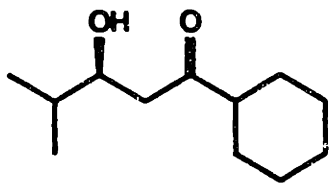
Physical Data for the Ketone Aldol Products

(5S)-5-Hydroxy-2,2,6-trimethylheptan-3-one



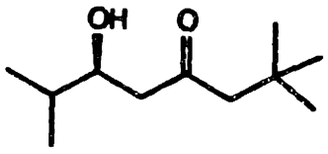
$[\alpha]^{22}_D$ -51.5° (*c* 1.19, CH_2Cl_2) for 81.6% ee (*S*)-alcohol; IR (film) 3540, 2980, 1710, 1490, 1380, 1080; ^1H NMR δ 0.92 (3H, d, *J*=6.8 Hz), 0.95 (3H, d, *J*=6.8 Hz), 1.15 (9H, s), 1.69 (1H, m), 2.51 (1H, dd, *J*=8.8, 17.6 Hz), 2.70 (1H, dd, *J*=17.6, 3.6 Hz), 3.21 (1H, d, *J*=4.0 Hz), 3.75 (1H, m); ^{13}C NMR 17.49, 18.26, 25.95, 32.77, 39.82, 48.80, 71.98, 217.33 MS (EI) m/e 154 (M^+-H_2O, 8.4), 97 (100); HRMS calcd for (M^+-H_2O) 154.1358, found 154.1357.

(3S)-5-Hydroxy-6-methyl-1-cyclohexylpentan-1-one



$[\alpha]^{22}_D$ -41.1° (*c* 3.80, CH_2Cl_2) for 81.6% ee (*S*)-alcohol; IR (film) 3540, 2950, 1710, 1465, 1380; ^1H NMR δ 0.91 (3H, d, *J*=6.8 Hz), 0.94 (3H, d, *J*=6.8 Hz), 1.26 (5H, m), 1.66 (2H, m), 1.82 (4H, m), 2.35 (1H, m), 2.50 (1H, dd, *J*=17.6, 10.8 Hz), 2.62 (1H, dd, *J*=17.6, 2.4 Hz), 3.12 (1H, d, *J*=2.4 Hz), 3.78 (1H, m); ^{13}C NMR 17.42, 18.13, 25.27, 25.55, 27.99, 32.84, 43.75, 51.10, 71.89, 215.18; MS (EI) m/e 180 (M^+-H_2O, 5.5), 155, 111, 83 (100); HRMS m/e calc for (M^+-H_2O) 180.1514, found 180.1513.

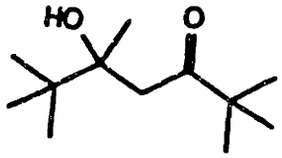
(6S)-6-Hydroxy-2,2,7-trimethyloctan-4-one



$[\alpha]^{22}_D$ -48.7° (c 1.52, CH_2Cl_2) for 81.6% ee (S)-alcohol; IR (film) 3500, 2980, 1710, 1480, 1360; ^1H NMR δ 0.94 (3H, d, *J*=6.8 Hz), 0.97 (3H, d, *J*=6.8 Hz), 1.06 (9H, s), 1.70 (1H, m), 2.38 (2H, s), 2.50 (1H, dd, *J*=16.4, 9.6 Hz), 2.61 (1H, dd, *J*=16.4, 3.2 Hz), 3.12 (1H, d, *J*=3.2 Hz), 3.83 (1H, m); ^{13}C NMR δ 17.78, 18.36, 29.71 31.08, 32.99, 48.25, 55.81, 72.23, 212.60; MS (EI) m/e 168 (M^+-H_2O, 0.9), 99, 97, 58, 57, 42 (100); HRMS m/e calcd for (M^+ - H_2O) 168.1514, found 168.1516.

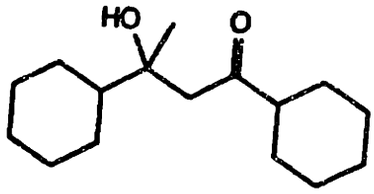
Physical Data for the Side Products of the Ketone Aldol Reactions

5-hydroxy-2,2,5,6,6-pentamethylheptan-3-one



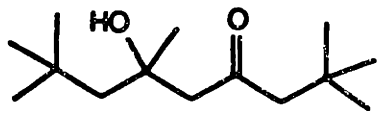
R_f 0.71 (pentane/ether, 4/1); IR (film) 3510, 2980.1695, 1375, 1275, 1090, 1015; ^1H NMR δ 0.96 (9H, s), 1.15 (12H, s), 2.47 (1H, d, *J*=16 Hz), 2.87 (1H, d, *J*=16 Hz), 4.63 (1H, s).

3-Hydroxy-3-methyl-1,3-dicyclohexylpropan-1-one



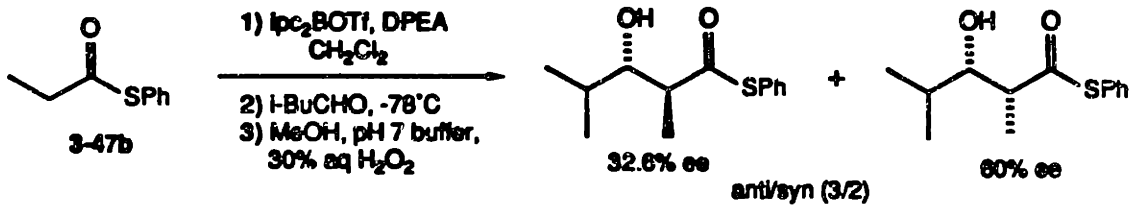
R_f 0.53 (pentane/ether, 4/1); IR (film) 3510, 2930, 1700, 1460, 1360, 1150; ^1H NMR δ 1.09 (3H, s), 1.24 (10H, m), 1.80 (11H, m), 2.31 (1H, m), 2.58 (2H, m), 4.16 (1H, s); MS (EI) m/e 234 (M^+-H_2O, 10.8), 169, 126, 111 (100).

6-Hydroxy-2,2,6,8,8-pentamethylnonan-4-one



Rf 0.68 (pentane/ether, 4/1); ^{1}H NMR δ 1.02 (18H, s), 1.30 (3H, s), 1.46 (1H, AB, *J*=14.0 Hz), 1.56 (1H AB, *J*=14.0 Hz), 2.30 (2H, s), 2.54 (1H, AB, *J*=16.8 Hz), 2.68 (1H, AB, *J*=16.8 Hz), 3.95 (1H, s).

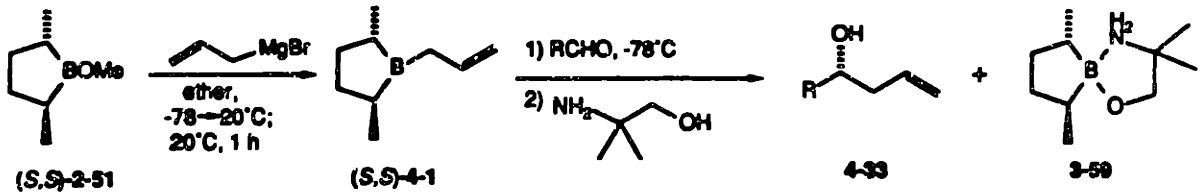
Aldol Reaction of S-Phenyl Propanethioate (3-47b) using $(Ipc)_2BOTf$ (3-75)



Triflic acid (83 μL, 0.934 mmol) was added dropwise to a magnetically stirred soltuion of $(Ipc)_2BH$ (243 mg, 0.85 mmol) in CH_2Cl_2 (2 mL) at 0°C and stirring was continued for 1 h. Diisopropylethylamine (228 μL, 1.316 mmol) was added and, after 10 min, the thioester (93 mL, 0.654 mmol) was added. The mixture was stirred for 5 h at 0°C. To the cooled (-78°C) mixture was added isobutyraldehyde (117 μL, 1.27 mmol). The mixture was warmed to 0°C and stirring was continued for 2 h. After usual oxidative workup {MeOH (2.5 mL), pH 7 buffer (2.5 mL), and 30% aq H_2O_2 (1.25 mL)} column chromatography (silica gel, CH_2Cl_2/MeOH, 98/2) gave 113 mg (72% yield) of a colorless oil. HPLC analysis (5% ether/hexane, 2.0mL/min) of the corresponding MTPA ester indicated syn/anti ratio of 2/3 and 60% ee for the syn- and 32.6% ee for the anti- diastereomer.

Alcohol R_f=0.27 (pentane/ether, 4/1); IR (film) 3500, 1700, 1450, 950; ^{1}H NMR δ 0.92 (3H, d, *J*=6.8 Hz), 1.05 (3H, d, *J*=6.8 Hz), 1.30 (3H, d, *J*=8.0 Hz), 1.77 (1H, m), 2.37 (1H, d, *J*=2.8 Hz), 2.97 (1H, dq, *J*=8.0, 4.0 Hz), 3.65 (1H, m), 7.42 (5H, m).

A Representative Procedure for the Allylboration using (*S,S*)-4-1

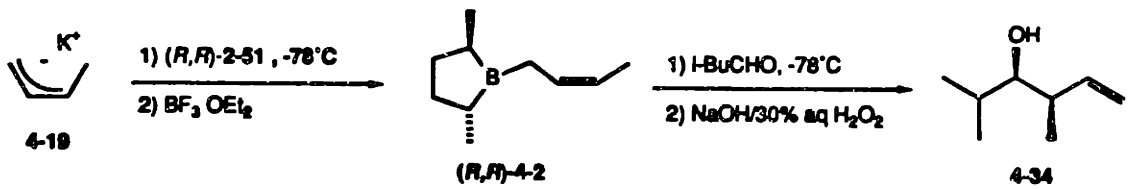


To a magnetically stirred solution of (*S,S*)-*B*-methoxy-2,5-dimethylborolane (*S,S*)-2-51 (0.234 g, 1.86 mmol) in ether (4 mL) was added an ethereal solution of allylmagnesium bromide (1.28 M, 1.32 mL, 1.69 mmol) at -78°C and stirring was continued for 15 min. Formation of a white precipitate was observed upon addition of the Grignard reagent. The mixture was warmed up to 20°C and stirred for 1 h at the temperature. Isobutyraldehyde (0.122 g, 1.69 mmol) was added dropwise to the recooled (-78°C) suspension and the mixture was stirred for 1 h. It was then slowly warmed to room temperature over 1 h. 2-Amino-2-methylpropanol (190 μL, 2.00 mmol) was added and the mixture was stirred for 1 h. All the volatile material was vacuum-transferred (40-50°C, 0.5-1.0 mmHg) and the remaing residue was washed with pentane (2 x 10 mL) and filtered. To the combined solution was added decane (112 mg) as an internal standard. Capillary GC analysis of the solution indicated 71.5% yield of the homoallylic alcohol. The solution was concentrated by fractional distillation through a Vigreux column (~30 cm) to ca. 1.0 mL and the residue was purified on a chromatographic column (silica gel, ether/pentane, 1/4). Solvents were removed from the fractions containing alcohol by fractional distillation and bulb-to bulb distillation of the residue *in vacuo* afforded 81 mg (42% yield) of pure homoallylic alcohol. $[\alpha]^{21.5}_{D}$ -1.74 (*c* 3.86, benzene); ^{1}H NMR δ 0.93 (3H, d, *J*=6.9 Hz), 0.95 (3H, d, *J*=6.9 Hz),

J=6.9 Hz), 1.65~1.76(2H, m), 2.05~2.37 (2H, m), 3.38~3.69 (1H,m), 5.11~5.18 (2H, m), 5.77~5.93 (1H, m).

HPLC analysis of the corresponding (*S*)-MTPA derivative {(*R*)-MTPACl, DMAP, pyridine, room temperature, 12 h} indicated 79.0% ee (85.1% ee, corrected for the purity of (*S,S*)-**2-51**) of (*S*)-alcohol derivative. (Retention time 38.2, 41.3 min for (*R*)- and (*S*)-alcohol derivatives, respectively, 0.3% ether/hexane, Chemcosorb Si60, 1.5 mL/min).

Reaction of (*R,R*)-**4-2** with an Achiral Aldehyde: A Representative Procedure with oxidative workup



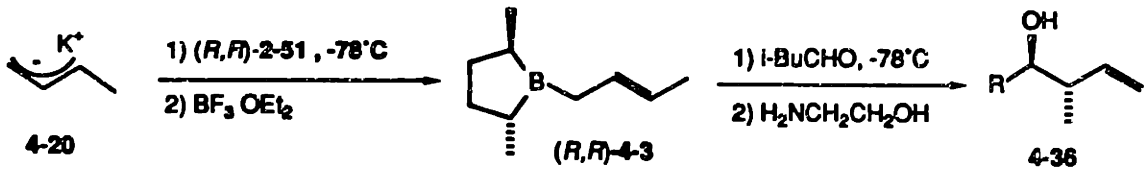
To a magnetically stirred soltuion of KO^{t}Bu (82 mg, 0.73 mmol) and *cis*-2-butene (0.18 mL, 2 mmol) in THF (0.8 mL) at -78°C, was added a hexane solution of n-BuLi (270 mL, 0.73 mmol). The resuting yellow-orange solution was stirred for 0.5 h at -50°C and recooled to -78°C. Methoxyborolane (*R,R*)-**2-51** (80 mL, 0.52 mmol) was added dropwise and the mixture was stirred for 0.5 h. BF_3·Et_2O (94 μL, 0.77 mmol) was added and, after 5 min stirring, isobutyraldehyde (70 μL, 0.765 mmol) was added dropwise. Stirring was continued for 3.5 h. 3 N NaOH (0.5 mL) and 30% aq H_2O_2 (0.3 mL) were added and the mixture was warmed to room temperature. After 0.5 h stirring, it was heated to 50-60°C for 1 h. To the recooled (20°C) solution were added ether (20 mL) and decane (25 μL). The organic layer was separated, dried over anhyd $MgSO_4$, and filtered. Capillary GC analysis of the filtrate indicated a 70% yield of a mixture of syn- and anti- alcohols in a ratio of 96/4. HPLC analysis of the bis-(*S*)-MTPA derivative of the corresponding 1,3-diol prepared as above indicated 91% ee (93% ee, corrected for the

purity of the starting methoxyborolane) of the major syn- isomer.

The crude 1,3-diol was purified on a chromatographic column (silica gel, ether, R_f=0.45). $[\alpha]^{25}_D$ -7.54° (*c* 0.83, $CHCl_3$); lit $[\alpha]^{22}_D$ +10.29° (*c* 0.91, $CHCl_3$) for the antipode: Masamune, S.; Choy, W.; Kerdesky, F.A.J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566.

^{1}H NMR of the homoallylic alcohol , δ 0.92 (3H, d, *J*=6.8 Hz), 0.96 (3H, d, *J*=6.8 Hz), 1.02 (3H, d, *J*=6.4 Hz), 1.76 (1H, m), 1.80 (1H, br s), 2.37 (1H, m), 3.17 (1H, dd, *J*=8.8, 5.6 Hz), 5.06 (1H, br d, *J*=12.0 Hz), 5.08 (1H, br d, *J*=17.2 Hz), 5.79 (1H, ddd, *J*=17.2, 12.0, 8.0 Hz).

Reaction of (*R,R*)-4-3 with an Achiral Aldehyde: A Representative procedure with nonoxidative workup.



4-20 (*R,R*)-4-3 4-36

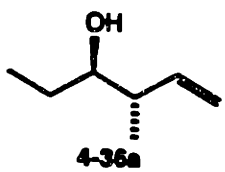
To a magnetically stirred solution of KO^{t}Bu (124 mg, 1.1 mmol) and trans-2-butene (0.30 mL, 3.3 mmol) in THF (0.8 mL) at -78°C, was added a hexane solution of n-BuLi (2.72 M, 370 mL, 1.0 mmol). The resulting yellow solution was stirred at -50~-47°C for 1 h. To the recooled (-78°C) mixture was added methoxyborolane (*R,R*)-2-51 (130 mL, 0.844 mmol) and stirring was continued for 30 min. BF_3·Et_2O (145 mL, 1.18 mmol) was added and, after 10 min stirring, isobutyraldehyde (108 mL, 1.18 mmol) was added. The mixture was stirred for 4 h at -78°C. After adding 2-aminoethanol (122 mg, 2.0 mmol), the reaction mixture was warmed to 20°C with stirring. Decane (40 mL) and pentane (45 mL) were added to the mixture and the suspension was stirred for 12 h at 25°C. The solution was filtered and the filtrate was washed with 1 N HCl solution. Capillary GC analysis of the organic phase indicated 76% yield of anti- and syn- alcohols

in a ratio of 96/4. The solution was concentrated to a volume of ~20 mL by fractionl distillation using a 30 cm Vigreux column and the residue was treated with a stream of ozone at -50°C for 15 min. The resulting blue solution was stirred for 10 min at -50°C and allowed to warm to room temperature. Nitrogen was passed through the soltuion to remove excess ozone and the mixture was recooled to -40°C. An ethereal solution of LAH (1.5 mL, 1.1 M) was added dropwise and the white suspension was stirred at 0°C for 10 min. Sat aq NaCl solution was added to quench excess hydride. Extraction with ether followed by drying ($MgSO_4$), filtration, and removal of solvent gave crude 1,3-diol as a colcrless oil. Derivatization of the 1,3-diol to the corresponding Mosher's ester {(*S*)-MTPACl, DMAP, pyridine} and HPLC analysis of the bis-MTPA ester indicated 95% ee {97% ee, corrected for the purity of (*R*,*R*)-**2-51**}.

The 1,3-diol was purified on a chromatographic column (silica gel, ether, R_f=0.42) to give pure 1,3-diol. $[\alpha]^{25}_D$ +17.6° (*c* 0.49, $CHCl_3$); lit. $[\alpha]^{22}_D$ +19.6° (*c* 0.75, $CHCl_3$): see ref 21.

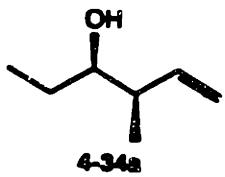
^{1}H NMR of the homoallylic alcohol **4-36b**, δ 0.92 (3H, d, *J*=6.8 Hz), 0.96 (3H, d, *J*=6.8 Hz), 1.03 (3H, d, *J*=6.8 Hz), 1.60 (1H br s, -OH), 1.76 (1H, m), 2.33 (1H, m), 3.10 (1H, m), 5.12 (1H, br d, *J*=16.8 Hz), 5.13 (1H, br d, *J*=12.8 Hz), 5.79 (1H, m).

Physical Data for **4-34a**, **4-36a**, **4-34c**, and **4-36c**



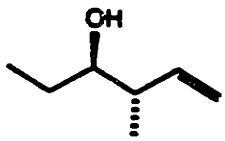
4-36a

^{1}H NMR δ 0.96 (3H, t, *J*=7.6 Hz), 1.02 (3H, d, *J*=7.0 Hz), 1.39 (1H, ddq, *J*=14.0, 8.8, 7.6 Hz), 1.55 (1H, dqd, *J*=14.0, 7.6, 4.0 Hz), 1.90 (1H, br s, -OH), 2.26 (1H, m), 3.37 (1H, m), 5.05 (1H, d, *J*=10.2 Hz), 5.06 (1H, d, *J*=18.0 Hz), 5.75 (1H, m).



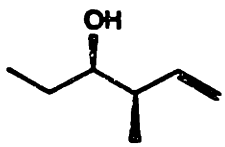
4-34a

^{1}H NMR δ 0.93 (3H, t, *J*=7.6 Hz), 1.0 (3H, d, *J*=6.8 Hz), 1.40 (1H, ddq, *J*=14.0, 10.5, 7.6 Hz), 1.56 (1H, dqd, *J*=14.0, 7.6, 3.5 Hz), 1.80 (1H, br s, -OH), 2.24 (1H, m), 3.33 (1H, ddd, *J*=10.5, 6.4, 3.5 Hz), 5.03 (1H, ddd, *J*=18.0, 10.2, 7.2 Hz).



4-36c

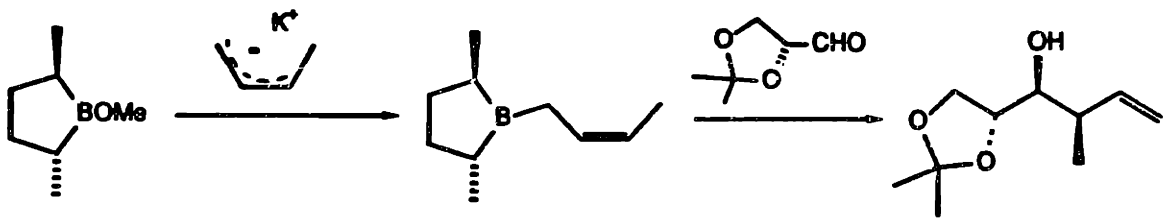
^{1}H NMR δ 0.94 (9H, s), 1.12 (3H, d, *J*=6.0 Hz), 1.60 (1H, br s, -OH), 2.57 (1H, m), 3.14 (1H, dd, *J*=6.8, 3.6 Hz), 5.07 (1H, d, *J*=19.6 Hz), 5.08 (1H, br d, *J*=9.6 Hz), 5.96 (1H, ddd, *J*=19.6, 9.6, 8.4 Hz).



4-34c

^{1}H NMR δ 0.97 (9H, s), 1.05 (3H, d, *J*=6.8 Hz), 1.62 (1H, br s, -OH), 2.49 (1H, m), 3.24 (1H, dd, *J*=5.4, 5.4 Hz), 4.99 (1H, br d, *J*=9.6 Hz), 5.02 (1H, br d, *J*=18.0 Hz), 5.89 (1H, ddd, J=18.0, 9.6, 6.8 Hz).

A Representative Procedure for the Crotylboration with Chiral Aldehyde 4-38



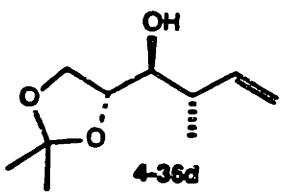
(*R,R*)-2-51 (*R,R*)-4-2 4-34d

To a magnetically stirred soltuion of KO^{t}Bu (124 mg, 1.1 mmol) in THF (1 mL) was added *cis*-2-butene (0.4 mL, 4.4 mmol) at -50°C. The solution was cooled to -78°C and a hexane soltuion of n-BuLi (2.72 M, 370 mL, 1mmol) was added dropwise over a period of 5 min. The resulting yellow suspension was stirred at -50°C for 25 min. To the recooled (-78°C) mixture was added (*R,R*)-2-51 (120 mL, 0.78 mmol) dropwise and stirring was continued for 30 min. $BF_3 \cdot Et_2O$ (128 mL, 1.04 mmol) was added, the

mixture was stirred for 5 min, and the aldehyde **4-38** (63 mg, 0.48 mmol) in THF (0.1 mL) was added. After stirring for 12 h at -78°C, 3 N NaOH (0.5 mL) and 30% aq H_2O_2 (0.3 mL) were added and the mixture was warmed to room temperature. After 15 min stirring at room temperature, ether (20 mL) was added and the organic phase was dried over anhyd Na_2SO_4. The solution was analyzed by capillary GC yielding a 66% yield with a composition of 91.6% of **4-34d**, 4.5% of **4-36d**, 2.3% of **4-37d**, and 1,6% of **4-35d**. 96.6% de (98.0% de, corrected for the purity of (*R*,*R*)-**2-51**) for the major syn-diastereomers.

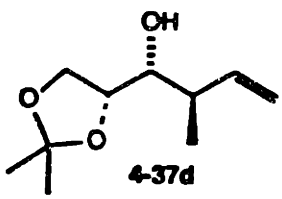
^{1}H NMR of **4-34d**, δ 1.08 (3H, d, *J*=6.0 Hz), 1.32 (3H, s), 1.40 (3H, s), 2.05 (1H, br s), 2.24 (1H, m), 3.63 (1H, m), 3.89 (1H, dd, *J*=8.6, 8.6 Hz), 3.96 (1H, dd, *J*=8.6, 8.6 Hz), 4.10 (1H, m), 5.01 (1H, br d, *J*=10.8 Hz), 5.05 (1H, br d, *J*=17.2 Hz), 5.73 (1H, m). $[\alpha]^{25}_D$ +45.5° (*c* 1.72, CH_2Cl_2); lit $[\alpha]^{23}_D$ +47.6° (*c* 2.1, CH_2Cl_2), ref 105d.

Physical Data for **4-36d**, **4-37d**, and **4-35d**



4-36d

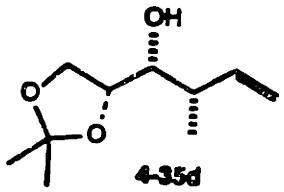
$[\alpha]^{25}_D$ +6.2° (*c* 0.7, CH_2Cl_2); lit $[\alpha]^{22}_D$ +6.3° (*c* 1.25, CH_2Cl2), ref 105d; ^{1}H NMR δ 1.10, (3H, d, *J*=7.0 Hz), 1.37 (3H, s), 1.43 (3H, s), 1.85 (1H, br s), 2.39 (1H, m), 3.59 (1H, dd, *J*=5.2, 5.2 Hz), 3.88 (1H, dd, *J*=7.4, 7.4 Hz), 3.96 (1H, dd, *J*=7.4, 6.0 Hz), 4.08 (1H, m), 5.15 (1H, d, *J*=16.0 Hz), 5.16 (1H, d, *J*=13.2 Hz), 5.88 (1H, ddd, *J*=16.0, 13.2, 8.8 Hz).



4-37d

$[\alpha]^{25}_D$ +16.5° (*c* 0.52, CH_2Cl_2); lit $[\alpha]^{23}_D$ +14.5° (*c* 0.95, CH_2Cl_2), ref 105d; ^{1}H NMR δ 1.09 (3H, d, *J*=7.0 Hz), 1.33 (3H, s), 1.40 (3H, s), 2.21 (1H, d, *J*=6.5 Hz), 2.24 (1H, m), 3.37 (1H, m), 3.72 (1H, dd, *J*=8.6, 8.6 Hz), 3.98 (1H, dd, *J*=8.6, 6.8 Hz), 4.08 (1H,

ddd, *J*=8.6, 6.8, 6.6 Hz), 5.04 (1H, dd, *J*=17.2, 2.4 Hz), 5.07 (1H, dd, *J*=10.8, 2.4 Hz), 5.86 (1H, ddd, *J*=17.2, 10.8, 8.0Hz).



4-35d

$[\alpha]^{25}_D$ -11.5° (*c* 0.9, $CHCl_3$); lit $[\alpha]^{22}_D$ -11.4° (*c* 0.9, $CHCl_3$), ref 105d; ^1H NMR d 1.07 (3H, d, *J*=7.0 Hz), 1.34 (3H, s), 1.40 (3H, s), 2.20 (1H, d, *J*=6.5 Hz), 2.26 (1H, m), 3.29 (1H, ddd, *J*=6.5, 6.8, 4.8 Hz), 3.72 (1H, dd, *J*=8.8, 6.4 Hz), 3.94 (1H, dd, *J*=8.8, 6.4 Hz), 4.13 (1H, ddd, *J*=6.4, 6.4, 4.8 Hz), 5.03 (1H, dd, *J*=10.4, 2.0 Hz), 5.08 (1H, dd, *J*=19.6, 2.0 Hz), 5.71 (1H, ddd, *J*=19.6, 10.4, 7.0 Hz).

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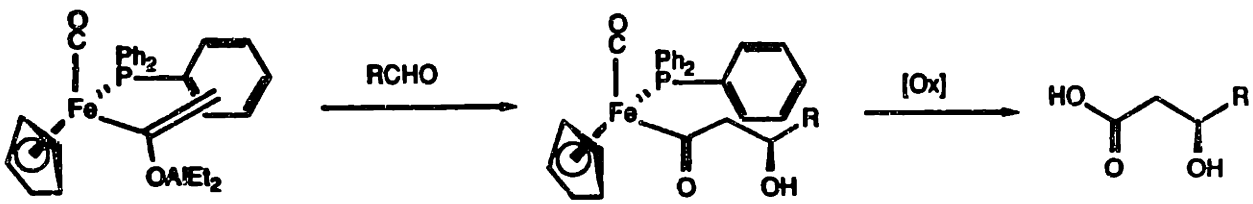
APPENDIX

LITERATURE SURVEY ON ASYMMETRIC ALDOL REACTIONS

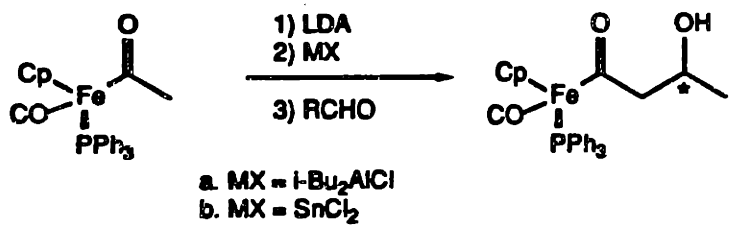
1. Preparation of 3-Hydroxycarbonyl Compounds.

Reagents A. Aluminum enolate derived from $(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)COCH_3$:

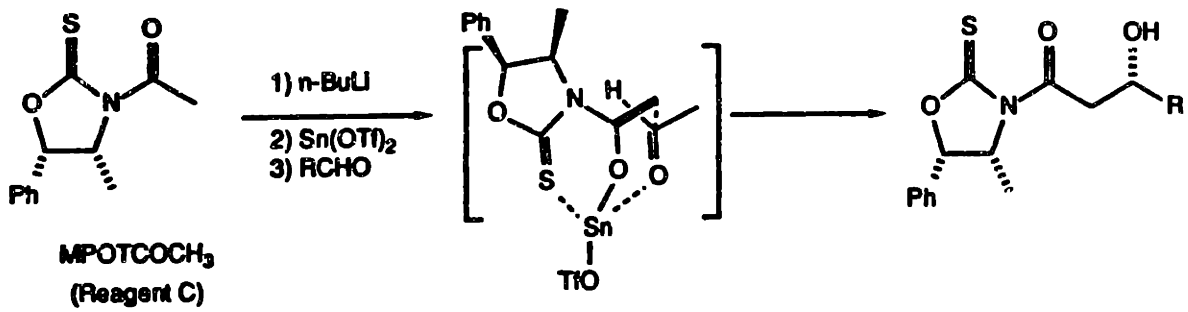
Davies, S.G.; Dordor, I.M.; Warner, P. *J. Chem. Soc., Chem. Commun.* **1984**, 956.

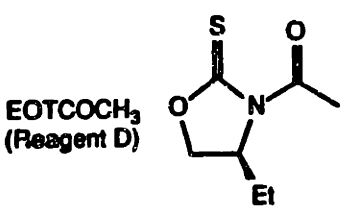


Reagent B Aluminum (a) or tin (b) enolate of $(\eta^5\text{-}Cp)Fe(CO)(PPh_3)COCH_3$: Liebeskind, L.S.; Welker, M.E. *Tetrahedron Lett.* **1984**, *25*, 4341.

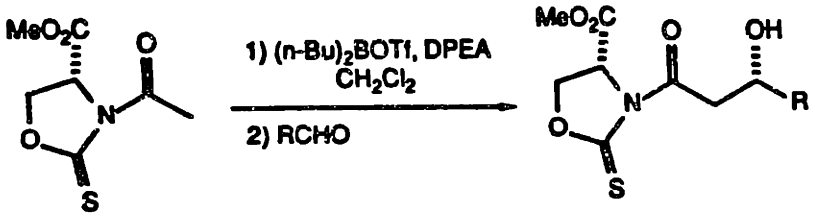


Reagent C $MPOTCOCH_3$, Reagent D $EOTCOCH_3$ (chiral 1,3-oxazolidine-2-thiones): Nagao, Y.; Yamada, S.; Kumagai, T.; Odirai, M.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1985**, 1418.

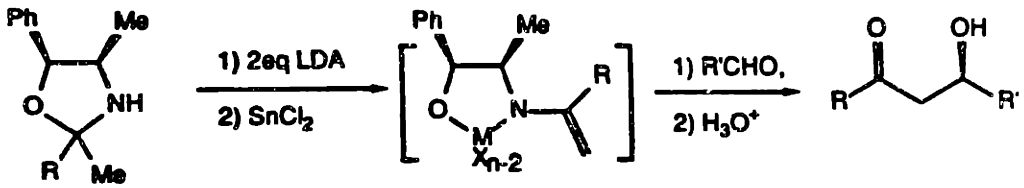




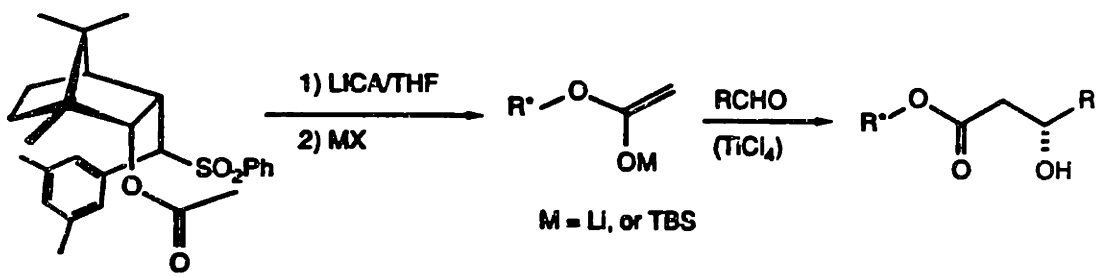
Reagent E Chiral 1,3-oxazolidine-2-thione: Hsiac, C.-N.; Liu, L.;Miller, M.J. *J.Org. Chem.* **1987**, *52*, 2201.



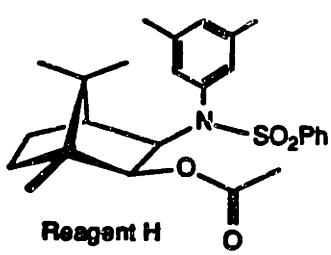
Reagent F Chiral 1,3-oxazolidine prepared from norephedrine: Narasaka, K.; Miwa, T.; Hayashi, H.; Ohta, M. *Chem. Lett.* **1984**, 1399.



Reagent G and H Chiral *O*-sylilketene acetals: Helmchen, G.; Leikauf, U.; Taufer-Knöpfel, I. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 874.

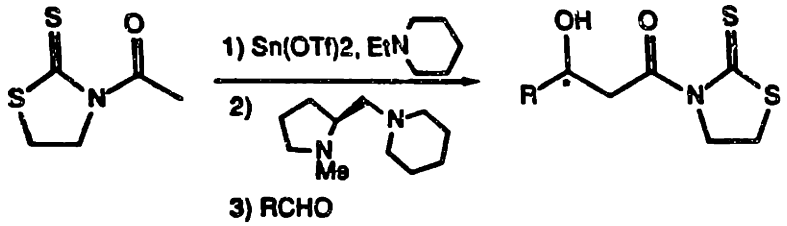


Reagent G

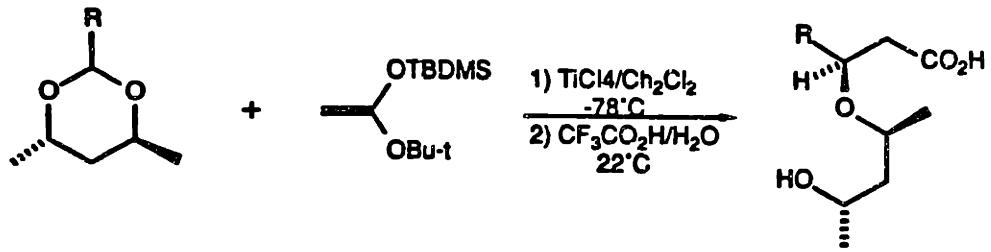


Reagent H

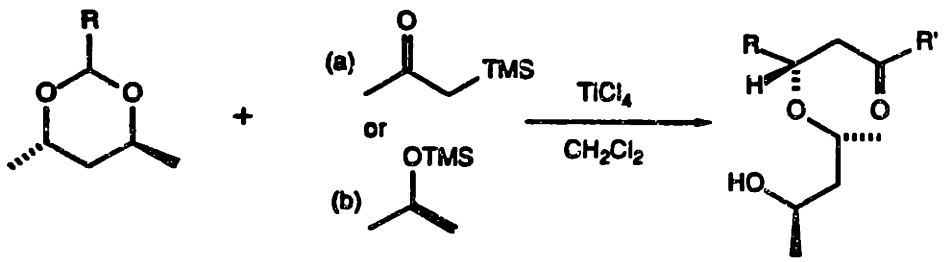
Reagent I Chiral tin enolate prepared from N-acetyl-1,3-thiazol-2-thione: Mukaiyama, T.; Iwasawa, N.; Stevens, R.W. *Tetrahedron* **1984**, *40*, 1381.



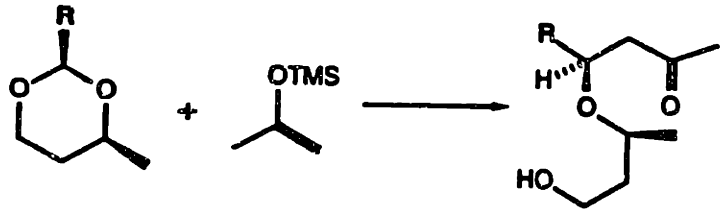
Reagent J. Chiral acetals with 1-t-butoxy-1-t-butyldimethylsiloxyethene: Elliott, J.D.; Stede, J.; Johnson, W.S. *Tetrahedron Lett.* **1985**, *26*, 2535.



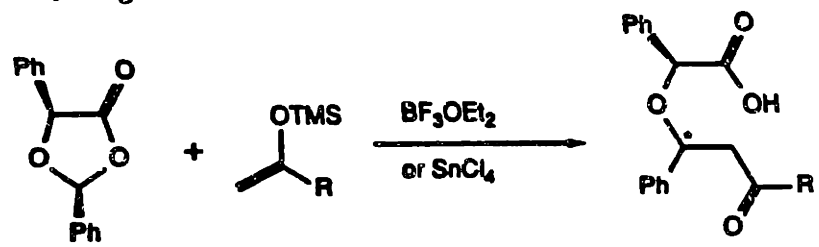
Reagent K Chiral acetals with α-silyl ketone (a) or silyl ether (b): Johnson, W.S.; Edington, C.; Elliott, J.D.; Silverman, I.R. *J. Am. Chem. Soc.* **1984**, *106*, 7588.



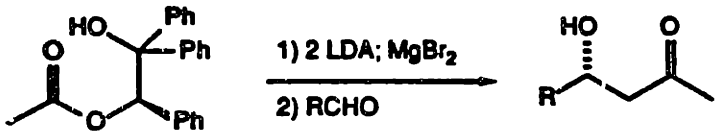
Reagent L Chiral acetal with silyl enol ether: Silverman, I.R.; Edington, C.; Elliott, J.D.; Johnson, W.S. *J. Org. Chem.* **1987**, *52*, 180-3.



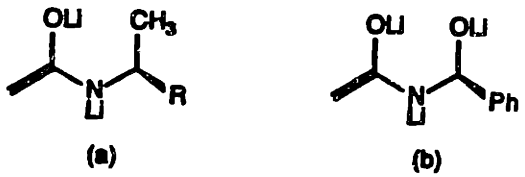
Reagent M Chiral 1,3-dioxolan-4-one with enol silyl ether: Mashraqui, S.H.; Kellogg, R.M. *J. Org. Chem.* **1984**, *49*, 2513.



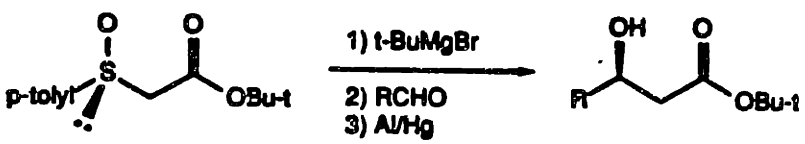
Reagent N (*R*)-2-Acetoxy-1,1,2-triphenylethanol: Braun, M.; Devant, R. *Tetrahedron Lett.* **1984**, *25*, 5031.



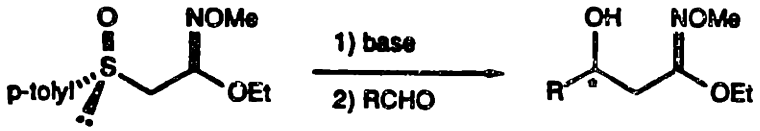
Reagent O Chiral acetamide (a and b): Devant, R.; Braun, M. *Chem. Ber.* **1986**, *119*, 2191.



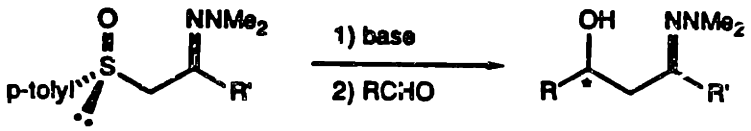
Reagent P Chiral t-butyl α-sulfinylacetate; Solladie, G. *Chimia* **1984**, *38*, 233.



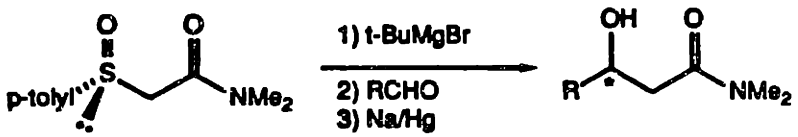
Reagent Q Ethyl (*R*)-2-(4-Methylphenylsulfinyl)-N-methoxyacetamidate: Bernardi, A.; Colombo, L.; Gennari, C.; Prati, L. *Tetrahedron* **1984**, *40*, 3769.



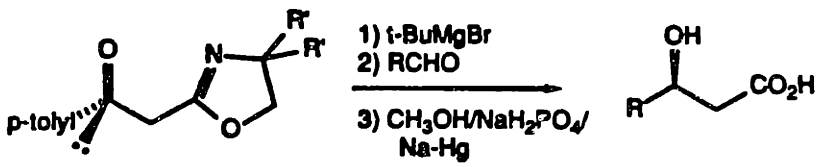
Reagent R Chiral α-sulfinyl hydrazone: Annunziata, R.; Cozzi, F.; Cinquini, M. *J. Chem. Soc., Perkin Trans. I* **1985**, 251.



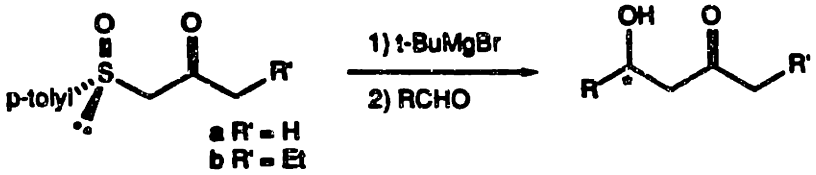
Reagent S Chiral α-sulfinyl-N,N-dimethylacetamide; Annunziata, R.; Cinquini, M.; Cozzi, F. *Ibid.* **1983**, 1138.



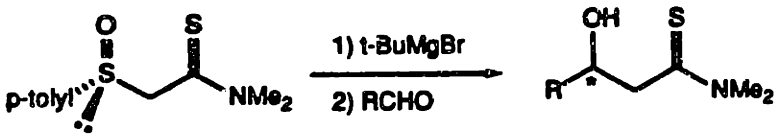
Reagent T Chiral 2-(arylsulfinylmethyl)oxazoline: Annunziata, R.; Cinquini, M.; Gilardi, A. *Synthesis* **1983**, 106.



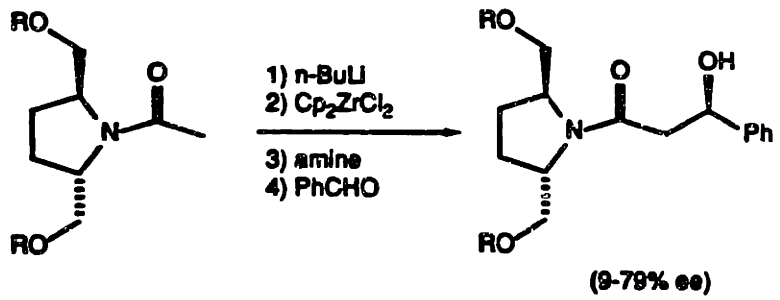
Reagent U Chiral 2-(arylsulfinylmethyl)ketone: Schneider, F.; Simon, R. *J. Chem. Soc., Chem Commun.* **1986**, 582.



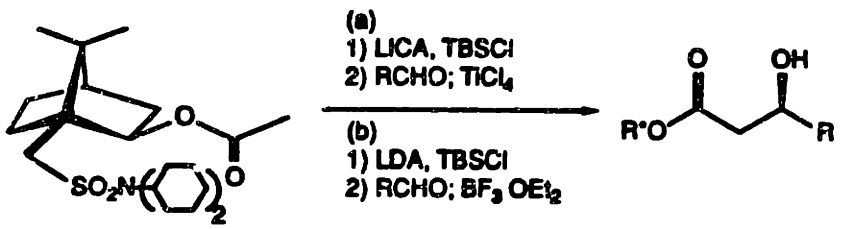
Reagent V Chiral 2-(arylsulfinylmethyl)-N,N-dimethylthioamide: Cinquini, M.; Manfredi, A.; Molinari, H.; Restelli, A. *Tetrahedron* **1985**, *41*, 4929-36.



Reagent W Chiral N-acetyl-2,5-dialkoxypyrrolidine: Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1985**, *26*, 5807.



Reagent X Chiral silyl ketene acetal: Oppolzer, W.; Marco-Contelles, J. *Helv. Chim. Acta* **1986**, *69*, 1699.



Reagent Y Chiral boron enolate of S-3-(3-ethyl)pentyl ethanethioate dprepared with 2,5-dimethylborolanyl triflate (Reagent 3-62 in this Thesis): Masamune, S.; Sato, T.; Kim, B.M.; Wollmann, T.A. *J. Am. Chem. Soc.* **1986**, *108*, 8279.

Table A.1 Preparation of 3-Hydroxycarbonyl Compounds

Aldehyde \ Reagent	A	B	C,D	E	F	G,H	I	J	K	L	M	N
	85-90[b]											75-85[b]
CH_3CHO	(92)	60 (69, a)	62[c] (52.4, C)									
EtCHO	(>98)	73 (68, a) 66 (84, b)				67 (86, G)	70 (90)					
n-PrCHO		74 (76, a) 66 (84, b)			60 (58)							(84)
n-BuCHO												
$n\text{-}C_5H_{10}CHO$												
$n\text{-}C_6H_{13}CHO$								98 (96)	96 (92, a) 92 (94, b)	84 (>98)		
									93 (94, a) 89 (94, b)	93 (92)		
$i\text{-}PrO_2C(CH_2)_2CHO$								90-93 (95)				
i-BuCHO			64[c] (63.6, C)									(90)
$Ph(CH_2)_2CHO$					59 (58)		76 (>90)					
$n\text{-}C_8H_{17}CHO$							65 (90)					
i-PrCHO	(>98)	76 (78, a) 74 (83, b)	68[c] (78, C) 60[c] (63, D)	58 (99)		59 (94, G) 62 (90, H)	63 (>90)		84 (92, b)			
3-PentCHO					60 (69)							
c-HexCHO					65 (73)		81 (88)	98 (94)	93 (96, a)	90 (94)		
t-BuCHO	(>98)				65 (86)							
PhCHO	(80.5)	81 (57, a)		73 (98)		(88, H)	79 (65)				(82-87) >90 (>98)[c]	(94)
												

Table A.1 continued

Aldehyde \ Reagent	O	P	Q	R	S	T	U	V	W	X	Y
CH_3CHO					68 (>99)	(53)		75 (64)			
EtCHO							67 (67, a) 40 (82, b)				
n-PrCHO						(36)				49 (84)	82 (91.2)
n-BuCHO	93 (56, b)										
$n\text{-}C_7H_{15}CHO$		80 (86)									
$n\text{-}C_8H_{17}CHO$		80 (83)								44 (84)	
											
$I\text{-}PrO_2C(CH_2)_2CHO$											
i-BuCHO	95 (66, b)[d] 93 (56, b)[e]				71 (98)	(48)		52 (69)			
$Ph(CH_2)_2CHO$							56 (76, a) 49 (76, b)				
$n\text{-}C_9H_{11}CHO$			(94)								
i-PrCHO			(72-84)	25 (56-88)	66 (95)	(22-48)		67-76 (81-90)		53 (98, a) 56 (92, b)	91 (91.5)
3-PentCHO											
c-HexCHO			(91)				60 (57', a) 40 (78, b)				95 (90.1)
t-BuCHO					56 (90)	(21-26)		40 (55)			71 (98.4)
PhCHO	96 (66, a) 96 (60, b)	85 (91)	(75) (86-88)	22 (50)					(9-79)	50 (84, a) 50 (90, b)	78 (92.8)
		65 (70)									

Captions for Table A.1.

a. Two numbers in each column correspond to yield and (in parenthesis) % ee, respectively.

b. General yields for all reactions.

c. Isolated yields of the major products.

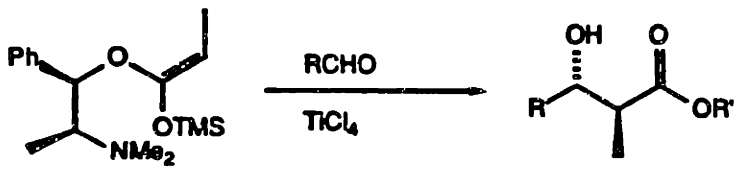
d. When R' = Ph.

e. When R' = β-naphthyl.

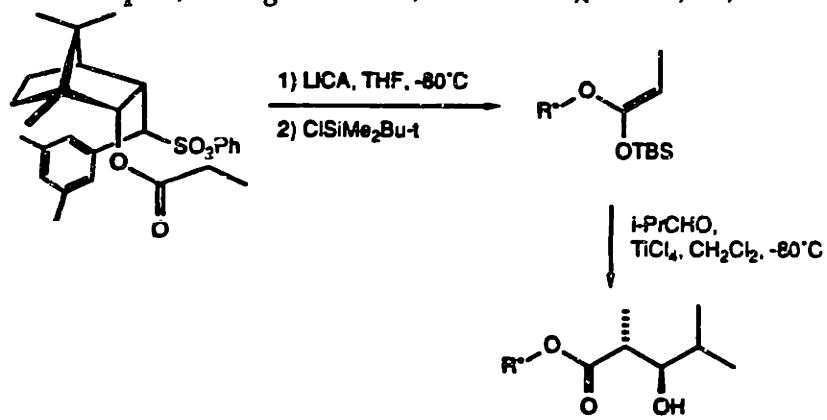
f. After removal of the chiral auxiliary.

2. Preparation of anti-3-Hydroxy-2-methylcarbonyl Compounds.

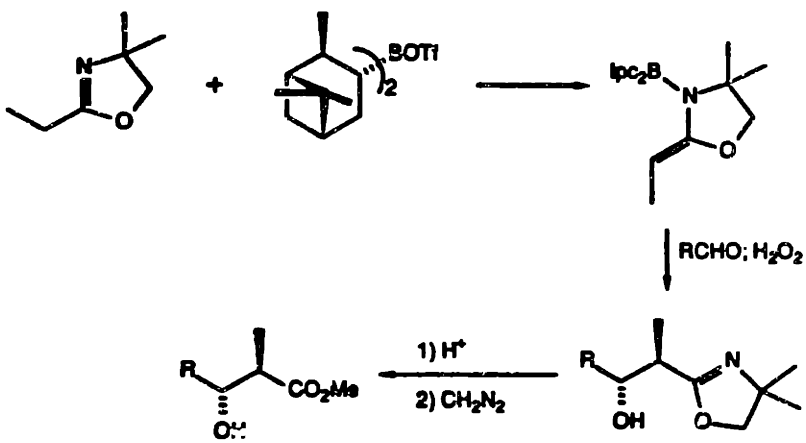
Reagent A Silyl Ketone acetals derived from N-methylephedrine: Gennari, C.; Bernardi, A.; Colombo, L.; Scolastico, C. *J. Am. Chem. Soc.* 1985, *107*, 5812, and Palazzi, C.; Colombo, L.; Gennari, C. *Tetrahedron Lett.* 1986, *27*, 1735.



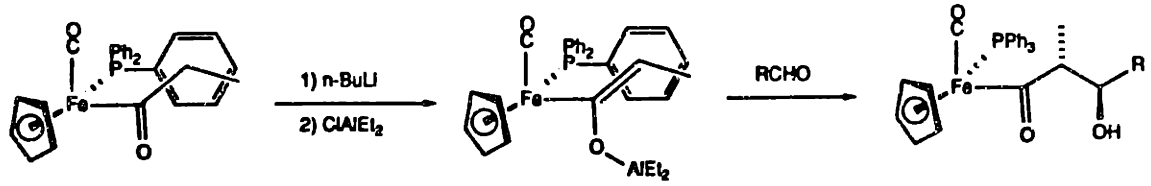
Reagent B Chiral silyl ketone acetal in the presence of $TiCl_4$: Helmechen, G.; Leikauf, U.; Taufer-Knopfel, I. *Angew. Chem., Int. Ed. Engl.* 1985, *24*, 874.



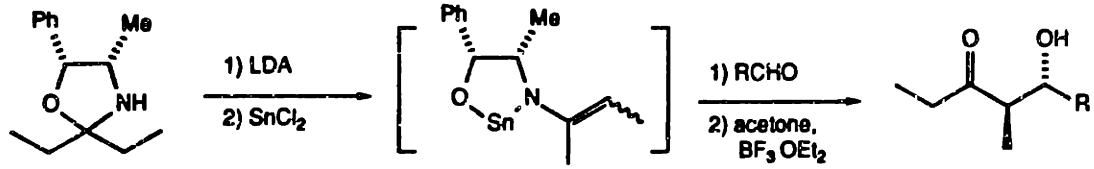
Reagent C Boron enolate of achiral oxazoline derived from diisopinocampheylborane: Meyers, A. I.; Yamamoto, Y. *Tetrahedron*, 1984, *40*, 2309.



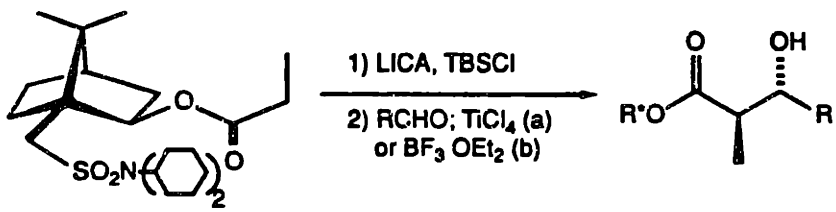
Reagent D Aluminum enolate derived from $(\eta^5\text{-Cp})Fe(CO)(PPh_3)COCH_2CH_3$: Davies, S.G.; Dordor-Hedgecock, I.M.; Warner, P. *Tetrahedron Lett.* **1985**, *26*, 2125.



Reagent E Chiral oxazolidine derived from 3-pentanone and norephedrine: Narasaka, K.; Miwa, T. *Chem. Lett.* **1985**, 1217.



Reagent F Chiral silylketene acetal: Oppolzer, W.; Marco-Contelles, J. *Helv. Chim. Acta* **1986**, *69*, 1699.



Readent G Boron enolate prepared from *S*-3-(3-ethyl)pentyl propanethioate and 2,5-dimethylborolanyl triflate, reagent **3-55** in this Thesis: Masamune, S.; Sato, T.; Kim, B.M.; Wollmann, T.A. *J. Am. Chem. Soc.* **1986**, *108*, 8279.

Table A.2 Preparation of anti-3-Hydroxy-2-methylcarbonyl Compounds[a]

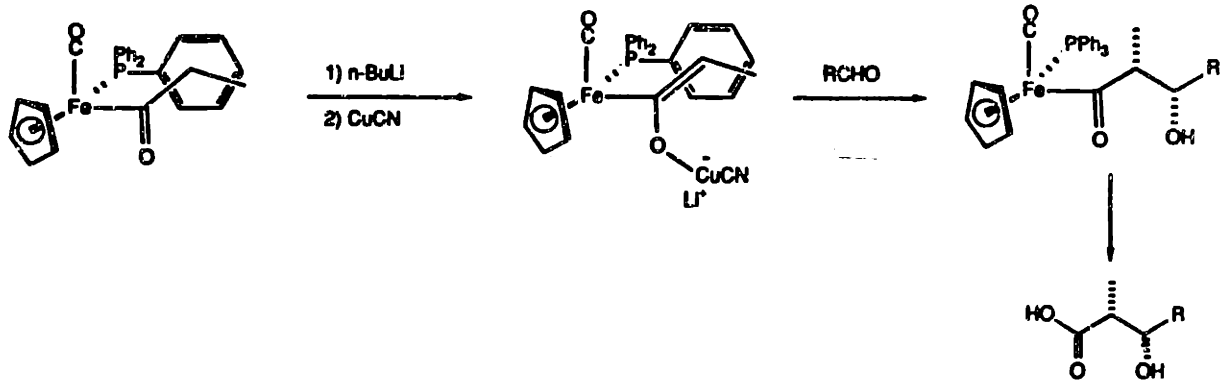
Aldehyde \ Reagent	A	B	C	D	E	F	G
CH_3CHO				- 15:1 96			
EtCHO			26 11.5:1 77		61 7.3:1 95	30 100:0 68 (a)	
n-PrCHO	88 4:1 91.0		22 10.1:1 77			50 15.7:1 86 (a)	91 97:3 97.9
n-$C_5H_{11}CH$)	60 3:1 93.0		25 9:1 77				
$Ph(CH_2)_2CHO$					77 7:1 92		
i-PrCHO		66 14.4:1 96.8	36 10.1:1 85	- 10:1 >98		60 54.6:1 85.1 (a) 58 2.7:1 - (b)	85 30:1 99.5
c-HexCHO			31 19:1 84		75 9:1 92		82 32:1 98.0
t-BuCHO			29 15.7:1 79	- 100:1 100	56 6:1 >95		95 30:1 99.9
PhCHO	80 5.7:1 94.0 (90) (>30:1) (94)					44 4.3:1 90.1 (a)	71 33:1 99.8
(E)-CH_3CH=CHCHO	78 4:1 91.0 (60) (>20:1) (67)						
(E)-PhCH=CHCHO	60 5.7:1 91.0 (50) (15:1) (86)						
$PhCH_2O(CH_2)_2CHO$							93 >30:1 97.1

Captions for Table A.2.

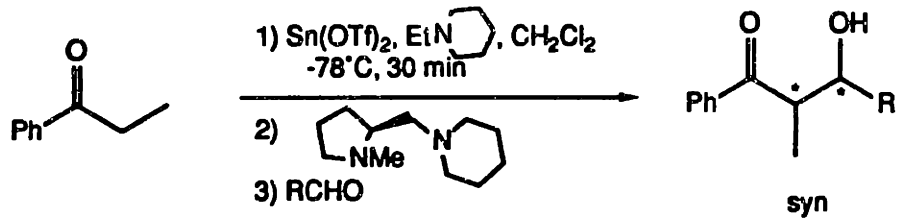
a. Three numbers in each column represent combined yield, anti/syn ratio, and % ee (or de) of anti isomer, respectively (left to right).

3. Preparation of syn-3-Hydroxy-2-methylcarbonyl Compounds.

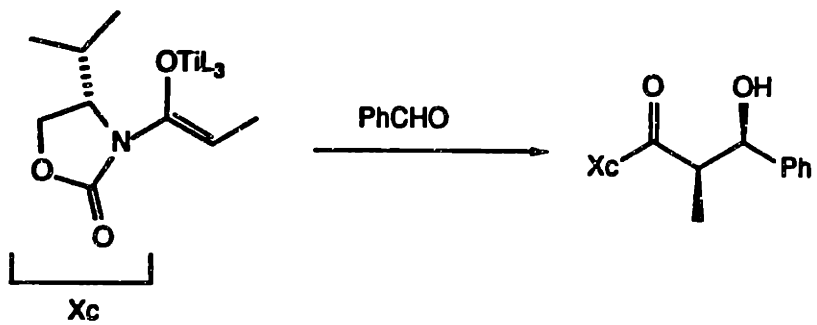
Reagent A Copper enolate derived from $(\eta^5\text{-Cp})Fe(CO)(PPh_3)COCH_2CH_3$: Davies, S.G.; Dordor-Hedgecock, I.M.; Warner, P. *Tetrahedron Lett.* **1985**, *26*, 2125.



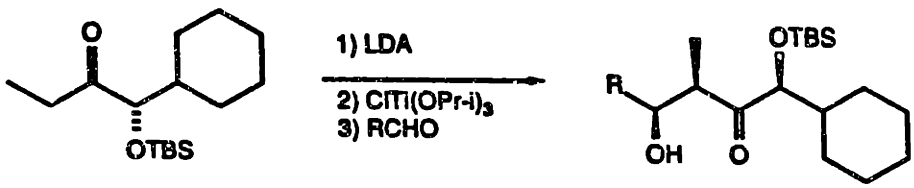
Reagent B Divalent tin enolate of aromatic ketone derived from chiral diamines: Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1982**, 1441.



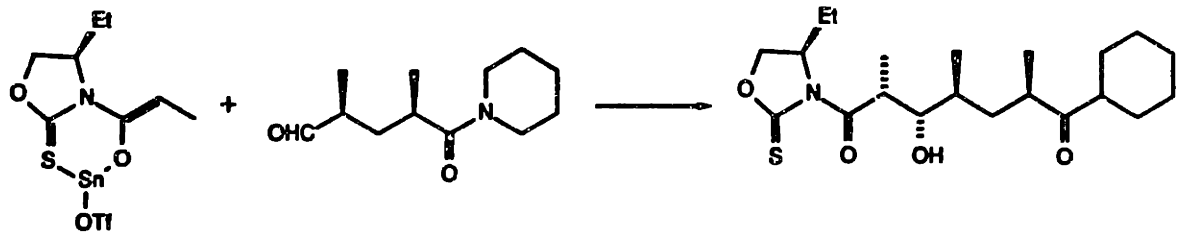
Reagent C Titanium enolate of chiral oxazolidone derivative: Nerz-Storms, M.; Thornton, E.R. *Tetrahedron Lett.* **1986**, *27*, 897.



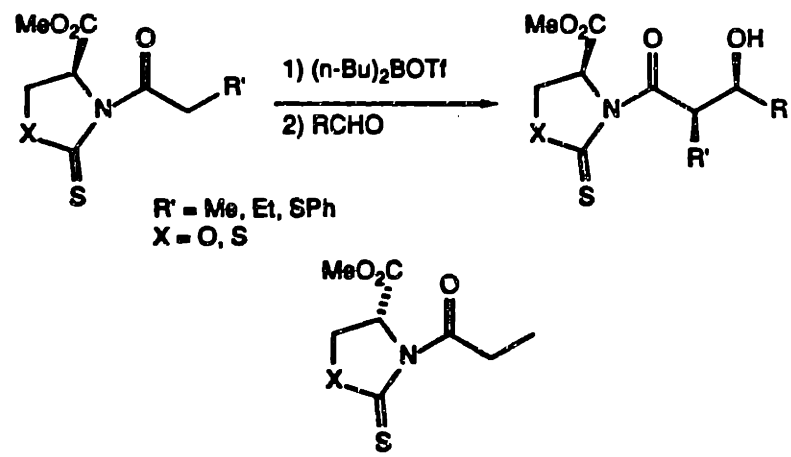
Reagent D Chiral titanium enolate of α-silyloxyketone derived from mandelic acid: Siegel, C.; Thornton, E.R. *Ibid.* 457.



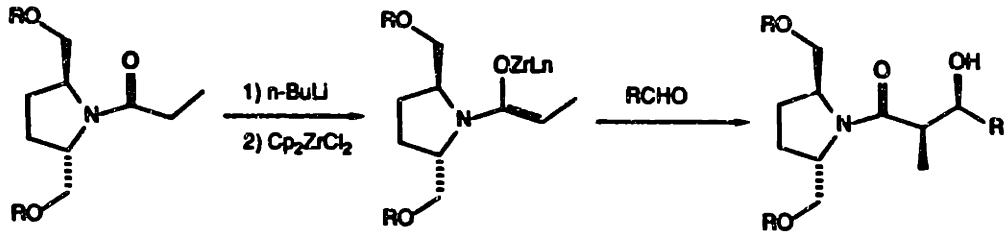
Reagent E Tin enolate of chiral 3-acyl-1,3-oxazolidine-2-thiones: Nagao, Y.; Yamada, S.; Kumagai, T.; Ochiai, M.; Fujita, E. *J. Chem. Soc., Chem. Commun.* 1985, 1418 and 1419.



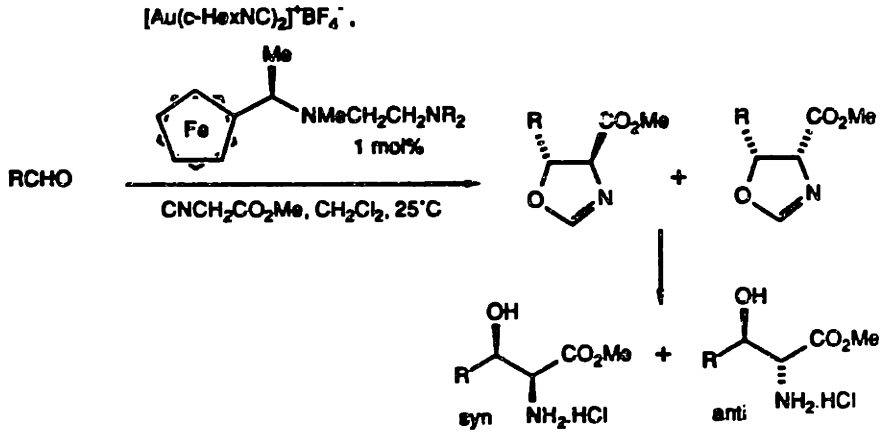
Reagent F Boron enolate of chiral acyl-1,3-thiazolidine-2-thiones: Hsiao, C.-N.; Ashburn, S.P.; Miller, M.J. *Tetrahedron Lett.* 1985, *26*, 4855. and Hsiao, C.-N.; Liu, L.; Miller, M.J. *J. Org. Chem.* 1987, *52*, 2201.



Reagent G Zirconium enolate of N-propionyl-2,5-dialkoxypyrrolidine: Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* 1985, *26*, 5807-10.



Reagent H Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* 1987, *108*, 6405.



Reagent I Evans, D.A.; Weber, A.E. *Ibid.* 6757-61.

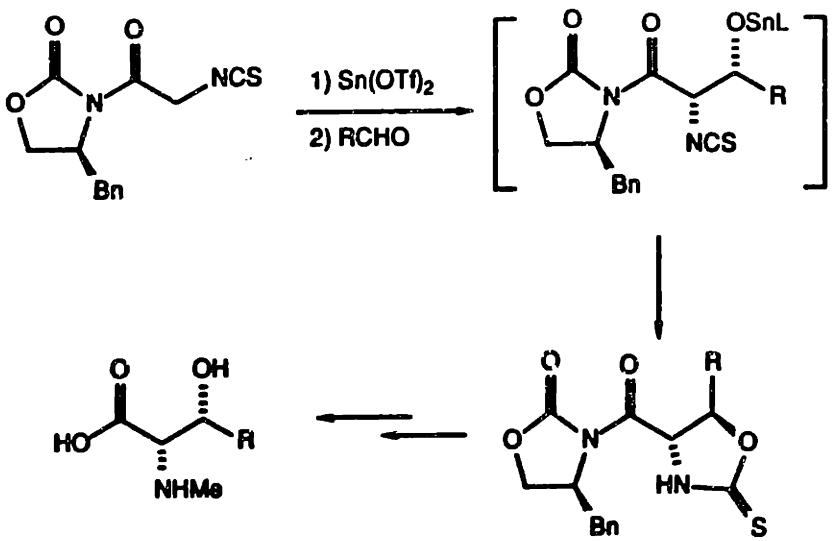
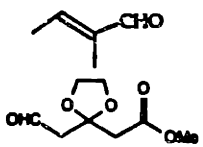


Table A.3 Preparation of syn-3-Hydroxy-2-methylcarbonyl Compounds

Aldehyde \ Reagent	A	B	C	D	E	F	G	H	I
				74-85 [b]					
CH_3CHO	- 7.1:1 >98							100 5.3:1 72	75 [c] 99:1 [d]
EtCHO				- 100:0 [e] 98			92 >49:1 >98		
n-PrCHO						82 100:0 [e] 99			
i-PrCHO	- 14.3:1 >98	69 >20:1 75		- 100:0 [e] >98	71 [c] >9.5:1 [d] >81 [d]	58-92 100:0 [e] 97-99	85 >49:1 >98	99 49:1 92	92 [c] 99:1 [d]
c-HexCHO		67 4:1 80						95 32:1 90 96 49:1 81	
t-BuCHO	- 25:1 >98	57 100:0 90						100 100:0 97	
PhCHO		74 6:1 80	- 97:3 90	- 100:0 [e] 98	74 [c] >5.1:1 [d] >71 [d]	67-95 100:0 [e] 96-98	88 >62:1 96.7	91-98 9:1 94-96	91 [c] 99:1 [d]
p-MePhCHO		72 8:1 80							
p-ClPhCHO		72 6:1 85							
p-MeOPhCHO		78 8:1 80							
CH_3CH=CHCHO							98 >49:1 >98		
(E)-n-PrCH=CHCHO								83-97 4:1 84-87	
								89 91:9 95	
						77 100:0 [e] >93			

Captions for Table A.3.

a. Three numbers in each column represent combined yield, syn/anti ratio, and % ee (or de) of syn isomer, respectively.

b. General yields for all reactions are given.

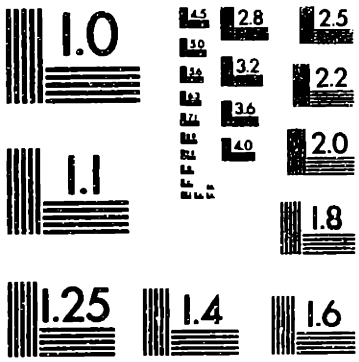
c. Isolated yield of major product.

d. Ratios of desired diastereomer vs. the sum of all other diastereomers are given.

e. No anti-aldol products were observed.

Biographical Note

The author, ByeongMoon Kim, was born in Kyungnam, Korea on October 23, 1957 and was raised in Pusan, Korea. After graduating from Pusan Senior High School in 1975, he entered the Seoul National University in Seoul, Korea. He received a B.S. in chemistry with honors in 1980. Continuing his study at the Graduate School of S.N.U. with Professor Eun Lee, he obtained a Graduate Fellowship from the Ministry of Education of Korean Government from 1980 to 1982, which also included reduction of military service as an officer. In 1982 he earned M.S. in chemistry. He then spent 6 months in the Korean Army to become a reserved second lieutenant. After briefly working for French-Korean Aromatics in Suwon, Korea as a part-time researcher, the author came to the Massachusetts Institute of Technology in September of 1983 and began working for Professor Masamune shortly thereafter. In June of 1985, he had the good fortune to marry ChoonWon Bahng. In 1986, he was elected to Sigma Xi. He was lucky to become a father in the spring of 1987 when his first son, Phillip, was born to him. After finishing his doctoral work, he will pursue postdoctoral studies at MIT with Professor K. Barry Sharpless.



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