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Organoboranes for Syntheses

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Foreword

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Preface

The discovery of hydroboration of olefins and acetylenes more than 40 years ago and subsequent study of the versatility of organoboranes altered the way organic chemists plan their syntheses. Today, it is almost impossible to carry out a major synthesis without involving organoboranes. This field of research has evolved considerably since its beginnings. Although it has become a mature area of organic chemistry, only a few monographs or books have been dedicated to this area. This led to a symposium dedicated to the topic of *Inorganic and Organic Syntheses via Boranes* that was held during the 218th National Meeting of the American Chemical Society (ACS) in New Orleans, Louisiana, August 22, 23 and 25, 1999. The symposium, sponsored by the ACS Divisions of Inorganic Chemistry, Inc. and Organic Chemistry, was well received by chemists from industry and academia alike and acted as a catalyst for this book.

This volume contains 16 chapters by leading boron chemists world-wide. The book is organized into three sections based on the symposium. The lead chapter reviews the current status of organoborane chemistry, which is followed by chapters discussing stoichiometric and catalytic methods, as well as asymmetric methods and synthesis.

This book, which discusses the current state of the art in organoborane chemistry for organic syntheses, is intended for synthetic chemists in academia and industry. This book can be adapted for a graduate course in organoborane or synthetic organic chemistry.

Acknowledgments

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Chapter 1

Recent Advances in Borane Chemistry

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Organoboranes are one of organic chemist's favorite reagents, used for functional group syntheses and carbon-carbon bond formations. Modern organic chemistry uses chiral organoboranes as reagents or catalysts for several transformations. They are also being examined for the syntheses of fluoroorganic compounds. Transition metal catalyzed coupling of organoboranes have become a preferred reaction of industrial chemists. This chapter (*1*) discusses some recent advances in the area of hydroboration and organoborane chemistry.

Introduction

Hydroboration (*2*) produces organoboranes, one of the most versatile intermediates currently available for organic chemists. For more than forty years since the discovery of the facile ether-catalyzed addition of borane across multiple bonds (*3*), organic chemists have become increasingly dependent on this reaction for a variety of transformations. Several new hydroborating agents of varying steric and electronic properties have become available and several novel applications also have ensued (*4*). Systematic study of the organoborane intermediates made available by hydroboration has revealed their remarkable

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versatility (5-7). A great majority of the substitution reactions of organoboranes proceed with complete retention of configuration in the organic group that is transferred from boron to some other element or group (Figure 1) (8). The last two decades has witnessed major applications of chiral organoboranes as reagents or catalysts (9-13). All these developments might make an impression that the chemistry of organoboranes has reached its peak. However, we believe that it is still in its formative years with more fascinating chemistry awaiting discovery. The recent developments discussed below should prove this point.

Versatile Organoboranes

The versatility of organoboranes was explored during the early years of hydroboration chemistry. Conversions to several classes of functional groups, such as alcohols, amines, ketones, alkenes, acetylenes, dienes, enynes, etc. were achieved with ease.

Figure 1. Versatile organoboranes

Asymmetric Synthesis via Boranes

The mandatory requirements of regulatory agencies around the world for the synthesis of enantiomerically pure pharmaceuticals gave an impetus to the area of asymmetric organic synthesis. Accordingly, the past two decades witnessed the extension of the versatility of organoboranes to include chiral molecules. A program of general asymmetric synthesis via organoboranes was developed. This included asymmetric hydroboration, asymmetric reduction, asymmetric allyl- and crotylboration, asymmetric homologation, asymmetric enolboration, asymmetric ring-opening reactions, etc. (9-13). α-Pinene turned out to be an excellent chiral auxiliary achieving nearly quantitative asymmetric induction for most of the reactions studied (Figure 2).
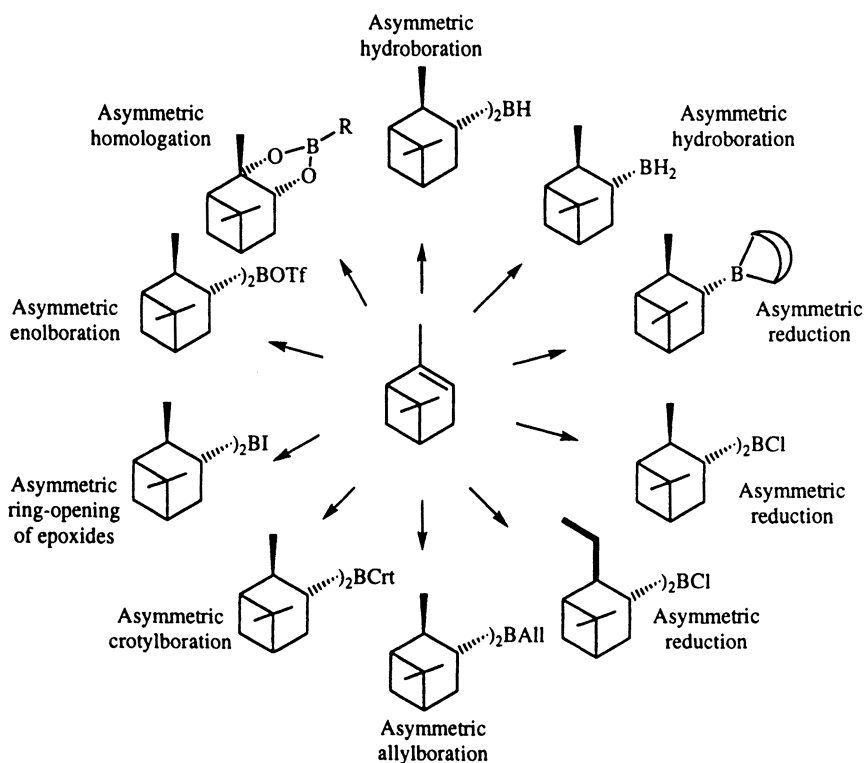
Figure 2. Pinane-based versatile reagents

It is impossible to highlight the utility of these chiral reagents for asymmetric syntheses in a short review such as this. Representative molecules

that have been synthesized using some of these reagents demonstrate that they have become part of the effective toolbox of modern day organic chemist.

Allyl- and Crotylboration

One of the carbon-carbon bond forming reactions involving organoboranes that continues to charm organic chemists is the asymmetric allyl- (*14*) and crotylboration (*15*). The list of compounds synthesized in recent years using asymmetric allyl- or crotylboration include Epothilones A and B (*16, 17*), Sanglifehrin A (18), Lankacidin (*19*), Acutiphycin (*20*), Tetronasin (*21*), etc. (Figure 3).

R = H, Epothilone A
R = Me, Epothilone B
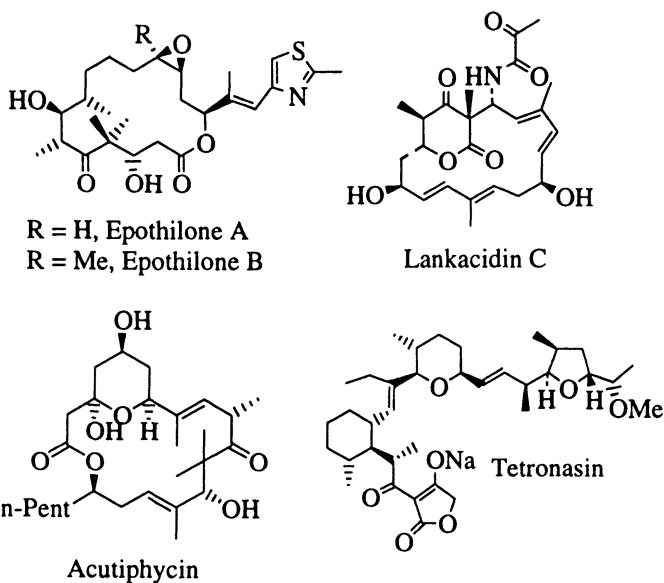
Lankacidin C

Acutiphycin

Tetronasin

Figure 3. Application of allyl and crotylboration

Our group utilized asymmetric allylboration-esterification-ring-closing metathesis as a general route to lactones (Figure 4) and synthesized Parasorbic acid, Goniothalamin, Massoia lactone, Hexadecanolide, Argentilactone, Mevinolic acid analogs, Umuravumbolide, Tarchonanthuslactone, Gloeosporone, etc. (*22-25*).
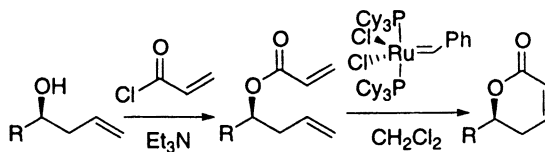
Figure 4. Allylboration-ring-closing metathesis for the synthesis of lactenones

Hoffmann has continued his pioneering work in asymmetric allylboration and synthesized several heterocyclic compounds (*26*). Soderquist has developed a new reagent, chiral *B*-allyl-10-trimethylsilyl-9-borabicyclo[3.3.2]-decane for allylboration reactions (*27*).

Enolboration

Mukaiyama pioneered the cross aldol reaction involving dialkylboron triflates (*28*) (Figure 5). Later developments by Evans, Masamune, and others brought this area to new heights (*29*). However, research in this direction was not complete until we developed a procedure to prepare *anti*-aldols using *B*-chlorodicyclohexylborane (*30*). This reagent has been utilized in several syntheses, especially in situations where the substrate controls the chirality.
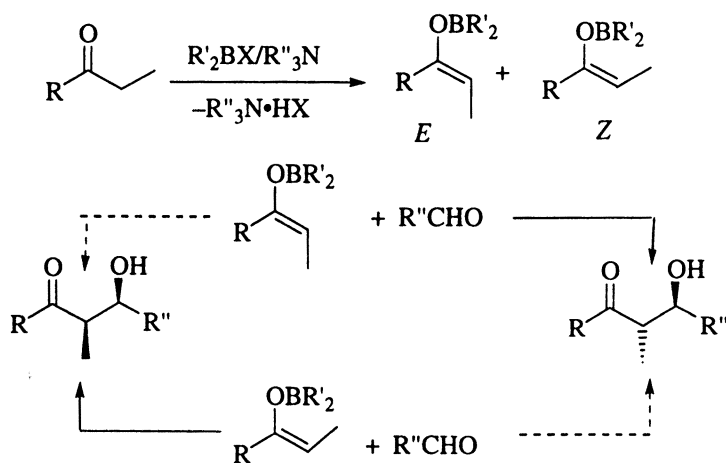

Figure 5. Synthesis of syn- or anti- 2-alkyl-1-hydroxy-3-ketones via stereoselective enolboration-aldolization reactions

Paterson developed asymmetric enolboration-aldolization involving diisopinocampheylboron triflate (*31, 32*). He has shown the utility of enolboration for the synthesis of various macrolide molecules. His recently completed target molecules include Concanamycin F (*33*) and the potential anticancer agent, Discodermolide (*34*) (Figure 6).

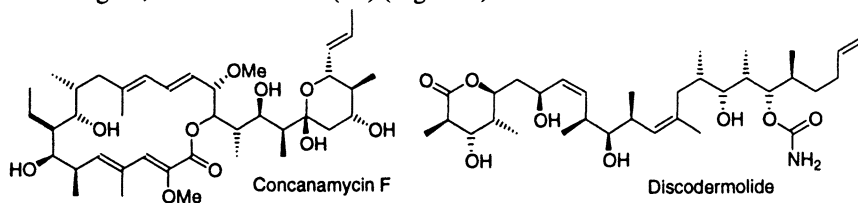Concanamycin F   Discodermolide

Figure 6. Targets completed via enolboration

Regioselectivity in Hydroboration: The Reaction of Fluoroolefins

Hydroboration of simple olefins provides, predominantly anti-Markovnikov products (*2*). The reaction can be readily rationalized by the electrophilic nature of borane. However, the hydroboration of olefins containing electron-withdrawing atoms or groups produces a considerable percentage of Markovnikov product as well, e.g., styrene, allyl chloride, and 3,3,3-trifluoropropene (Figure 7). Trimethylvinylsilane provided an equal mixture of Markovnikov and anti-Markovnikov products (*35*). Replacing the methyl groups with chlorine atoms increased the Markovnikov product to 90% (Figure 7) (*36*).
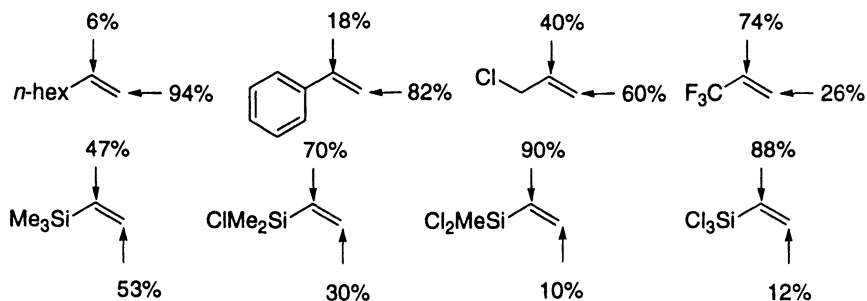

Figure 7. Regioselectivity in hydroboration with BH₃•THF

Due to the importance of fluoroorganic molecules in agricultural, material, and medicinal chemistry, we re-investigated the hydroboration of fluoroolefins.

Several hydroborating agents have become available since the original research of Phillips and Stone (*37*). Our recent study led to the Markovnikov hydroboration of fluoroolefins with dihaloboranes (*38*). Regioselective anti-Markovnikov hydroboration can be achieved by changing the hydroborating agent to dicyclohexylborane (Figure 8) (*39*). A similar reversal in regioselectivity by changing the hydroborating agent was observed by Jones and coworkers for the hydroboration of dichloro- and trichloromethylvinylsilanes as well (*40*).
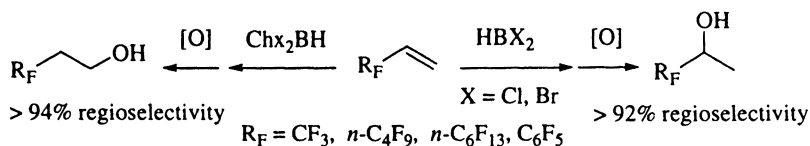

Figure 8. Regioselective hydroboration of fluoroolefins

Catalytic Hydroboration of Fluoroolefins

In 1985, Mannig and Noth reported the first rhodium catalyzed hydroboration of olefins with the relatively less reactive catecholborane (Figure 9) (*41*). This led to a systematic study of catalytic hydroboration by various researchers, *albeit* limited to relatively few olefins (*42*).
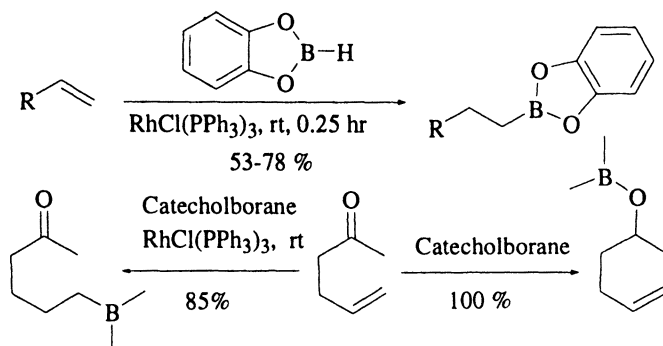

Figure 9. Catalytic hydroboration

The asymmetric version of this reaction was restricted primarily to styrene derivatives. Various chiral phosphines were examined to achieve high

enantioselectivity. BINAP turned out to be the best chiral auxiliary (*42*) (Figure 10).
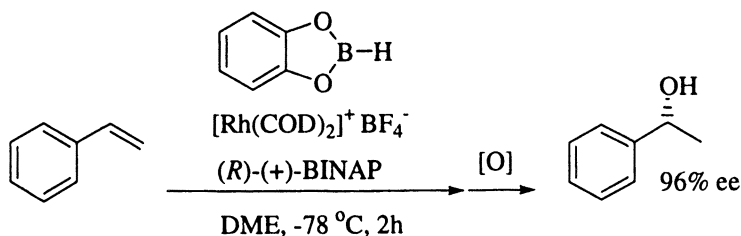

Figure 10. Catalytic asymmetric hydroboration

The catalytic hydroboration reaction of fluorinated olefins also provided both Markovnikov and anti-Markovnikov products by the prudent choice of the catalyst and reagent mixture (*43*). Thus, catecholborane in the presence of cationic Rh catalysts affords anti-Markovnikov hydroboration whereas pinacolborane in the presence of neutral Rh catalysts provide anti-Markovnikov products (Figure 11). We have achieved up to 70% enantioselectivity for catalytic asymmetric hydroboration of fluoroolefins (*39*). The search for an optimal chiral ligand continues.
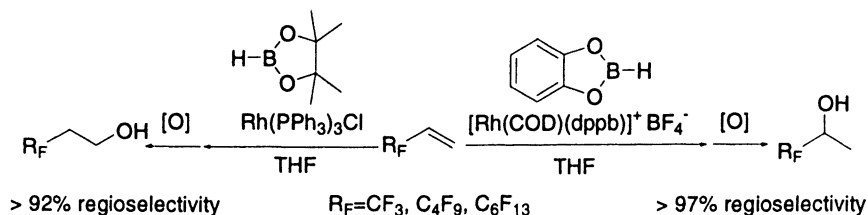

> 92% regioselectivity $R_F=CF_3, C_4F_9, C_6F_{13}$ > 97% regioselectivity

Figure 11. Catalytic hydroboration of fluoroolefins

Borane Catalysts in Organic Syntheses

Oxazaborolidines

The past fifteen years witnessed the development of oxazaborolidines as catalysts for various organic reactions (*44*). The Itsuno-Corey asymmetric reduction is a prominent example (Figure 12) (*45, 46*). This chemistry led

organic chemists to examine a wide variety of β-amino alcohols and amino acids for the preparation of oxazaborolidines (*47,48*).
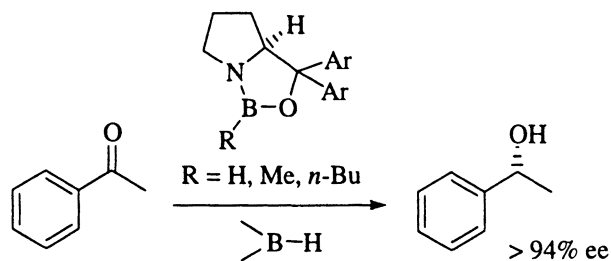

Figure 12. Oxazaborolidine catalyzed reduction of ketones

Oxazaborolidines have also been used as catalysts in atrop enantioselective ring-opening (*49*), asymmetric addition of diethylzinc to aldehydes (*50*), asymmetric Diels-Alder reactions (*51, 52*), aldol reactions (*53*), Rh catalyzed hydroboration (*54*), etc.

Acyloxyboranes

Hisashi Yamamoto has developed several chiral acyloxyboranes (CABs) as catalysts in various organic transformations, such as allylsilation (*55*) Diels-Alder reaction (*56*), aldol reaction (*57*) (Figure 13), etc.
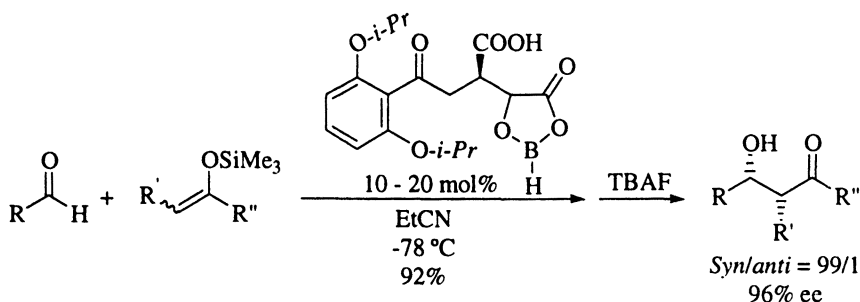

Figure 13. CAB catalyzed aldol reaction

Dioxaborolanes

Pietruska and coworkers reported asymmetric cyclopropanation of chiral *B*-vinyl-1,3,2-dioxaborolanes with diazomethane in the presence of Pd catalyst (*58*) (Figure 14). The cyclopropylboronates were utilized for subsequent reactions, such as Suzuki coupling, Matteson homologation, etc.
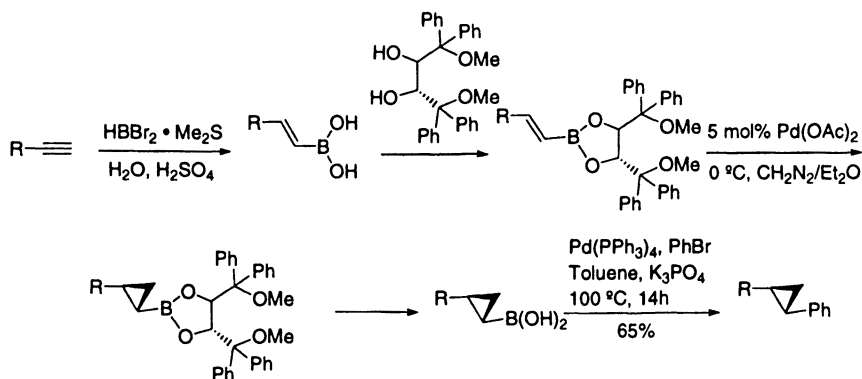
Figure 14. Stoichiometric cyclopropanation reaction via dioxaborolanes

Charette has shown the utility of dioxaborolanes as catalyst for asymmetric cyclopropanation reaction (*59*) (Figure 15).
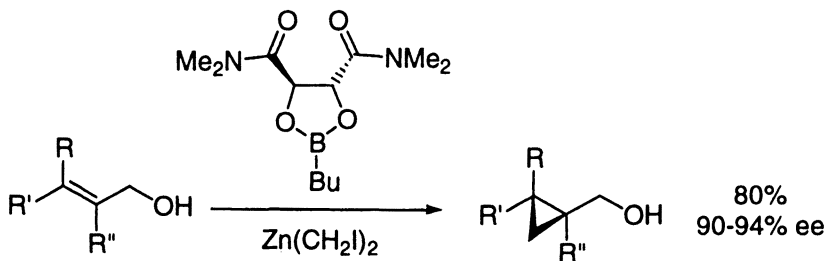
Figure 15. Dioxaborolane catalyzed cyclopropanation reaction

Suzuki Coupling

Carbon-carbon bond forming reactions with organoboranes were developed during the 1970s. Several methods for the synthesis of *E,E-*, *E,Z-*, and *Z,Z-*dienes, enynes, and diynes emerged during this period (*6*). An example of the synthesis of *E,Z*-diene is shown in Figure 16.
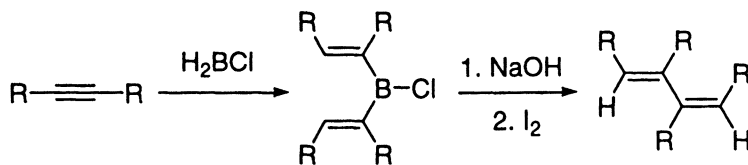

Figure 16. Synthesis of E,Z-diene via hydroboration

The utility of these reactions were dramatically improved by the cross-coupling reactions involving transition metals as catalysts. The most prominent among these is the Suzuki coupling (Figure 17) (*60-62*). These reactions allow for aryl-aryl couplings also (*62*). Recently Buchwald (*63*) and Fu (*64*) developed modified phosphines which will allow the inclusion of aryl chlorides in Suzuki coupling reactions.
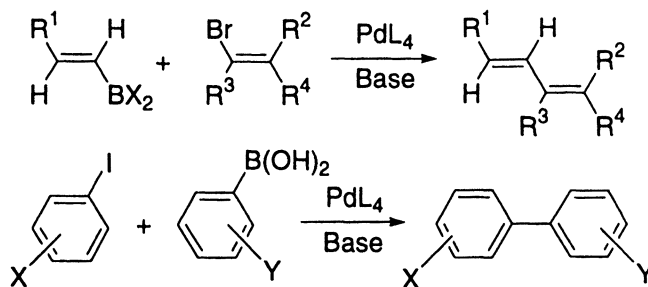

Figure 17. Suzuki coupling reaction

An application of Suzuki coupling for the synthesis of diospyrin, a potential agent against Leishmaniasis and related parasitic protozoan diseases is shown in figure 18 (*65*).
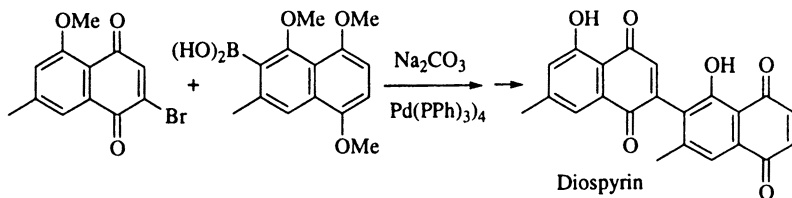
Figure 18. Application of Suzuki coupling reaction

Haloboration

Stereoselective addition of B-Br across a terminal acetylene (haloboration) was first reported by Blackborow (*66*). Suzuki and coworkers examined the intermediate obtained from the haloboration of alkynes with *B*-bromo and *B*-iodo-9-borabicyclo[3.3.1]nonanes for various organoborane reactions. Suzuki has reviewed the applications of haloboration for organic syntheses (*67-69*). A recent application involving the 1,4-addition of a halovinyl-9-BBN to methyl vinyl ketone (*70*) for the synthesis of a promising anti-cancer agent, 12,13-desoxyepothilone B due to Danishefsky and coworkers is shown in Figure 19 (*71*).
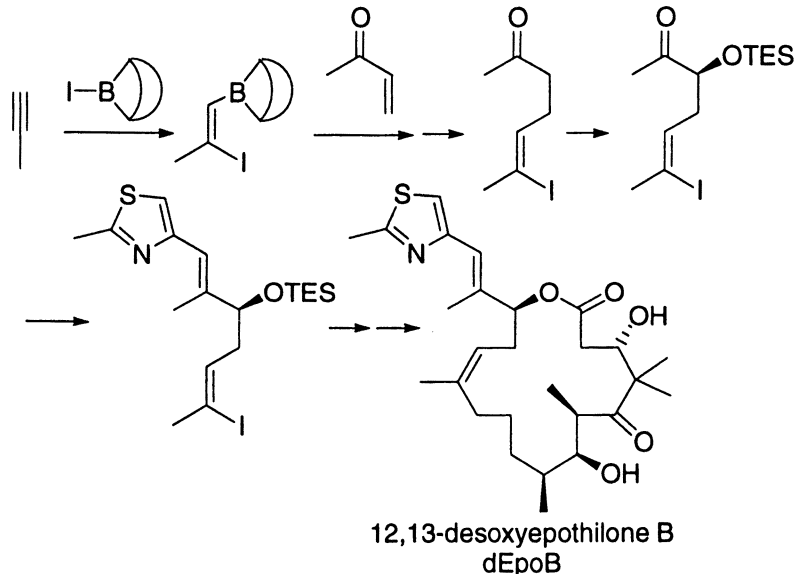

12,13-desoxyepothilone B
dEpoB

Figure 19. Application of haloboration: Synthesis of 12,13-desoxyepothiloneB

Conclusion

In conclusion, we have highlighted some of the recent applications of hydroboration and organoborane chemistry. Further examples of this rich area of organic chemistry can be found in all of the subsequent chapters in this volume. The organoborane continent is truly vast.

Acknowledgment

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Lithium Aminoborohydrides: Reagents with Multiple Personalities

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This chapter describes newly discovered reactions and synthetic utilities of lithium aminoborohydrides (LABs) including: (1) the reduction of nitriles to amines, (2) the direct synthesis of amine-borane complexes from LABs and benzylic or alkyl halides (nitrogen transfer), and (3) the "tandem nitrogen transfer/reduction" of halogen-substituted benzonitriles to give the corresponding aminobenzylamines.

Introduction

In 1984, Hutchins and coworkers (*1*) reported the preparation (Figure 1) and reducing properties of sodium aminoborohydrides. These reagents were

$$H_3B:HN(CH_3)_2 \xrightarrow[\text{THF}]{\text{NaH}} NaH_3BN(CH_3)_2$$

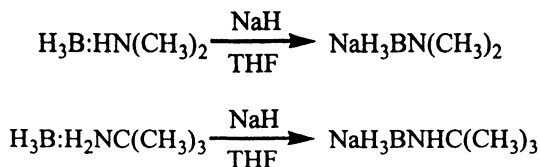$$H_3B:H_2NC(CH_3)_3 \xrightarrow[\text{THF}]{\text{NaH}} NaH_3BNHC(CH_3)_3$$

Figure 1. Preparation of sodium aminoborohydrides.

reported to reduce aldehydes and ketones to alcohols, esters to alcohols, and primary amides to amines in good to excellent yields. Several anomalous reactions were also reported with sodium dimethylaminoborohydride in which the dimethylamine portion of the reagent was transferred to give the corresponding tertiary amine from an alkyl iodide and the corresponding amino alcohol from an epoxide (Figure 2).
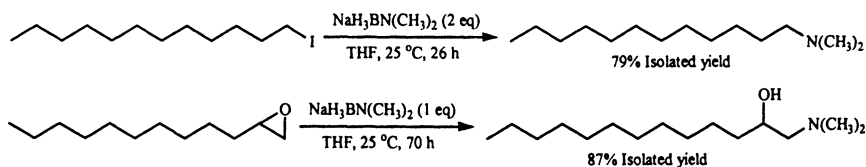

Figure 2. Reaction of sodium aminoborohydrides with alkyl iodides and expoxides.

Several years ago, we reported the synthesis and synthetic utility of lithium aminoborohydrides (LABs): a new class of powerful, safe, and highly selective reducing agents (*2, 3*). These reagents performed many of the transformations for which lithium aluminum hydride is usually used. Thus, the following reduction reactions were carried out with LABs: aldehydes and ketones to alcohols, esters to alcohols, α,β-unsaturated ketones to allylic alcohols, α,β-unsaturated esters to allylic alcohols, alkyl halides to hydrocarbons, azides to amines, and epoxides to alcohols. These reduction reactions are summarized in Figure 3.

We had not, until recently, however, observed any of the nitrogen transfer reactions with LABs reported earlier by Hutchins. This summary will describe recently observed reactions of LABs, which display their multiple personalities (properties) and utility in synthetic organic chemistry.

Recently Reported Reduction Reactions

Before embarking on a discussion of new reactions, it will be useful to describe recently reported examples of the synthetic utility of the reducing capabilities of the LABs. Myers has recently described a practical synthesis of chiral alcohols employing pseudoephedrine as a chiral auxiliary (*4*). An amide of pseudoephedrine is first deprotonated with LDA and then alkylated with the appropriate alkyl halide to give the substituted amide with 97-99% de. The amide is then reduced to the alcohol with lithium pyrrolidinoborohydride to give

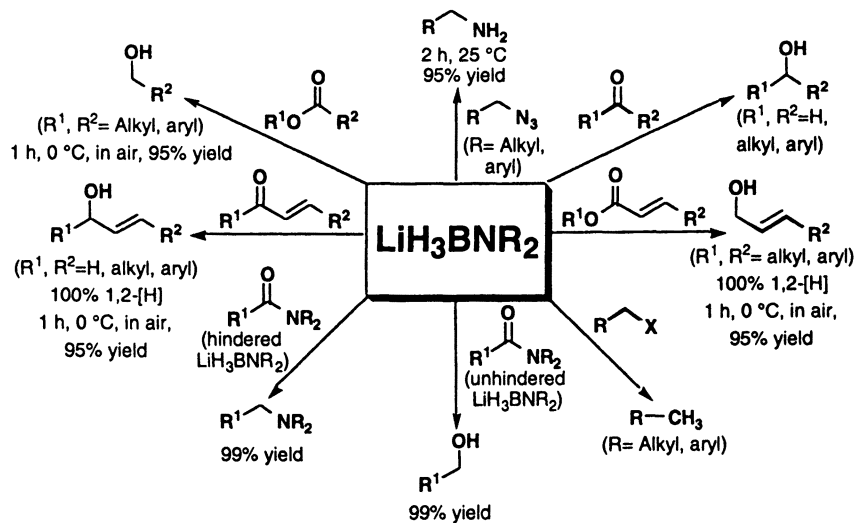the desired chiral alcohol in high chemical yield and greater than 97-99% ee (Figure 4, Table I).

Figure 3. Summary of the reduction reactions of lithium aminoborohydrides. (Reproduced from reference 2. Copyright 1994 American Chemical Society.)
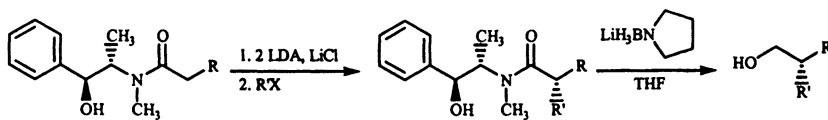

Figure 4. Reductive cleavage of pseudoephedrine amides with lithium pyrrolidinoborohydride.

In the last entry of Table I, it is noted that the reduction had to be done with lithium aminoborohydride (LiH$_3$BNH$_2$). Myers further expanded the utility of this reagent with additional examples of the reduction of alkylated pseudoephedrine amides to chiral alcohols of high ee (Table II), and the reduction of *N,N*-disubstituted dodecanecarboxamides and 1-adamantanecarbox-amides to the corresponding alcohols, respectively (Table III) (5).

Table I. Reduction of Pseudoephedrine Amides with Lithium Pyrrolidinoborohydride

R	R'	Alkylated Amide		Alcohol	
		de, %	Yield, %	ee, %	Yield, %
CH_3	$CH_2C_6H_5$	>99	90	99	84
CH_3	$(CH_2)_3CH_3$	>99	80	99	81
$CH_2C_6H_5$	CH_3	97	95	97	87
$CH_2C_6H_5$	$(CH_2)_3CH_3$	98	90	98	88
$(CH_2)_3CH_3$	$CH_2C_6H_5$	>99	87	99	88
$C_6H_5{}^a$	CH_2CH_3	>99	92	88	80

[a]Reduction with LiH_3BNH_2

SOURCE: Reproduced from reference 4. Copyright 1994 American Chemical Society.
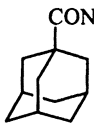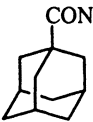
Table II. Reduction of Pseudoephedrine Amides with Lithium Aminoborohydride

Amide	dc, %	Temp, °C	Time, h	Alcohol	Yield, %	ee, %
	≥99	23	2.5		92	≥95
	≥99	23	4.0		90	90
	98	0	4.0		83	93
	≥99	23	9.0		88	≥95
	≥99	60	12.0		91	≥95
	≥95	23	12		84	94

Reactions run with LiH$_2$BNH$_2$ (4.0-4.5 equiv) generated in situ at 0 °C.

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Table III. Reduction of Amides with Lithium Aminoborohydride

Amide	Temp, °C	Time, h	Isol. Yield Alcohol, %	Isol. Yield Amine, %
$CH_3(CH_2)_{10}CONEt_2$	23	1.3	94	<5
CONEt₂ (adamantane structure)	23	10.0	88	8
$CH_3(CH_2)_{10}CON(i\text{-}Pr)_2$	23	6.0	68	28
CON(i-Pr)₂ (adamantane structure)	66	1.7	47	51

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The ability of LABs to reduce α,β-unsaturated ketones to the corresponding allylic alcohol was recently utilized by Marshall in a key step in the synthesis of rubifolide (Figure 5) (6).

$R = CH_2CH_2Si(CH_3)_3$
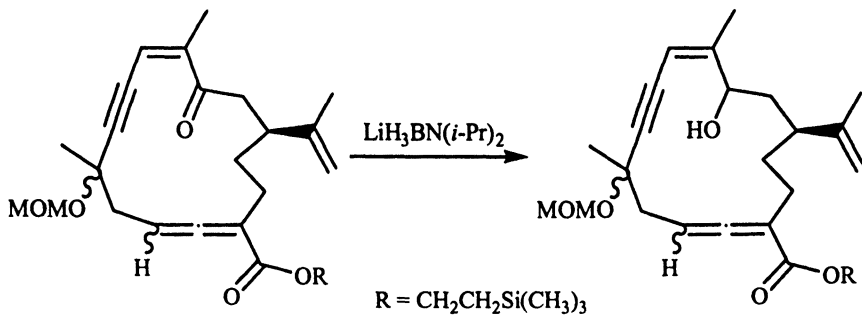
Figure 5. Reduction of an allylic alcohol with lithium diisopropylaminoborohydride.

Chiral LAB Reducing Agents

To date, there has been only one report in the literature describing chiral LABs and their use as reducing agents. In 1995, Kagan (7) reported the preparation of two chiral lithium dialkoxyaminoborohydrides. These reagents readily reduced methyl iodide to methane (Figure 6).

^{11}B NMR: -16.4 δ
(d, J_{BH} = 61 Hz)

^{11}B NMR: +0.31 δ (s)

^{11}B NMR: -13.8 δ
(d, J_{BH} = 56 Hz)

^{11}B NMR: +0.51 δ (s)
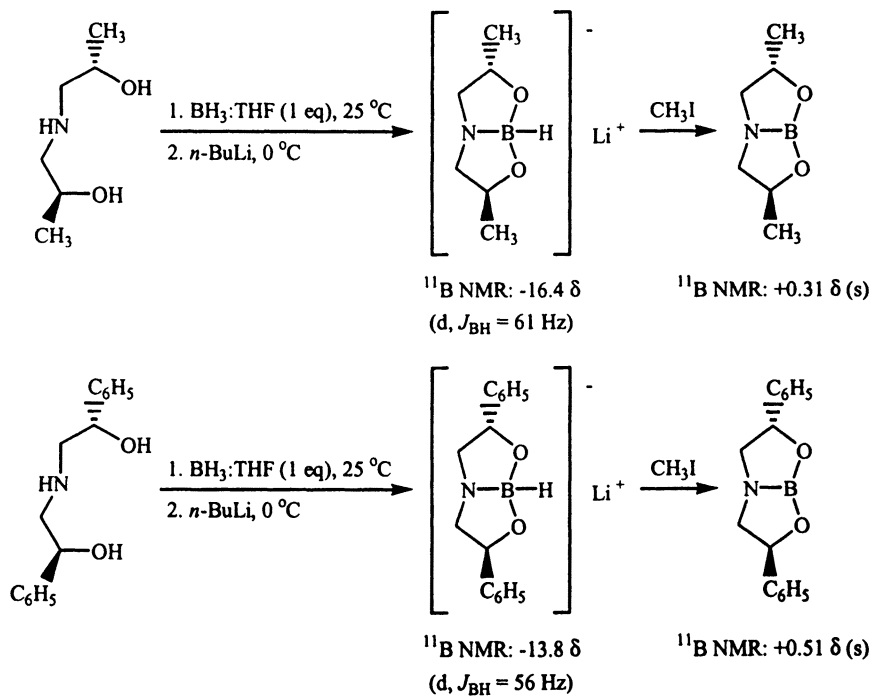
Figure 6. Preparation of chiral lithium dialkoxyaminoborohydrides.

Unfortunately, reduction of acetophenone with these reagents afforded 1-phenyl-ethanol with only 5-9% ee (Figure 7).

Reduction of Nitriles

Since the discovery of the LABs, we have constantly been encouraged to investigate the reduction of nitriles. This investigation has recently been conducted, and portions of the results reported (8). Simple aliphatic nitriles are not reduced with LABs – the substrates are recovered in high yield. In fact, it is possible to reduce the following functional groups in the presence of a nitrile group: aldehyde, ketone, ester, and epoxide. Investigation of the reaction of lithium dimethylaminoborohydride with a series of phenylacetonitriles

Figure 7. Reduction of acetophenone with chiral lithium dialkoxyaminoborohydrides.
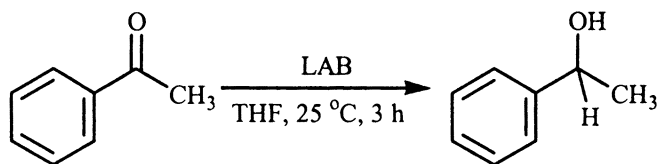
Equivalents	1.1	1.8
Isol. Yield, %	93	90
ee, %	9 (R)	5 (S)

uncovered another of the personalities of the LABS – that they can function as bases (unpublished results). Treatment of phenylacetonitrile with $LiH_3BN(CH_3)_2$ in THF followed by quenching with D_2O gave no 2-phenylethylamine and an 81% recovery of phenylacetonitrile, which was monodeuterated. Treatment of 2-phenylpropionitrile with $LiH_3BN(CH_3)_2$ under the same conditions gave a 22% isolated yield of 2-phenylpropylamine and a 66% recovery of 2-deuterio-2-phenylpropionitrile. Reduction of 2-methyl-2-phenylpropionitrile, which contains no hydrogen alpha to the nitrile group, with $LiH_3BN(CH_3)_2$ gave a 57% isolated yield of 2-methyl-2-phenylpropylamine. These reactions are summarized in Figure 8.
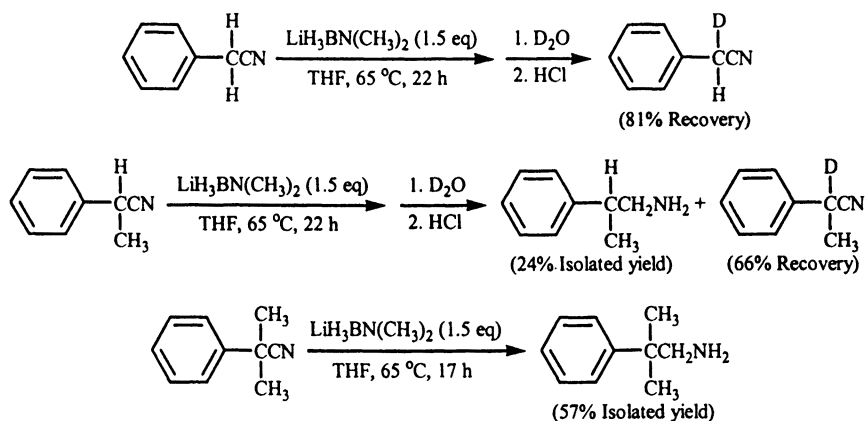
Figure 8. Reaction of phenylacetonitriles with lithium dimethylaminoborohydride.

The situation is different with aromatic nitriles. Treatment of benzonitrile with lithium dimethylaminoborohydride in THF at room temperature gave only recovered starting material. Increasing the temperature to 65 °C, however, afforded a 75% isolated yield of benzylamine. Simple, non-reactive functional groups, such as alkyl groups or alkoxy groups are well tolerated, and excellent isolated yields of the corresponding benzylamines were obtained (Figure 9). The temperature sensitivity of the nitrile group reduction in benzonitriles permits the selective reduction of sensitive functional groups in the presence of the nitrile group. Thus, treatment of ethyl 4-cyanobenzoate with lithium pyrrolidino-borohydride in THF at room temperature afforded a 99% GC yield of 4-cyanobenzyl alcohol. Surprisingly, similar treatment of 4-cyanobenzyl bromide with lithium dimethylaminoborohydride afforded a 78% yield of the nitrogen transfer product 4-cyanobenzylamine borane complex (Figure 10). The nitrogen transfer reaction will be discussed subsequently.
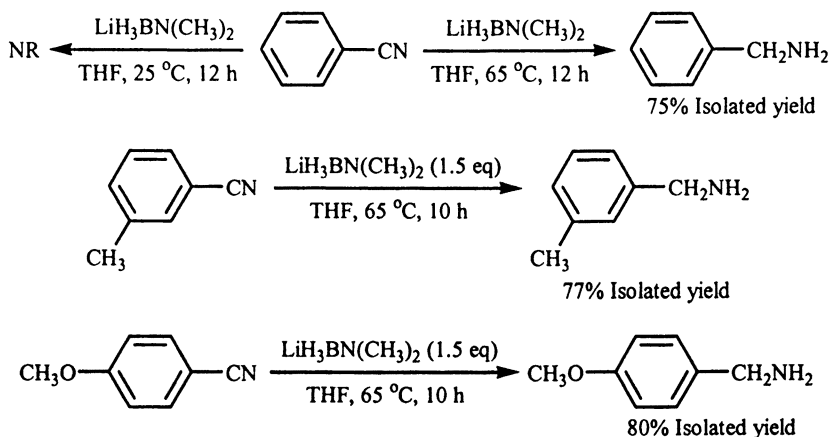
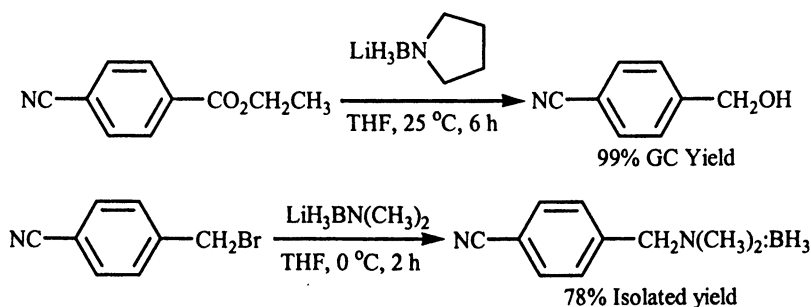Figure 9. Reduction of benzonitriles with lithium dimethylaminoborohydride.

Figure 10. Selective reductions of functional groups in benzonitriles.

Nitrogen Transfer Reactions

During the time we were studying the nitrogen transfer reaction discovered with 4-cyanobenzyl bromide and lithium dimethylaminoborohydride, Vedejs (9) reported an example of this reaction with aziridines. Treatment of 2-methylaziridine with BH_3 first gave the borane complex which was deprotonated with sodium hydride to give the corresponding sodium aminoborohydride. Treatment of the sodium aminoborohydride with methyl iodide afforded a 1:10 mixture of two isomeric N-methylaziridine borane complexes (Figure 11).

We recently described our expanded study of the synthesis of tertiary amine-boranes from benzyl and alkyl halides (Figure 12) (10). This reaction has

an advantage in the preparation of monoalkylated amines, since the amine produced is protected from further alkylation as the amine-borane complex. This chemistry has been extended to the preparation of complex diamines and also simple aliphatic amines (Figure 13).
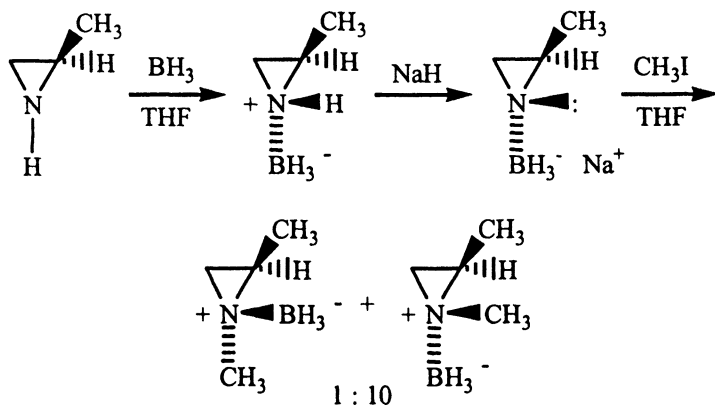
Figure 11. Nitrogen transfer reactions with sodium aziridinylborohydrides.
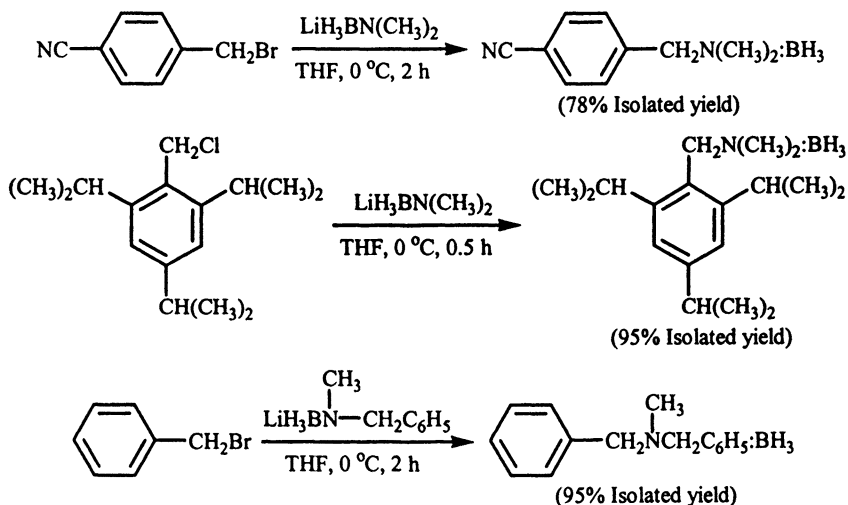
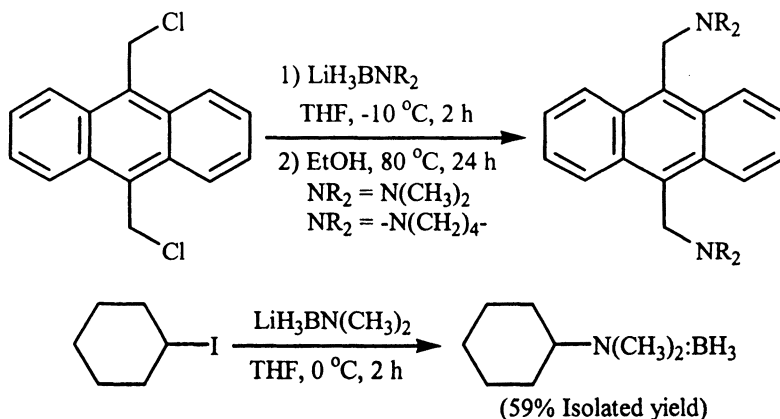*Figure 12. Nitrogen transfer reactions with benzyl halides and lithium dialkylaminoborohydrides.*

Figure 13. Lithium dialkylaminoborohydrides in the synthesis of complex diamines and simple aliphatic amines.

Tandem Nitrogen Transfer/Reduction Reactions

The reaction of benzonitriles containing halogens has provided some very interesting results. Treatment of 4-chlorobenzonitrile with lithium dimethylaminoborohydride in refluxing THF afforded a 55 % yield of a mixture of 4-chlorobenzylamine (the expected product), benzylamine (the result of dechlorination and reduction), and 4-chloro-*N,N*-dimethylbenzylamine. In contrast, reaction of 2-chlorobenzonitrile with lithium dimethylaminoboro-hydride under the same conditions gave a 91% isolated yield of a 70/30 mixture of 2-(dimethylamino)benzylamine (the result of nucleophilic aromatic substitution of the chlorine by the dimethylamino group, another example of nitrogen transfer, followed by reduction of the nitrile group) and 2-chlorobenzylamine (Figure 14). We have designated this displacement/reduction sequence as tandem amination/reduction.

The tandem amination/reduction was further studied with other halogenated benzonitriles. Treatment of 2-fluorobenzonitrile and 4-fluorobenzo-nitrile with lithium pyrrolidinoborohydride in THF at reflux afforded 73% and 89% yields, respectively, of the corresponding pyrrolidinobenzonitriles (Figure 15). Reaction of 2-chlorobenzonitrrile with lithium pyrrolidinoborohydride under similar conditions gave analogous results to those obtained with lithium dimethylaminoborohydride – a 70/30 mixture of 2-(pyrrolidino)benzylamine and

2-chlorobenzylamine. Treatment of 2-chlorobenzonitrile with pyrrolidine under similar conditions gave only recovered starting material (Figure 16).
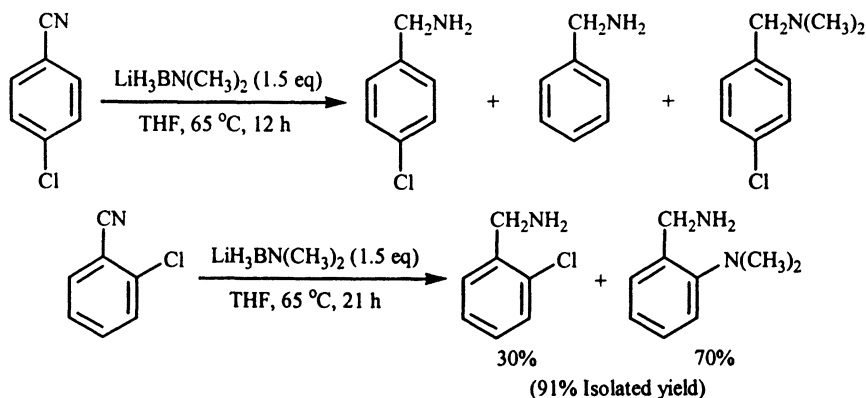

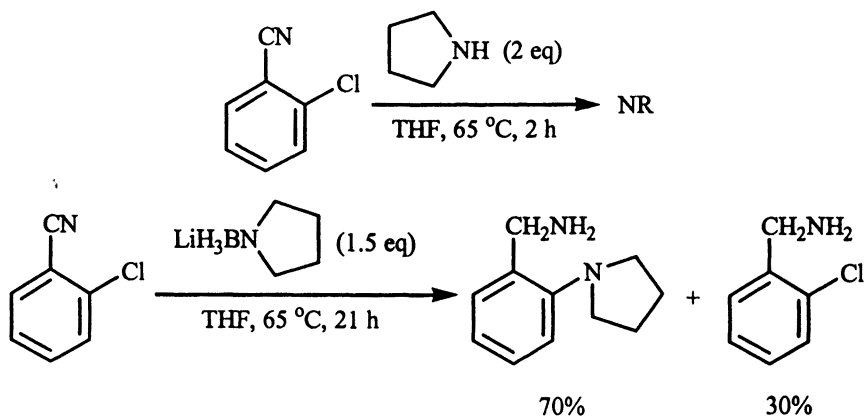Figure 14. Reaction of chlorobenzonitriles with lithium dimethylaminoborohydride.

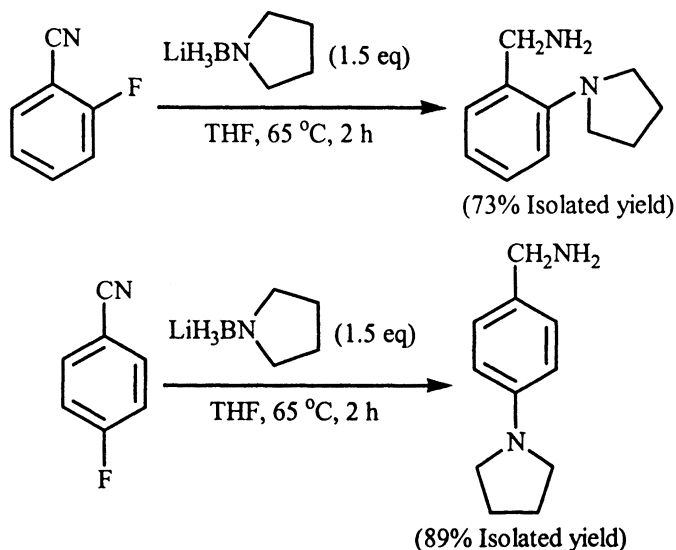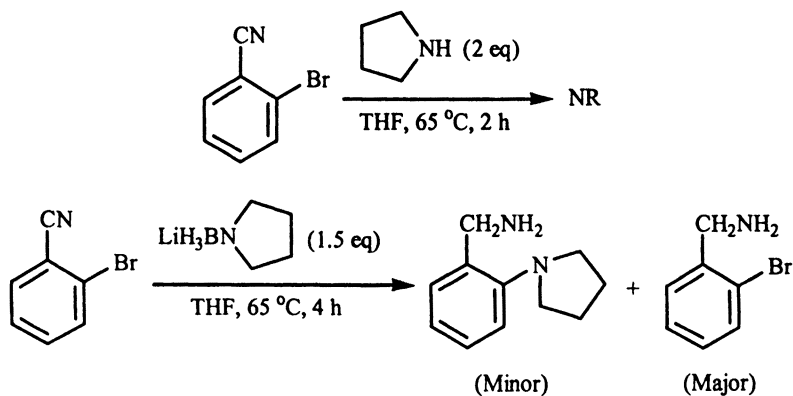Figure 15. Reaction of 2-chlorobenzonitrile with pyrrolidine and lithium pyrrolidinoborohydride.

Figure 16. Reaction 2-fluoro- and 4-fluorobenzonitrile with lithium pyrrolidinoborohydride.

Reaction of 2-bromobenzonitrile with lithium pyrrolidinoborohydride gave 2-bromobenzylamine as the major product, with the tandem reduction product becoming the minor product. Treatment of 2-bromobenzonitrile with pyrrolidine under similar conditions afforded only recovered starting material (Figure 17).

Figure 17. Reaction of 2-bromobenzonitrile with pyrrolidine and lithium pyrrolidinoborohydride.

Conclusions

Since the initial discovery of lithium aminoborohydrides (LABs) in 1994, these reagents have found increasing use in organic synthesis. With the discovery of the broader personalities of these reagents described in this paper, we have opened a whole new frontier of LAB chemistry which is only beginning to be explored.

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Chapter 3

New Stereoselective Transformations Involving Organoboranes and Organozinc Compounds

Applications of the Boron–Zinc Chain Reaction and the Diastereoselective Migration of Organoboranes

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The boron-zinc exchange is an unique way for preparing chiral secondary alkylzinc reagents which are configurationally stable over a wide temperature scale. Coupled with the thermal rearrangement of tertiary organoboranes, a broad range of open-chain and cyclic polyfunctional molecules have been prepared. In addition, several examples of a diastereoselective remote C-H activation have been studied.

Introduction

Although organoboranes have found numerous applications in organic synthesis (*1-3*), there is still a need to increase their reactivity with many classes of organic electrophiles, especially in the case of alkylboranes. The boron-zinc exchange reaction constitutes an excellent method for increasing the reactivity of organoboranes, since the resulting organozincs react smoothly with a wide range

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of electrophiles in the presence of a transition metal catalyst such as Cu(I), Pd(0), and Ni(II) salts (*4*). In this chapter, two new aspects of the chemistry of organoboranes involving transmetalations to organozinc compounds will be presented: the preparation of chiral secondary diorganozinc derivatives and the diastereoselective thermal migration of organoboranes.

## The boron-zinc exchange reaction as a source of polyfunctional organozincs

The boron-zinc exchange reaction constitutes a very mild method for preparing polyfunctional primary or secondary diorganozincs (*5*). A broad range of functional groups like an ester, cyanide, or iodide are tolerated. The exchange reaction is best performed with Et$_2$Zn for primary organoboranes, whereas secondary organoboranes require the use of *i*-Pr$_2$Zn. In the case of the functionalized olefins **1** or **2**, the hydroboration products react with Et$_2$Zn within 1 h at 0 °C affording the desired organozinc derivatives which can be readily allylated with allyl bromide in the presence of CuCN · 2 LiCl (*6,7*). Remarkably, neither the acidic hydrogens at the alpha position of the ester functions, nor the quinoline ring interfere with the exchange reaction (Scheme 1).

1) Et$_2$BH, Et$_2$O
2) Et$_2$Zn (2 equiv)
   neat, 0 °C, 1 h

3) CuCN · 2 LiCl cat.
   allyl bromide

1

EtO$_2$C
EtO$_2$C

overall yield: 86 %

1) Et$_2$BH, Et$_2$O
2) Et$_2$Zn (2 equiv)
   CH$_2$Cl$_2$, rt, 0.5 h

3) CuCN · 2 LiCl cat.
   allyl bromide

2

AcO

overall yield: 95 %
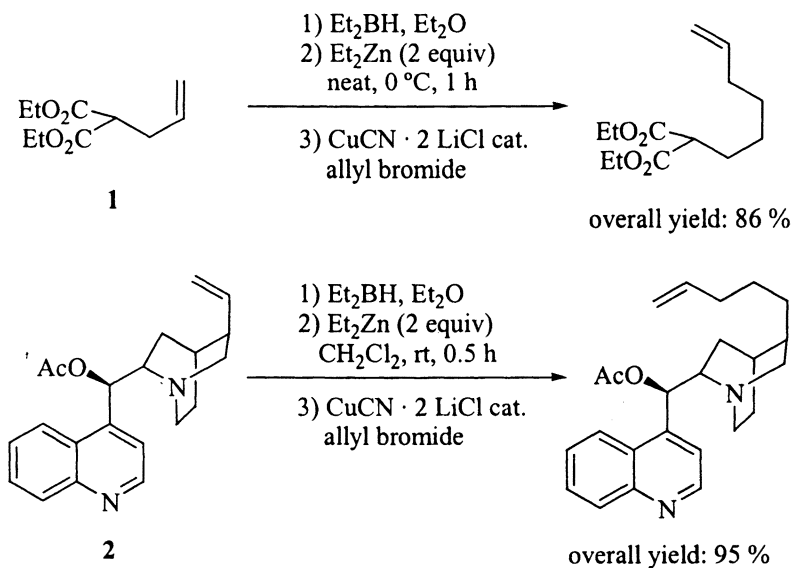
Scheme 1: Hydroboration of functionalized olefins

Preparation of chiral secondary dialkylzincs

Because of the high covalent character of the carbon-zinc bond, secondary organozincs of type 3 have a high configurational stability and are excellent candidates for the preparation of chiral secondary alkyl organometallics (Scheme 2). To be synthetically useful, the boron-zinc exchange has to be stereoselective, the formed organozinc derivatives should be configurationally stable under the reaction conditions used (solvents, temperature, additives), and finally the reaction of the chiral zinc organometallic with an electrophile has to be stereoselective (either retention or inversion).
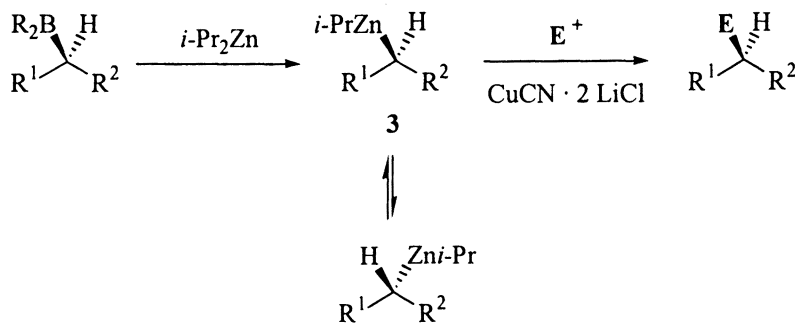
Scheme 2: the problem of the configurational stability of diorganozincs

Fortunately, all these conditions are fulfilled and the asymmetric hydroboration of 1-phenylcyclopentene with (-)-IpcBH$_2$ gives the secondary organoborane **4** (94 % *ee*) which, after treatment with Et$_2$BH (50 °C, 16 h), reacts with *i*-Pr$_2$Zn in THF (25 °C, 4 h) furnishing the secondary mixed diorganozinc reagent **5**. The treatment with Et$_2$BH is required to exchange the bulky terpenyl ligand. The allylation of **5** in the presence of CuCN · 2LiCl provides the desired product **6** with an excellent *trans:cis* ratio of 98:2. This result demonstrates the configurational stability of **5** as well as its stereoselective reaction with an electrophile (Scheme 3).

An extension to acyclic systems is possible. *Z*- and *E*-styrenes **7**, e. g., undergo the same sequence of reactions furnishing in the first case the secondary alkylzinc reagent *anti*-**8**, whereas with *E*-styrene the *syn*-organozinc reagent (*syn*-**8**) is obtained preferentially (*8*). After allylation, the expected products *anti*-**9** and *syn*-**9** are obtained. Excellent results are also obtained with the cross-coupling of the chiral organozincs with 1-bromoalkynes as shown in Scheme 4. In this case an almost perfect *anti:syn* selectivity is observed (> 99:1). This is certainly due to the mild reaction conditions used for this cross-coupling (-50 °C) (*9*).
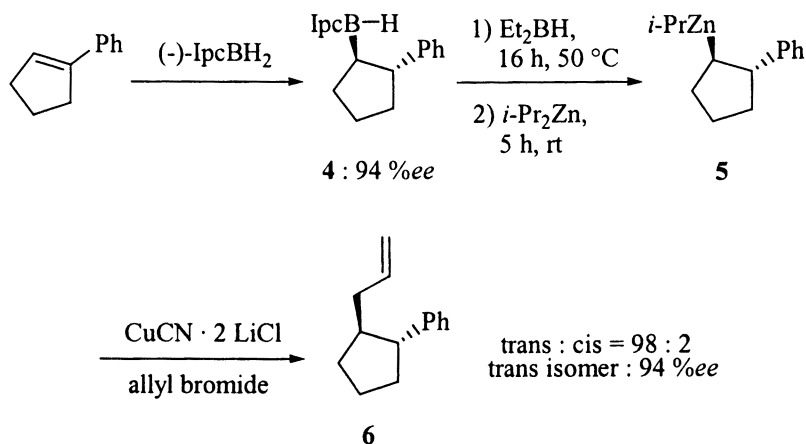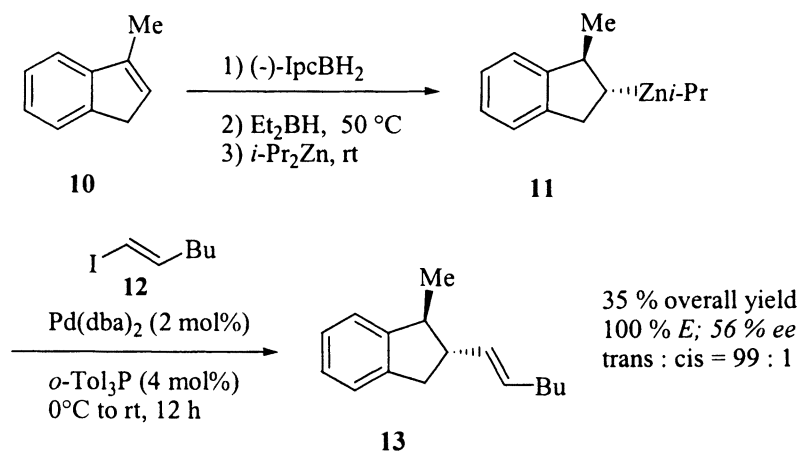
Scheme 3: The stereoselective preparation of chiral cyclic diorganozincs

Pd(0)-catalyzed reactions also occur with retention of configuration. Thus, the hydroboration of 3-methylindene **10**, followed by a boron-zinc exchange reaction with *i*-Pr$_2$Zn, gives the secondary dialkylzinc reagent **11** which undergoes a Pd(0)-catalyzed reaction with alkenyl iodides, such as **12**, providing only the *trans*-indene **13** (Scheme 5) (*10*).
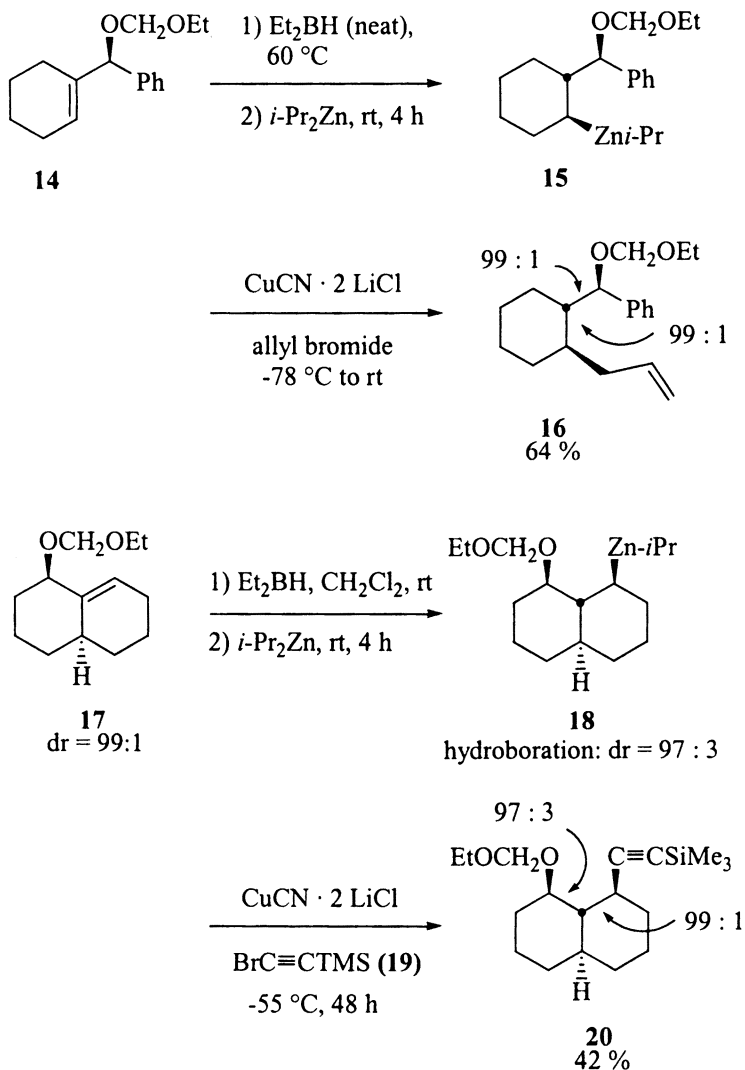
The asymmetric hydroboration constitutes an excellent way for preparing chiral organoboranes (*11,12*). However, the diastereoselective hydroboration of compounds readily obtained in optically pure form is a viable alternative. Thus, the hydroboration of the allylic ether **14** is completely diastereoselective and gives a diastereometrically pure organoborane which, after boron-zinc exchange, affords the stereochemically pure diorganozinc reagent **15**. Allylation of **15** in the presence of a Cu(I) salt affords product **16** in 64 % overall yield (Scheme 6). Starting with the bicyclic alcohol **17**, it is possible to control 4 chiral centers. The hydroboration of **17** with Et$_2$BH furnishes selectively the corresponding organoborane which after boron-zinc exchange results in the organozinc derivative **18**. A copper-mediated cross-coupling with bromoalkyne **19** furnishes compound **20** as one major diastereomer (Scheme 6) (*13*). The examples of schemes 3-6 demonstrate that the boron-zinc exchange is an excellent method for preparing chiral secondary organozinc reagents, both in cyclic and acyclic system. These organometallics should be of great utility for the preparation of complex organic molecules.
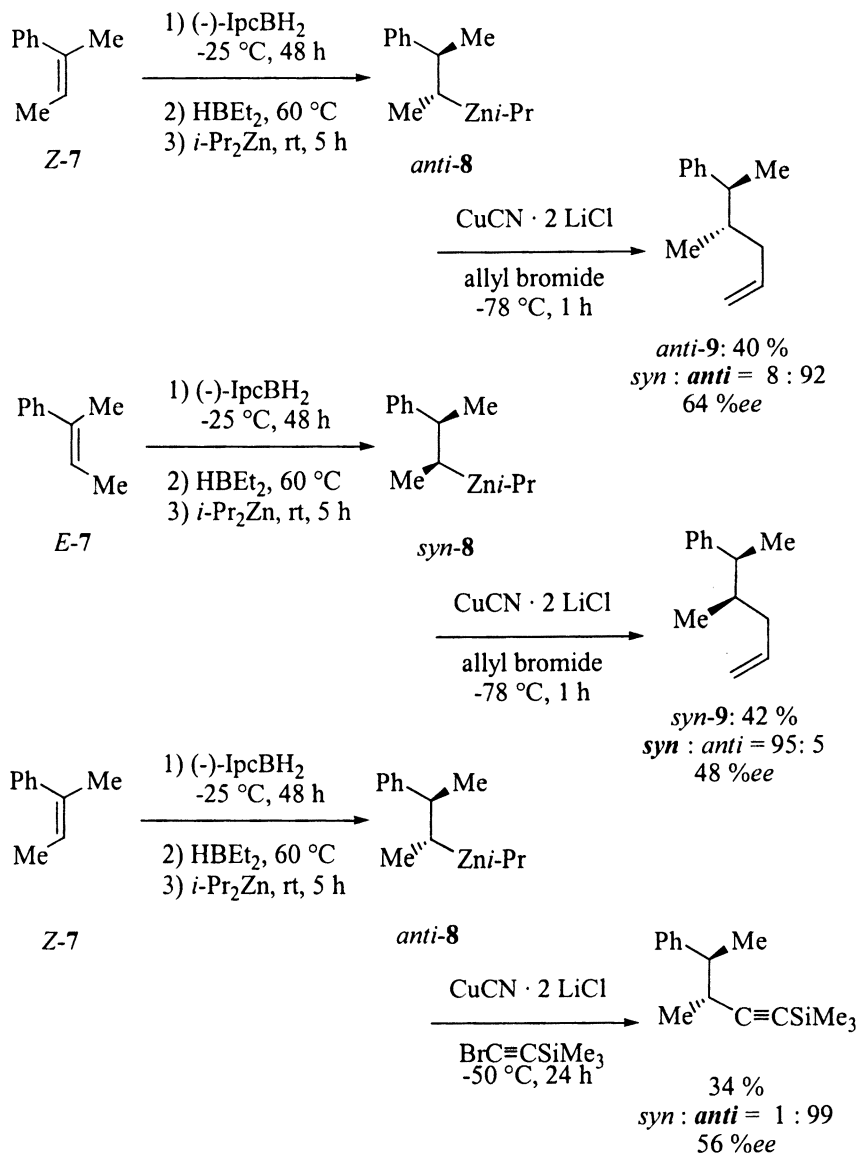
Scheme 4: The stereoselective preparation of chiral acyclic diorganozincs

Me

10

1) (-)-IpcBH$_2$

2) Et$_2$BH, 50 °C
3) i-Pr$_2$Zn, rt

Me

$\cdots$Zni-Pr

11

$I\diagup\diagdown$Bu

12

Pd(dba)$_2$ (2 mol%)

o-Tol$_3$P (4 mol%)
0°C to rt, 12 h

Me

$\cdots$$\diagup\diagdown$Bu

13

35 % overall yield
100 % *E; 56 % ee*
trans : cis = 99 : 1

Scheme 5: Pd(0)-catalyzed cross-coupling with chiral diorganozincs

Scheme 6: Diastereoselective hydroboration and stereoselective B/Zn-exchange

The diastereoselective thermal migration of organoboranes

The activation of non-activated C-H bonds is an important research field (*14*). In most cases, transition metal complexes have been used for this purpose (*14-19*). In this chapter, we wish to describe a stereoselective allylic C-H activation involving the thermal rearrangement of organoboranes (Scheme 7) (*20-22*). The observed stereochemistry may be best explained by a dehydroboration-rehydroboration mechanism, but mechanistic studies indicate that a more complex pathway involving a second molecule of BH_3 may be involved.
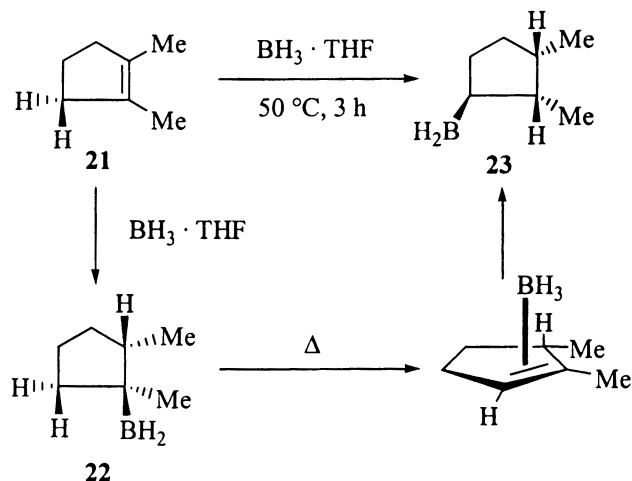
Scheme 7:Thermal migration of cyclic boranes

Thus, the hydroboration of the tetrasubstituted olefin **21** first produces the normal hydroboration product which undergoes a 1,2-migration at 50 °C, due to the steric hindrance of the resulting tertiary organoborane **22**, leading to the new secondary organoborane **23**. The reaction proceeds well with several bicyclic systems (Scheme 8) (*23*).

In the case of the symmetrical bicyclic olefin **24**, only one stereomeric migration product **25** is obtained leading after amination to the secondary amine **26**. In the case of the unsymmetrical bicyclic ring systems **27** and **28**, only a migration in the five membered ring is observed leading respectively to the amine **29** and alcohol **30** as a single diastereomer. Interestingly, in the case of the unsymmetrically substituted cyclopentene derivatives **31** and **32**, a regioselective migration occurs for **31** furnishing after oxidation the alcohol **33** as only one diastereomer. In the case of **32**, a fast rearrangement occurs for the intermediate tertiary organoborane **34**, but for **35** a prolonged heating of 48 h is necessary leading to a mixture of the alcohols **36** and **37** after oxidation (Scheme 9).
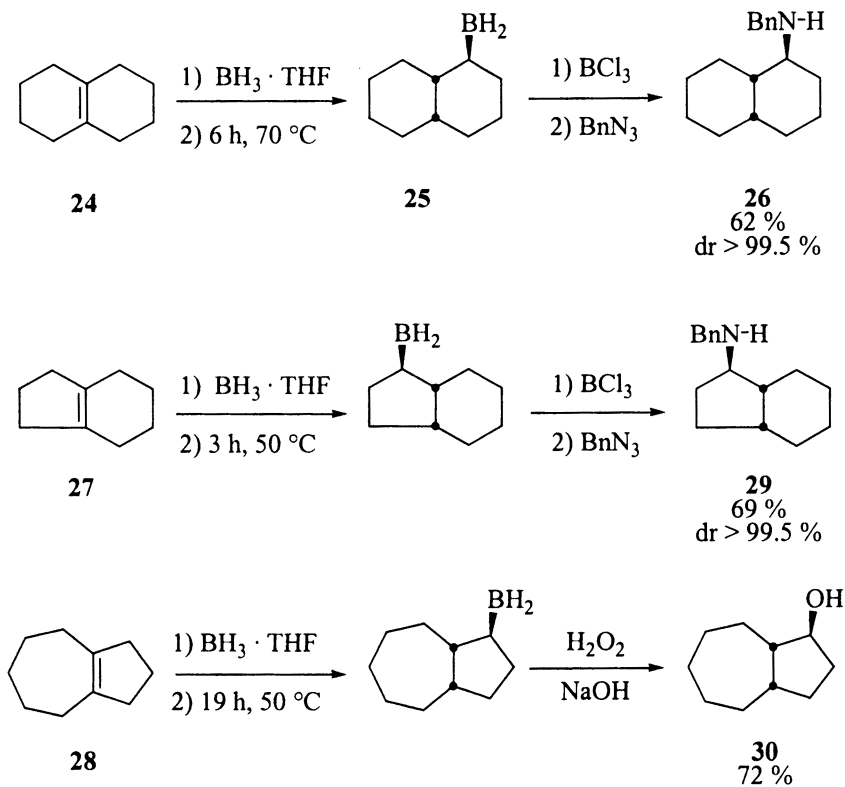
Scheme 8: Stereoselective preparation of bicyclic boranes via thermal migration
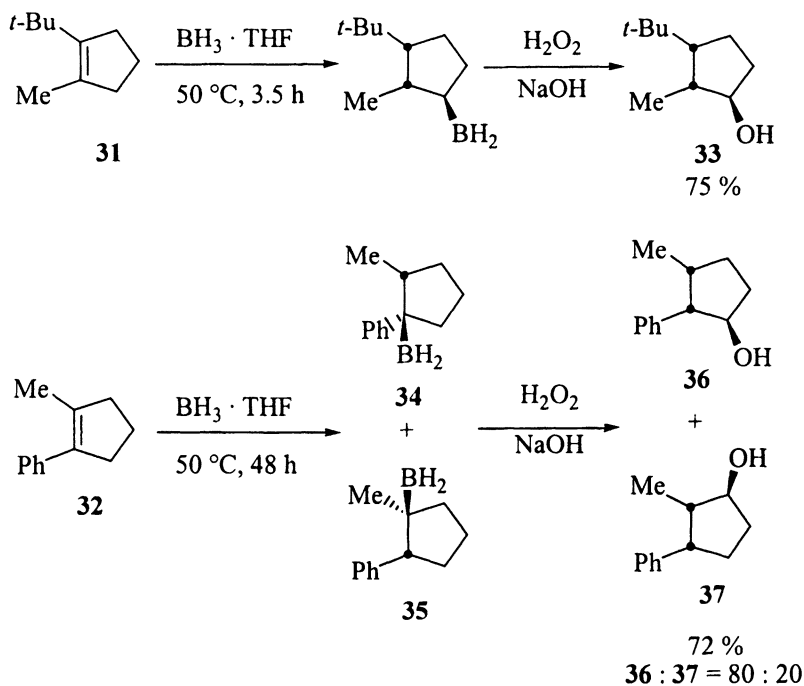
Scheme 9: The thermal migration of unsymmetrical hydroborated cyclopentenes

For *exo*-alkylidene cyclopentane derivatives such as **38** (Scheme 10), an exclusive rearrangement in the five membered ring is observed leading after amination to the *trans*-cyclopentane derivative **39** in 77 % yield (*24*). Remarkably, in the case of four membered rings such as **40** (Scheme 10), a new rearrangement of the intermediate tertiary organoborane **41** occurs affording the boracycle **42** furnishing the *meso*-1,4-diol **43** as only isomer after alkaline oxidation (*23*).

Open-chain tetrasubstituted olefins are also good substrates for the hydroboration/ thermal migration sequence (*24*). Thus, the hydroboration of Z- and E-stilbenes **44** with $BH_3 \cdot$ THF followed by heating the reaction mixtures at 70 °C for 12 h furnishes after oxidation with H_2O_2 respectively the two diastereoisomeric diols *syn*- and *anti*-**45** with excellent stereoselectivity (dr > 99.5 %) and 90 % yield (Scheme 11). The intermediate organoboranes *syn*- or *anti*-**46** can also be converted into a secondary amine by treatment with BCl_3 and benzyl azide (*22,25*). By the reaction with ethylene, *syn*-**46** leads to the corresponding diethylorganoborane which after treatment with Et_2Zn (10 equiv, 0 °C, 3 h) affords a mixed organozinc reagent (Scheme 12) which in the presence of CuCN $\cdot$ 2LiCl undergoes allylation, alkynylation or benzoylation reactions in satisfactory yields (*24*).
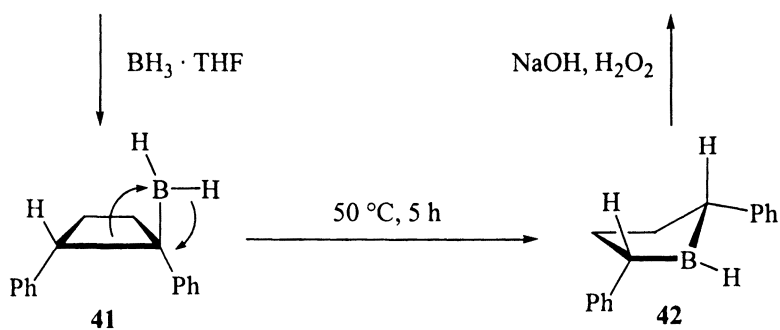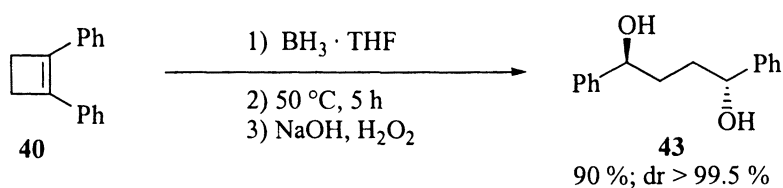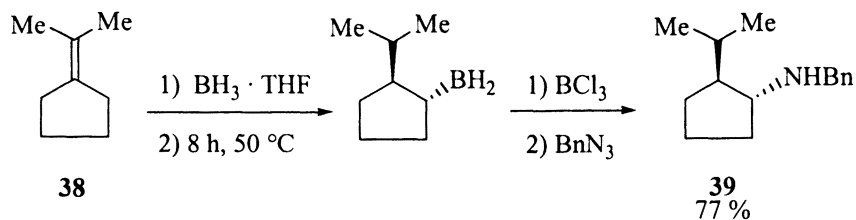
Scheme 10: Hydroboration of cyclobutenes and thermal migration
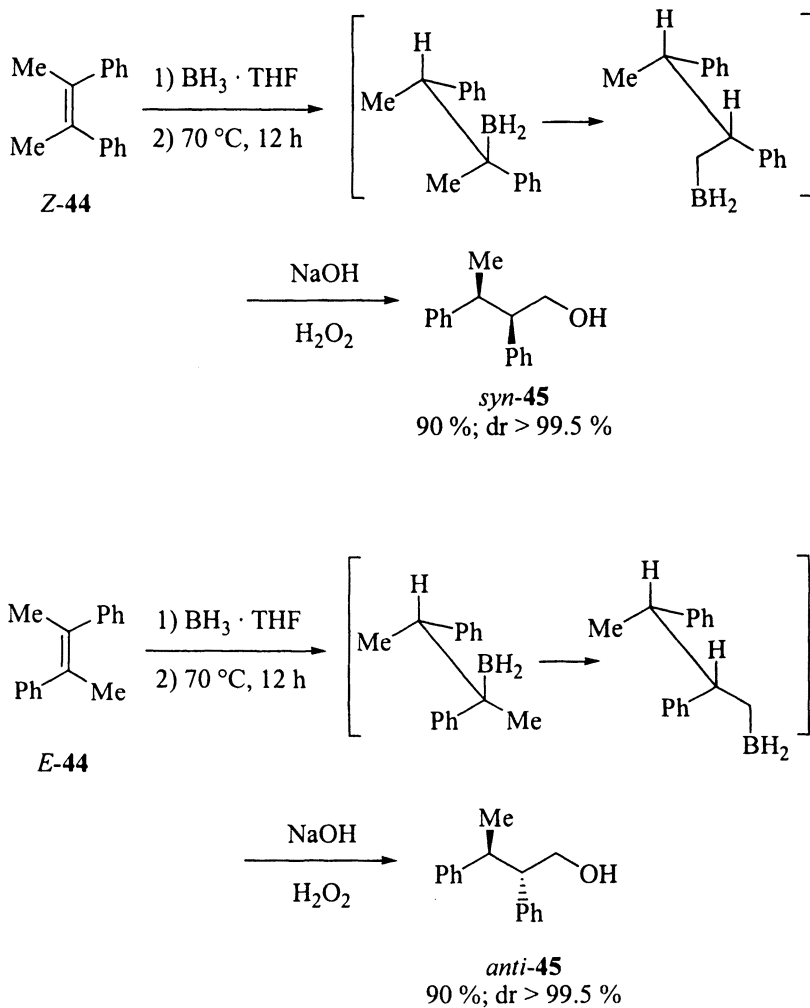
Scheme 11: Thermal migration of acyclic organoboranes
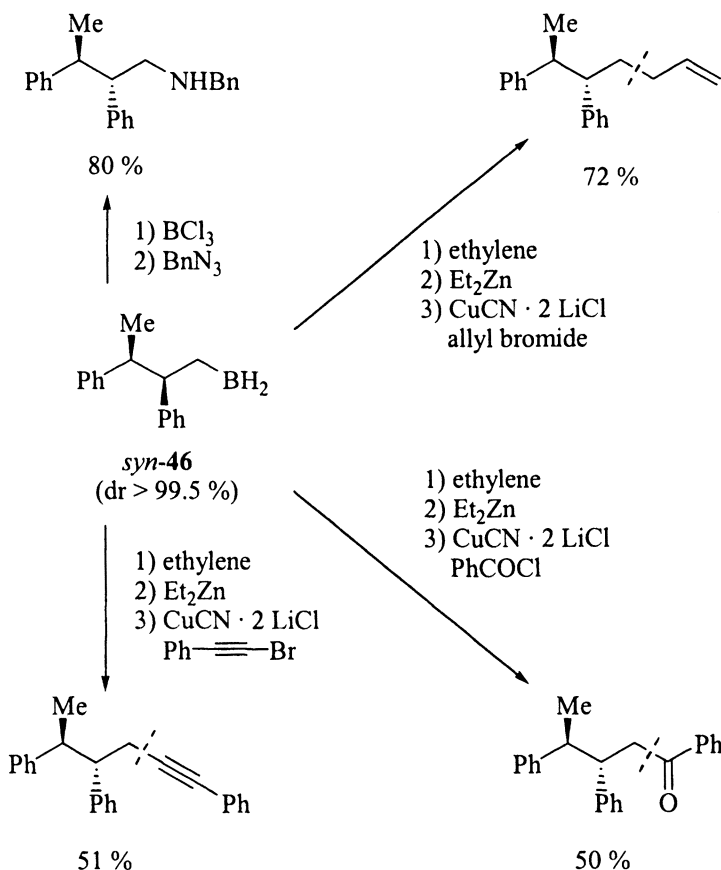
Scheme 12: Conversion of migrated organoboranes to various products

Starting with the ethyl-substituted olefin **47**, there are two possibilities for the migration since two diastereotopic hydrogen atoms H^a and H^b can undergo the migration via **48** after the initial hydroboration. Only one of these two hydrogens undergoes selectively the rearrangement leading to the secondary organoborane **49**. This may be explained by assuming that the most stable borane-olefin complex **50** is formed having the bulky benzyl and the methyl group in a trans-arrangement. After oxidative workup (NaOH, H$_2$O$_2$) or copper-mediated allylation, the expected products **51** and **52** are obtained as only one diastereomer (Scheme 13; dr > 99.5 %).
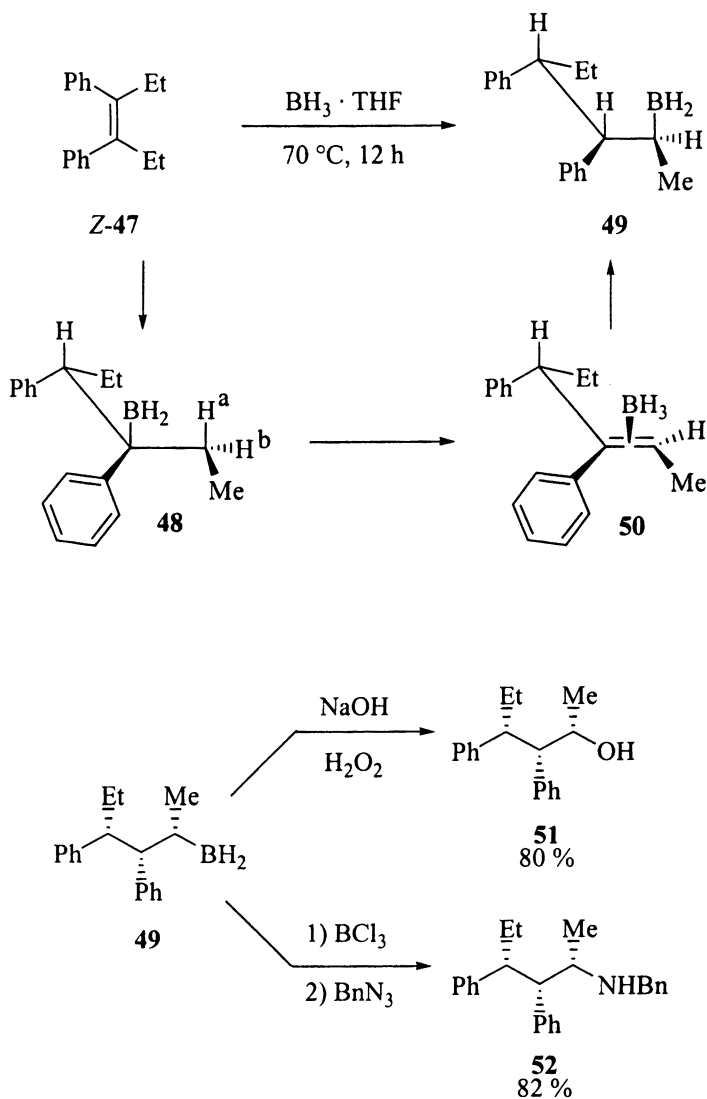
Scheme 13: Diastereoselective thermal borane migration

This method can be used to control the configuration of three contiguous centers in an open-chain system. Thus, the *Z*- and *E*-ethyl substituted stilbenes **47** afford, after hydroboration and thermal migration, the diastereomerically pure

organoboranes **53** and **54**. These can be transmetalated to the corresponding organozinc reagents by the treatment with *i*-Pr$_2$Zn (rt, 2 h) with retention of configuration. After a copper-mediated allylation reaction the products **55** and **56** are obtained (Scheme 14) (*26*).
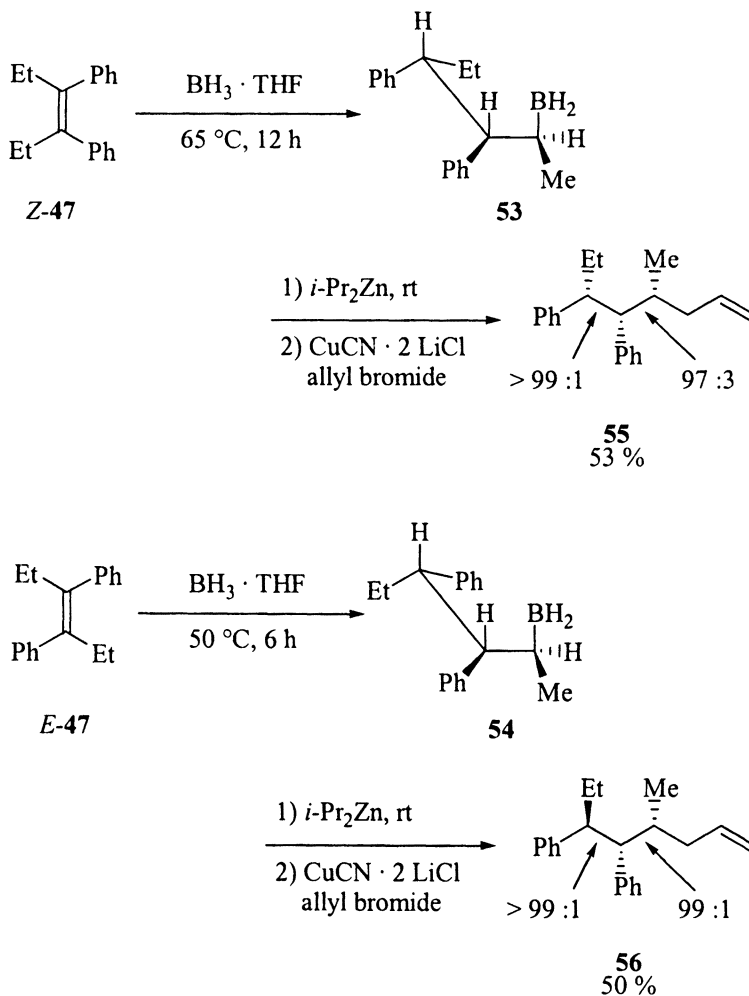
Scheme 14: Diastereoselective preparation of acyclic molecules via the thermal borane migration

Interestingly, the unsymmetrically substituted olefin **57** provides after hydroboration with BH$_3$ · THF and thermal migration only the organoborane **58**. This excellent regioselectivity is obtained despite the initial unselective hydroboration leading to **59** and **60**. The intermediate tertiary organoborane bearing an ethyl substituent (**59**) undergoes a fast thermal rearrangement. On the other hand, the organoborane having a methyl as substituent (**60**), undergoes a preferential dehydroboration via the boron-olefin complex **61** leading to **59** which is then converted into **58**. The rearranged organoborane **58** can be converted into the amine **62** (79 %), the ketone **63** (69 %), and the alkyne **64** (66 %) with excellent diastereoselectivities and satisfactory yields (Scheme 15) (*26*).
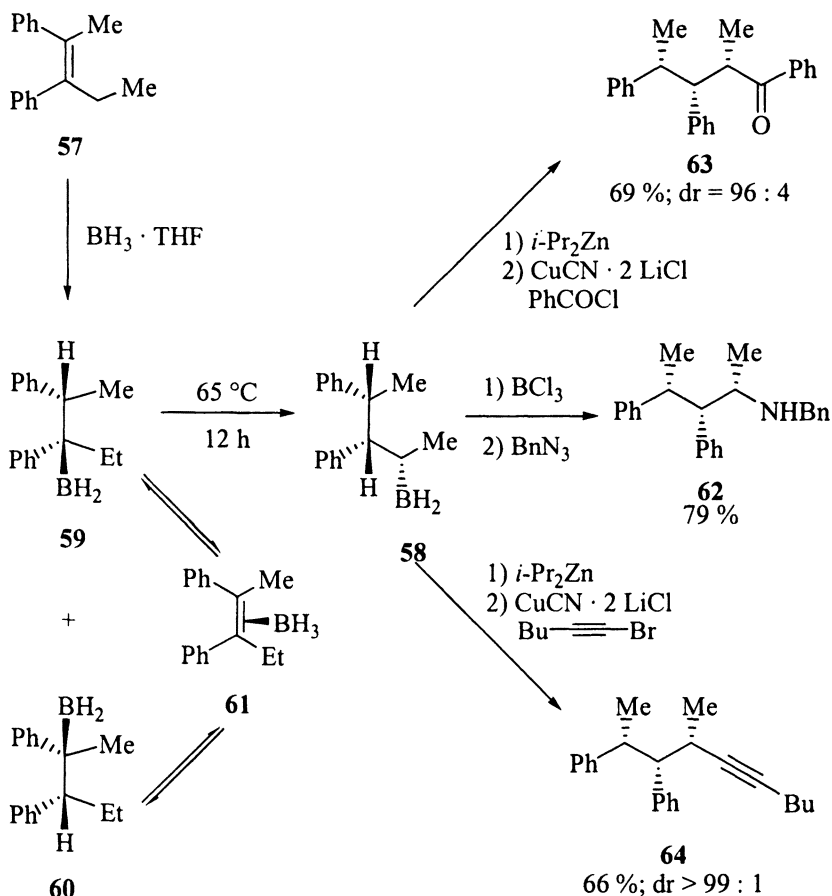
Scheme 15: The regioselective migration of acyclic tertiary boranes

The remote activation of C-H bonds is an important synthetic goal and some especially crowded tetrasubstituted olefins undergo such a reaction. Furthermore, in all the examples studied, this activation proceeds with high diastereoselectivity. Thus, the two *tert*-butyl substituted olefins **65** and **66** undergo, after the initial hydroboration and migration, an insertion into a remote C-H bond forming the boracycles **67** and **68** which after oxidation furnish the two diols **69** and **70** as one diastereoisomer (Scheme 16) (*24*).

Conclusion

The boron-zinc exchange is an excellent method for activating the C-B bond and allows the transition metal catalyzed reactions with many types of electrophiles. Furthermore, it allows an unique access to chiral secondary alkylzinc organometallics, without the need of any stabilizing neighboring heteroatom. The thermal rearrangement of organoboranes is a powerful method for controlling stereocenters in cyclic and acyclic molecules. With appropriate substrates, diastereoselective remote C-H activation reaction can be accomplished.

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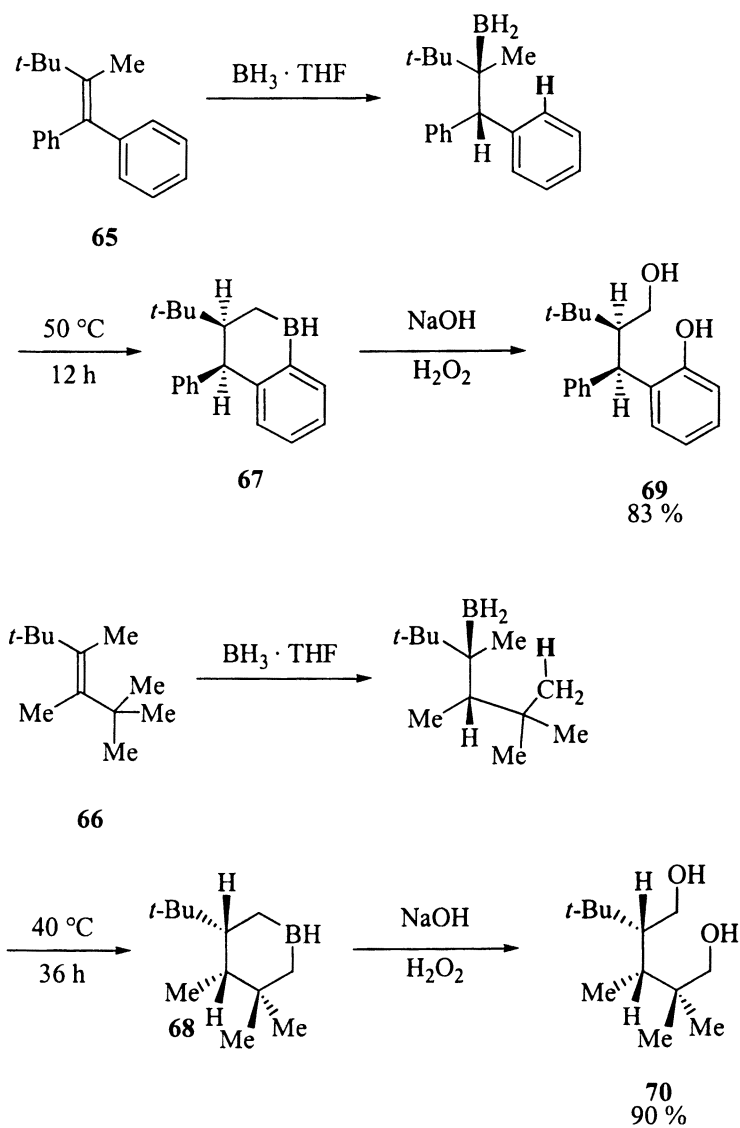
Scheme 16: Remote C-H activation

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Chapter 4

Synthesis and Cyclizations of Conjugated Systems Derived from Organoboranes

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Conjugated systems, including 1,3-butadienes, diene–allenes, enyne–allenes, enediynes, dienediynes, and enediallenes, were synthesized via organoboranes. A wide array of cascade cyclization reactions involving high energy intermediates, such as *o*-isotoluenes, biradicals, *o*-quinodimethanes, benzocyclobutadienes, and enyne–ketenes, were initiated from these unsaturated compounds.

Introduction

Unsaturated compounds are inherently reactive because transformation of a π bond to a σ bond provides ca. 20 kcal/mol of energy. This energy could be used to power a variety of chemical transformations. The Diels-Alder reaction is a classical example. Cycloaddition of 1,3-butadiene with ethylene gives cyclohexene with an exchange of two π bonds in the reactants for two σ bonds in the product. Each chain extension of the radical polymerization of ethylene is sustained by the

conversion of a π bond to a σ bond. The cobalt-mediated [2 + 2 + 2] cycloaddition reaction of a diacetylene with an alkyne produces a substituted benzene, trading three π bonds in the reactants for three σ bonds in the product (*1*). The aromaticity of the resulting benzene ring provides additional driving force for the reaction.

The γ-trialkylsilyl-substituted allylboranes 1 and allenylboranes 2 and 3 have found useful applications in the synthesis of unsaturated compounds. The trimethyltin chloride-induced transformations of the organoborate complexes 4 also provide easy entries to a variety of unsaturated molecules for subsequent synthetic elaborations.
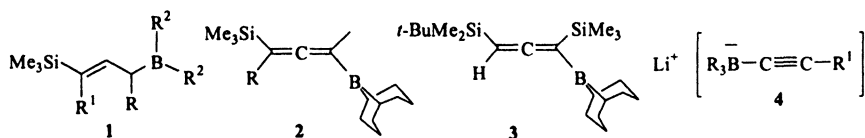
Results and Discussion

1,3-Butadienes via γ-(Trialkylsilyl)allylboranes

Hydroboration of **5** with 9-borabicyclo[3.3.1]nonane (9-BBN-H) furnished the γ-(trimethylsilyl)allylboranes **1** (Scheme 1) (*2–6*). Condensation of **1a** with a variety of aldehydes produced **6** in situ. Subsequent treatment with sodium hydroxide to induce a *syn* elimination and concentrated sulfuric acid to induce an *anti* elimination furnished the terminal 1,3-butadienes **7** and **8**, respectively. The high geometry purity of the resulting 1,3-butadienes could be attributed to high diastereoselectivity during condensation. Similarly, all four geometric isomers of representative internal 1,3-butadienes were synthesized from **1b** and related compounds with high isomeric purity.
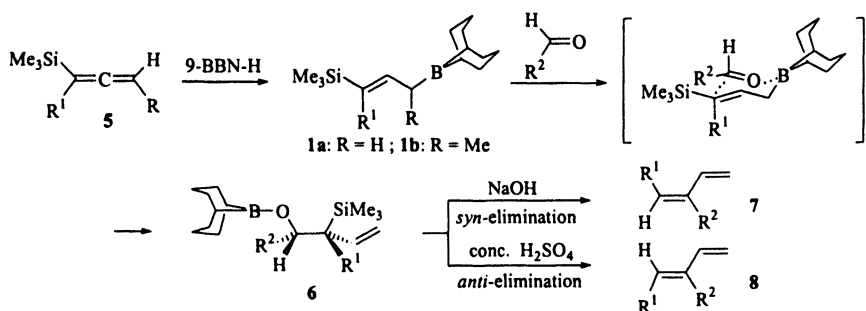
Scheme 1. Stereoselective Synthesis of 1,3-Butadienes.

5-Methylene-1,3-cyclohexadienes (*o*-Isotoluenes) and Diene–Allenes

Treatment of 4-methyl-2,3-pentadienal (**9**) with **1a** (R = H, R^1 = Me) followed by 2-aminoethanol afforded the condensation adduct **11a** with high diastereoselectivity (Scheme 2) (*7*). Interestingly, with **1b** (R = Me, R^1 = Me) the *Z* isomer was produced predominantly. The preference for the *Z* isomer was attributed to the α methyl group in **1b** favoring the axial position in the chair-like transition state **10** in order to avoid a severe *gauche* interaction that would occur between the rigid 9-BBN ligand and the equatorial α methyl group. Treatment of **11** with KH promoted a *syn* elimination reaction to produce the *o*-isotoluenes **13**. Apparently, the initially formed enyne–allenes **12** underwent a facile electrocyclic reaction to form **13**. On the other hand, treatment with concentrated sulfuric acid afforded the expected diene–allenes **14**.
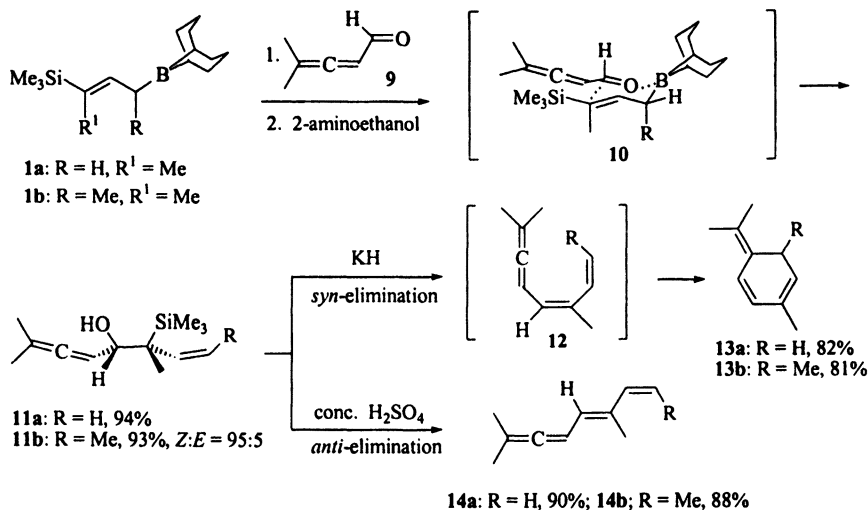
Scheme 2. o-Isotoluenes and Diene–Allenes via B-Allyl-9-BBN.

Similarly, condensation of **9** with **1c** furnished **16**, leading to the *o*-isotoluene **13b** and the diene–allene **18** (Scheme 3). The disubstituted double bond in **16** and **18** has exclusively the *E* geometry (>98%). Apparently, the less rigid cyclohexyl ligands alleviate the *gauche* interaction in the transition state. The 1,3-diaxial interaction with the methyl group at the γ position now predominates, pushing the α methyl group toward the equatorial position and producing the *E* geometry.
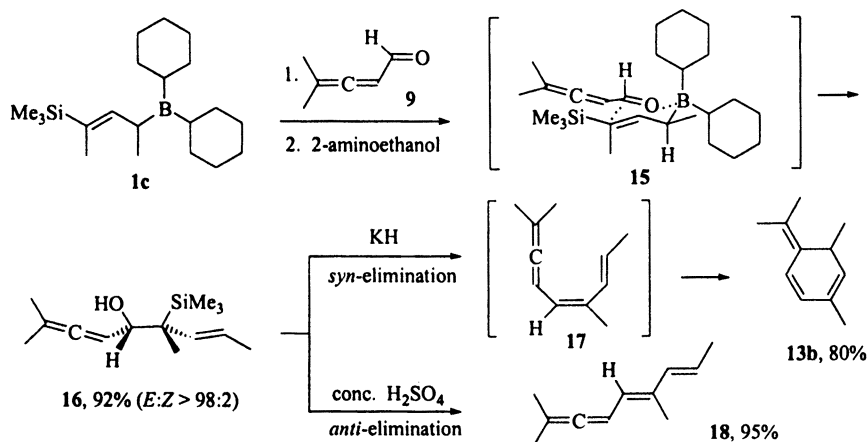
Scheme 3. o-Isotoluenes and Diene–Allenes via B-Allyldicyclohexylboranes.

Synthesis and Cascade Radical Cyclizations of Enyne–Allenes

Lithiation of **19** with *t*-butyllithium followed by *B*-methoxy-9-BBN and 4/3 $BF_3 \cdot OEt_2$ produced in situ the allenylboranes **2** (Scheme 4) (*8,9*). Subsequent condensation with **9** furnished **20** with high diastereoselectivity, allowing stereoselective transformations to the (*E*)-enyne–allenes **21** and the (*Z*)-enyne–allenes **22**.
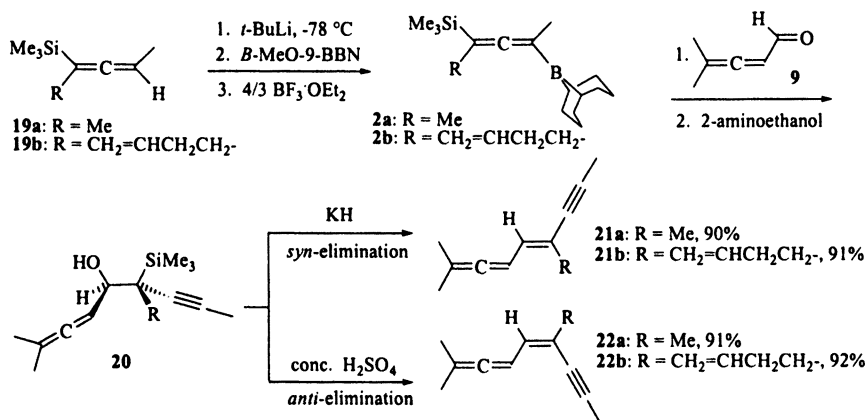
Scheme 4. Stereoselective Synthesis of Enyne–Allenes.

The Myers cyclization of enyne–allenes under mild thermal conditions provides an easy access to the α,3-didehydrotoluene biradicals (*10–18*). Thermolysis of **22b** in refluxing benzene generated the biradical **23** (Scheme 5). The phenyl radical center in **23** was then captured by the double bond intramolecularly, giving rise to the biradical **24**. A subsequent 1,5-hydrogen shift produced the *o*-quinodimethane **25**, which in turn underwent a [1,5] sigmatropic hydrogen shift to afford the indan **26**.
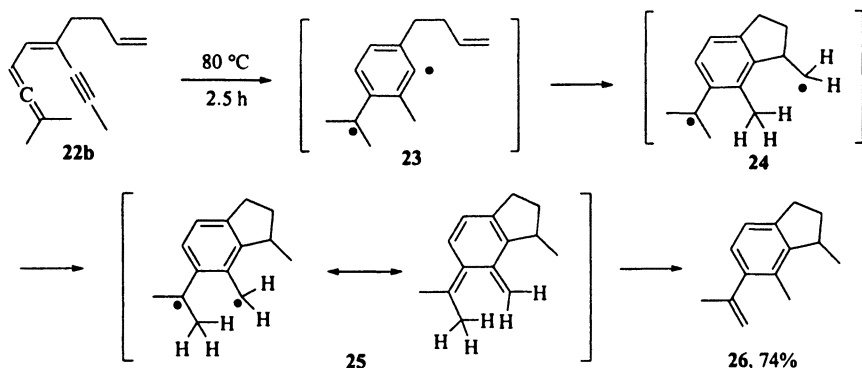
Scheme 5. Cascade Radical Cyclization of Biradicals from Enyne–Allenes.

By starting from the enyne–allene **27**, the *o*-quinodimethane **28** was captured in an intramolecular Diels-Alder reaction to give **29** having the tetracyclic steroidal skeleton (Scheme 6) (*19,20*). It is worth noting that this cascade reaction could involve an energy loss of more than 100 kcal/mol with conversion of four π bonds in **27** to four σ bonds in **29** along with the formation of a benzene ring.
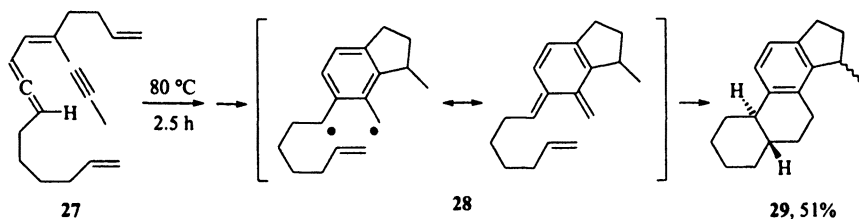
Scheme 6. Thermally-Induced One-Step Construction of the Steroidal Skeleton.

Enediynes via Allenylboranes

Condensation of **2a** with the acetylenic aldehyde **30** produced both **31a** and **31b** with low diastereoselectivity (Scheme 7) (21). Consequently, a mixture of the *E* and the *Z* isomers of the enediyne **32** was obtained. The poor selectivity of the condensation step is presumably due to a relatively small difference in steric demands between the cylindrical acetylenic moiety and the hydrogen atom of the aldehyde carbonyl in **30**.
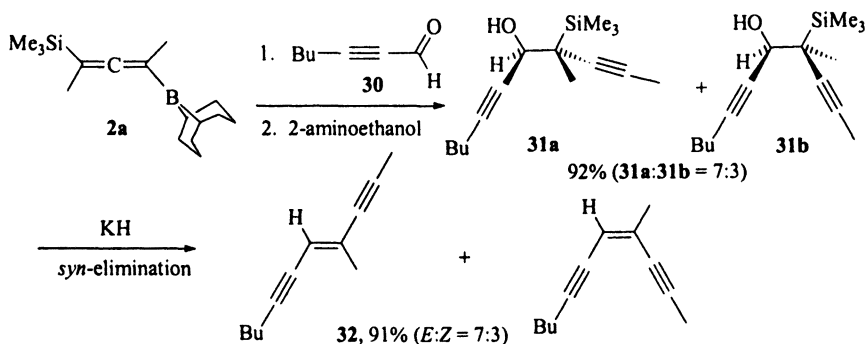
Scheme 7. Synthesis of Enediynes.

In order to improve diastereoselectivity with the acetylenic aldehydes, the allenylborane **3** with a greater difference of the steric demands of the two groups at the γ carbon (*t*-butyldimethylsilyl vs. hydrogen) than that of **2a** (trimethylsilyl vs. methyl) was prepared for condensation with **30** (Scheme 8). Essentially only **33** was produced, leading to the enediynes **34** and **35** with high isomeric purity.
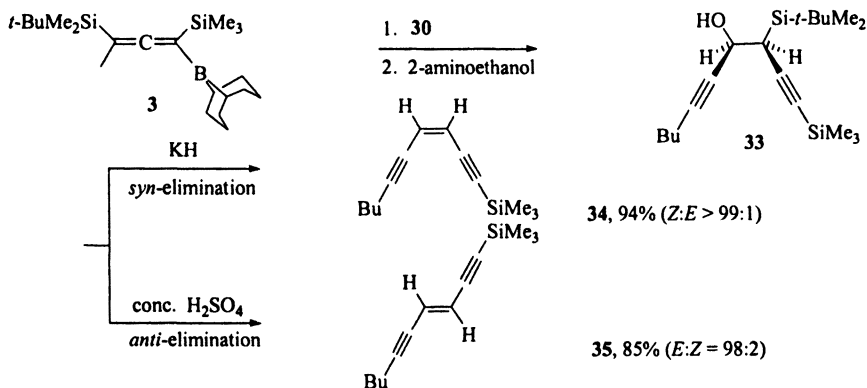
Scheme 8. Stereoselective Synthesis of Enediynes.

Dienediynes and Benzocyclobutadienes

The dienediynes **38** were readily synthesized via condensation of **3** with the enynyl aldehydes **36** followed by a *syn* elimination reaction of **37** (Scheme 9) (*22*). A variety of substituents could be placed at one of the acetylenic termini.

38a: R = Me₃Si, 78%; 38b: R = Bu, 80%
38c: R = Ph, 83%; 38d: R = isopropenyl, 81%
38e: R = 1-cyclohexenyl, 81%
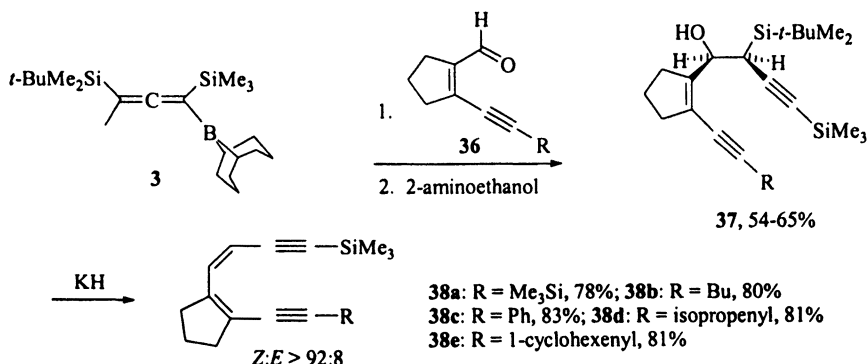
Scheme 9. Stereoselective Synthesis of Dienediynes.

On exposure to tetrabutylammoniun fluoride (TBAF) for desilylation, the dienediynes **38** underwent interesting cascade cyclizations to form unusual structures. For example, an initial electrocyclic reaction of the desilylated dienediyne **39** generated the enediallene **40**, which in turn underwent a second electrocyclic reaction to afford the benzocyclobutadiene **41** (Scheme 10). Dimerization of **41** in a Diels-Alder manner furnished **42** and subsequently the angular dimer **43**.
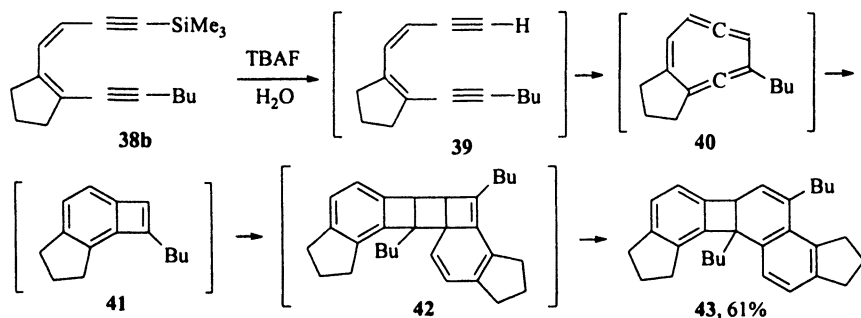
Scheme 10. Dimerization of Dienediynes via Benzocyclobutadienes.

Surprisingly, the presence of an isopropenyl group on the four-membered ring in **44** dramatically altered the dimerization pathway. A formal [4 + 4] cycloaddition reaction occurred, producing the 1,5-cyclooctadiene **45** (Scheme 11). The trans geometry of **45** was unequivocally established by an X-ray structure determination.
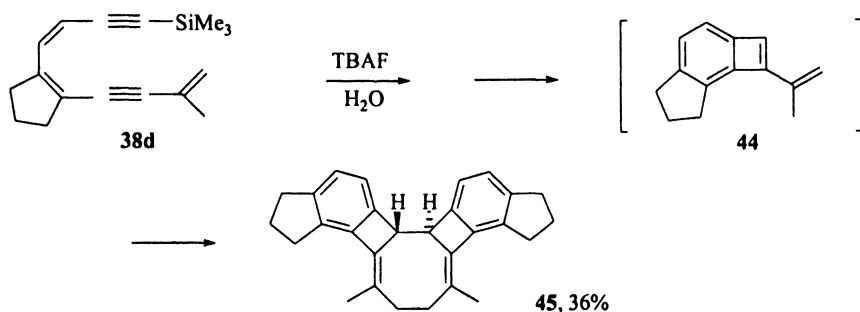
Scheme 11. *Formal [4 + 4] cycloaddition of 1-Alkenylbenzocyclobutadiene.*

The presence of a terminal alkynyl group in **46** and consequently in the condensation adduct **47** made it possible to use the Pd(PPh₃)₄-catalyzed cross-coupling reaction between **47** and aryl iodides to produce **48** (Scheme 12) (*23*). Subsequently, a variety of the aryl-substituted dienediynes **49** were obtained.

49a: R = H, 98%; **49b**: R = 4-Me₃Si, 98%
49c: R = 2-iodo, 95%; **49d**: R = 3-iodo, 72%
49e: R = 4-iodo, 84%
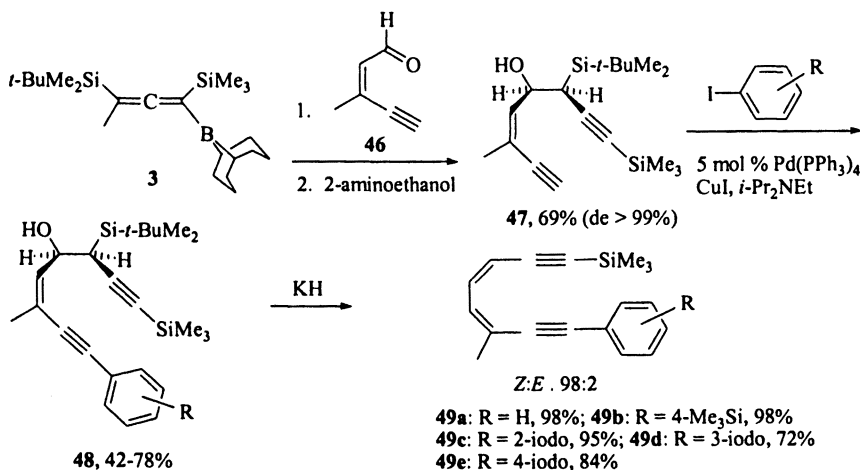
Scheme 12. *Stereoselective Synthesis of 1-Aryl-Substituted Dienediynes.*

Interestingly, the presence of a phenyl substituent on the four-membered ring of the benzocyclobutadienes **50** also changed the course of dimerization. The linear dimers **52** were produced presumably via an initial formation of the *syn* dimers **51**.

52a: R = H, 74%; **52b**: R = 4-Me₃Si, 54%
52c: R = 2-iodo, 47%; **52d**: R = 3-iodo, 40%
52e: R = 4-iodo, 43%
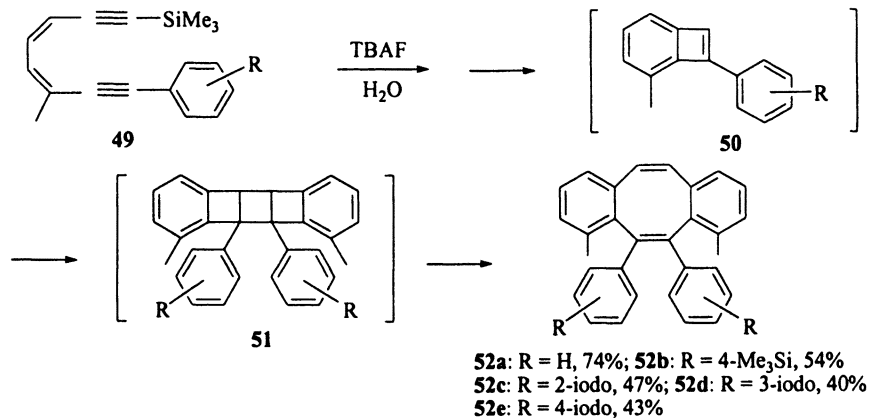
Scheme 13. Dibenzocyclooctatetraenes via 1-Aryl-Substituted Dienediynes.

A repeat of the coupling and dimerization sequence with **52e** produced the trimer **53**. Coupling of 1,4-diiodobenzene with two equiv of **47** appeared to lead to the oligomers/polymers **54** having multiple dibenzo[*a,e*]cyclooctenyl units.
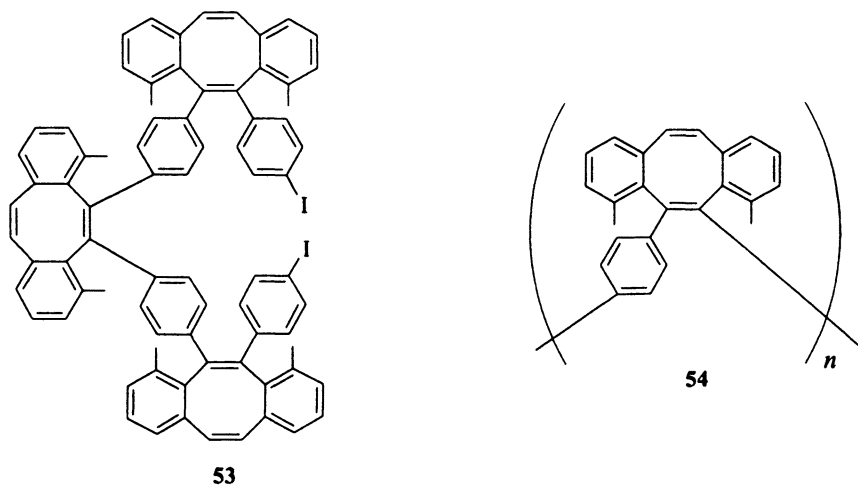
o-Isotoluenes via Diene–Allenes Derived from Organoborates

Hydroboration of 1-hexyne with dicyclohexylborane produced the alkenylborane **55**, which on treatment with the lithium acetylide **56** furnished the organoborate complex **57** (Scheme 14) (*24*). Trimethyltin chloride then induced a stereoselective migration of the 1-hexenyl group to the adjacent acetylenic carbon to afford the diene–allene **58** and subsequently the *o*-isotoluenes **59** and **60**. A variety of other *o*-isotoluenes were likewise synthesized.
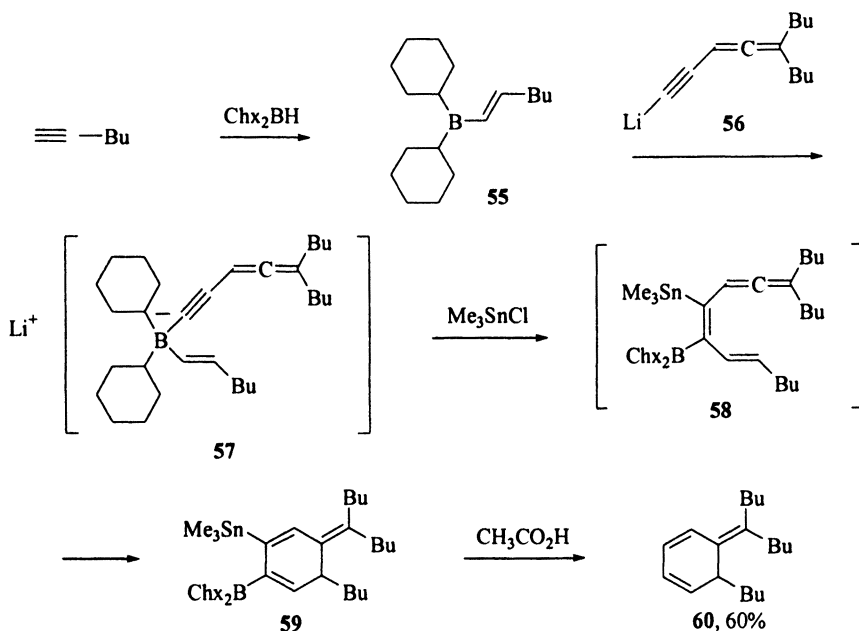
Scheme 14. o-Isotoluenes via Organoborates.

o-Quinodimethanes via Enediallenes

By using the allenylborane **61** to form the organoborate complex **63**, the trimethyltin chloride-induced transformation led to the enediallene **64** (Scheme 15) (*25*). After an electrocyclic reaction, the *o*-quinodimethane **65** was produced, which then underwent a [1,5] sigmatropic hydrogen shift to furnish **66**. Oxidation with alkaline hydrogen peroxide followed by protonolysis with acetic acid then produced the phenol **67**.
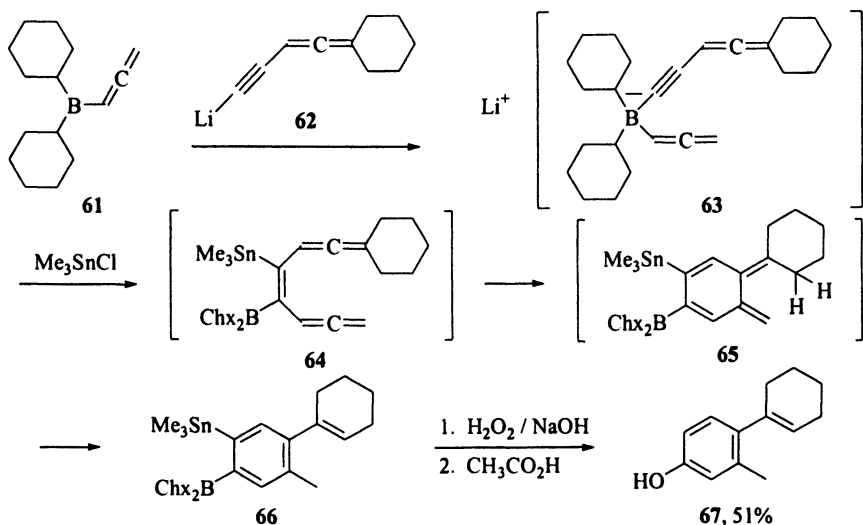
Scheme 15. *o-Quinodimethanes via Organoborates*

Enediynes via the Trimethyltin-Substituted Alkenylboranes

The boron and the tin appendages in **68** were exploited for consecutive couplings with terminal alkynyl derivatives to afford the enediynes **72** having a tetrasubstituted central carbon–carbon double bond (Scheme 16) (*26*). Sequential treatment of **68**, generated in situ from triethylborane and 1-lithio-1-hexyne, with butyllithium, CuBr SMe$_2$, 1-bromo-1-alkynes (**69**), and iodine furnished the enynyl iodides **70** in a single operation. The subsequent Pd(PPh$_3$)$_4$-catalyzed cross-coupling with 1-alkynylzinc chlorides **71** produced the enediynes **72**.
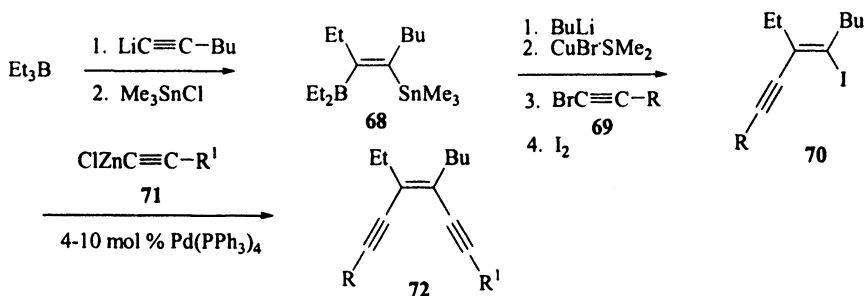
Scheme 16. *Stereoselective Synthesis of Enediynes via Alkenylboranes.*

In the cases where R^1 is an ethoxyl group, thermolysis at 132 °C induced a retro-ene reaction with the elimination of an ethylene to generate enyne–ketenes. Specifically, **72a** was converted to the enyne–ketene **73**, which then underwent a Moore cyclization reaction to form the biradical **74** (Scheme 17) (*27*). A 1,5-hydrogen shift afforded the biradical **75**, which decayed via intramolecular routes to give the chromanol **76**, the phenols **77** and **78**, and the spiro ketone **79**.
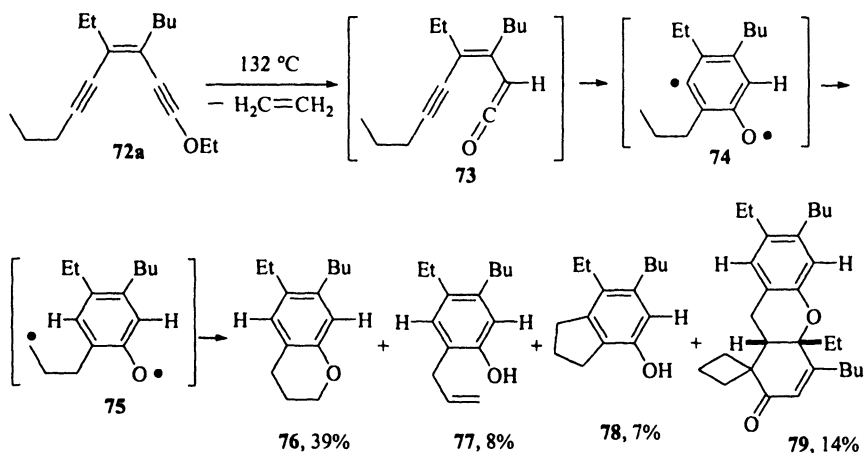
Scheme 17. Thermolysis of Enediynyl Ethyl Ether.

Conclusions

Condensation of γ-(trialkylsilyl)allylboranes and allenylboranes with simple aldehydes and conjugated allenic, acetylenic, and enynyl aldehydes followed by a stereoselective elimination of trialkylsilanol produced 1,3-butadienes, diene–allenes, enyne–allenes, enediynes, and dienediynes with high isomeric purity. The trimethyltin chloride-induced transformations of 1-alkynyltrialkylborates also provided easy access to a variety of unsaturated compounds. High energy intermediates, such as *o*-isotoluenes, biradicals, *o*-quinodimethanes, benzocyclobutadienes, and enyne–ketenes, were derived from these unsaturated molecules for subsequent synthetic elaborations.

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Chapter 5

New Organic Synthetic Methods Using the NaBH₄/I₂ System

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Research efforts in this laboratory revealed that the readily accessible and easy to handle NaBH₄/I₂ reagent system can be used in place of other hydride reagents in several synthetic applications. The diborane generated using the NaBH₄/I₂ reagent system has been used for the preparation of iodoborane-amine complexes that have good synthetic potential. An interesting catalytic process involving hydroboration with weak complexes of borane and Lewis bases followed by exchange of the alkyl group to catechol borane has been developed. The H₃B:THF prepared *in situ* in THF using NaBH₄ and I₂ is useful for reduction of functional groups.

Introduction

The sodium borohydride is one of the most widely used reagents in chemistry. It is certainly a reagent of choice for the reduction of organic functional groups, especially for the reduction of aldehydes and ketones (*1*). The carboxylic acids, esters, amides and nitriles are resistant towards NaBH₄ under

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65

ambient conditions (*1*). Historically, Brown and Subba Rao (*2*) discovered the hydroboration of carbon-carbon double bonds during their efforts to increase the reactivity of $NaBH_4$ using $AlCl_3$ (*2*). This discovery followed the development of various methods of generation of diborane using Lewis acids and $NaBH_4$ (*3*).

Although borane is now commercially available in various forms (e.g. $H_3B:THF$, $H_3B:SMe_2$ and $H_3B:NR_3$ (*3*), efforts are still continuing for developing more convenient methods of reductions using $NaBH_4$ along with additives. For example, it has been reported that the $NaBH_4/R_2SeBr_2$ combination reduces amides and nitriles to the corresponding amines (*4*). At the time, we have been investigating the generation of B_2H_6 using I_2 and $NaBH_4$ (*5*). It occurred to us that a systematic investigation on the synthetic applications of the readily accessible and easy to handle $NaBH_4/I_2$ combination should yield fruitful results. Hence, we have undertaken efforts to explore the synthetic possibilities of this reagent system. We describe here the results of these studies. Our preliminary reports also prompted other scientists to investigate the synthetic applications of the $NaBH_4/I_2$ system. Their results are also described here.

Generation of B_2H_6 Using $NaBH_4$ and I_2

In 1965, it has been reported that the reaction of $NaBH_4$ with I_2 gives diborane in >90% yield (eq 1) (*6*).

$$2\,NaBH_4 \;+\; I_2 \quad \xrightarrow[\text{25°C}]{\text{diglyme}} \quad 2NaI \;+\; H_2 \;+\; B_2H_6 \qquad (1)$$
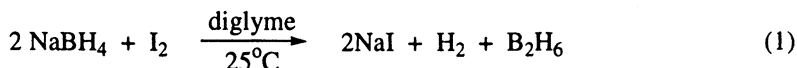
These authors used a vacuum line technique and isolated the diborane in a series of liquid nitrogen traps (*6*). The diborane generated in this way was found to be free of any detectable impurities compared to the diborane generated using $NaBH_4$ and $F_3B:OEt_2$ that contains trace amounts of BF_3. The advantage of diborane generated using the $NaBH_4/I_2$ has been also demonstrated in the reduction of dianisylketone **1** (*7*). Whereas the B_2H_6 generated using $NaBH_4$ and I_2 gave the desired secondary alcohol **3**, the reaction of "B_2H_6" obtained from $NaBH_4$ and $F_3B:OEt_2$ led to over reduction to the compound **2** due to the presence of BF_3 impurity (*7*).

Clearly, the complication due to the presence of BF_3 is prevented when the B_2H_6 generated from $NaBH_4/I_2$ is used. Since the I_2 is readily accessible and more easy to handle compared to $F_3B:OEt_2$, it is surprising that the $NaBH_4/I_2$ system has not received attention for a long time. This may have been due to the non-availability of a detailed procedure for the diborane generation using the $NaBH_4/I_2$ combination, as suggested by Lane in a review article describing synthetic applications of diborane (*8*). Further, the use of vacuum line technique

by the original authors (*6*) might have also played a role in driving away the bench-top synthetic chemists from using this simple, convenient reagent system.
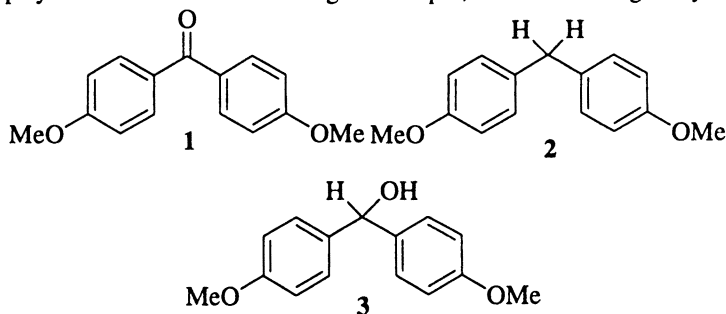
We were looking for a simple way of preparation of diborane for applications using the NaBH$_4$/I$_2$ reagent system. We have observed that the same apparatus assembly recommended by Brown for the generation of B$_2$H$_6$ from NaBH$_4$/F$_3$B:OEt$_2$ in diglyme can be used for the preparation of B$_2$H$_6$ from NaBH$_4$ and I$_2$ (*3*). Thus, I$_2$ in diglyme is added slowly to a slurry of NaBH$_4$ in diglyme and the evolved mixture of B$_2$H$_6$ and H$_2$ gases are bubbled through a solution containing appropriate Lewis bases to obtain the corresponding BH$_3$ complexes (*5,6*). We have followed this procedure for the preparation of H$_3$B:THF or Ph(Et)$_2$N:BH$_3$ for hydroboration and other synthetic applications (Scheme 1) (*5*).
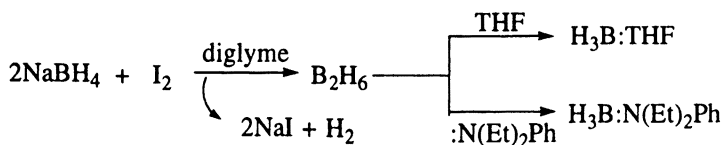
Scheme 1: Generation of diborane from NaBH$_4$ and I$_2$ in diglyme

Synthetic Applications of Ph(Et)$_2$N:BH$_3$ prepared Using NaBH$_4$ and I$_2$ for B$_2$H$_6$ Generation

The Ph(Et)$_2$N:BH$_3$ complex has been used in the hydroboration of representative olefins (*5*).

The Itsuno-Corey oxazaborolidine-H$_3$B:THF reduction, the CBS process, is the method of choice for obtaining high level of asymmetric induction (>95% ee) in the reduction of ketones (*9-11*). We have shown that the CBS

oxazaborolidine can be readily prepared using $Ph(Et)_2N:BH_3$ for synthetic applications (Scheme 2) (12).

$$2NaBH_4 + I_2 \xrightarrow{\text{diglyme}} B_2H_6 \xrightarrow{Ph(Et)_2N:} Ph(Et)_2N:BH_3$$
$$\searrow 2NaI + H_2$$

CBS catalyst

95% ee
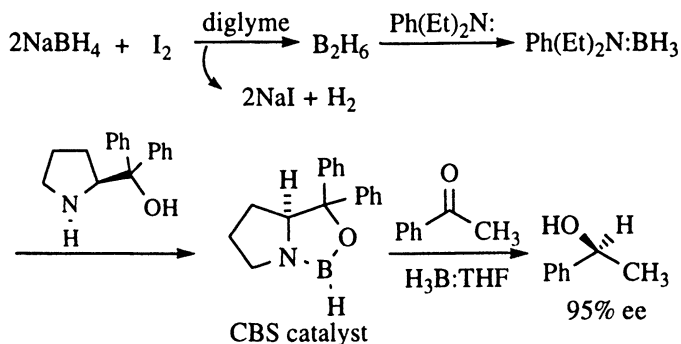
Scheme 2: Insitu generation of oxazaborolidine and its utilization in catalytic asymmetric reductions

Synthetic Applications of $I_2BH:N(C_2H_5)_2Ph$ and $I_3B:N(C_2H_5)_2Ph$ Complexes

The iodoborane-N,N-diethylaniline complexes have been prepared through the reaction of $BH_3:N(C_2H_5)_2Ph$ with appropriate amount of I_2 at 0-25° C (Scheme 3) (13,14).

$$Ph(C_2H_5)_2N:BH_3 \xrightarrow{\text{Benzene}}$$

$\xrightarrow{0.5I_2} IBH_2:N(C_2H_5)_2Ph$

$\xrightarrow{I_2} I_2BH:N(C_2H_5)_2Ph$

$\xrightarrow{1.5I_2} I_3B:N(C_2H_5)_2Ph$
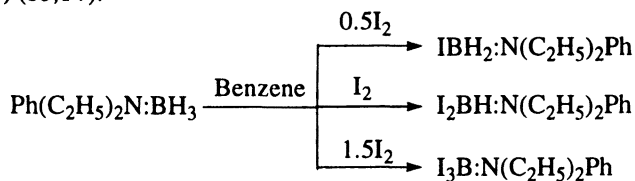
Scheme 3: Preparation of B-iodoborane-N,N-diethylaniline complexes

We have examined the applications of IBH_2 and I_2BH complexes for hydroboration of alkenes to obtain dialkyl and mono alkyl boranes. Unfortunately, these species disproportionate and hence the dialkyl and trialkyl boranes were not formed cleanly. Fortunately, however, the HBI_2 and BI_3 complexes are found to be useful for iodinations of alcohols, reductive iodinations of carbonyl compounds and hydroiodination of alkenes and alkynes.

Alcohols react with $Ph(Et)_2N:BHI_2$ to give the corresponding iodides in good yields (Scheme 4) (13).

$$RCH_2OH \xrightarrow[\text{Benzene, 25°C}]{Ph(Et)_2N:BHI_2} RCH_2I$$

80-85%

 ∿OH ⟶ I

exo/endo   80-85%
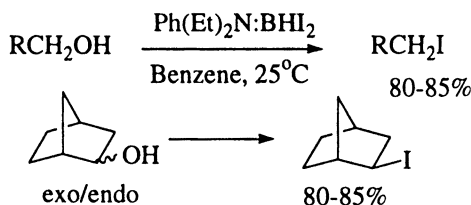
Scheme 4: Iodinatination of alcohols using Ph(Et)₂N:BHI₂

The aldehydes, ketones and carboxylic acids undergo reductive iodination under these conditions (Scheme 5) (*14*).

$$\underset{R \quad R'}{\overset{O}{\|}}C \xrightarrow[\text{Benzene, 25°C}]{Ph(Et)_2N:BHI_2} \overset{I}{\underset{82\%}{RCHR'}}$$

R' = H,alkyl,aryl

$$HOOC(CH_2)_8COOH \longrightarrow ICH_2(CH_2)_8CH_2I$$

60%
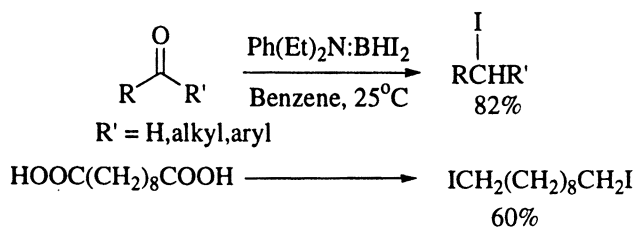
Scheme 5: Reductive iodinations using Ph(Et)₂N:BHI₂

The "HI" species can be readily generated using Ph(Et)₂N:BI₃ and CH₃COOH for synthetic applications (Scheme 6) (*15*).

$$Ph(Et)_2N:BI_3 \xrightarrow[\text{Benzene, 25°C}]{CH_3COOH} HI$$

$$R{-}HC{=}CH_2 \xrightarrow{HI} \overset{I}{\underset{R \quad CH_3}{}}$$

82-84%

$$\diagup\!\!\diagdown\!(CH_2)_8COOCH_3 \xrightarrow{HI} \overset{I}{\underset{H_3C \quad (CH_2)_8COOCH_3}{}}$$

80%
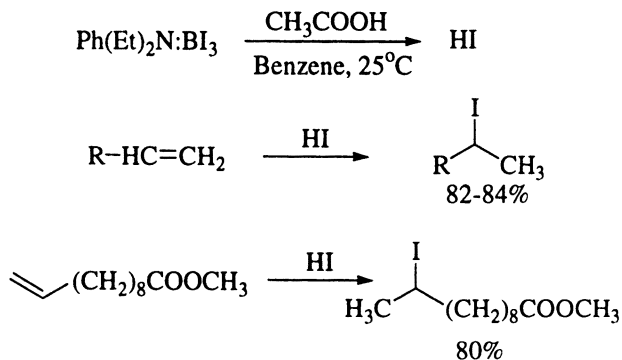
Scheme 6: In situ generation of 'HI' and its reaction with olefins

Shibasaki et al followed this method of "HI" generation for hydroiodination of an alkynyl ketone (eq 2) (*16*).

$$H_3C \overset{CH}{\underset{O}{\diagdown}} O \quad \xrightarrow[\substack{CH_3COOH \\ Benzene, 25°C \\ 14h}]{Ph(Et)_2N:BH_3} \quad H_3C \overset{I}{\underset{O}{\diagdown}} CH_2 \quad O \qquad \qquad (2)$$

95%
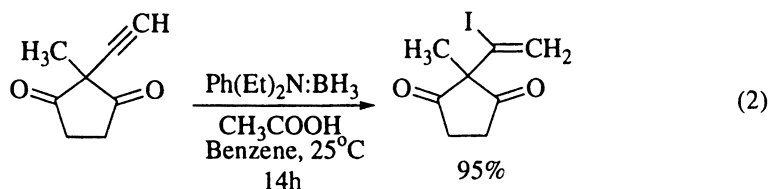
Kabalka et al found that the $Ph(Et)_2N:BI_3$ is useful for cleavage of ethers (*17*), lactones (*18*) and reduction of sulphonates and sulphoxides (*19*) (Scheme 7).

$$PhCOCH_3 \quad \xrightarrow[\substack{CH_3COOH \\ Benzene, 25°C}]{Ph(Et)_2N:BI_3} \quad PhOH \;+\; CH_3I$$

$$O \overset{}{\diagup} R^1 \quad \xrightarrow[\substack{R^2OH, 25°C}]{Ph(Et)_2N:BI_3} \quad R^1 \overset{I}{\diagup} (CH_2)_2COOR^2$$

82-90%

$$R \overset{O}{\underset{O}{\overset{\|}{S}}} X \quad \xrightarrow[\substack{R = alkyl, 25°C \\ R = aryl, 80°C}]{Ph(Et)_2N:BI_3} \quad R-S-S-R$$

22-95%

$$R \overset{O}{\overset{\|}{S}} R \quad \xrightarrow[\substack{25°C}]{Ph(Et)_2N:BI_3} \quad R-S-R$$

77-80%
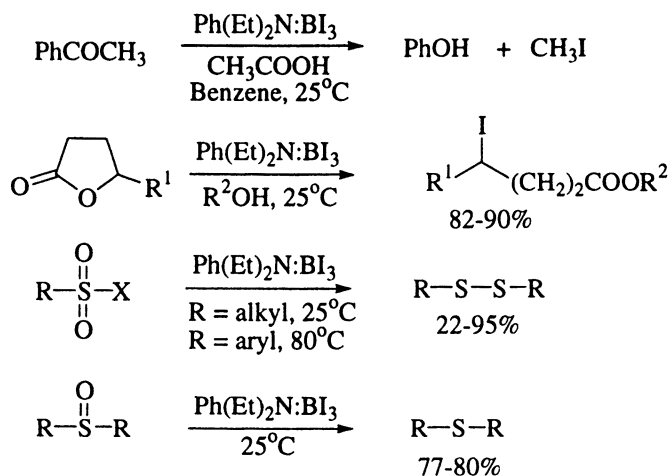
Scheme 7: Synthetic applications of Ph(Et)$_2$N:BI$_3$

The BI_3 complex has also been used in the cleavage of carbamates (eq 3) (*20*).

$$\underset{\underset{CH_2OOEt}{N}}{\overset{Ph \quad Ph}{\diagdown}} \quad \xrightarrow[\substack{25°C, 8h}]{Ph(Et)_2N:BI_3} \quad \underset{\underset{H}{N}}{\overset{Ph \quad Ph}{\diagdown}} \quad 87\% \qquad (3)$$
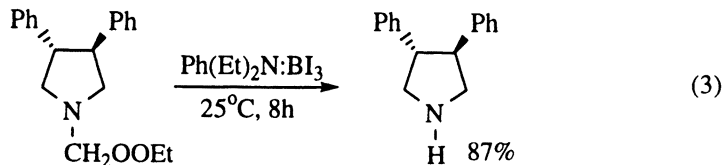
Synthetic Applications of Catecholborane prepared Using B_2H_6 Generated from $NaBH_4$ and I_2

Catecholborane is one of the widely used hydroborating and reducing agents with a very rich chemistry (*21,22*). It can be readily made *in situ* by passing B_2H_6, prepared using $NaBH_4$ and I_2 through a solution of catechol in benzene (eq 4) (*23,24*).

$$2NaBH_4 \ + \ I_2 \ \xrightarrow[\text{2NaI + H}_2]{\text{diglyme}} \ B_2H_6 \ \xrightarrow[\substack{\text{Benzene} \\ 25^\circ\text{C}}]{} \quad \text{(structure)} \tag{4}$$
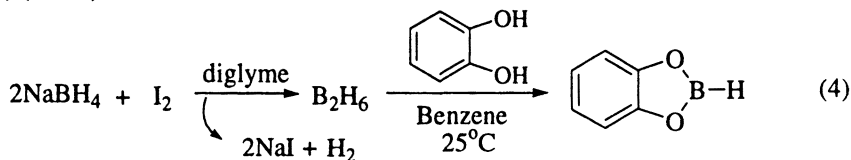
Generally, hydroboration of olefins and alkynes with catecholborane requires elevated temperatures (70-100°C) (*21,22*). In recent years, there have been sustained interest in achieving catacholborane hydroboration under ambient conditions using transition metal catalysts (*25-27*). We have observed that small amounts of H_3B:THF or H_3B:N(Et)$_2$Ph also facilitate the formation of alkenylcatecholborane under ambient conditions through an interesting hydroboration-exchange mechanism (Scheme 8) (*23,24*).

$$R\text{-}C\equiv C\text{-}H \ \xrightarrow[\substack{H_3B:THF, \ 25^\circ C \\ \text{(catalyst)}}]{} \quad \text{(structures)}$$
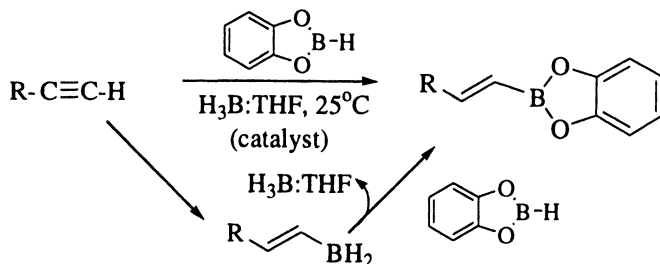
Scheme 8: Hydroboration of acetylenes using catecholborane, catalysed by H_3B:THF

Recently, Fu observed that *N,N*-dimethylacetamide facilitates catecholborane hydroboration under ambient conditions (*28*). Further, it was observed that the reaction of catecholborane with the amide leads to the formation of the corresponding H_3B:amide complex. These observations further illustrate the scope of the above mentioned hydroboration-exchange mechanistic pathway.

Reduction of Functional groups Using NaBH₄/I₂ in THF

Reduction of Carboxylic Acids

While we have been investigating the synthetic applications of B_2H_6 and H_3B Lewis base complexes as discussed above, we came across a report on the use of R_2SeBr_2 for activation of $NaBH_4$ towards the reduction of carboxylic acid amides and esters in THF (*4*). These authors have also shown that the reaction of $NaBH_4$ with R_2SeBr_2 in THF gives H_3B:THF. Since the more readily accessible and easy to handle I_2 reacts with $NaBH_4$ to give B_2H_6, this reagent system in THF would also give H_3B:THF *in situ* and hence would be useful for similar synthetic applications. Indeed, the $NaBH_4/I_2$ combination in THF results in the formation of H_3B:THF as indicated by the quantitative formation of the inert Ph_3P:BH_3 upon addition of Ph_3P to the solution (*29*). The reagent system is useful for the reduction of carboxylic acids under ambient conditions to obtain the corresponding alcohols (**4-12**) in good yields with some selectivities (*30*).

$CH_3(CH_2)_8CH_2OH$

4
95%

5
93%

6
92%

7
98%

8
89%

9
95%

10
82%

11
87%

12
82%
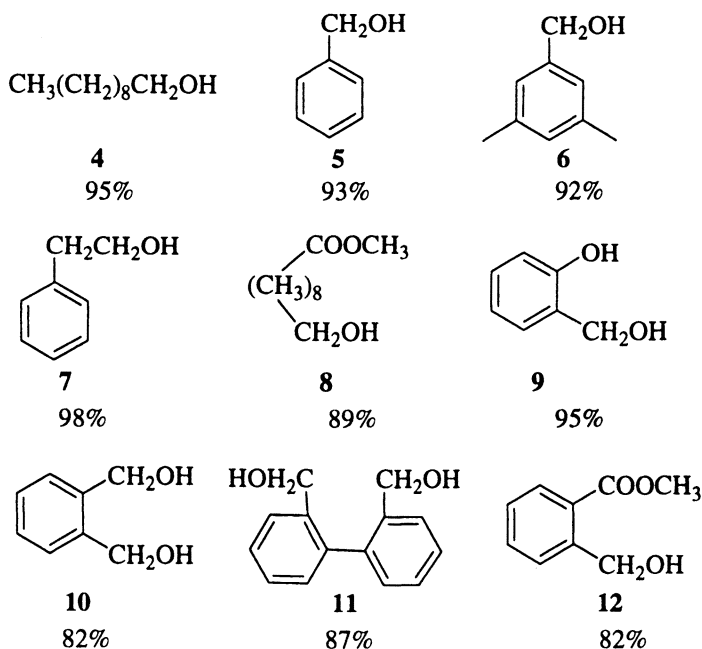
Hydroboration of Olefins

The use of the $NaBH_4/I_2$ reagent system in THF for the hydroboration of alkenes has been examined using representative olefins (*29,31*). The corresponding anti-Markovnikov alcohols (**13-15**) have been isolated after $H_2O_2/NaOH$ or $H_2O_2/NaOAc$ oxidation.

$n\text{-}C_8H_{17}CH_2CH_2OH$

13

92%

14

81%

$HO\diagdown\diagup(CH_2)_8COOCH_3$

15

78%
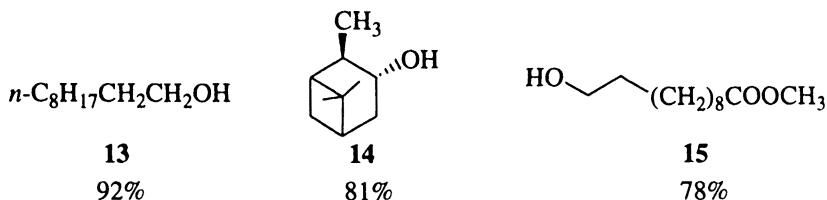
Interestingly, selective reduction of carboxylic acid moiety in an olefinic acid has been achieved by first forming the corresponding acyloxyborohydride before the addition of I_2 (Scheme 9) (*30*).

$(CH_2)_8COOH \xrightarrow[0°C]{NaBH_4} (CH_2)_8COO\overset{-}{B}H_3\overset{+}{Na}$

$0.5I_2$

$NaI + 0.5H_2$

$(CH_2)_8CH_2OB=O \longleftarrow (CH_2)_8COOBH_2$

$\Big| H_2O$

$(CH_2)_8CH_2OH$

89%
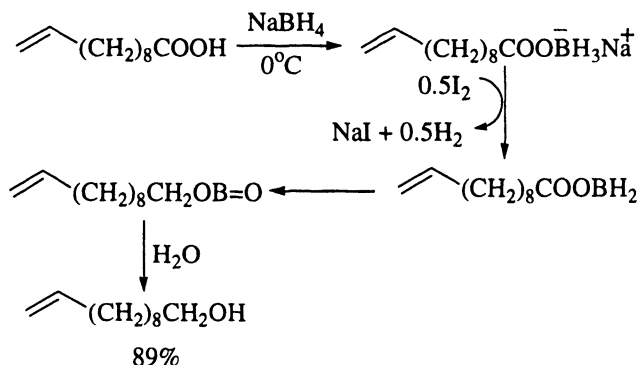
Scheme 9: Selective reductions using NaBH₄ and I₂ in THF

It may be of interest to note that this acyloxyborohydride intermediate leads to the hydroboration of the olefinic moiety in 12h in the absence of I_2. The corresponding hydroxy carboxylic acid was obtained after $H_2O_2/NaOH$ oxidation and acidification (Scheme 10) (*32*).

$$\text{/\\/(CH}_2)_8\text{COO}\bar{\text{B}}\text{H}_3\overset{+}{\text{Na}} \xrightarrow[\text{25}^\circ\text{C}]{\text{THF, 12h}}$$

1. H$_2$O$_2$/NaOH

2. H$_3$O$^+$

HO—/\\—(CH$_2$)$_8$COOH

85%
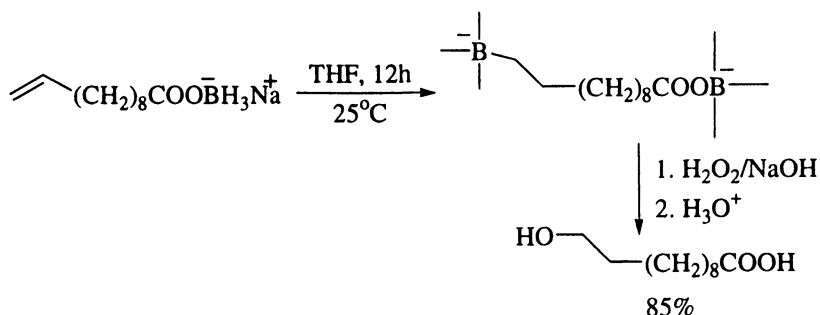
Scheme 10: Hydroboration of 10-undecenoic acid using NaBH$_4$

Reduction of Carboxylic Acid Esters, Amides and Nitriles

The NaBH$_4$/I$_2$ system in THF readily reduces carboxylic acid esters under refluxing conditions (eq 5) (*29*).

$$\text{CH}_3(\text{CH}_2)_8\text{COOCH}_3 \xrightarrow[\text{2. 70}^\circ\text{C, 0.5h}]{\text{1. NaBH}_4/\text{I}_2/\text{THF}} \xrightarrow{\text{H}_2\text{O}} \text{CH}_3(\text{CH}_2)_8\text{CH}_2\text{OH} \qquad (5)$$

85-89%
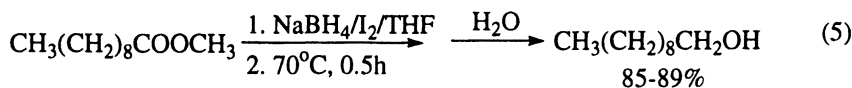
Various carboxylic acid amides and imides have been also reduced to the corresponding amines by the NaBH$_4$/I$_2$ reagent system under reflux conditions in THF (Scheme 11) (*29*).

$$\text{PhCONH}_2 \xrightarrow[\text{2. 70}^\circ\text{C, 3h}]{\text{1. NaBH}_4/\text{I}_2/\text{THF}} \xrightarrow{\text{NaOH}} \text{PhCH}_2\text{NH}_2$$

70%

PhNHCOCH$_3$ ⟶ PhNHCH$_2$CH$_3$

75%

76%
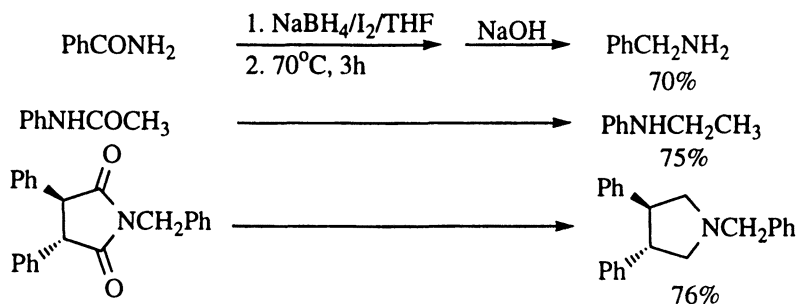
Scheme 11: Reduction of amides using NaBH$_4$ and I$_2$ in THF

The nitriles have been also reduced to the corresponding amines by the NaBH$_4$/I$_2$ system in THF (eq 6) (*29*).

$$\text{RCN} \xrightarrow[\text{2. } 70^\circ C, 3h]{\text{1. NaBH}_4/\text{I}_2/\text{THF}} \xrightarrow{\text{NaOH}} \underset{70\text{-}75\%}{\text{RCH}_2\text{NH}_2} \qquad (6)$$
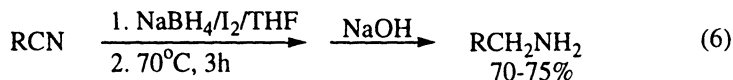
Reduction of amides containing sensitive functional groups should be carried out at under ambient conditions. Obviously, the reaction requires longer reaction time under these conditions (eq 7) (*33*).

$$\qquad (7)$$

70%
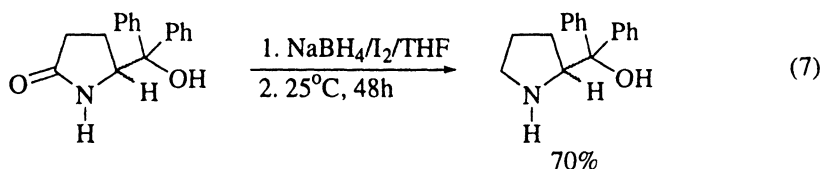
Reduction of Amino Acids and Their Derivatives

The chiral amino alcohols are important organic compounds used in asymmetric synthesis (*34,35*) in resolution of racemic mixtures (*36*), in the synthesis of pharmaceuticals (*37-39*) and insecticidal compounds (*40*). They have been prepared by the reduction of the readily accessible amino acids by a variety of reagents including LiAlH$_4$ (*41*) and H$_3$B:SMe$_2$ (*42,43*). The method employing LiAlH$_4$ is one of the most commonly used procedures but on large scale it suffers from the disadvantage of the cost, inflammability and laborious isolation procedures.

Therefore, a cheaper, safer and a simpler procedure was very much sought after. Prompted by our report on the reduction of carboxylic acids to alcohols by the NaBH$_4$/I$_2$ system (*30*), Meyers and his coworkers (*44*) examined the reduction of amino acids using this reagent system (eq 8). They have reported that the NaBH$_4$/I$_2$ combination is an excellent reagent system for the conversion of amino acids to amino alcohols (*44*).

$$\qquad (8)$$

R = *t*-Bu, *s*-Bu, *i*-Pr, Ph, CH$_2$Ph, CH$_2$CH$_2$SCH$_3$

65-94%
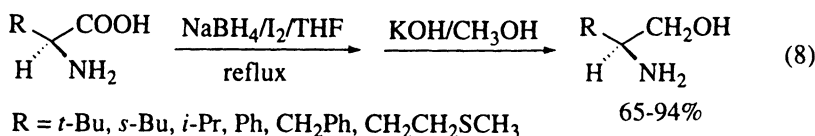
It has been reported that the transformation has been routinely carried out in 10g to a molar scale without any difficulty (*44*). Furthermore, the process is convenient from a safety and cost stand point while producing optically pure materials.

The *N*-acyl amino acids give the corresponding *N*-alkyl amino alcohols under these conditions (eq 9) (*44*).

$$R \overset{COOH}{\underset{H \quad NHCOR'}{\diagup}} \xrightarrow[\text{reflux}]{NaBH_4/I_2/THF} \xrightarrow{KOH/CH_3OH} R \overset{CH_2OH}{\underset{H \quad NHCH_2R'}{\diagup}} \tag{9}$$

$$R = CH_2Ph; R' = H, CH_3 \qquad 73\text{-}83\%$$
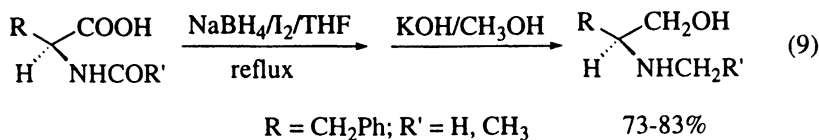
However, the *N*-carbamate protecting group remains unaffected (eq 10) (*44*).

The chiral amino alcohols have been used by Meyers and others to prepare a variety of useful compounds with very rich chemistry (*34*). Hence, the preparation of chiral amino alcohols from the readily available chiral amino acids using the simple, convenient NaBH$_4$/I$_2$ reagent system should facilitate research activities in this exciting area of research and development (*34*).

$$\tag{10}$$
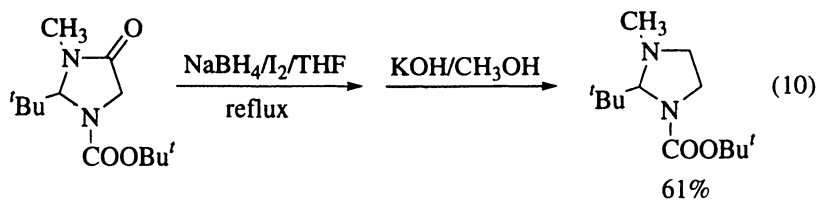
Other Synthetic Applications of NaBH$_4$/I$_2$ in THF

The NaBH$_4$/I$_2$ system has been also employed in the reduction of azoarenes and azoxyarenes to the corresponding hydrazobenzenes in good yields (eq 11) (*45*).

$$Z-\langle\!\rangle-N=N-\langle\!\rangle-Z \xrightarrow[\text{rt, 2.5h-4h}]{NaBH_4/I_2/THF}$$

$$Z-\langle\!\rangle-NH-NH-\langle\!\rangle-Z \tag{11}$$

$$Z = H, CH_3, Cl, OCH_3 \qquad 60\text{-}75\%$$
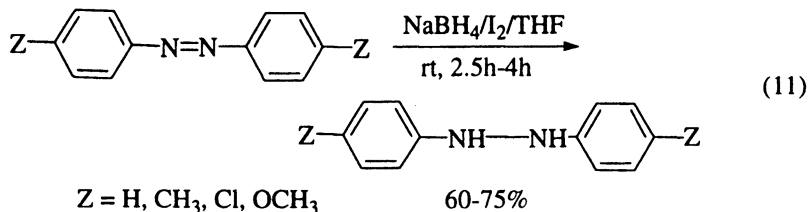
A facile, selective cleavage of allyl ethers has been reported (eq 12) (*46*).

$$RO\diagdown\!\diagup \xrightarrow[0°C]{NaBH_4/I_2} ROH \tag{12}$$

$$53\text{-}96\%$$
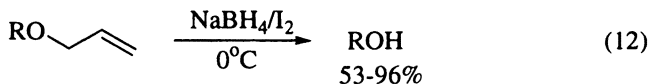
Conclusions

The results of the investigations described here on the synthetic applications of the $NaBH_4/I_2$ reagent system should further widen the scope of synthetic applications of $NaBH_4$ and borane reagents. The I_2 and $NaBH_4$ starting materials are more easy to handle and relatively more stable towards atmospheric air and moisture compared to other hydride reducing agents. Hence, the processes employing the $NaBH_4/I_2$ reagent combination should be useful in large scale applications.

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Cross-Coupling Reaction of Organoboron Compounds with Organic Electrophiles

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The palladium-catalyzed cross-coupling reaction between different types of organoboron compounds, sp^2-, sp^3-, and sp-hybridized carbon-boron compounds and various organic electrophiles in the presence of base provides a powerful and general methodology for the formation of carbon-carbon bonds. The coupling reaction offers several advantages: ready availability of reagents, mild reaction conditions, water stability, toleration of a broad range of functional groups, good regio- and stereoselectivity, insignificant effect of steric hindrance, small amount of catalysts, application in one-pot synthesis, nontoxic reaction, and easy separation of inorganic boron compounds. An overview of the coupling reaction will be presented.

Coupling Reactions of SP^2 Hybridized C-B Compounds

Vinylic Boron Compounds *(1)*

Reaction with Vinylic Halide. Synthesis of Conjugated Alkadienes

The stereo- and regioselective synthesis of conjugated alkadienes are of great importance in organic chemistry. A number of methods for the preparation of conjugated dienes and polyenes were developed uitilizing

organometallic compounds. Although these methods were useful, the scope of many of these reactions was limited by the nature of the organometallic reagents involved or the procedure employed. The most promising procedure for preparing conjugated dienes or enynes in a stereoselective manner was based on the direct cross-coupling reaction of stereodefined haloalkenes or haloalkynes with stereodefined alkenylboron compounds in the presence of transition-metal catalysts. In spite of the efforts by many workers to find such cross-coupling reactions, there were no successful reports when we began this work.

At the initial stage of our exploration, we considered that the reason of difficulty in the coupling seemed to be based on the following feature. The common mechanism of transition-metal catalyzed cross-coupling reactions between organometallic compounds and organic halides involves sequential (a) oxidative addition, (b) transmetalation, and (c) reductive elimination. We felt that one of the major reasons why 1-alkenylboranes did not react with 1-alkenyl- or 1-alkynyl halides appeared to be step b, where the transmetalation process between R'MX (M = transition-metal; X = halogen) and the organoboranes does not occur readily because of the weak carbanion character of organic groups in the organoboranes. To overcome this defect,

Table 1. Cross-coupling Reaction of 1 with 2
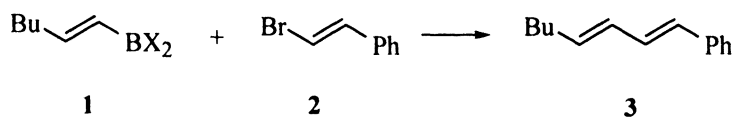
1^a	Catalyst (mol%)	Base (Equiv / 2)	Solvent	Reac. time(h)	Yield (%) of 3
1b	PdL_4 (3)	None	THF	6	0
1b	PdL_4 (3)	None	Benzene	6	0
1a	PdL_4 (3)	2M NaOEt(2)-EtOH	THF	2	73
1b	PdL_4 (1)	2M NaOEt(2)-EtOH	Benzene	2	86

a) **1a**, $X_2 = (Sia)_2$; **1b**, $X_2 = $ b) $L = PPh_3$
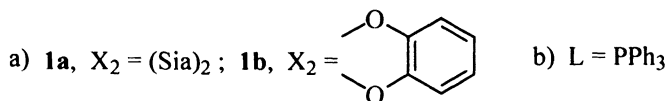
we proposed to use tetracoordinated organoboranes, instead of tricoordinated organoboron compounds. For example, the methyl group in

tetramethylborate was reported to be five times more electronegative than the methyl group of trimethylborane *(2)*. Such a process is also expected in a case of the reaction of triorganoboranes in the presence of base. Actually, we found that the cross-coupling reaction of vinylic boron compounds with vinylic halides proceeds smoothly in the presence of base to give the expected conjugated alkadienes and alkenynes stereo- and regioselectively in excellent yields (Table 1). Although the coupling reaction of (E)-1-alkenylboranes, readily obtained via the hydroboration of appropriate alkynes with disiamylborane or dicyclohexylborane, proceeds smoothly with (E)- and (Z)-1-alkenyl bromides and iodides to give the corresponding dienes readily (Table 2), (Z)-1-alkenylboranes, prepared by hydroboration of 1-haloalkynes followed by the reaction with *t*-butyllithium, gave product yields, near 50% (Table 3).

Table 2. Cross-coupling Reaction of (E)-1-Vinyldisiamylboranes

1-Alkenyl-borane	1-Alkenyl bromide	Product	Yield/% (Purity/%)
Bu ⁀ B(Sia)$_2$	Br ⁀ Ph	Bu ⁀ Ph	86 (98)
Bu ⁀ B(Sia)$_2$	Br ⁀ Hex	Bu ⁀ Hex	88 (99)
Ph ⁀ B(Sia)$_2$	Br ⁀ Ph	Ph ⁀ Ph	89 (98)

Reaction conditions: Pd(PPh$_3$)$_4$/NaOEt/benzene/reflux/2 h

Fortunately, it became apparent that high yields and stereoselectivities could be achieved by coupling (Z)-1-alkenyl halides with (Z)-1-alkenyldialkoxyboranes, instead of disiamyl- and dicyclohexylborane derivatives, shown in Table 3 *(3)*. Consequently, the cross-coupling reaction of 1-alkenylboranes with 1-alkenyl halides can be achieved for nearly all conjugated alkadienes. The reaction has been applied to syntheses of many natural and unnatural compounds which have conjugated alkadiene structures *(4)*. For example, Burk et al. have most recently reported that the Suzuki Coupling of (Z)-methyl 2-acetamido-3-bromoacrylate having several functional groups, with a variety of vinylboronic acids furnishes corresponding coupling products in excellent yields (eq 1)*(5)*.

Table 3. Cross-coupling of (Z)-1-Hexenyldisiamyl- or (Z)-1-Hexenyl-diisopropoxyborane
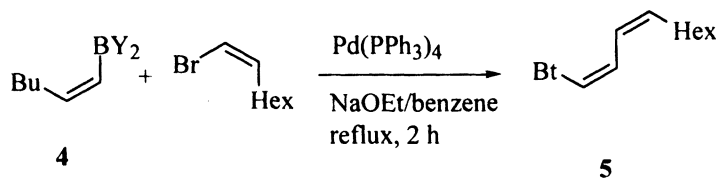
BY$_2$ in **4**	Yield(%) of **5**	Purity(%) of **5**
B(Sia)$_2$	49	>98
B(OPr^i)$_2$	87	>99

$$\tag{1}$$

94%
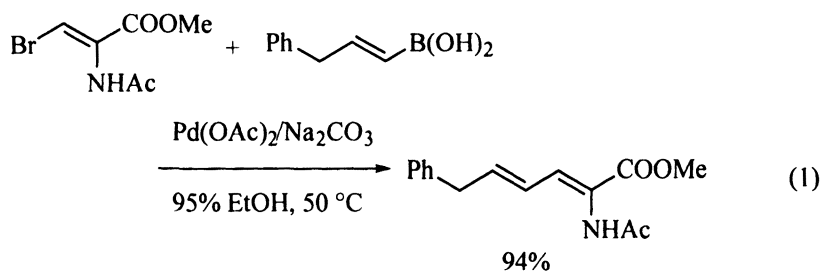
Mechanism of the Vinyl-vinyl Cross-coupling

The principal features of the cross-coupling reaction are as follows: (a) Small catalytic amounts of palladium complexes (1-3 mol %) are required to obtain the coupling products. (b) The coupling reactions are highly regio- and stereoselective and take place while retaining the original configurations of both the starting alkenylboranes and the haloalkenes. The isomeric purity of the products generally exceeds 97%. (c) A base is required to carry out a successful coupling. In the initial stage of the study, as mentioned in the introduction, we considered that tetracoordinated organoboron compounds facilitate the transfer of organic groups from the boron to the palladium complex in the transmetalation step. In order to check this possibility, lithium (1-hexenyl)methyldisiamylborate was examined as shown in eq 2. The coupling product, however, was obtained only in 9%. On the other hand, it was found that (trichlorovinyl)palladium(II) complexes (**6** and **9**) both prepared as pure solids, reacted with vinylborane (**7**) to give diene (**8**), as depicted in eqs 3 and 4, thus suggesting that vinylalkoxypalladium(II) compounds were intermediates in these cross-copupling reactions.

Consequently, we now consider the reaction proceeds through the catalytic cycle shown Figure 1.

$$Bu\diagdown\diagup\overset{\overset{Me}{|}}{\underset{\underset{(Sia)_2}{|}}{B}} + Br\diagup\diagdown_{Ph} \xrightarrow{Pd(PPh_3)_4} Bu\diagup\diagdown\diagup\diagdown_{Ph} \quad (2)$$

yield: 9 %

$$\underset{6}{\overset{\overset{Cl}{|}}{\underset{\underset{Cl}{|}}{Cl}}C=C{\overset{}{\underset{}{PdCl\text{-}L_2}}}} + \underset{7}{Hex\diagup\diagdown B\langle\overset{O}{\underset{O}{}}\rangle} \xrightarrow[17\,h]{r.t.} \text{no reaction}$$

NaOMe $\downarrow$ r.t./2 h

$$\underset{Cl}{\overset{\overset{Cl}{|}}{Cl}}C=C\diagup\diagdown_{Hex} \quad (3)$$

8 89 %

$$\underset{9}{\overset{\overset{Cl}{|}}{\underset{\underset{Cl}{|}}{Cl}}C=C{\overset{}{\underset{}{PdOMe\text{-}L_2}}}} + 7 \xrightarrow[(r.t.,\ 1\ h)]{r.t.,\ 15\ min} \begin{array}{c} \textbf{8} \\ 66\ \% \\ (95\ \%) \end{array} \quad (4)$$
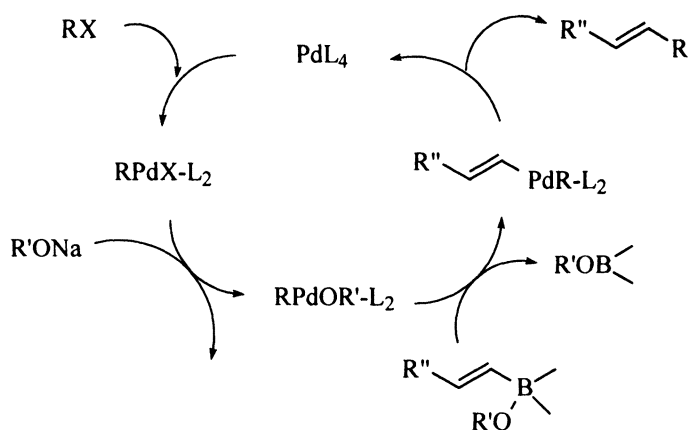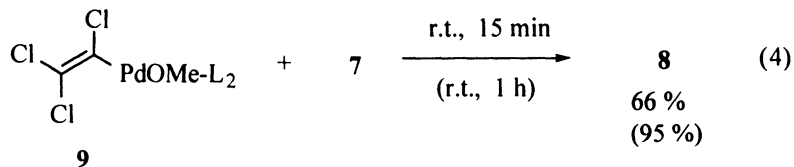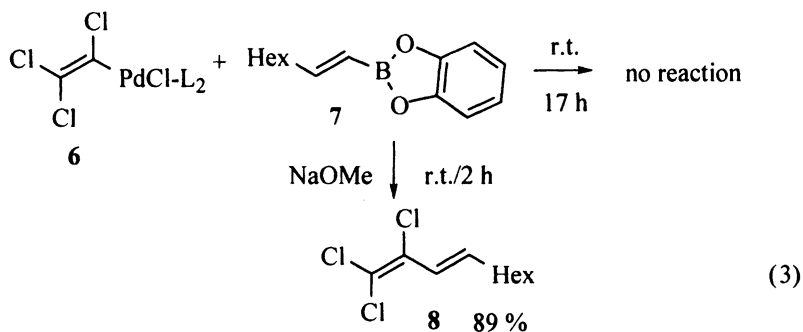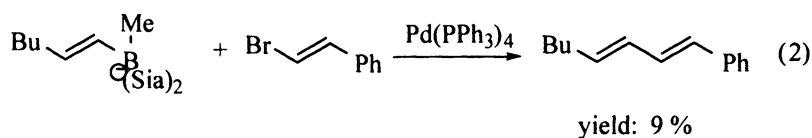
Figure 1. Catalytic cycle for the coupling reaction of alkenylboranes with haloalkenes.

1-Alkynyl halides also react with a number of 1-alkenylboranes to provide conjugated (E)- and (Z)-enynes in high yields stereo- and regioselectively.

Reaction with Aryl Halides

As described in the previous section, it was discovered that vinylic boron compounds readily react with vinylic halides to give coupling products. Consequently, we next attempted to examine the reaction of 1-alkenylboranes with haloarenes which have also sp^2 hybridized carbon-halogen bonds, and found that the reaction takes place smoothly. Representative results are exhibited in Table 4.

Table 4. Cross-Coupling Reaction of 10 with Iodobenzene
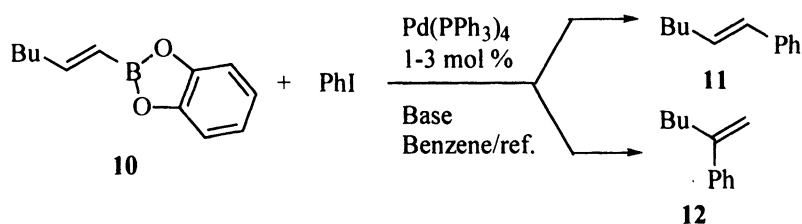
Base	Reaction time (h)	Product yield (%)	Ratio of **11** : **12**
None	6	0	
NaOEt	2	100	100 : 0
NaOMe	2	100	100 : 0
NaOH	2	100	100 : 0
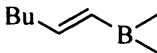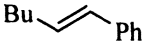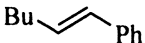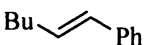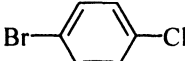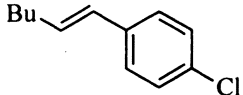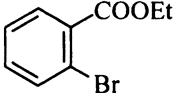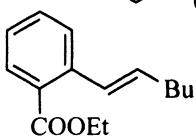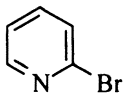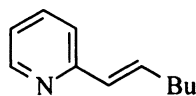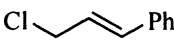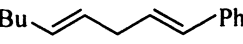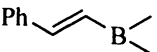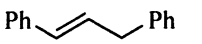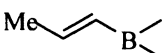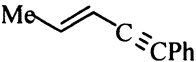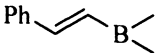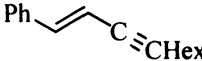
This reaction has the advantage that only one product (**11**) (head-to-head coupling product) is formed. Additional results are shown in Table 5. Aromatic bromides and iodides easily react with vinylic boron compounds, but organic chlorides do not participated, except the reactive allylic and benzylic derivatives. Heteroaromatic halides can be used as coupling partners. *Ortho*-substituents on benzene ring do not give difficulty. Thus, the cross-coupling reaction is used for the synthesis of benzo-fused heteroaromatic compounds (eq 5) *(6)*.

Aromatic Boron Compounds *(4a,4d)*

Reaction with Aromatic Halides. Synthesis of Biaryls
The first method to prepare biaryls by the cross-coupling of arylboranes

Table 5. Coupling of 1-Alkenylboranes with Various Organic Halides

1-Alkenylborane	Halide	Product[a]	Yield (%)
Bu—CH=CH—B<	PhI	Bu—CH=CH—Ph	100
	PhBr	Bu—CH=CH—Ph	98
	PhCl	Bu—CH=CH—Ph	3
	Br—C6H4—Cl	Bu—CH=CH—C6H4—Cl	100
	o-(COOEt)C6H4—Br	o-(COOEt)C6H4—CH=CH—Bu	87
	2-pyridyl—Br	2-pyridyl—CH=CH—Bu	83
	Cl—CH2—CH=CH—Ph	Bu—CH=CH—CH2—CH=CH—Ph	89
Ph—CH=CH—B<	PhCH2Br	Ph—CH=CH—CH2—Ph	97
Me—CH=CH—B<	BrC≡CPh	Me—CH=CH—C≡CPh	93
Ph—CH=CH—B<	BrC≡CHex	Ph—CH=CH—C≡CHex	95

a) Isomeric purity, > 98 %

with haloarenes was observed in 1981 (eq 6) *(7)*. The reaction proceeds even under heterogeneous conditions to give the corresponding coupling products selectively in high yields. After this discovery, various modifications have been made to the reaction conditions. As the bases, Na_2CO_3, $NaHCO_3$, Tl_2CO_3, K_3PO, etc. are employed. In some cases, CsF or Bu_4NF can be used instead of usual bases (eq 7) *(8)*. Phosphine-based palladium catalysts are generally used since they are stable on prolonged heating; however, extremely high coupling reaction rate can be sometimes achieved by using palladium catalysts without a phosphine ligand such as $Pd(OAc)_2$, $[(\eta^3\text{-}C_3H_5)PdCl]_2$, and $Pd_2(dba)_3$.

$$(5)$$

$$(6)$$

$$(7)$$
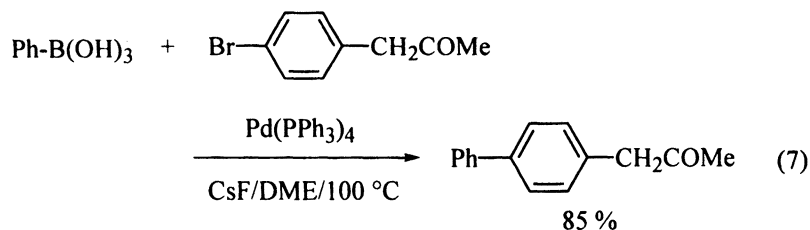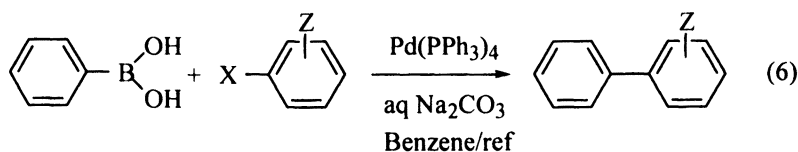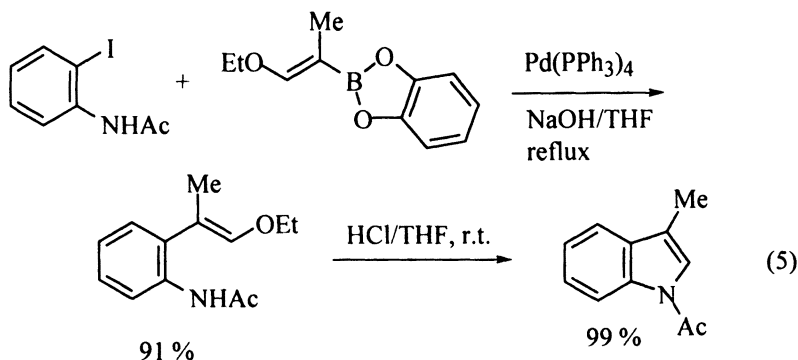
Reaction of Arylboronic Acids Having Highly Steric Hindrance or Electron-withdrawing Functionalities

Sterically hindered *ortho*-disubstituted arylboronic acids such as mesitylboronic acid *(9)* or arylboronic acids with electron-withdrawing substituents *(10)* do not provide satisfactory results due to the steric hindrance and competitive hydrolytic deboronation. Consequently, we reinvestigated the coupling reactions of sterically hindered arylboronic aids having two *ortho*-substituents or functional groups which accelerate hydrolytic deboronation. It was discovered that this difficulty can be overcome by using suitable bases and solvent systems; examples are shown in eqs 8 and 9 *(11)*. This procedure gives an excellent method for the synthesis of biaryls.

Recently, the anti-HIV alkaloids, michellamine A **(15)** and B **(16)** have been synthesized. The tetraaryl skeleton of the michellamines was constructed by formation, first, of the inner (nonstereogenic) biaryl axis and subsequently of the two other (stereogenic) axes by using a double Suzuki-type cross-coupling reaction between the dinaphtalene ditriflate **(13)** and isoquinolineboronic acid **(14)** (Fig 2) *(12)*.

$$Pd(PPh_3)_4 \; (2 \text{ mol } \%)$$
$$Ba(OH)_2 \; (1.5 \text{ mol } \%)$$
$$DME\text{-}H_2O/80 \, °C/ \; 13 \text{ h}$$

(8)

94 %

$$Pd(PPh_3)_4 \; (2 \text{ mol } \%)$$
$$K_3PO_4 \; (1.5 \text{ mol } \%)$$
$$DMF/100 \, °C/4 \text{ h}$$

(9)

85 %
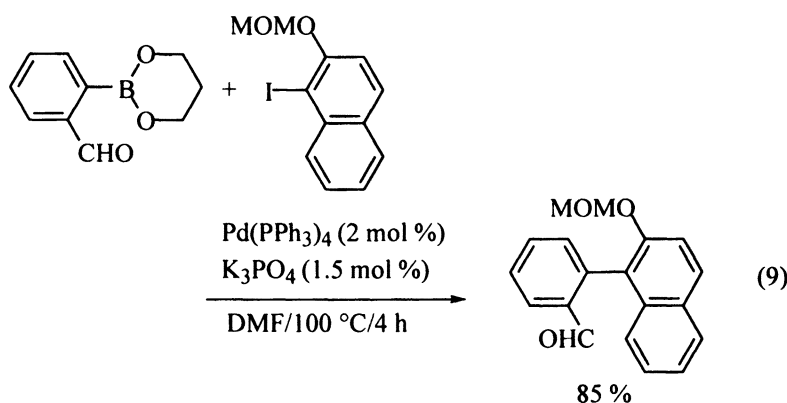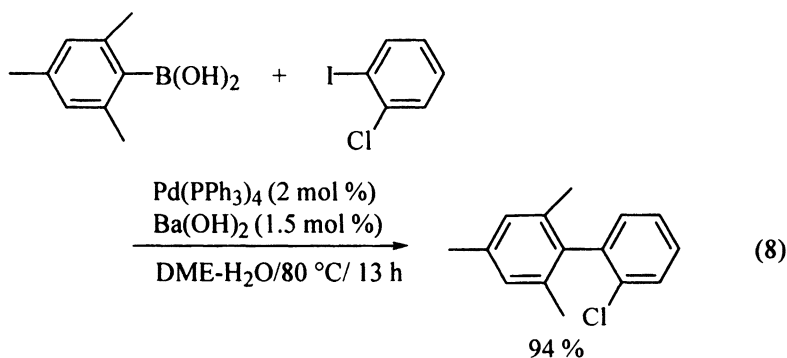
The coupling reaction has been used extensively in the synthesis of natural products and pharmaceuticals. In addition, the reaction is also widely utilized for the synthesis of polymeric compounds(4).

Coupling with Aromatic Chlorides

The palladium-catalyzed Suzuki-coupling reaction of aryl bromides, iodids, and triflates is a general method employed for the formation of C-C bonds. The use of aryl chlorides as chemical feedstock in coupling was reported difficult but would economically benefit a number of industrial processes. Most recently, Buchwald *(13)*, Fu *(14)*, and other workers *(15-17)* have reported phosphine-modified palladium-mediated coupling reactions which employ inexpensive aryl chlorides as substrates. The use of a bulky phosphine or phosphine-containing moiety in ancillary ligation was shown to be fundamental in triggering the observed catalytic behavier.

Coupling Reaction of SP³ Hybridized C-B Compounds *(18)*

Although alkylmagnesium, -zinc, -tin, and -aluminum reagents were successfully used for some of cross-coupling reactions with organic
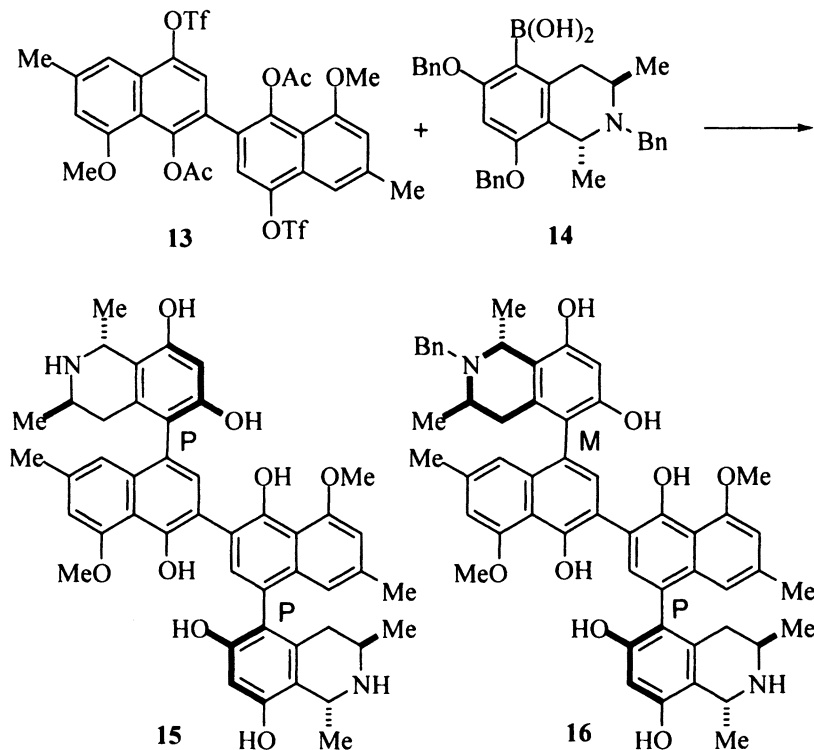
Figure 2. Synthesis of Michellamines A (15) and B (16).

halides, the reaction of alkylboranes is particularly useful when one wishes to start from alkenes via hydroboration. As described previously, it was reported that palladium-catalyzed cross-coupling reaction of 1-alkenyl- and arylboron compounds with organic halides proceeds smoothly in the presence of base to give corresponding coupling products in high yields stereo- and regio-selectively.

Alkylboranes are readily prepared by hydroboration of alkenes, which is essentially quantitative and proceeds through a *cis*-Markovnikov addition from the less hindered side of double bond. Since alkylboranes thus obtained are also quite inert toward many functional groups, the coupling can be carried out without protecting these groups. To confirm the advantages, we examined the cross-coupling of alkylboranes with organic halides using Pd(PPh$_3$)$_4$ and base. Unfortunately, we were unable to obtain coupling products. Initially, the difficulty was considered to be the reductive elimination step (see, Figure 1). Hayashi et al.*(19)* reported an effective catalyst at the reductive elimination step for the cross-coupling of Grignard and alkylzinc reagents with organic halides, which is dichloro[1,1'-bis(diphenylphosphino)ferrocene]-palladium(II) [PdCl$_2$(dppf)]. Therefore, we used this catalyst for the reaction of alkylboranes with organic halides, and discovered that the reaction occurs readily to give coupling products

selectively in excellent yields. Examples of the result are depicted in eq 10-11.

Danishefsky et al. have reported a total synthesis of the promising anticancer agent (-)-epothilone B using the Suzuki coupling of B-alkyl-boranes with vinylic halides as shown in eq 12 *(20)* and a related compound *(21)*.

$$
\text{Br} + \text{B} \quad \xrightarrow[\substack{\text{NaOH} \\ \text{THF/65 °C}}]{\substack{\text{PdCl}_2(\text{dppf}) \\ (3 \text{ mol \%})}} \quad \tag{10}
$$

88 %

$$
\text{Br} + \text{B}-\text{C}_8\text{H}_{17} \quad \longrightarrow \quad \text{C}_8\text{H}_{17} \tag{11}
$$

94 %

$$
\xrightarrow[\text{Cs}_2\text{CO}_3/\text{H}_2\text{O-DMF}]{\text{Pd(dppf)}_2/\text{Ph}_3\text{As}}
$$

$$
\xrightarrow{\text{several steps}} \quad \text{(-)-Epothilone B} \tag{12}
$$

77%
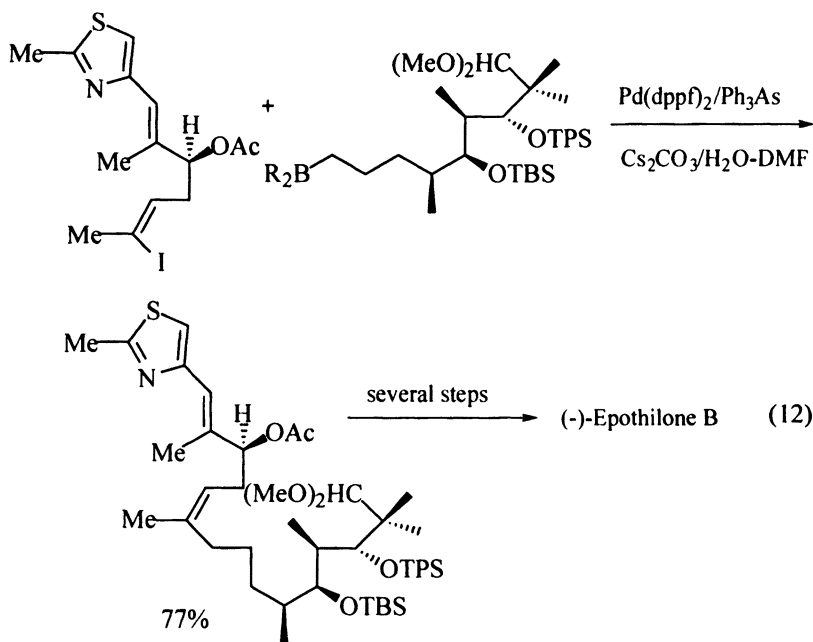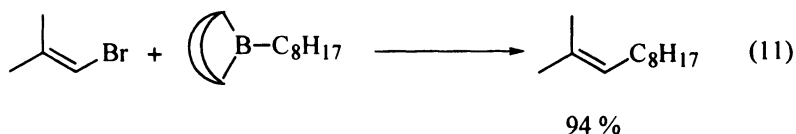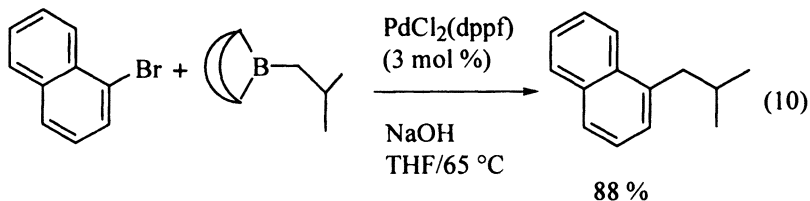
Base Problem

In cross-coupling reactions of organoboron compounds, the presence of bases is essential; no reaction occurs without bases. On the other hand, there

are many organic compounds, sensitive toward bases. Consequently, careful uses of bases are required in such cases. For example, Table 6 shows that the selection of base and solvent provides markedly different yields of coupling products. By carefully selecting the reaction conditions high yields of the desired coupling products can be achieved (eqs 13 and 14).

Table 6. Solvent and Base Effects on the Cross-Coupling Reaction[a]
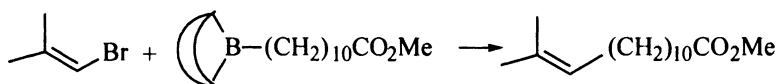
Solvent	Base (equiv)	Temp.(°C)	Time (h)	Yield (%)
DMF	KOAc (4)	50	18	18
DMF	K_2CO_3 (2)	50	18	64
CH_3CN	K_2CO_3 (4)	50	18	46
DMF	K_3PO_4 (4)	50	20	92

a) Catalyst: $PdCl_2$(dppf)

(13)

88 %

(14)

84 %
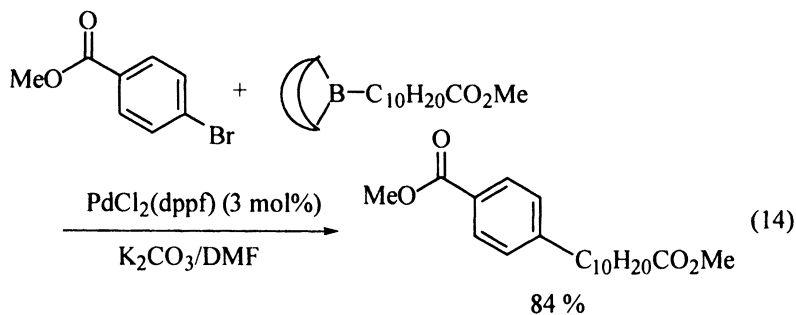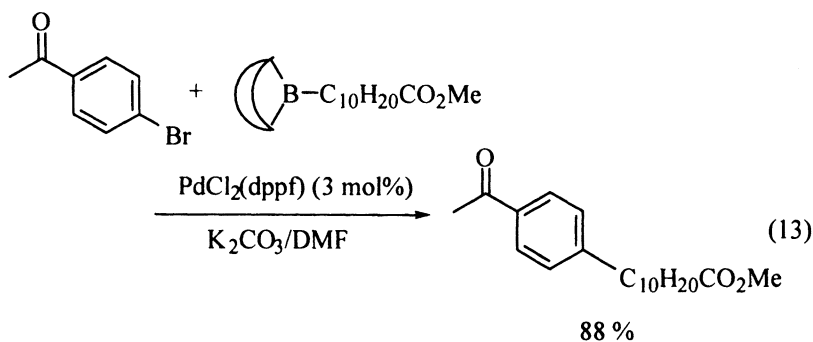
Coupling Reactions of SP Hybridized C-B Compounds

Alkynylboranes have long been known to be useful synthetic intermediates. Compared to other organoboranes, they are stronger Lewis acids and are easily hydrolyzed. Because of this property, alkynylboron compounds have not been employed in the Suzuki coupling reaction, in which the presence of bases is essential. Recently, Soderquist et al. have found that the addition of B-methoxy-9-borabicyclo[3.3.1]nonane to alkynyllithium reagents gives stable complexes **17** which undergo efficient Suzuki coupling to produce a variety of alkynyl derivatives **18** (eq 15, Table 7)*(22)*. Almost at the same time, Fürstner and Seidel reported the same reaction *(23)*.

17

$$\xrightarrow[\text{Pd(PPh}_3)_4 \text{ / no base}]{\text{R'Br}} \quad R \textemdash\!\!\equiv\!\!\textemdash R' \qquad (15)$$

18
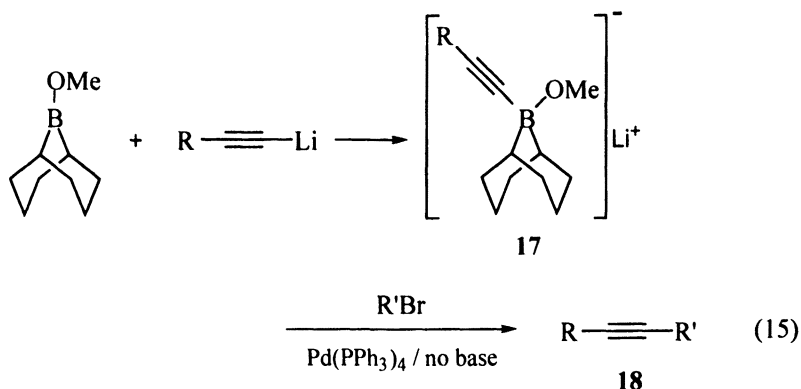
Table 7. Coupling Products from 17

R	R'	Yield (%)[a] of **18**
n-Bu	Ph	60 (92)
SiMe	Ph	64
Ph	Ph	94
n-Bu	*p*-MeOPh	62 (68)
SiMe$_3$	CH$_2$=CPh	88
t-Bu	*cis*-CH=CH-t-Bu	56

a) Isolated yields (GC yields)

In Summary, the Suzuki coupling reaction has become an important method in organic chemistry. Although it is impossible to give a detail overview, there are a number of detailed reviews available *(4)*.

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Chapter 7

Rhodium-Catalyzed Addition Reactions of Organoboronic Acids

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The rhodium-catalyzed addition of aryl- and 1-alkenylboronic acids to α,β-unsaturated ketones, aldehydes, esters, and amides gave the conjugate 1,4-addition products in high yields. The rhodium(I) complexes also catalyzed the 1,2-addition of organoboronic acids to aldehydes or N-sulfonyl aldimines. The efficiency of protocol was demonstrated in the asymmetric addition reactions of organoboronic acids in the presence of a rhodium(acac)/ BINAP complex.

1. Introduction

Intermolecular transfer reactions of organoboron compounds such as the Grignard-type reaction are rare; however, several methods have been reported for the conjugate addition to enones (Scheme 1). Trialkylboranes add to acyclic and cyclic enones in the presence of a small amount of air or a radical initiator (1). Both 9-(1-alkenyl)-9-BBN (2, 3) and 1-alkenylboron fluorides (4, 5) in situ generated from boronic acid and BF_3 add to acyclic enones via a chair-like, six-membered transition state because of their high Lewis acidity for coordination to a carbonyl oxygen. The metal-catalyzed addition reaction of organoboron compounds has not yet been well developed, but the addition of $NaBPh_4$ or arylboronic acids to enones catalyzed by $Pd(OAc)_2$ in the presence of $SbCl_3$ was recently demonstrated by Uemura (6). The catalytic cycle involves a unique process proceeding through a sequence of oxidative addition of the Ar-B bond to palladium(0) giving an Ar-Pd(II)-B(OH)$_2$ species and its addition to enone.

$$—CH=CH-\overset{\overset{O}{\|}}{C}— \xrightarrow{R_3B/O_2} —\overset{\overset{R}{|}}{CH}-CH_2-\overset{\overset{O}{\|}}{C}—$$

$$—CH=CH-\overset{\overset{O}{\|}}{C}— \xrightarrow{RCH=CHB(OH)_2/BF_3} \overset{RCH=CH}{\underset{}{—\overset{|}{CH}-CH_2-\overset{\overset{O}{\|}}{C}—}}$$

$$—CH=CH-\overset{\overset{O}{\|}}{C}— \xrightarrow{9\text{-}(RCH=CH)\text{-}9\text{-}BBN} \overset{RCH=CH}{\underset{}{—\overset{|}{CH}-CH_2-\overset{\overset{O}{\|}}{C}—}}$$

$$—CH=CH-\overset{\overset{O}{\|}}{C}— \xrightarrow[Pd(OAc)_2/SbCl_3]{PhB(OH)_2} \overset{Ph}{\underset{}{—\overset{|}{CH}-CH_2-\overset{\overset{O}{\|}}{C}—}}$$
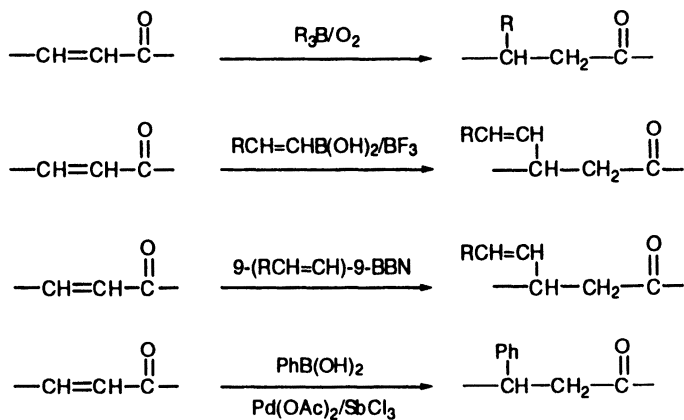
Scheme 1. 1,4-Addition of Organoboron Compounds

Recently, we found that rhodium(I) complexes catalyze various addition reactions of organoboronic acids, including the conjugate 1,4-addition to α,β-unsaturated ketones, aldehydes, esters, and amides, and the 1,2-addition to aldehydes and imines. The cross-coupling reaction of organoboron compounds proceeding through the transmetalation to palladium(II) halide has been proved to be a quite general technique for a wide range of selective carbon-carbon bond formation (7-10). The present transmetalation reaction from boron to rhodium(I) will provide another carbon-carbon bond forming reaction *via* the addition reactions of organoboronic acids.

The following abbreviations are used for ligands. cod = 1,5-cyclooctadiene, coe = cyclooctene, dppf = 1,1'-bis(diphenylphosphino)ferrocene, $Ph_2P(CH_2)_nPPh_2$: dppe (n=2), dppp (n=3), dppb (n=4)

2. Rhodium-Catalyzed Conjugate 1,4-Additions

Various rhodium(I) complexes catalyze the addition reaction of aryl- and 1-alkenylboronic acids to α,β-unsaturated ketones (*11*), esters (*12*), and amides (*12*) in an aqueous solvent (Scheme 2). The cationic rhodium(I) complexes such as $[Rh(CO)(PPh_3)_2]ClO_4$, $[Rh(cod)]BF_4$, $[Rh(cod)(CH_3CN)_2]BF_4$, or its combination with a diphosphine ligand having large P-Rh-P angles (dppp or dppb) efficiently catalyzes the reaction. The neutral complexes, *in situ* generated from $Rh(acac)(CO)_2$, $Rh(acac)(CH_2=CH_2)_2$, or $Rh(acac)(coe)_2$ and dppp or dppb, are also highly effective whereas (halogeno)rhodium complexes such as

$$R^1\text{—}CH\text{=}CH\text{—}\overset{\overset{\displaystyle O}{\|}}{C}\text{—}R^2 \xrightarrow[\text{Rh catalyst (3 mol\%)}]{\text{Ph–B(OH)}_2} R^1\text{—}\overset{\overset{\displaystyle Ph}{|}}{C}H\text{—}CH_2\text{—}\overset{\overset{\displaystyle O}{\|}}{C}\text{—}R^2$$
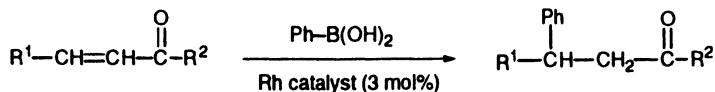
entry	R^1	R^2	catalyst/ligand/solvent	temp	yield/%
1	CH_3	C_4H_9	$Rh(acac)(CO)_2$/dppb/aq. MeOH	50	96
2	Ph	CH_3		50	99
3	Ph	Ph		50	86
4	-$CH_2)_2$-		$Rh(acac)(CO)_2$/dppp/aq. EtOH	50	72
5	-$(CH_2)_3$-			50	92
6	H	H	$Rh(acac)(CO)_2$/dppb/aq. MeOH	50	59
7	MeO_2C	OMe	$[Rh(acac)(MeCN)_2]BF_4$/aq. EtOH	25	84
8	Ph	OMe		50	87
9	H	OMe		80	60
10	CH_3	OMe		100	82
11	CH_3	$NHCH_2Ph$	$Rh(acac)(coe)_2$/dppm/aq. dioxane	100	XX

Scheme 2. Additions to α,β-Unsaturated Carbonyl Compounds

$RhCl(PPh_3)_3$ and $RhCl(CO)(PPh_3)_2$ do not give good results. The reaction was preliminarily studied in aqueous DMF, but the reaction is slow in such donating solvents coordinating to the rhodium metal center. Less polar solvents such as aqueous alcohols, DME, and dioxane will significantly shorten the reaction times. Although the reaction proceeds to some extent in the absence of water by using an arylboronic ester, the presence of some water is, in general, critical to improve yields because often no reaction is observed in the absence of water even in alcohol solvents. The addition of a base such as NaOH, NaOAc, and Et_3N retards the reaction, which is in sharp contrast to the effect of a base on the palladium-catalyzed cross-coupling reaction of organoboronic acids.

Phenylboronic acid adds to various acyclic and cyclic α,β-unsaturated carbonyl compounds (Scheme 2). The reaction is fast in more electron-deficient substrates and highly dependent on the substituents which may affect the rate of insertion of the double bond into the rhodium-carbon bond. For example, the

additions to both dimethyl fumarate and maleate smoothly proceed at room temperature (entry 7), but the additions to cinnamate, acrylate, and crotonate are carried out at 50 °C, 80 °C and 100 °C to complete the slow reactions (entries 8-10). Thus, the relative reactivity is parallel to the order of rhodium/alkene complex stability and the insertion rate which can be estimated by the LUMO energy level of alkenes. However, the additions to trisubstituted unsaturated ketones and esters are significantly slow. The rhodium complexes catalyze a similar reaction of 1-alkenylboronic acids, but all attempts at the addition of alkylboronic acids or trialkylboranes having a β-hydrogen are unsuccessful.

The addition to a sterically hindered enone is shown in Scheme 3. The reaction is very slow with neutral complexes, but a phosphine-free cationic rhodium selectively gives a β-addition product.

$PhB(OH)_2$

$[Rh(cod)(MeCN)_2]BF_4$/aq. dioxane
100 °C/16h

93%
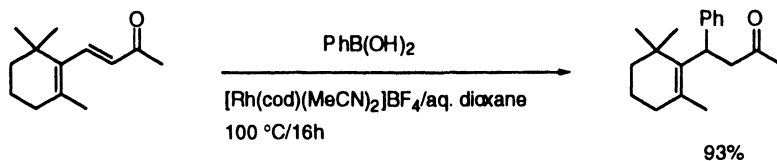
Scheme 3. Addition to β-Ionone

More recently, it was reported that potassium alkenyl and aryl-trifluoroborates undergo similar addition to enones in the presence of a Rh(I) catalyst (Scheme 4) (13). It was found that the reaction proceeds more rapidly than with the corresponding boronic acids, and the choice of catalyst ligand does not significantly influence the overall catalyst efficiency.

$R^1B(OH)_2$

KHF_2/H_2O
rt

$[R^1\text{-}BF_3]K$

$R^2-CH=CH-\overset{O}{\overset{\|}{C}}-R^3$

$Rh(acac)(CO)_2/dppb$ or PPh_3
MeOH-H_2O, 50 °C

$R^2-\overset{R^1}{\underset{|}{CH}}-CH_2-\overset{O}{\overset{\|}{C}}-R^3$
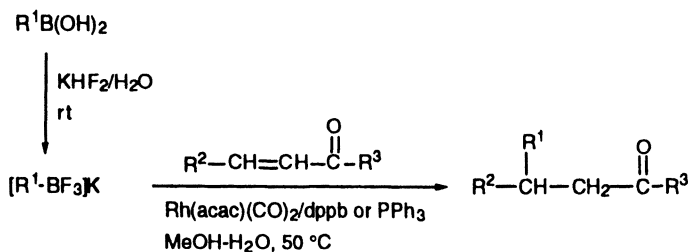
Scheme 4. 1,4-Addition of Organotrifluoroborates
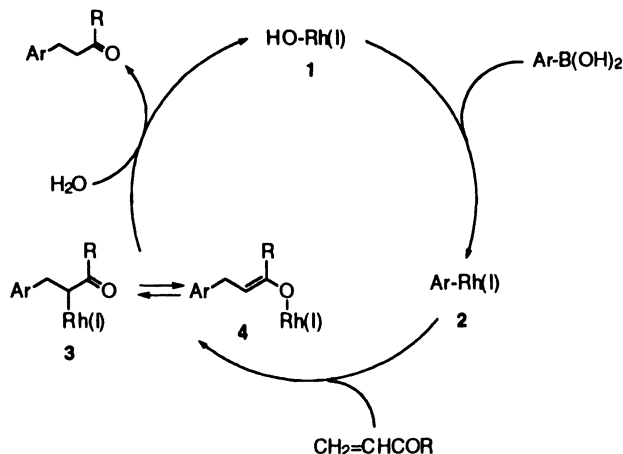
Scheme 5. Catalytic Cycle for 1,4-Addition

Work on mechanistic details is in progress, but the present transformation may result from a catalytic cycle that involves the transmetalation between the hydroxo-rhodium(I) species **1** and arylboronic acid giving an arylrhodium(I) complex **2**, and the insertion of an enone to the Ar-Rh bond. The hydrolysis of the rhodium(I) enolate with water reproduces **1**, as shown in Scheme 5. The arylrhodium(I)-arylphosphine complexes **2** are unstable such as to preclude isolation in pure form, but they have been reasonably speculated to be the key intermediates carrying out various coupling reactions with organic halides and the addition to alkenes and alkynes. Preliminary results indicated a sequence of the formation of the ArRh(I) species and its addition to unsaturated ketones (Scheme 6). A Michael product is obtained indeed when the *in situ* preparation of phenylrhodium(I) from a Vaska complex is followed by the addition to methyl vinyl ketone at room temperature in an aqueous DMF solution.

a) PhLi/THF/-78 °C; b) MVK/DMF-H₂O/0-20 °C/16 h
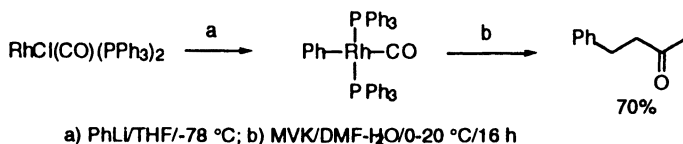
Scheme 6. Insertion of MVK into the C-Rh Bond

Another indirect evidence for the catalytic cycle is that the addition of phenylboronic acid to methyl acrylate accompanies with the β-hydride elimination giving a Heck product (Scheme 7). The reaction exceptionally affords a dipheny ester (8%) which is derived from the β-hydride elimination giving methyl cinnamate. The results suggest the mechanism for forming a rhodium species bound to the α-carbon, though such by-product is not observed or is in a negligibly small amount in the addition to other substrates shown in Scheme 2.
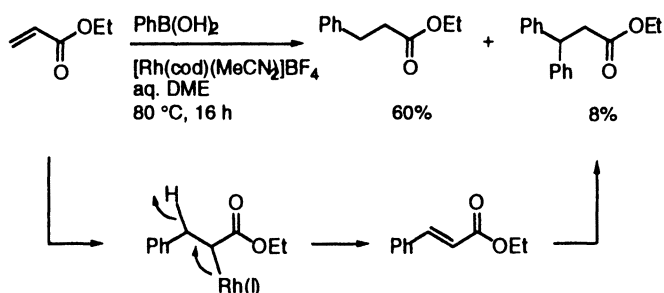
Scheme 7. β-Hydride Elimination from Rh Intermediate

The next insertion step of an α,β-unsaturated carbonyl compound into the Rh-C bond provides **3** which is in equilibrium with the rhodium-enolate **4**. The synthesis of rhodium enolate and its application to catalytic aldol chemistry was extensively studied by Heathcock (*14*). The η^1 oxygen-bound rhodium enolate complexes, synthesized from $RhCl(CO)(PMe_3)_2$ and potassium enolates or silyl enolates, exhibit a dynamic equilibrium between the O-bound and C-bound forms which are sufficiently nucleophilic to condense with carbonyl compounds. Thus, the hydrolysis of the rhodium enolate **4** with water reproduces a (hydroxo)rhodium complex **1** which would be a key intermediate for the transmetalation. The high oxophilicity of the boron center and the basicity of transition metal hydroxides would induce the transmetalation from boron to the (hydroxo)rhodium(I) species, which can be rationalized by a related reaction with (alkoxo)- or (hydroxo)palladium(II) complexes demonstrated in the palladium-catalyzed cross-coupling reaction of organoboronic acids (*7-10*).

On the other hand, the fact that the reaction of organoboronic esters takes place in the absence of water might account for the transmetalation under anhydrous conditions between organoboronic esters and **7**; however, the experimental results do not support this process (Scheme 8). The addition of the phenylboronic ester of diethylene glycol to 1,3-diphenylpropen-1-one (calcon)

with [Rh(cod)(MeCN)$_2$]BF$_4$ (3 mol%) at 100 °C in dioxane indeed produces 1,3,3-triphenylpropan-1-one in 87% yield, but the treatment of the reaction mixture with benzaldehyde gives no aldol product of **5**.
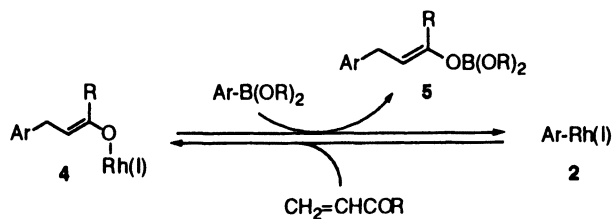
Scheme 8. *Catalytic Cycle under Anhydrous Conditions*

The related metal-catalyzed 1,4-addition reaction is shown in Scheme 9 (*15*). The conjugate addition of arylmercury halides or tetraarylstananes to enones is catalyzed by palladium(II) chloride in an acidic solution. The mechanism is reported to proceed through the transmetalation giving Ar-Pd-Cl, the insertion of enone to the C-Pd bond, and finally, the protonolysis of the C-Pd or the O-Pd bond with acid. Thus, both reactions catalyzed by rhodium(I) and palladium(II) complexes are concluded to proceed through a quite similar process.
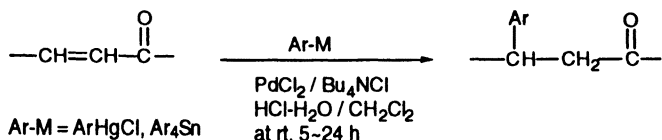
Scheme 9. 1,4-Addition Catalyzed by PdCl$_2$

3. Asymmetric 1,4-Addition

Since chiral phosphine ligands are the chiral auxiliaries most extensively studied for transition metal-catalyzed asymmetric reactions, one can use the accumulated knowledge of the chiral phosphine ligands for the asymmetric reaction. The effects of commercially available chiral ligands on the enantiomer excess are summarized in Scheme 10 (*16*). Although the

complexes *in situ* generated from four ligands including BINAP, DIOP, CHIRAPHOS, and Me-DuPHOS give high yields of the addition product, BINAP is found to be the best ligand achieving both high yields and high asymmetric induction. These ligands were originally designed for asymmetric hydrogenation, but they also works well in the conjugate addition because both reactions involve a quite similar molecular recognition mechanism.
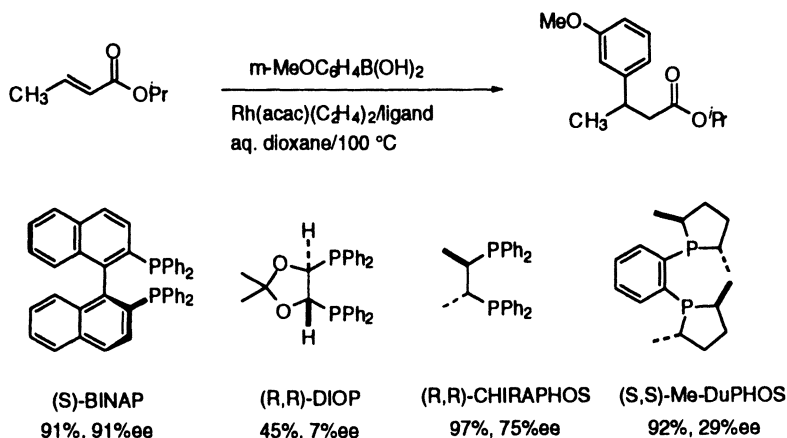
Scheme 10. Effect of Chiral Ligand on Enantioselectivity

    The asymmetric 1,4-addition of aryl- and 1-alkenylboronic acids to the representative Michael acceptors are summarized in Scheme 11 (*11, 16*). The reaction is efficiently catalyzed at 100 °C by a rhodium complex *in situ* generated by mixing $Rh(acac)(CH_2=CH_2)_2$ with (S)-BINAP. It is interesting that the enantioselectivity is kept constant at the reaction temperature ranging between 40-120 °C in the addition to 2-cyclohexenone. High enantioselectivity exceeding 90%ee is readily achieved for cyclic and acyclic α,β-unsaturated ketones (*16*), esters (*12*), and amides (*12*). Organoboronic acids are used in large excess (in general, more than 2 equivalents), because the protodeboronation of organoboronic acids with water reduces the yields of the addition products.

    The addition of phenylboronic acid to 2-cyclohexenone with Rh/(S)-BINAP affords (S)-3-phenylcyclohexanone (entry 1). On the other hand, the addition of phenylboronic acid to *trans*-crotonates produces (R)-3-phenylbutanoates. Scheme 12 shows the stereochemical pathway forming these products of (S) or (R) configuration for 2-cyclohexenone and crotonates.

$$R^1-CH=CH-\overset{\overset{\displaystyle O}{\|}}{C}-R^2 \xrightarrow[\substack{\text{Rh(acac)(C}_2\text{H}_4)_2/\text{(S)-BINAP} \\ \text{aq. dioxane/100 °C}}]{R^3-B(OH)_2} R^1-\overset{\overset{\displaystyle R^3}{|}}{CH}-CH_2-\overset{\overset{\displaystyle O}{\|}}{C}-R^2$$
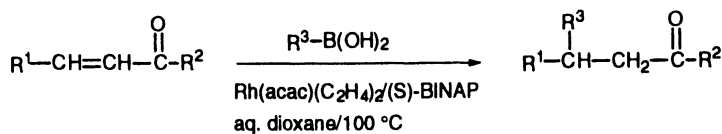
entry	R^1	R^2	$R^3B(OH)_2$	yield/%	%ee
1	-(CH$_2$)$_3$-		PhB(OH)$_2$	93	97
2	-(CH$_2$)$_3$-		p-MeOC$_6$H$_4$B(OH)$_2$	97	96
3	-(CH$_2$)$_3$-		m-ClC$_6$H$_4$B(OH)$_2$	96	96
4	-(CH$_2$)$_3$-		(E)-C$_5$H$_{11}$CH=CHB(OH)$_2$	88	94
5	-(CH$_2$)$_2$-			64	96
6	2-C$_3$H$_7$	CH$_3$	PhB(OH)$_2$	82	97
7	C$_5$H$_{11}$	CH$_3$		88	92
8	CH$_3$	O^{i}Pr	p-MeC$_6$H$_4$B(OH)$_2$	89	92
9	CH$_3$	O^{i}Pr	p-MeOC$_6$H$_4$B(OH)$_2$	82	92
10	CH$_3$	O^{i}Pr	m-MeOC$_6$H$_4$B(OH)$_2$	91	91
11	CH$_3$	O^{i}Pr	o-MeOC$_6$H$_4$B(OH)$_2$	43	98
12	CH$_3$	NHCH$_2$Ph	PhB(OH)$_2$	67	95

Scheme 11. *Asymmetric 1,4-Addition with Rh(I)-BINAP*

The (S)-BINAP/rhodium intermediate should have an open space at the lower part of the vacant coordination site, the upper part being blocked by one of the phenyl rings of the BINAP ligand (Scheme 12). Thus, α,β-unsaturated ketones and esters coordinate to the rhodium at its open space, avoiding the interaction between the phenyl group and the substituents around the double bond, which undergoes migratory insertion to form a stereogenic carbon center.

The bulkiness of both the ester group (R') and the β-substituent (R) significantly affects the enantioselectivity and the reaction rate. For example, the addition of *m*-methoxyphenylboronic acid to a series of crotonates reveals selectivities which suggest that the enantioselectivity improves with increasing the bulkiness of R': ethyl crotonate (81%, 87%ee), benzyl crotonate (97%, 87%ee), isopropyl crotonate (91%, 91%ee), cyclohexyl crotonate (97%, 91%ee),
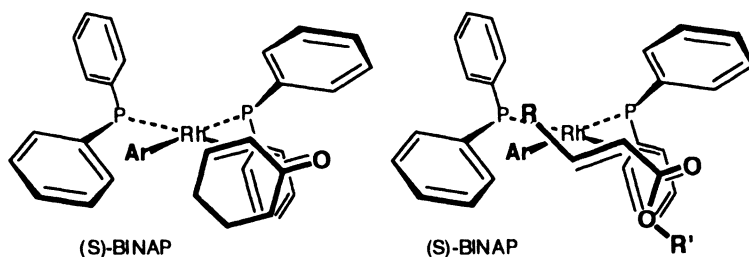
Scheme 12. Transition State for Asymmetric 1,4-Addition

and *t*-butyl crotonate (54%, 92%ee). On the other hand, the addition of *p*-methylphenylboronic acid to isopropyl cinnamate results in 48%ee. Thus, the large steric interaction between Ar and β-substituent (R) reverses the effect to decreise the enantioselectivity.

4. Rhodium-Catalyzed 1,2-Addition to Aldehydes and Imines

The efficiency of transmetalation from boron to rhodium in the conjugate addition to various Michael acceptors encouraged us to extend the protocol to the addition of aryl- and 1-alkenylboronic acids to aldehydes in an aqueous solution (Scheme 13) (*17*). The reaction is well catalyzed by the phosphine complexes having a large P-Rh-P angle such as dppf which may affect the rate of carbonyl insertion into the Rh-C bond. The reaction is sensitive to electronic effects both in aldehydes and arylboronic acids, suggesting the mechanism proceeds through the nucleophilic attack of the aryl group to the carbonyl. Thus, the reaction is facilitated in the presence of an electron-withdrawing group in aromatic aldehydes and a donating group in arylboronic acids. On the other hand, the addition to electron-rich aldehydes and the arylation with electron-deficient arylboronic acids are very slow. The additions to aliphatic aldehydes such as hexanal and cyclohexanecarbaldehyde are very slow at 80 °C due to their lower electrophilicity than that of aromatic aldehydes. The reaction is specific for aldehydes. Aromatic ketones, esters, nitriles, halides (Cl, Br) are unreactive as evidenced by the recovery of these substrates. (*E*)-1-Hexenylboronic acid participates in the catalytic reaction, retaining its stereochemistry.

The proposed catalytic cycle is shown in Scheme 14, which is based on the previous observations at the conjugate 1,4-addition reaction. The insertion of

$$\underset{\underset{H}{|}}{\overset{\underset{R}{|}}{C}}{=}O \quad + \quad Ph{-}B(OH)_2 \quad \xrightarrow[\text{aq. dioxane/80 °C}]{Rh(acac)(CO)_2/dppf} \quad R{-}\underset{OH}{\overset{Ph}{C}}H$$
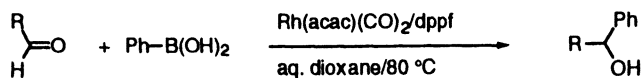
entry	R	yield/%
1	p-CF$_3$C$_6$H$_4$	97
2	p-NO$_2$C$_6$H$_4$	0
3	p-NCC$_6$H$_4$	97
4	p-MeCOC$_6$H$_4$	93
5	p-MeO$_2$CC$_6$H$_4$	82
6	p-MeC$_6$H$_4$	48 (76 at 95 °C)
7	n-C$_5$H$_{11}$	69
8	cyclo-C$_6$H$_{11}$	45 (95 at 95 °C)

Scheme 13. *Rhodium-Catalyzed Addition to Aldehydes*
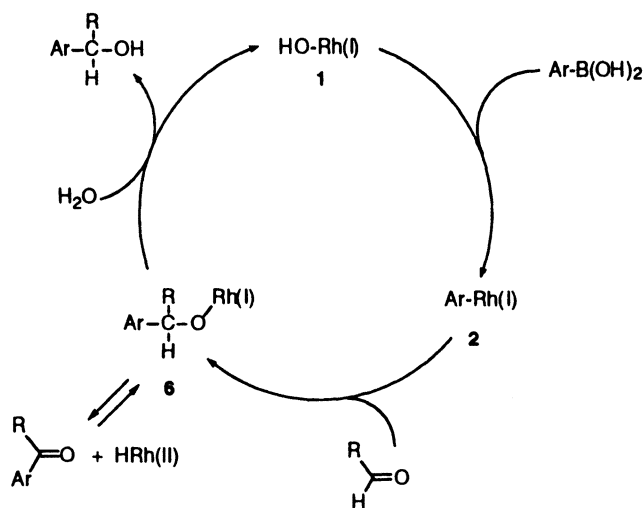
Scheme 14. *Catalytic Cycle for 1,2-Addition to Aldehydes*

carbonyl groups into the metal-carbon bonds is not a popular reaction in transition metal compounds, but this step will lead to (alkoxo)rhodium(I) species **6** and its hydrolysis with water because a similar addition reaction of Me-Rh or Ph-Rh to carbon dioxide yields a (carboxylato)rhodium(I) complex. The formation of ketone *via* the β-hydride elimination from **6** in the absence of water also supports the existence of an (alkoxo)rhodium intermediate.

More recently, a large accelerating effect of ligand was found in bulky and donating trialkylphosphines such as tri(isopropyl)phosphine and tri(*t*-butyl)phosphine when using one equivalent of phosphine to the rhodium metal (Scheme 15) (*18*). The use of a rhodium(I)-tri(*t*-butyl)phosphine complex allowed the quantitative addition of organoboronic acids to aromatic aldehydes at room temperature.

$$R{-}CHO + PhB(OH)_2 \xrightarrow[\text{DME-H}_2\text{O/rt}]{\text{Rh(acac)(coe)}_2\text{/t-Bu}_3\text{P (3 mol\%)}} R{-}CH(Ph)OH$$
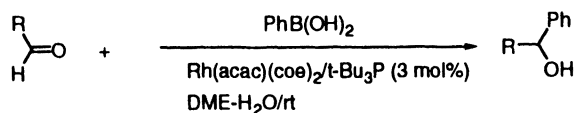
entry	RCHO	time/h	yield/%
1	p-O$_2$NC$_6$H$_4$CHO	16	94
2	p-NCC$_6$H$_4$CHO	16	94
	p-MeOC$_6$H$_4$CHO	16	99

Scheme 15. Large accelerating effect of tri(t-butyl)phosphine

The addition of arylboronic acids to N-sulfonyl aldimines in an aqueous solvent give an addition product of the corresponding aldehyde because the imines are readily hydrolyzed to the aldehyde before addition to the C-N double bond. The use of Ph$_4$BNa in place of phenylboronic acid allows the catalytic addition to various N-sulfonyl imines in the absence of water (Scheme 16) (*19*). The cationic rhodium complexes such as [Rh(cod)(MeCN)$_2$]BF$_4$/dppb are found to be the most efficient catalyst for both aromatic and aliphatic N-sulfonyl imines whereas no reactions are observed for N-alkyl and N-aryl imine derivatives. The mechanism involving the insertion of imine into the carbon-rhodium bond and the subsequent transmetalation between arylboron compounds can be consistent with other related addition reactions of organostannanes and organosilanes. The cationic rhodium complex exhibited high catalyst efficiency over the neutral complexes,

probably due to its high reactivity on the transmetalation with organoboronic acids or by high Lewis acidity on the coordination of imine to the rhodium metal center.
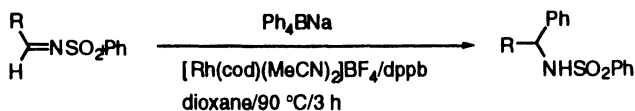
entry	imine	time/h	yield/%
1	$PhCH=NSO_2Ph$	3	89
2	$p\text{-}MeOC_6H_4CH=NSO_2Ph$	3	94
3	$p\text{-}FC_6H_4CH=NSO_2Ph$	3	91
4	$o\text{-}MeC_6H_4CH=NSO_2Ph$	16	90 (16 h)
5	$C_5H_{11}CH=NSO_2Ph$	3	59

Scheme 16. Addition to N-Sulfonyl Aldimines
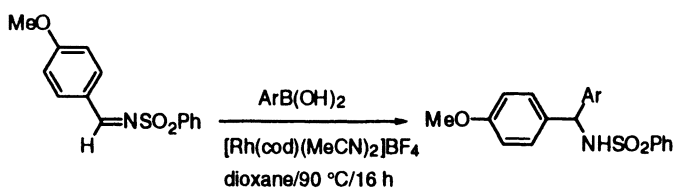
$ArB(OH)_2 = $ 4-$MeC_6H_4B(OH)_2$ (95%), 2-$MeC_6H_4B(OH)_2$ (75%)
3-$ClC_6H_4B(OH)_2$ (96%), 4-$CF_3C_6H_4B(OH)_2$ (87%)

Scheme 17. Addition of ARB(OH)$_2$ to N-Sulfonyl Aldimines

It was recently found that the arylation of N-sulfonyl aldimines with arylboronic acids or esters can be carried out in the presence of $[Rh(cod)(MeCN)_2]BF_4$ (Scheme 17) (20). Arylboronic acids freshly crystallized

from water, arylboroxine (ArBO)$_3$, and arylboronic esters of ethylene glycol afforded similarly good results for aryl aldimines.

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Chapter 8

Arylboron Catalysts for Stereoselective Organic Transformations

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Arylboron compounds with electron-withdrawing aromatic groups such as triarylborons, diarylborinic acids, and arylboronic acids represent a new class of air-stable and water-tolerant Lewis acid or Brønsted acid catalysts in organic synthesis. In particular, arylboronic acids are showing to be powerful tools in the design of chiral boron catalysts.

1. Introduction

The classical boron Lewis acids, BX_3, RBX_2 and R_2BX (X = F, Cl, Br, OTf) are now popular tools in organic synthesis. In general, these are used stoichiometrically in organic transformations under anhydrous conditions, since the presence of even a small amount of water causes rapid decomposition or deactivation of the promoters. To obviate some of these inherent problems, the potential of *arylboron compounds with electron-withdrawing aromatic groups* as a new class of boron catalysts has recently been demonstrated. This chapter provides a comprehensive summary of the organic transformations catalyzed by arylboron compounds **1–11**, which have been developed in our laboratory.

Ar–B(Ar)Ar

1 (Ar=C₆F₅)

OH / Ar–B(Ar)Ar

2 (Ar=C₆F₅)
3 (Ar= 3,5-(CF₃)₂C₆H₃)

OH / Ar–B(Ar)OH

4 (Ar=C₆F₅)
5 (Ar=3,5-(CF₃)₂C₆H₃)
6 (Ar=3,4,5-F₃C₆H₂)

7a (Ar=H)
7b (Ar=3,5-(CF₃)₂C₆H₃)

8 (Ar=3,5-(CF₃)₂C₆H₃)

9 (Ar=3,5-(CF₃)₂C₆H₃)

10d (Ar= 3,5-(CF₃)₂C₆H₃)

11a (Ar=H)
11b (Ar=mesityl)
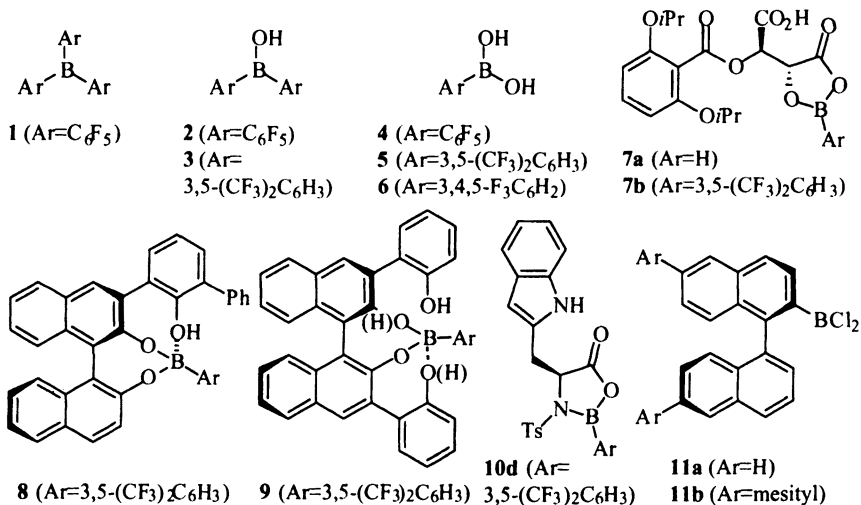
2. Triarylboron

Tris(pentafluorophenyl)boron (**1**) is a convenient, commercially available Lewis acid of comparable strength to BF₃, but without the problems associated with reactive B–F bonds. Although its primary commercial application is as a co-catalyst in metallocene-mediated olefin polymerization, its potential as a Lewis acid catalyst for organic transformations is now recognized as being much more extensive. This compound is very thermally stable, even at 270 °C, and is soluble in many organic solvents (*1, 2*). Although **1** catalyzes various reactions most effectively under anhydrous conditions, **1** exposed to air is also available.

Mukaiyama aldol reactions of various silyl enol ethers or ketene silyl acetals with aldehydes or other electrophiles like chloromethyl methyl ether and trimethylorthoformate proceed smoothly in the presence of 2 mol% of **1** (eq 1) (*3, 5*). These reactions can be carried out in aqueous media, so that the reaction of silyl enol ethers with an aqueous solution of formaldehyde does not present any problems. Triphenylboron catalyzes no aldol-type reactions.

Conjugate addition of silyl enol ethers to α,β-unsaturated ketones proceeds regioselectively in the presence of 2 mol% of **1** (*3, 5*). The product can be isolated as a synthetically valuable silyl enol ether when the crude product is worked-up without exposure to acid (eq 1).

$$\text{(1)}$$

1) **1** (2-10 mol%) R¹CHO
2) HCl or TBAF

1) **1** (2 mol%) R⁵CH=CHCOR⁶
2) HCl or TBAF
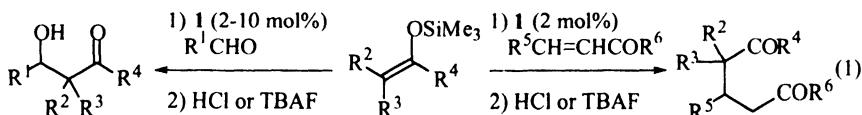
Tris(pentafluorophenyl)boron **1** (anhydrous grade) is a highly active catalyst for the Mannich reaction between ketene silyl acetals and imines because of its stability and comparatively low bond energy and affinity towards nitrogen-containing compounds (eq 2) (*4*, *5*). *N*-Benzylimines are useful substrates because the β-benzylamino acid esters produced can be readily debenzylated by hydrogenolysis over palladium on carbon. In most cases, the condensation proceeds smoothly, even with aliphatic enolizable imines derived from primary or secondary aliphatic aldehydes, and the *syn/anti* stereoselectivity in these condensations of *N*-benzylidenebenzylamine is dependent on the geometry of the ketene silyl acetal double bond: (*E*)- and (*Z*)-ketene silyl acetals give *anti* and *syn* products, respectively, as the major diastereomers.

$$\text{1) } \mathbf{1} \text{ (0.2-10 mol\%)} \quad \text{toluene} \quad \text{2) NaHCO}_3 \text{ aq.} \tag{2}$$

Examples

R^1=Ph, R^2=R^3=H, R^4=t-Bu: 99% R^1=Pr, R^2=R^3=H, R^4=t-Bu: >99%

R^1=Ph, R^2=H, R^3=Me, R^4=Et: >99% R^1=sec-Bu, R^2=R^3=H, R^4=t-Bu: >99%
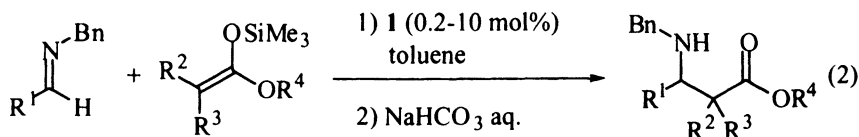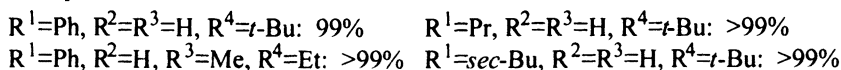
The use of *N*-trialkylsilylimines can be advantageous, since the protecting *N*-substituent can easily be cleaved from the β-amino acid esters produced. The reaction of mono- or disubstituted ketene silyl acetals with *N*-trimethylsilyl-benzylideneamine in the presence of 10 mol% of **1** gives the corresponding β-amino acid esters in good yield (eq 3) (*5*). β-Lactams have also been synthesized in moderate yield by *in situ* treatment of the intermediate with MeMgBr (eq 3) (*5*).

Examples

R^2=H, R^3=Me, R^4=Et (*E:Z*=85:15): 82%, *syn:anti*=84:16

R^2=R^3=R^4=Me: 83%
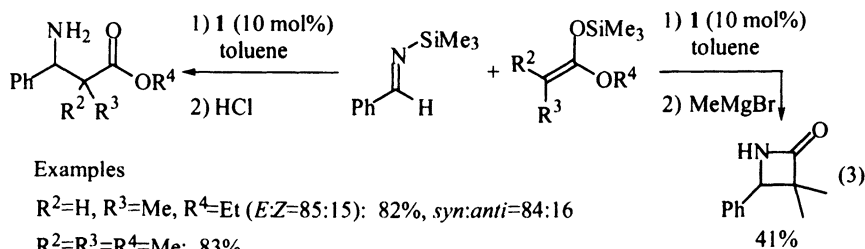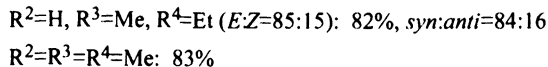
The acid-promoted rearrangement of epoxides to carbonyl compounds is a well-known synthetic transformation. $BF_3 \cdot OEt_2$ appears to be the most widely used Lewis acid for this purpose (*6*). It is often consumed in the course of these reactions, and is thus a reagent rather than a catalyst. We have found **1** to be a highly efficient catalyst in the rearrangement (*7*). The rearrangement of trisubstituted epoxides readily takes place in the presence of catalytic amounts of **1** (anhydrous grade), resulting in a highly selective alkyl shift to give the

corresponding aldehydes. The exceptional bulkiness of **1** may play a role in ensuring the high selectivity of this process. In contrast, treatment of **12** with $BF_3 \cdot OEt_2$ affords a diastereomeric mixture in a 33:67 ratio (alkyl shift:hydride shift) (eq 4).

$$\underset{\textbf{12}}{Bu} \xrightarrow[\text{toluene, 60 °C}]{\textbf{1 (1 mol\%)}} \underset{>99\% \text{ (alkyl shift:hydride shift=98 : 2)}}{OHC\text{-}Bu + Bu}$$ (4)
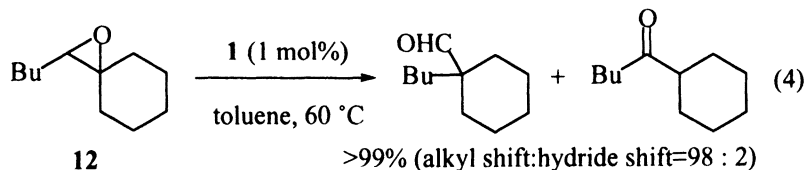
3. Diarylborinic Acids

Diarylborinic acids bearing electron-withdrawing aromatic groups, **2** and **3**, are effective catalysts for Mukaiyama aldol condensation (*8*). The catalytic activities of **2** and **3** are much higher than those of the corresponding arylboronic acids. It is noteworthy that small amounts of (*E*)-isomeric dehydrated products have been isolated in reactions catalyzed by **2** and **3**. In contrast, no dehydrated products have been isolated in the presence of **1**, despite its high catalytic activity. The dehydration is strongly favored in THF, and (*E*)-α,β-enones are obtained in high yields. In reactions of α-substituted β-hydroxy carbonyl compounds, α,β-enones are preferentially obtained from *anti* aldols, while most of the *syn* aldols are recovered. This dehydration thus represents a useful and convenient method for isolating pure *syn* aldols from *syn/anti* isomeric mixtures (eq 5).

$$\underset{R^3}{\overset{OH \quad O}{R^1 \diagdown R^2}} \xrightarrow[\text{THF, ambient temp.}]{\textbf{2 (5-10 mol\%)}} \underset{R^3}{\overset{O}{R^1 \diagdown R^2}} + \underset{R^3}{\overset{OH \quad O}{R^1 \diagdown R^2}}$$ (5)
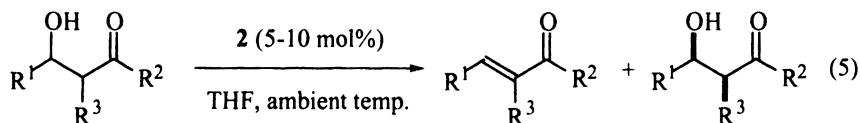
Examples

R^1=Ph(CH$_2$)$_2$, R^2=Ph, R^3=Me (*syn:anti*=71:29): 35%   65% (>99% *syn*)
R^1=R^2=Ph, R^3=H: >99%
R^1=Ph(CH$_2$)$_2$, R^2=Ph, R^3=H: >99%
R^1=Ph(CH$_2$)$_2$, R^2=Bu, R^3=H: 97%

Reaction of the β-hydroxy function with **2** leads to a cyclic intermediate **13**, which should be susceptible to dehydration. Subsequent transformation to α,β-enones occurs via an enolate intermediate **14**, resulting from selective abstraction of a pseudoaxial α-proton perpendicular to the carbonyl face. A cyclic intermediate formed from a *syn* aldol and a diarylborinic acid would be thermodynamically less stable than **13**, thus dehydration to (*E*)-α,β-enones occurs selectively for *anti* aldols.

$$13 \longrightarrow 14$$
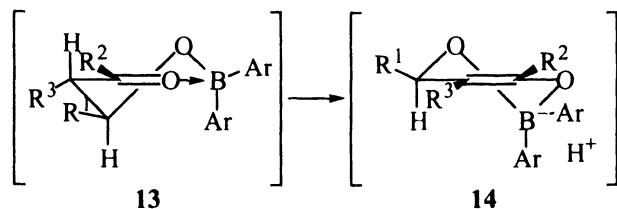
Oppenauer (OPP) oxidation is one of the most useful methods for transforming secondary alcohols into ketones. Functional groups such as carbon–carbon double and triple bonds, aldehydes, amino groups, halogens, or sulfur-containing groups are not affected by this reaction, which is a great advantage over many oxygen-transferring oxidation processes. We have found **2** to be a suitable OPP catalyst for primary and secondary allylic and benzylic alcohols (*9*). Borinic acid **2**, which can be readily handled in air, is a stronger Lewis acid than **4**, although it is weaker than **1** (*8*).

OPP catalysis has been carried out using 1–2 mol% of **2** in the presence of pivalaldehyde as a hydride acceptor in toluene (eq 6). Most allylic alcohols are oxidized to α,β-enals and α,β-enones in high yields. Primary and sterically less-hindered secondary benzylic alcohols are oxidized reasonably efficiently in good yields. The catalytic activity of **2** is much higher than those of other diarylborinic acids; in contrast, **4** is inert. Surprisingly, **1** is also active as a catalyst for the present oxidations. The latter result can be explained in terms of the *in situ* generation of **2** from **1**, and by this being the actual active catalyst. In fact, we have ascertained by ^{19}F-NMR analyses that **1** gradually undergoes conversion to **2** and pentafluorobenzene, and finally to **4**, under these reaction conditions. In general, triarylborons and diarylborinic acids bearing electron-withdrawing substituents on their aryl groups are relatively stable in acidic aqueous solutions, but are unstable in neutral and basic aqueous solutions, undergoing conversion to arylboronic acids and arenes. Removal of water by magnesium sulfate efficiently prevents the inactivation of **2**.

$$R^1\text{-CH(OH)-}R^2 \xrightarrow[\text{\textit{t}-BuCHO (3 equiv), MgSO}_4\text{ (1 equiv)}]{\textbf{2 (1 or 2 mol\%)}} R^1\text{-CO-}R^2 \quad (6)$$

toluene, rt

Examples

95%   >99%   90%
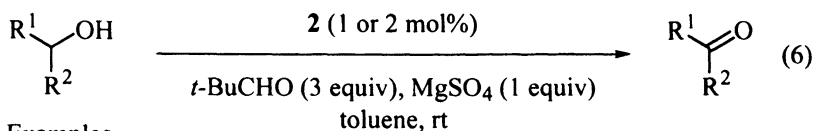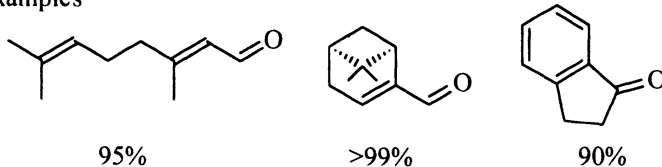
In the oxidation of a diastereomeric mixture of carveol (*syn:anti* = 42:58), the *syn* alcohol is stereoselectively oxidized, while the *anti* alcohol is recovered in

98% diastereomeric purity (eq 7). This shows that the catalytic activity of **2** is very sensitive to steric hindrance in the alcohols.

$$syn{:}anti=42{:}58 \qquad \text{48\% yield} \qquad \text{52\% yield} \tag{7}$$

48% yield

52% yield
(98% *anti*)
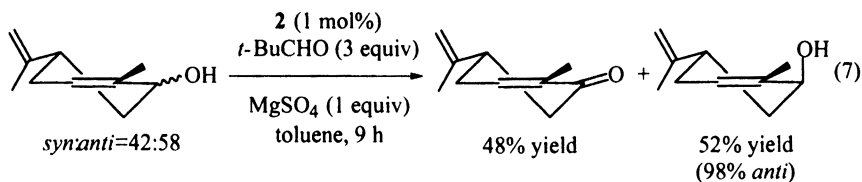
4. Arylboronic Acids

There are several different routes to carboxamides. In most cases, a carboxylic acid is converted to a more reactive intermediate, e.g. an acid chloride, which is then allowed to react with an amine. For practical reasons, it is preferable to form the reactive intermediate *in situ*. We have found that arylboronic acids bearing electron-withdrawing aromatic groups, e.g. **6** and **5**, act as highly efficient catalysts in the amidation of carboxylic acids with amines (*10*). The catalysts are useful in the amide condensation of amines and carboxylic acids and lactamization of amino acids (eq 8). The catalytic amidation of optically active aliphatic α-hydroxy carboxylic acids with benzylamine proceeds with no measurable loss (<2%) of enantiomeric purity under reflux conditions in toluene (eq 8).

$$R^1CO_2H \; + \; R^2R^3NH \; \xrightarrow[\substack{\text{toluene, xylene, or mesitylene}\\ \text{reflux}}]{\textbf{6} \, (1 \, mol\%)} \; R^1CONHR^2R^3 \tag{8}$$

Examples

99%   95%   93%   96% (>98% ee)
6 (10 mol%)
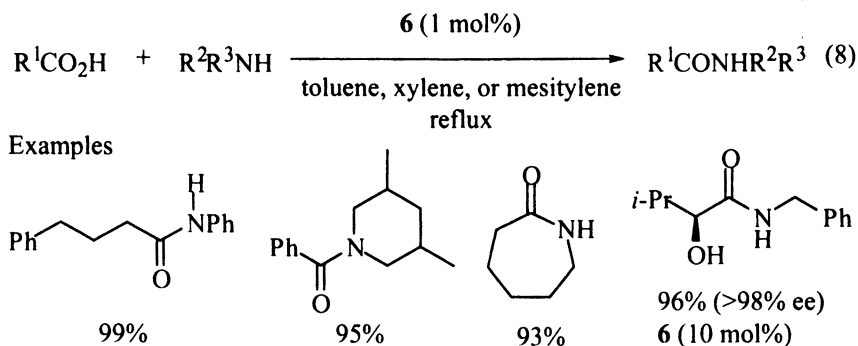
The mechanism that we have proposed to explain boron-catalyzed amidation is depicted in Scheme 1. In general, arylboronic acids contain varying amounts of cyclic trimeric anhydrides (boroxines). The rate-determining step is the generation of **15**.

Scheme 1
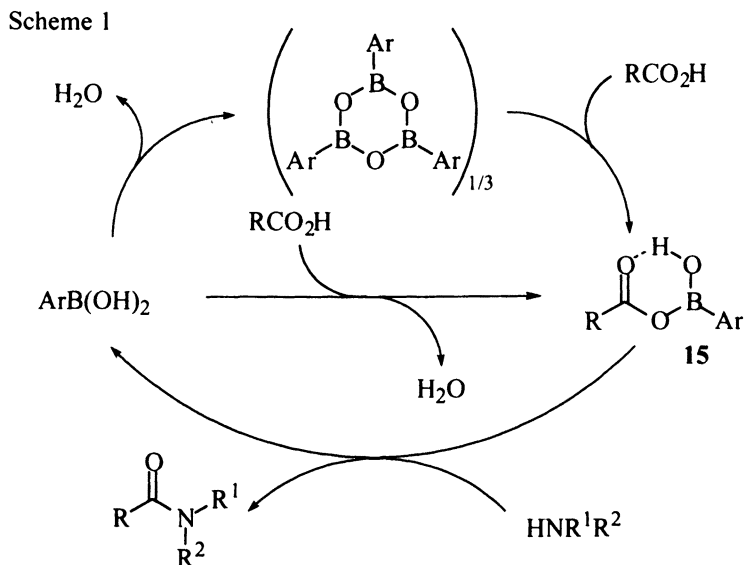
Boronic acid **5** is amenable to the regioselective protection of amino groups (*11, 12*). For example, the synthesis of verbacine (**18**) has been accomplished by addition of cinnamoyl chloride to a 1:1 mixture of **16** and **5** in dichloromethane to give **18** as the major product in 53% yield, together with recovered **16**, the monocinnamamide acylated at *N*-11 of **16**, and the dicinnamamide acylated at both *N*-6 and *N*-11 (eq 9). The acylation of **16** with acyl chloride in the absence of boronic acid gives only the dicinnamamide. The efficiency of the present regioselective acylation can be attributed to the stability of a 1,3-diaza-2-boracyclohexane unit. Thus, the presumed six-membered cyclic intermediate **17** can be expected to undergo acylation with the free amino group at *N*-6.

17 (Ar= 3,5-(CF$_3$)$_2$C$_6$H$_3$)

(*E*)-PhCH=CHCOCl

CH$_2$Cl$_2$, -78 °C

(9)

Verbacine (**18**)
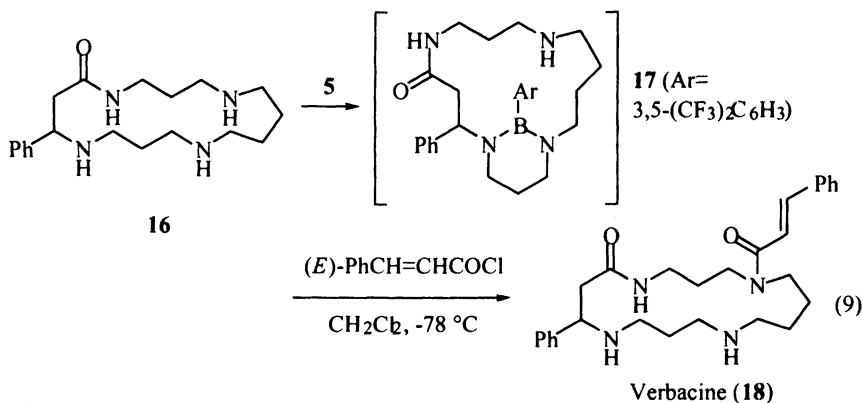
5. Chiral Arylboron Catalysts

Enantioselective Mukaiyama-aldol and Sakurai-Hosomi allylation reactions catalyzed by chiral Lewis acid are currently of great interest because of their utility for the introduction of asymmetric centers and functional groups.

Arylboronic acids bearing electron-withdrawing aromatic groups are highly effective Lewis acid, which are suitable for the design of chiral Lewis acids.

We have reported **7a** to be a good catalyst (20 mol%) for the enantioselective Mukaiyama condensation of simple enol silyl ethers with various aldehydes (eq 10) (*13*). The rate of the aldol reaction is accelerated without reducing the enantioselectivity by using 10–20 mol% of **7b** (*15*). Regardless of the stereochemistry of the enol silyl ethers, *syn* aldols are obtained highly selectively through the acyclic transition-state mechanism. Judging from the configurations of the products, **7** should effectively cover the *si* face of the carbonyl upon coordination.

$$R^1CHO \; + \; R^2 \overset{OSiMe_3}{\underset{R^3}{\diagup}} \quad \xrightarrow[\text{2) 1}N \text{ HCl or TBAF}]{\substack{\text{1) 7 (10-20 mol\%)} \\ \text{EtCN, }-78\,°C}} \quad R^1 \overset{OH \;\; O}{\underset{R^2}{\diagup}} R^3 \quad (10)$$

Examples

(83%), 97% ee *syn*
syn:anti=>95:5
(**7b** (20 mol%))

cf. (57%), 95% ee *syn*
syn:anti=>95:5
(**7a** (20 mol%))

(92%), 96% ee *syn*
syn:anti=99:1
(**7b** (10 mol%))

cf. (86%), 95% ee *syn*
syn:anti=95:5
(**7a** (20 mol%))
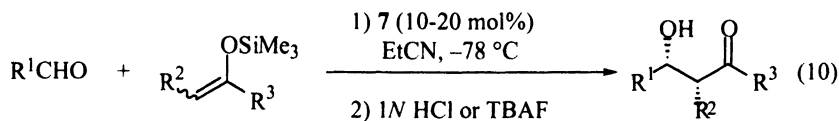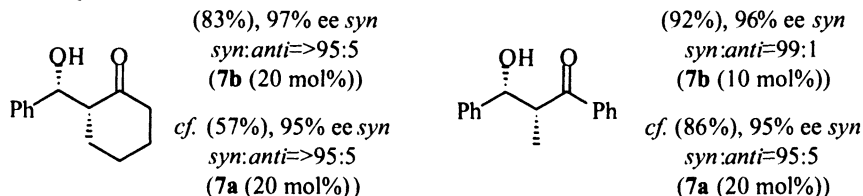
We have also found **7a** to have good catalytic activity in the Sakurai-Hosomi allylation reaction of aldehydes, leading to homoallylic alcohols with high enantiomeric excesses (eq 11) (*16*). γ-Alkylated allylsilanes exhibit excellent diastereo- and enantioselectivities, affording *syn* homoallylic alcohols of even higher optical purity. Regardless of the geometry of the starting allylsilane, the predominant isomer produced is of *syn* configuration, which can be predicted on the basis of an extended transition-state model similar to that for the 7-catalyzed aldol reaction (*13–15*). The boron substituent of **7** has a strong influence on the chemical yield and the enantiomeric excess of the allylation adduct, with the 3,5-bis(trifluoromethyl)phenyl group being most effective (*17*).

$$R^1CHO \; + \; R^2 \overset{R^3}{\diagup}\diagdown SiMe_3 \quad \xrightarrow[\text{2) TBAF}]{\substack{\text{1) 7 (10-20 mol\%)} \\ \text{EtCN, }-78\,°C}} \quad R^1 \overset{OH \;\; R^3}{\underset{R^2}{\diagup}}\diagdown \quad (11)$$
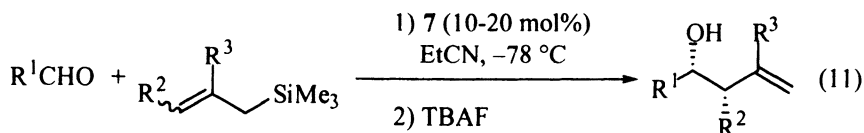
Examples

R^1=Ph, R^2=H, R^3=Me: 99% yield, 88% ee (**7b** (20 mol%))

cf. 68% yield, 82% ee (**7a** (20 mol%))

R^1=Ph, R^2=R^3=Me:(82%), 91% ee *syn, syn:anti*=94:6 (**7b** (20 mol%))

cf. (63%), 92% ee *syn, syn:anti*=96:4 (**7a** (20 mol%))

The asymmetric Diels-Alder reaction is currently of great interest because of its potential to introduce several asymmetric centers simultaneously during carbon–carbon bond formation.

Use of Brønsted acid-assisted chiral Lewis acids (BLAs) **19** has led to high selectivity through the double effect of intramolecular hydrogen-bonding interaction and attractive π-π donor-acceptor interaction in the transition state (eq 12) (*18, 20, 21*). Extremely high enantioselectivity and *exo*-selectivity has been realized for cycloadditions of α-substituted α,β-enals to dienes. The absolute stereopreference can be easily understood in terms of the most favorable transition-state assembly **20**. Coordination of the proton of the 2-hydroxyphenyl group to the oxygen of the adjacent B–O bond in **20** plays an important role in asymmetric induction; this hydrogen-bonding interaction via a Brønsted acid enhances both the Lewis acidity of boron and the π-basicity of the phenoxy moiety.

>99% yield, >99% exo, 94%ee [*S*]

Other examples

(*R*)-**19a** (10 mol%)
91% yield, 91% endo
40% ee [*R*]

(*R*)-**19b** (10 mol%)
85% yield, 86% endo
92% ee [*R*]
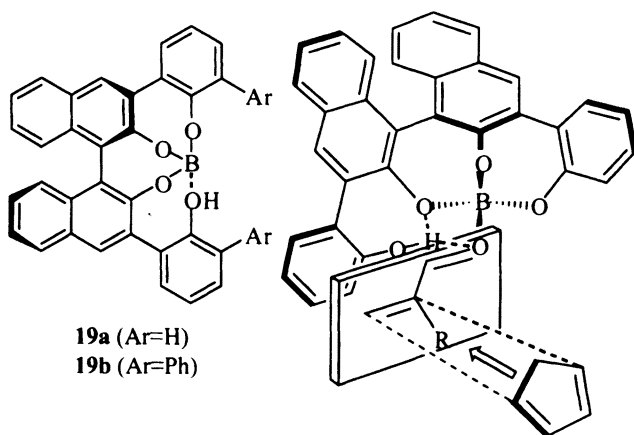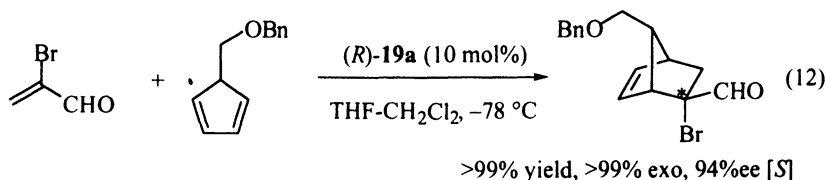
19a (Ar=H)
19b (Ar=Ph)

Transition-state assembly **20**

BLA **19a** is one of the best catalysts for the enantioselective cycloaddition. However, the corresponding reactions of α-unsubstituted α,β-enals such as acrolein and crotonaldehyde exhibit low enantioselectivity and/or reactivity. The range of dienophiles applicable for less reactive dienes is rather limited. The use of **5** in the preparation of BLAs greatly enhances their catalytic activity and asymmetric-inducing ability. We have developed a more practical BLA, **8**, which shows greater catalytic activity in the enantioselective cycloaddition of both α-substituted and α-unsubstituted α,β-enals to various dienes (Scheme 2) (*19–21*). The high enantioselectivity and stereochemical results attained in this reaction can be understood in terms of the transition-state model **21**.

Scheme 2

Transition-state assembly **21**

Examples

(*R*)-**8** (5 mol%)
>99% yield
>99% ee [*R*]

(*R*)-**8** (10 mol%)
95% yield
99% ee

(*R*)-**8** (20 mol%)
94% yield
95% ee [*S*]

(*R*)-**8** (30 mol%)
95% yield
80% ee [*R*]
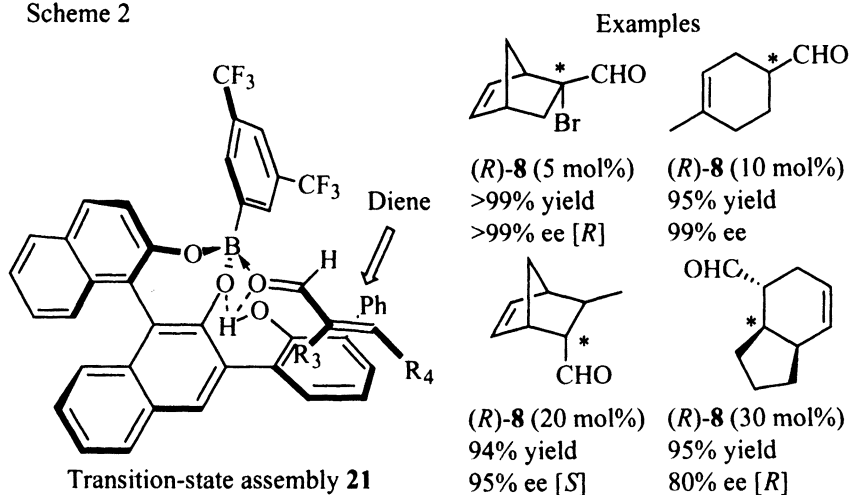
BLA **8** is prepared from a chiral triol and monomeric **5** in the presence of powdered 4 Å molecular sieves in dichloromethane/THF. Although molecular sieves are essential for dehydration, they may also facilitate the aryloxy ligand exchange reaction. Arylboronic acids usually exist as mixtures of the monomer, trimer, and oligomers. To prevent oligomerization of **5** in preparing the catalyst, THF is needed as an additive (eq 13) (*21*).

1) water
   THF
   CH₂Cl₂, rt
2) MS 4A

$$\qquad\qquad (R)\text{-}\mathbf{8} \qquad (13)$$
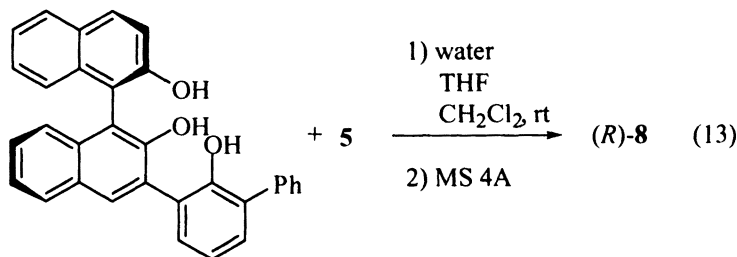
The absolute stereopreference observed in the Diels-Alder reaction catalyzed by (R)-8 is opposite to that found with catalysis by (R)-19a. This implies that the presence of the 3,5-bis(trifluoromethyl)phenyl group greatly affects the asymmetric induction of BLAs. In fact, the use of BLAs 19a and 9, prepared from the same chiral tetraol, in Diels-Alder reactions leads to the opposite enantiomers with high selectivity (eq 14) (21).
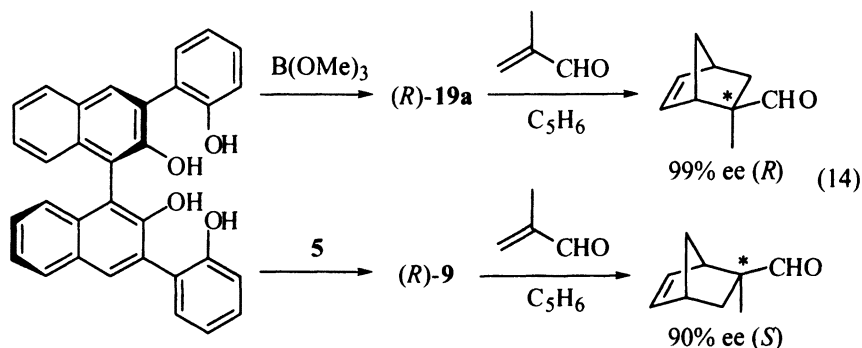
Since our group (22) and Helmchen's (23) independently announced a new class of chiral acyloxyboranes derived from N-sulfonylamino acids and borane•THF, chiral 1,3,2-oxazaborolidines, their utility as chiral Lewis acid catalysts in enantioselective synthesis has been convincingly demonstrated (26). In particular, Corey's tryptophan-derived chiral oxazaborolidines 10a and 10b are highly effective for not only Mukaiyama aldol reactions (24) but also Diels–Alder reactions (25). More than 20 mol% of 10b is required for the former reaction, however. Actually, the reaction of the trimethylsilyl enol ether derived from cyclopentanone with benzaldehyde afforded the aldol products in only 71% yield even in the presence of 40 mol% of 10b (24). We recently succeeded in renewing 10b as a new and extremely active catalyst 10d using arylboron dichlorides as Lewis acid components (26).

Catalyst 10d was prepared simply by treatment of N-(p-toluenesulfonyl)-(S)-tryptophan with 3,5-bis(trifluoromethyl)phenylboron dichloride and subsequent removal of the produced HCl in vacuo (eq 15) (26). The B-Aryloxazaborolidine could not be prepared from the arylboronic acid.
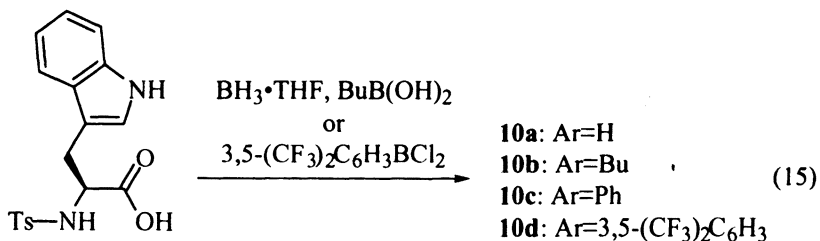
Our initial studies were conducted with benzaldehyde and the trimethylsilyl enol ether derived from acetophenone at −78 °C in propionitrile in the presence of **10** (eq 16) (*26*). Following Corey's procedure using **10b**, we obtained the aldol adducts in low yields. However, when **10c** was used, the chemical yield was improved strikingly. Furthermore, when **10d** was used, the catalytic activity and the enantioselectivity were increased to a turnover of 25 and 91~93% ee, respectively.

In the reaction of benzaldehyde with the trimethylsilyl enol ether of cyclohexanone, both substrates were sequentially added in a solution of **10d** in propionitrile at −78 °C according to Corey's procedure (*24*). The reaction proceeded quantitatively to give the aldol products in 78:22 *syn/anti* ratio, and the optical yield of *syn* adduct was 89% ee. The reaction of butyraldehyde with the (*Z*)-trimethylsilyl enol ether derived from propiophenone, however, did not proceed well. Fortunately, the reaction proceeded cleanly by adding trimethylsilyl enol ether followed by butyraldehyde to afford only the *syn* aldol adduct with more than 99% ee. The *syn* selection observed in both reactions suggests that the reaction occurs *via* extended transition state assemblies.

10b (10 mol%)	38%, 82% ee	15%, 82% ee
10c (10 mol%)	88%, 79% ee	11%, 82% ee
10d (10 mol%)	91%, 93% ee	4%, 68% ee
10d (4 mol%)	94%, 91% ee	4%, 72% ee

Other examplex
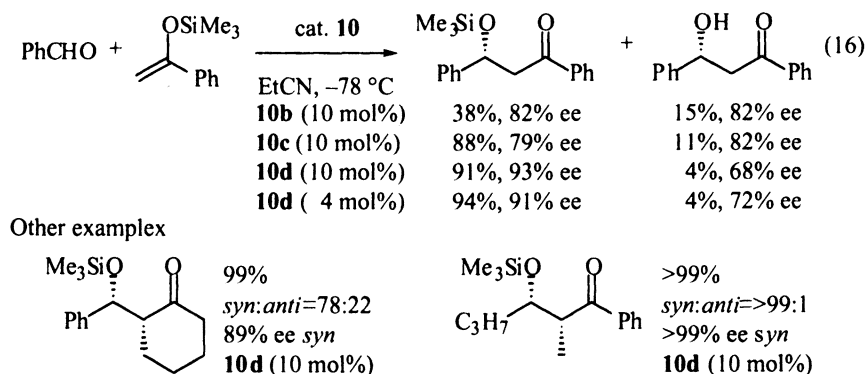
Chiral alkyldihaloboranes are among the most powerful of chiral Lewis acids. However, since these compounds are often prone to facile decomposition to alkanes or alkenes by protonolysis or β-hydride elimination, it is difficult to recover them as alkylboronic acids. Aryldichloroboranes are more stable and can be reused as the corresponding boronic acids. We have developed chiral aryldichloroboranes **11**, bearing binaphthyl skeletons with axial chirality, as asymmetric catalysts (*27*). (*R*)-2-Dihydroxyboryl-1,1'-binaphthyl (**22**) can be synthesized in several steps from (*R*)-binaphthol (*27*). Conversion of (*R*)-**22** to (*R*)-**11** has been achieved by two different methods: one via exchange of the methanol boronate with trichloroborane (*Method A*), and the other via exchange of the anhydrides of boronic acids with trichloroborane (*Method B*) (Scheme 3).

The Diels-Alder reaction of cyclopentadiene with methyl acrylate proceeds smoothly at −78 °C in the presence of 10 mol% of (*R*)-**11**, to give the only *endo*

adduct in high yield. Catalyst **11b** showed the highest asymmetric induction. The absolute configuration of the *endo* adduct is consistent with the naphthyl moiety shielding the *re* face of the coordinated methyl acrylate, leading to attack by cyclopentadiene at the *si* face, as shown in **23**. Coordination of the methyl acrylate with the *re* face exposed, as shown in **24**, is unfavorable due to steric interaction between the alkene and the naphthyl moiety. Increased enantioselectivity obtained using **11b** can be understood in terms of steric repulsion between the alkene and mesityl groups.

Scheme 3

23 (favored) **24** (unfavorable)
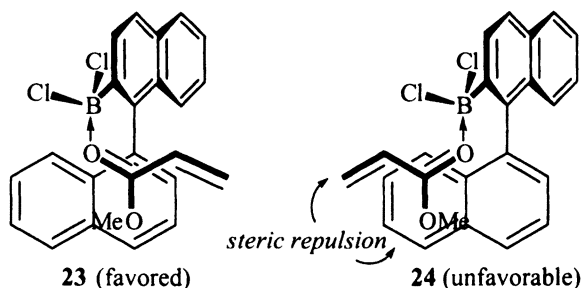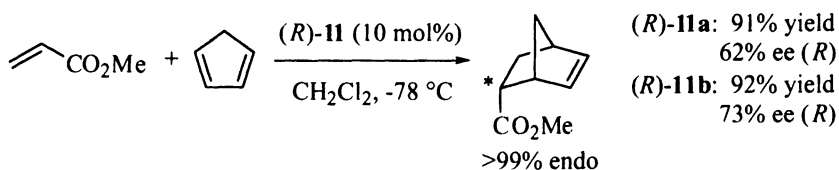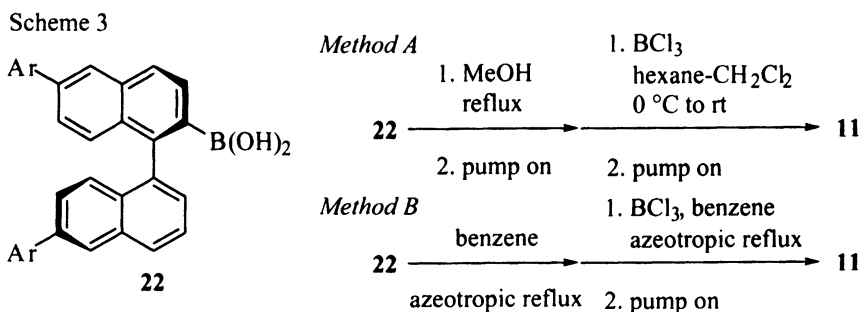
6. Conclusions

Arylboron compounds with electron-withdrawing substituents are useful as air-stable acid catalysts in performing various organic transformations, and as significant components of chiral acid catalysts. Despite these impressive recent advances, many unsolved problems remain. These include limitations with regard to the scope of reactions and frequently encountered practical problems associated with catalyst preparation and use. Nonetheless, continued exploratory research on the catalytic applications of arylboron compounds and on the development of reusable chiral arylboron catalysts can be expected to provide powerful and practical methods for carrying out acid-catalyzed organic transformations.

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Chapter 9

Asymmetric Reduction of α-Functionalized Ketones with Organoboron-Based Chiral Reducing Agents

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Asymmetric reductions of α-functionalized ketones, such as α-hydroxy ketones, α-halo ketones, α-sulfonoxy ketones, 1,2-diketones, α-keto acetals or thio ketals, acyl cyanides and α-amino or imino ketones with boron-based chiral reducing agents in a stoichiometric or catalytic manner have been reviewed. The oxazaborolidine-catalyzed borane reduction of protected α-hydroxy ketones, α-keto acetals and α-sulfonoxy ketones has been discussed in more detail.

One of the simplest and most useful methods for the preparation of optically active secondary alcohols is the asymmetric reduction of prochiral ketones. Over the past decades, a variety of asymmetric reducing agents have been extensively reported (*1-3*). However, most of the early experiments in this area gave disappointingly low optical yields (*4-7*). Moreover, because reactive species of the reducing systems are generally unknown, there has been no reliable information on the mechanistic basis for enantioselectivity. In recent years, significant advances have been made in the asymmetric ketone reduction area using chirally modified aluminumhydrides, borohydrides and borane derivatives

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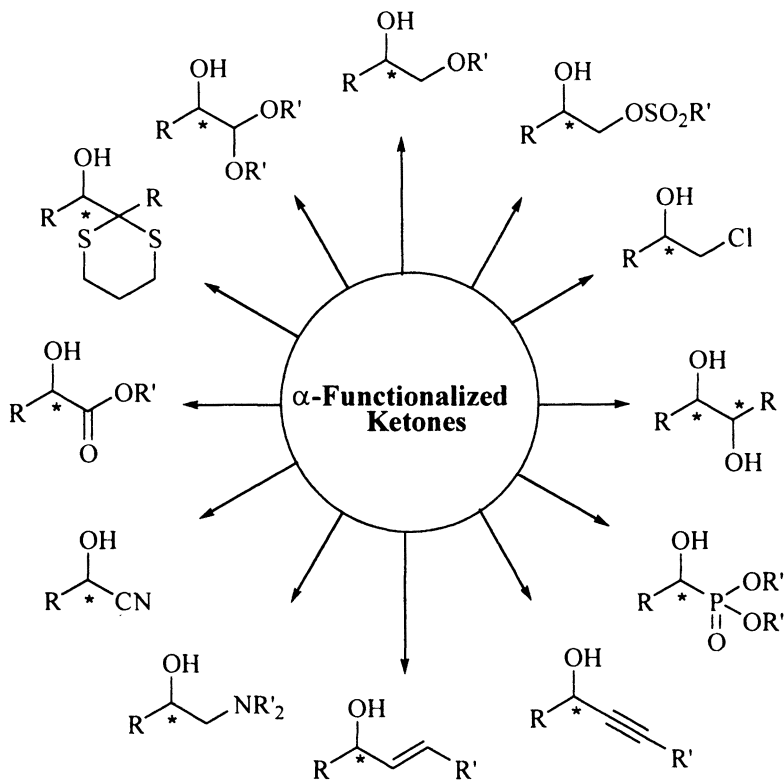
Figure 1. Asymmetric reduction of α-functionalized ketones

which produce high enantioselectivity. Of these reagents, structurally well-defined reducing agents, such as Binal H, K-Glucoride, Alpine-borane and Dip-Chloride™ have proven to be the most promising (*8*). However, limitations to the use of these stoichiometric reagents are availability, cost, ease of product purification and chiral auxiliary recovery on large scale. Following the pioneering works of Itsuno (*9*) and Corey (*10, 11*), a number of oxazaborolidine-catalyzed asymmetric borane reduction of prochiral ketones has been extensively studied (*12-15*). This method provides an impetus for asymmetric reduction, because oxazaborolidines can be easily prepared from chiral β-amino alcohols and provide high enantioselectivity with predictable absolute configurations.

On the other hand, optically active 1,2-diols, α-hydroxy acetals or thio ketals, halohydrins, α-sulfonoxy alcohols, α-hydroxy esters, cyanohydrins, β-amino

alcohols, α-phosphonyl alcohols, allylic alcohols, propargyl alcohols have found widespread use as chiral building blocks and numerous applications as chiral auxiliaries, ligands or intermediates for asymmetric synthesis. These chiral compounds can be prepared by asymmetric reduction of the corresponding α-functionalized prochiral ketones (Figure 1). In this chapter, attention has been focused on the recent advances in the asymmetric reduction of such α−functionalized ketones with organoboron-based chiral reducing agents in a stoichiometric and catalytic manner. In addition, we have described our recent results for oxazaborolidine-catalyzed borane reduction of α-protected hydroxy ketones, α-keto acetals and α-sulfonoxy ketones more in detail.

Chiral Borohydrides: Potassium 9-*O*-(1,2:5,6-di-*O*-isopropylidene-α-D-glucopyranosyl)-9-boratabicyclo[3.3.1]nonane (K Glucoride, 1) and Potassium 9-*O*-(1,2-*O*-isopropylidene-5-deoxy-α-D-xylofuranosyl)-9-boratabicyclo[3.3.1]nonane (K Xylide, 2). The chiral borohydrides, 1 and 2 were easily prepared by treating excess potassium hydride with the corresponding borinic esters (*16, 17*) (Figure 2). We identified that 1 was an unusually efficient reagent for the reduction of hindered aromatic ketones and α-keto esters. The hydride 2 has proven to be the most promising reagent for the asymmetric reduction of α-keto acetals (*18*).

$$Y = \overset{O}{\underset{O}{>\!\!\!<}}\!\!\!< \quad \text{K Glucoride, 1}$$

$$Y = Me \quad \text{K Xylide, 2}$$

Alpine-borane, 3   DIP-Cl, 4

BH = 9-BBN
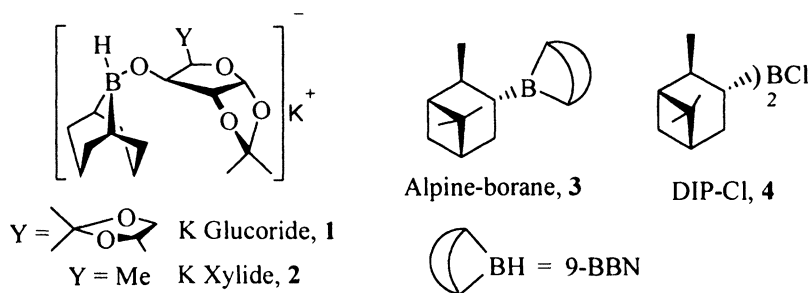
Figure 2. Representative chiral borohydrides and organoboranes

Chiral Organoboranes: *B*-Isopinocampheyl-9-borabicyclo[3.3.1]nonane (Alpine-borane® 3) and *B*-chlorodiisopinocampheylborane (Ipc₂BCl, DIP-Chloride™ 4) (Figure 2). The first successful chiral organoborane reducing agent 3 was prepared from hydroboration of α-pinene with 9-BBN (*19*). Although this reagent gives poor selectivity for the simple ketones, the reagent is excellent for the reduction of α,β-acetylenic ketones, α-halo ketones, α-keto

esters and acyl cyanides (*20-22*). The reagent **4** was prepared by treating diisopino-campheylborane (Ipc$_2$BH) with hydrogen chloride in ethyl ether (*23*), by the direct hydroboration of α-pinene with monochloroborane (*24*) or by *in situ* reaction of α-pinene, NaBH$_4$ and BCl$_3$ (*25*) (Figure 2). Although the reduction with **4** requires a stoichiometric amount of this reagent (*26*), it is a versatile chiral reducing agent to provide high enantioselectivities for the reduction of not only aralkyl ketones and α-hindered aliphatic ketones (*23*), but also functionalized ketones, such as perfluoroalkyl ketones (*27-29*), halo ketones (*30*), diketones (*31-35*), α- or β-hydroxy ketones (*36*), α-ketophosphonate (*37*), α-keto acids (*38*), α-amino ketones (*39, 40*), and hindered α,β-acetylenic ketones (*41*). In addition, both isomers of this reagent are available from the corresponding enantiomer of α-pinene.

Oxazaborolidine Catalysts: The oxazaborolidines used as catalyst are easily prepared from the reaction of chiral β–amino alcohols with borane-THF, borane-dimethyl sufide (BMS), trimethylboroxine or alkyl (or aryl)boronic acid (*12, 13, 14, 15*). The ketone reduction generally occurs even at ambient temperature and in the presence of 2 mol% of the catalyst to provide the product alcohols in high enantiomeric excess (*ee*) with predictable absolute configurations. The detailed mechanistic study for the catalytic and stereo-chemical course of the reduction have been well established (*10, 42*). Since the oxazaborolidine-catalyzed borane reduction have proven to be highly effective for the asymmetric reduction of different types of ketones, this method have been widely applied to syntheses of chiral drugs, catalytic ligands, natural products, and synthetic intermediates (*12*). On the other hand, borane-THF, BMS and catecholborane have been so far most commonly used as borane carriers for the reduction. However, these kinds of borane carriers are not free from certain disadvantages for large scale applications, because of the low concentration and stability of borane-THF, and high volatility, flammability, unpleasant odor of BMS and high sensitivity to air and moisture. In contrast, it has been known that the amine-borane complexes offer the advantages of being soluble in most common solvents at high concentration and lower sensitivity to air and moisture. Therefore, the use of more stable borane carrier in the catalytic reduction provides more practically useful method in their large scale applications. Very recently, successful oxazaboroli-dine-catalyzed ketone reductions using an amine-borane complex, *N,N*-diethylaniline-borane (DEANB), as a borane carrier have been reported (*43, 44*).

Asymmetric Reduction of α-Functionalized Ketones
Protected α-hydroxy ketones. Enantiomerically pure terminal 1,2-diols are important synthetic intermediates for numerous applications (*45, 46*). We first

compared oxazaborloidine-catalyzed borane reduction of 2-*tert*-butyldimethyl-siloxyacetophenone using five structurally diverse oxazaborolidines selected as representative catalysts, namely, Itsuno's reagent (**5**) (*9*), CBS reagent (**6**) (*10*, *11*), Garcia's reagent (**7**) (*47*), Pfizer's reagent (**8**) (*48*) and Sepracor's reagent (**9**) (*49*) (Figure 3). Among the catalysts examined, the CBS reagent **6a** provided the best result showing 1-phenyl-1,2-ethanediol with almost 100 % *ee*. In the same reduction for other aromatic analogues using **6a** as catalyst, we obtained the product diols in almost 100 % *ee* except the cases for *o*-tolyl and 1-naphthyl derivatives (*50*). Interestingly, the reduction of *o*-tolyl and 1-naphthyl analogues provided lower enantioselectivity such as 58 % *ee* and 75 % *ee*, respectively. These results indicate the asymmetric induction was sensitive to steric effects of the substituent proximal to the carbonyl group. This is a common phenomenon in oxazaborolidine-catalyzed reduction (*51*). In the case of aliphatic analogues, somewhat lower enantioselectivities were obtained. However, the case having a cyclohexyl group again produced very high enantioselectivity (Figure 4). We also examined the effect of different protecting groups on the asymmetric induction. We compared the CBS reduction of α-hydroxyacetophenone protected with different groups, such as tetrahydropyranyl (THP), methoxy-methyl (MOM), 1-ethoxyethyl (EE), and pivaloyl (Piv) groups. Of the protecting groups examined, THP group provided the best result to give >99 % *ee*. For α-hydroxyacetophenone itself, the reduction exhibited only 3 % *ee*. Next we examined the effect of borane carriers for the same reduction. Surprisingly, *N*-phenyl-amine-borane complexes such as *N,N*-diethylaniline-borane (DEANB), *N*-ethyl-*N*-isopropylaniline-borane (Aldrich: Bach-EI) and *N*-phenylmorpholine-borane (PHMOB) complexes furnished very high *ee* approaching 100 % *ee*, although borane-THF, borane-dimethylsulfide (BMS) and catecholborane also provided high *ee*. This method again afforded very high *ee* for most aromatic derivatives except for *ortho* substituted analogues. Unlike the reduction of α-siloxy derivatives, the reduction also provided high *ee* for aliphatic analogues. This offers more practically useful method for the preparation of optically active terminal 1,2-diols. In this reaction, the use of other amine-borane reagents, such as pyridine-borane derivatives and trialkyamine-borane derivatives afforded slow reduction and low enantio-selectivities (Cho, B. T.; Chun, Y. S., unpublished results, *52*) (Figure 5). The reason for this is unclear. It may be attributable to differential dissociation of amine-borane adducts leading to liberation of free BH$_3$, which coordinates with the oxazaborolidine to initiate catalytic asymmetric reduction. This assumption is based on easier dissociation of *N*-phenylamine-borane complexes to the free borane compared to other amine-borane complexes (*53*).

a, R = H; b, R = Me; c, R = n-Bu; d, R = Ph
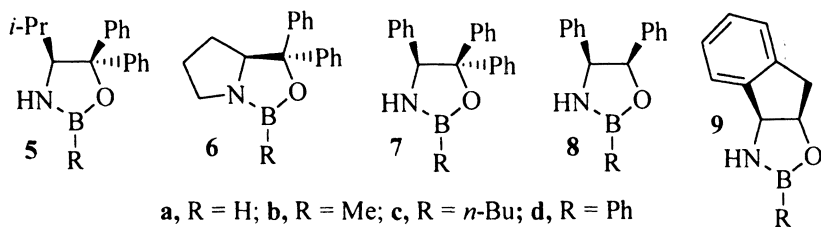
Figure 3. Selected oxazaborolidines
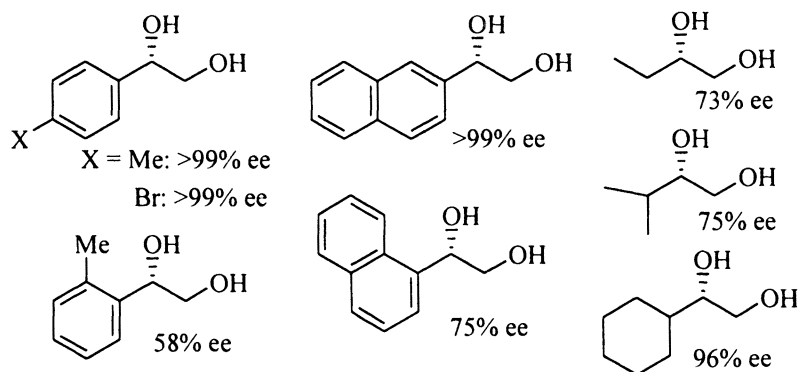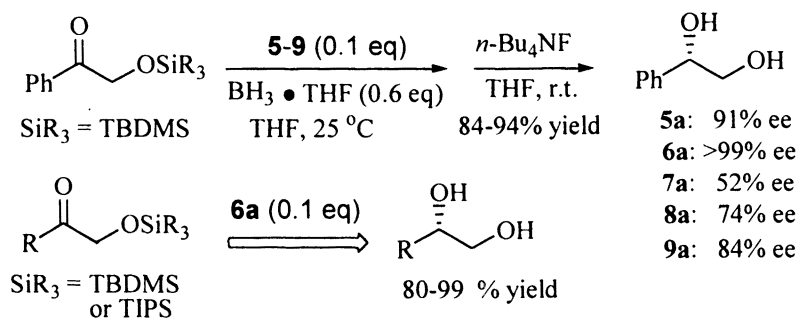
Figure 4. Oxazaborolidine-catalyzed borane reduction of α-siloxy ketones
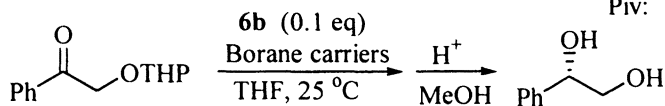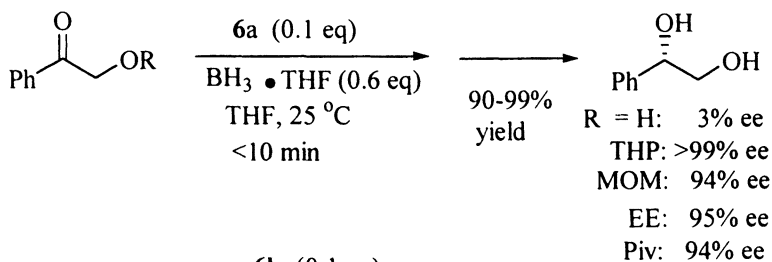
Borane carrier = BMS, 99% ee; catecholborane, 96% ee;
DEANB, >99% ee, Bach-EI, >99% ee, PHOMB, >99% ee;
i-Pr$_2$EtN-BH$_3$, 85% ee (3h); Et$_3$N-BH$_3$, 68% ee (24h)

X = p-Me: >99% ee
  o-Me: 23% ee
  p-Cl: 95% ee
  m-Cl: 90% ee
  m-AcO: 92% ee
  p-MeO: 95% ee

>99% ee

19% ee

R = Et: 88% ee
  i-Pr: 91% ee
  t-Bu: 97% ee
  c-Hex: 97% ee
  n-C$_8$H$_{17}$: 90% ee
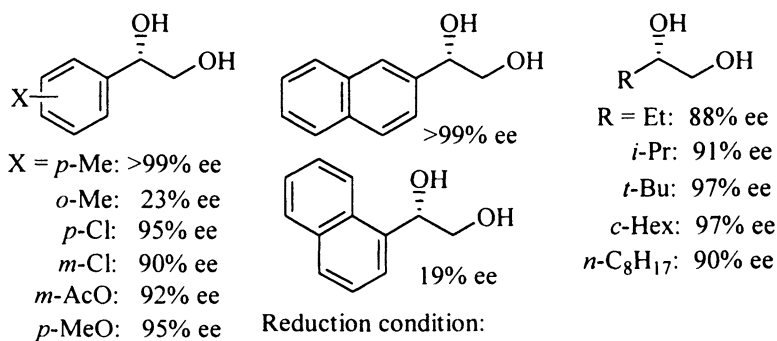
Reduction condition:
6b (0.1 eq), DEANB (1.0 eq), THF, 25 °C

Figure 5. CBS reduction of THP-protected α-hydroxy ketones using N-phenylamine-borane complexes efficiently produces terminal 1,2-diols with very high ee

α-Halo ketones. Asymmetric reduction of α-haloacetophenone derivatives has permitted the highly efficient preparation of a number of chiral β-blockers by amination of the corresponding optically active halohydrins or styrene oxides (*54-58*). Most of oxazaborolidine-catalyzed reduction of α-halo acetophenone provided optically active 2-halo-1-phenylethanol with high *ee* (92-96% *ee*) (*49, 59, 60*), whereas the chiral borohydrides, **1** and **2** affored 77 % ee and 92% *ee*, respectively (*16, 17*). The organoborane reagents, **3** and **4** also produced high *ee* (*8, 20*) (Figure 6).
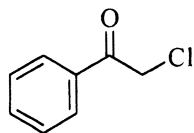
1 (1.1 eq), -78 °C, 77% ee, *S*
2 (1.1 eq), -78 °C, 92% ee, *S*
3 (neat), r.t, 96.2% ee, *R*
4, -25 °C, 95% ee, *R*
6a (0.02 eq), BH_3-THF (0.5 eq), 96.5% ee, *S*
8c (0.05 eq), BMS (0.5 eq), 92% ee, *R*
9b (0.1 eq), BH_3-THF (0.8 eq), -20 °C, 96% ee, *S*

Figure 6. Asymmetric reduction of 2-chloroacetophenone with various boron-based asymmetric reducing agents

α-**Sulfonoxy ketones**. Although asymmetric reduction of α-halo ketones may be a useful method in obtaining optically active halohydrins and epoxides, the use of α-halo ketones on large scale suffers from disadvantages such as severe irritations to skin and eyes, and light-sensitivity of the compounds. In contrast, α-sulfonoxy ketone derivatives can be easily handled, because they are not irritant and stored under usual condition for a long time as well as easily prepared by reacting methyl ketones with Koser's reagent, tosyl or mesyloxyiodobenzene (*61*, *62*). We compared asymmetric reduction of 2-tosyloxyacetophenone ketones using each of oxazaborolidine selected as the catalyst and various borane reagents as the borane carrier. Among them, the CBS catalyst **6b** and borane reagents such as BH_3-THF, BMS, Bach-El and DEANB provided the best results to give the correponding α-sulfonoxy alcohol in very high *ee*. No significant effects among different sulfonoxy groups were observed. The CBS reduction of most aromatic α-sulfonoxy ketones using Bach-El as the hydride source furnished excellent *ee*. These α-sulfonoxy alcohols were readily converted to epoxides under basic conditions with no racemization. This offers a very convenint and practically useful method for preparation of optically active epoxides (Cho, B. T.; Choi, O. K.; Yang, W. K., unpublished results) (Figure 7).

1,2-Diketones. Chiral 1,2-diols have been extensively utilized as ligands and chiral auxiliaries for asymmetric synthesis. The CBS reduction of 1,2-diketones, such as benzil and heterocyclic derivatives furnishes optically active hydrobenzoins with excellent ee (>99 % *ee*) and good de (64-86 % *de*) (*63*) (Figure 8), whereas the reagent **1** afforded hydrobenzoin in 70 % ee with 34 % *de* (Cho, B. T., unpublished results).

cat. (0.1 eq)

Bach-EI (1.0 eq)
THF, 25 °C

NaOH
ether

cat =
6b: 97 %ee
7b: 70 %ee
9b: 80 %ee

Borane carrier =

Bach-EI: 97% ee
DEANB: 97% ee
PHMOB: 90% ee
BH$_3$-THF: 96% ee

6b (0.1 eq)
borane carrier
THF, 25 °C

NaOH
ether

6b (0.1 eq)
Bach-EI (1.0 eq)

THF, 25 °C

R = Ms: 96% ee
Ts: 97% ee
p-Ns: 97% ee

Ar⎯⎯OR

6b (0.1 eq)
Bach-EI (1.0 eq)

THF, 25 °C

NaOH
ether

X = *o*-Cl: 80% ee
m-Cl: >99% ee
p-Cl: >99% ee
p-Me: 97% ee
p-NO$_2$: 95% ee

98% ee
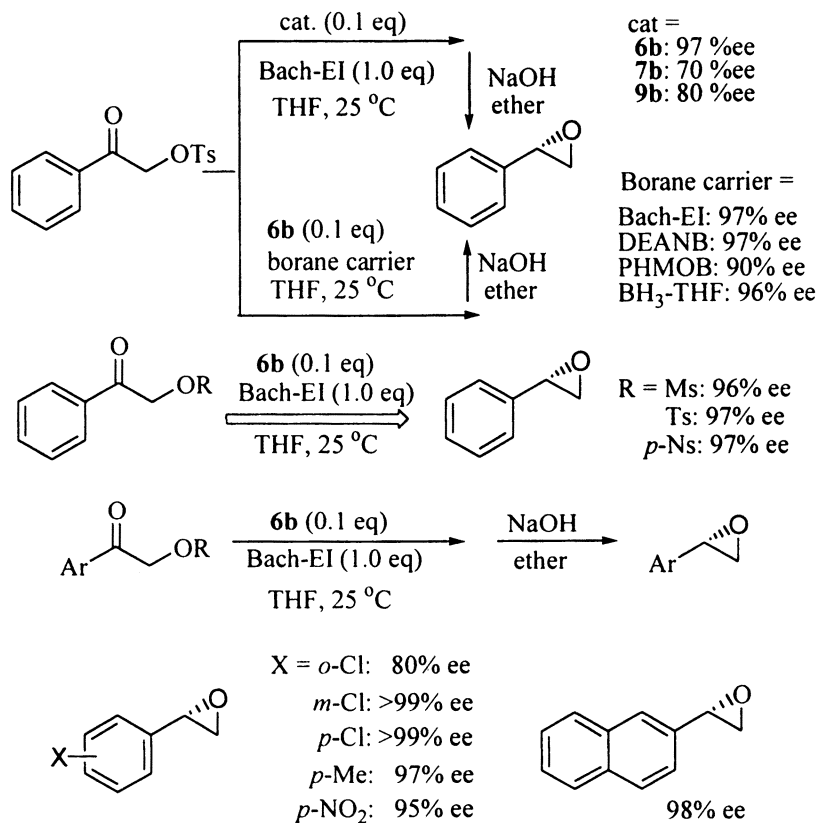
*Figure 7. CBS reduction of α-sulfonoxy ketones to valuable
terminal epoxides with excellent ee*

6a (0.1 eq)

BMS
PhMe, 45 °C

Ar =
Substituted phenyl,
2-furyl or 2-thienyl

>99% ee
68-84 de
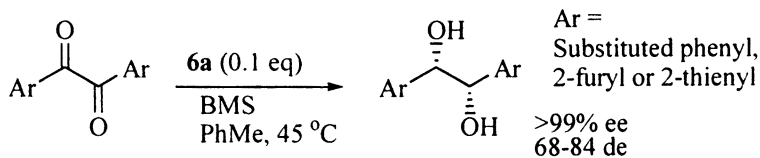
Figure 8. CBS reduction of 1,2-diketones

α-Keto acetals and thio ketals. Optically active α-hydroxy aldehydes are not only useful chiral building blocks for the synthesis of natural products, but also important substrates for diastereofacial selective reactions of the carbonyl groups, *e.g.* nucleophilic 1,2-addition or aldol reactions, and cycloadditions. The chiral hydride **2** efficiently reduced α-keto acetals to the corresponding α-hydroxy acetals in high *ee* for both aliphatic and aromatic analogues (*18*). The CBS reduction provided excellent *ee* for aromatic analogues and moderate ee for aliphatic analogues (*64*). Also, the CBS reduction for both acyclic and cyclic α-keto thioketals was highly enantioselective (*65*) (Figure 9).
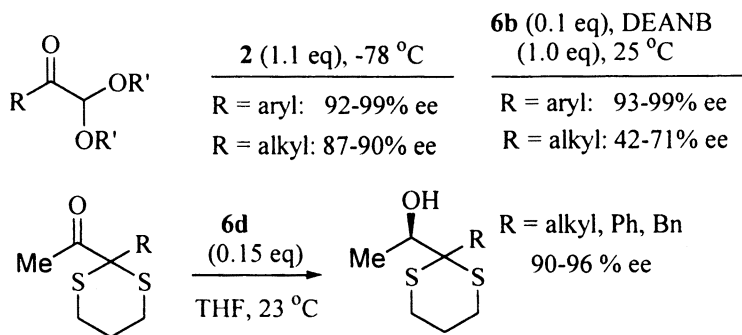
Figure 9. Asymmetric reduction of α–keto acetals or thioketals

Acyl cyanides. Owing to their broad synthetic potential, optically active cyanohydrins have attracted attention as staring materials for the preparation of several important classes of compounds, such as α-hydroxy acids and esters, acyloins, α-hydroxy aldehydes, β-amino alcohols and β-hydroxy-α-amino acids (*66, 67*). Acyl cyanides are rapidly reduced by the chiral organoborane reagent **3** to cyanohydrines, and converted by NaBH₄/CoCl₂ to the corresponding 1,2-amino alcohols of high *ee* (*23*) (Figure 10).

α-Amino and imino ketones. Enantiomerically pure β-amino arylethanol-amine derivatives are playing an increasingly important role as chiral drugs (*54, 55, 56, 57, 58, 68, 69*). One of the most convenient methods for preparation of the amino alcohol may be the asymmetric reduction of the corresponding α-amino or imino ketones. Oxazaborolidine-catalyzed borane reduction of α-imino ketones gave the corresponding β-amino alcohols in high *ee* (*70, 71*). The reagent **4** also afforded high *ee* (*39*), whereas **1** provided moderate ee (*72*) (Figure 10).
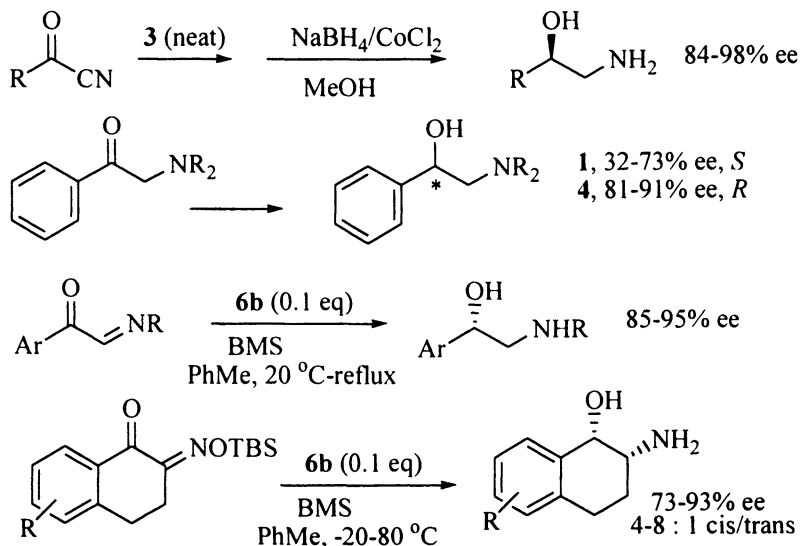
Figure 10 . Asymmetric reduction of acyl cyanides and α-amino or imino ketones produced optically acive β-amino alcohols

In summary, this chapter shows that organoboron-based asymmetric reducing agents, such as K Glucoride (**1**), K Xylide (**2**), Alpine-borane (**3**), Dip-Chloride™ (**4**) and oxazaborolidine-catalyzed boranes are highly effective for the reduction of a variety of α-functionalized ketones. We have established a convenient and simple procedure for the preparation of terminal 1,2-diols, α-hydroxy acetals and epoxides with very high optical purity via oxazaborolidine-catalyzed borane reduction using *N*-phenylamine-borane complexes as the hydride source.

Acknowledgments

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Chapter 10

Enantioselective Cyclopropanation Using Dioxaborolane Ligands

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Enantiopure cyclopropanes are important subunits found in several natural products. This chapter will highlight our efforts to design a stoichiometric chiral additive for the enantioselective cyclopropanation of allylic alcohols (Eq 1). Some preliminary mechanistic features of the cyclopropanation reaction in the presence of dioxaborolane **1** and related analogs will also be presented.

$$\text{(1)}$$

yield ≥ 80%
ee : 90-94%

136
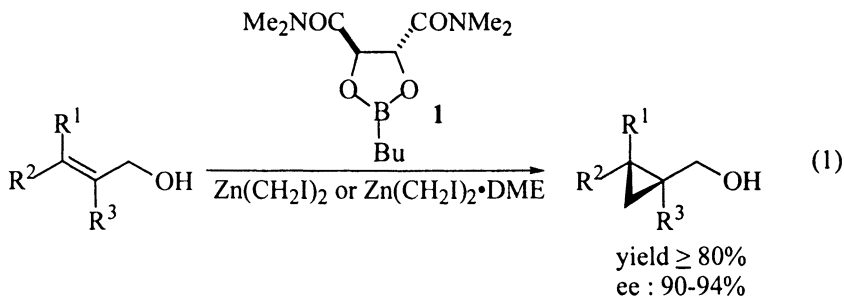
I. Synthesis

The chiral dioxaborolane **1** can be prepared using either one of two procedures. Originally, this dioxaborolane was generated under dehydrating conditions by using two readily available precursors : *N, N, N ', N '*-tetramethyl-L-tartaramide **2** and butylboronic acid **3** (Eq 2). These two precursors are commercially available, or easily prepared from tartaric acid (in the case of the tartaramide (*44*)) and from butyl magnesium bromide and trimethyl borate (in the case of the butylboronic acid (*45*)).

$$\text{(2)}$$
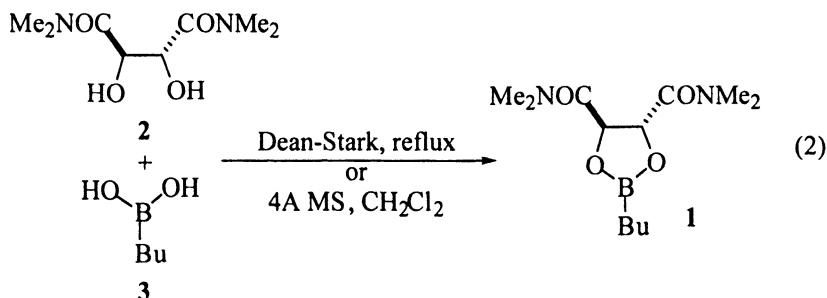
It is not that convenient to store alkylboronic acids since these compounds are quite oxygen-sensitive. Indeed, **3** is gradually oxidized to generate boric acid and butanol when exposed to air for long periods of time. Furthermore, they also tend to form boroxines under dehydrating conditions, which are themselves oxygen sensitive.

The second procedure takes into account the possible complications that could be encountered and it takes advantage of the use of the air-stable diethanolamine derivative **4**. Treatment of **4** with tartaramide **2**, under biphasic conditions generates the dioxaborolane ligand **1** (Eq 3). Although this second protocol requires one extra step, it is overall more efficient and more convenient than the previous one since both precursors are stable to storage.

$$\text{(3)}$$
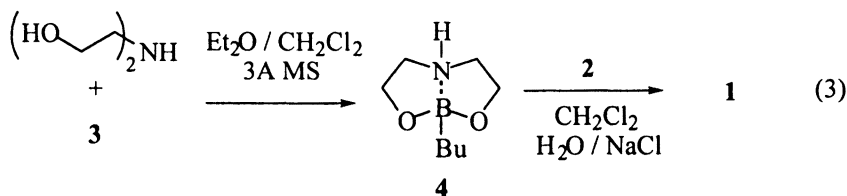
II. Scope

The dioxaborolane ligand **1** has been found to effectively convert allylic alcohols to their corresponding enantioenriched cyclopropylmethanols in high yields and high enantiomeric excesses. The $Zn(CH_2I)_2$ reagent or its DME

complex is the optimal cyclopropanating reagent (Figure 1) (*30-33*). The dioxaborolane-mediated enantioselective cyclopropanation proceeds well for *cis-*, *trans-*, trisubstituted and tetrasubstituted allylic alcohols. Chiral cyclopropylstannanes and cyclopropyl iodides can also be generated using this method. Representative examples are illustrated in Figure 1.

95% yield
94% ee

93% yield
91% ee

85% yield
94% ee

96% yield
85% ee

85% yield
88% ee

88% yield
90% ee

83% yield
90% ee
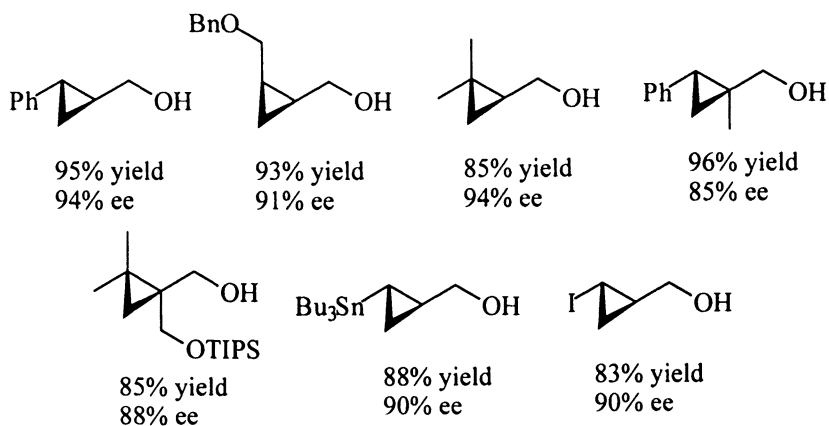
Figure 1 : Representative examples of enantioenriched cyclopropylmethanols obtained from allylic alcohols using the dioxaborolane ligand 1 and bis(iodomethyl)zinc.

The dioxaborolane-mediated cyclopropanation can also be used in the reagent-controlled cyclopropanation of chiral non-racemic *E*-allylic alcohols (*46*) to effectively give *anti*-cyclopropylmethanols (*47*) (Figure 2).

Conversely, the cyclopropanation of *Z*-allylic alcohols produces mainly the *syn*- isomer. The *anti*-selective cyclopropanation of chiral *E*-allylic alcohols is quite unique since the same reaction carried in the absence of the chiral additive produces the *syn* isomer (*48*). However, the level of *anti*-selectivity is highly dependant upon the nature and size of the substituents on the alkene and on the allylic position.

98% yield
<1 : 200 *syn : anti*

92% yield
<1 : 200 *syn : anti*

84% yield
1 : 32 *syn : anti*
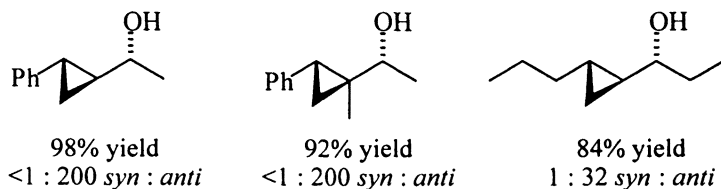
Figure 2 : Representative examples of enantioenriched cyclopropylmethanols obtained from chiral allylic alcohols using the dioxaborolane ligand 1 and bis(iodomethyl)zinc.

The dioxaborolane-mediated cyclopropanation has also been used for the chemo- and enantioselective cyclopropanation of conjugated and unconjugated polyenes (*49, 32*). In these cases, the reaction displays a high level of chemoselectivity for the allylic alcohol alkene. This methodology was also extended to homoallylic alcohols (*32*), and allylic carbamates (*32*). The synthesis of enantioenriched 1,2,3-trisubstituted cyclopropanes is also possible by using more substituted and functionalized iodoalkylzinc reagents (*50*) (Figure 3). These reagents are prepared by treating the corresponding diiodoalkane with 2 equivalents of diethylzinc (*51*).
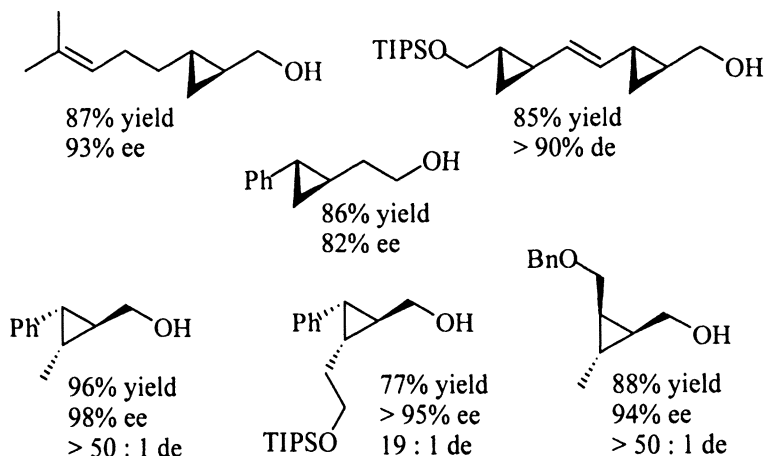
Figure 3 : Representative examples of enantioenriched cyclopropylmethanols obtained from polyenes, homoallylic alcohols using the dioxaborolane ligand 1 and bis(iodomethyl)zinc and allylic alcohols from functionalized zinc reagents.

III. Mechanistic Considerations

The dioxaborolane ligand **1** was designed such that it possesses both, a Lewis basic site (the amide groups) that will chelate to the cyclopropanating reagent (bis(iodomethyl)zinc) and a Lewis acidic site (the boron center) that will allow binding to the allylic alcohol (or its corresponding zinc alkoxide). According to our studies, the first step of the reaction is the deprotonation of the alcohol by the cyclopropanating reagent to form a zinc alkoxide and methyl iodide. It is postulated that the resulting basic zinc alkoxide covalently binds to the boron center to form a tetracoordinate borate intermediate. Boron NMR of the reaction mixture indicates that a new species appearing at about 10 ppm is formed in small amounts. This chemical shift is consistent with the formation of a tetracoordinate boron species corresponding to (RO)$_3$BBu. It is believed that the zinc reagent then complexes one of the amide groups, and a subsequent diastereoselective intramolecular delivery of the methylene group on one of the

two faces of the double bond leads to the product. This species is converted to the corresponding cyclopropylmethanol upon work-up (Figure 4).
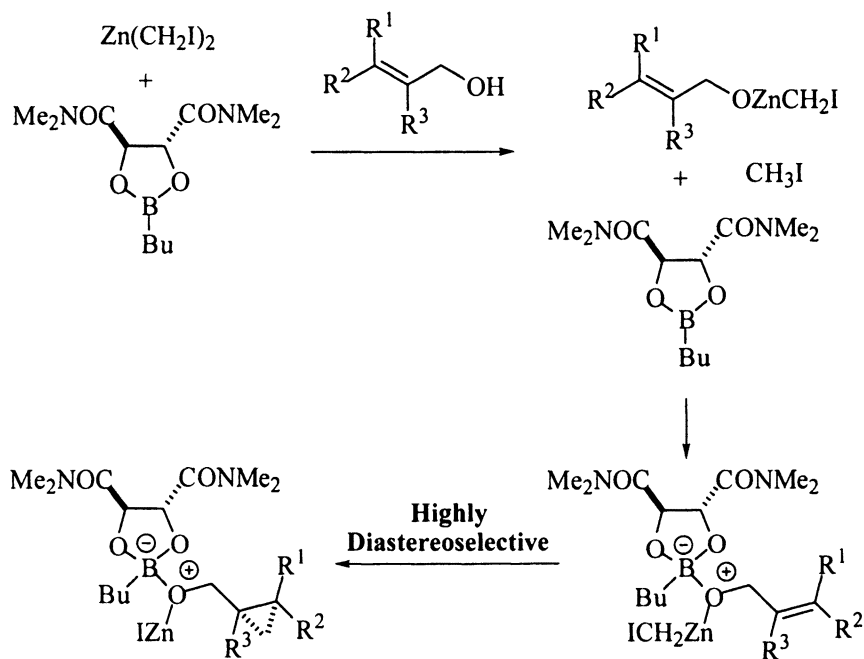
Figure 4 : Proposed mechanism of the dioxaborolane ligand 1.

The following transition state model shown in Figure 5 is consistent with the observed absolute configuration of the cyclopropane. The butyl substituent adopts a pseudoequatorial position and the allylic alkoxide a pseudoaxial position. It is believed that the reacting conformer is that in which the $A^{1,3}$ strain is minimized.
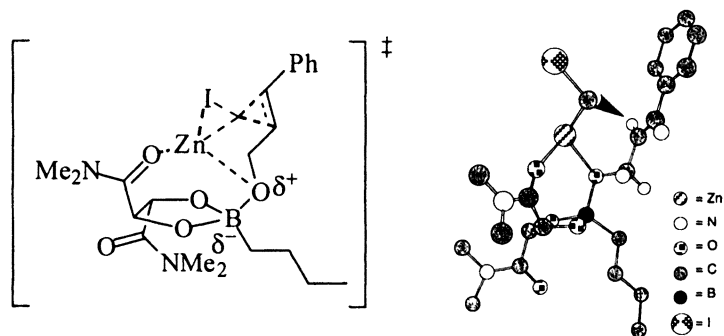
Figure 5 : Chem 3D representation of the proposed transition state using dioxaborolane 1 and the zinc alkoxide of cinnamyl alcohol.

IV. Other Dioxaborolanes

The dioxaborolane structure was altered to understand the importance of the acidic and basic sites, and to better understand the essential structural features of the chiral additive for high enantioselectivities.

The acidic site was first removed by replacing the boron center by a tetrahedral carbon. Racemic cyclopropylmethanol was obtained in quantitative yield when cinnamyl alcohol was cyclopropanated in the presence of dimethyl tartramide **5** under the usual conditions (Eq 4). This information suggests that the boron is necessary to bring the substrate and the ligand together and that the chiral additive does not act strictly as an activator of the bis(iodomethyl)zinc reagent.

$$ Ph \diagdown \diagup OH \xrightarrow[Zn(CH_2I)_2 \,/\, CH_2Cl_2]{} Ph \diagdown \diagup OH \qquad (4) $$

> 95% yield
0% ee
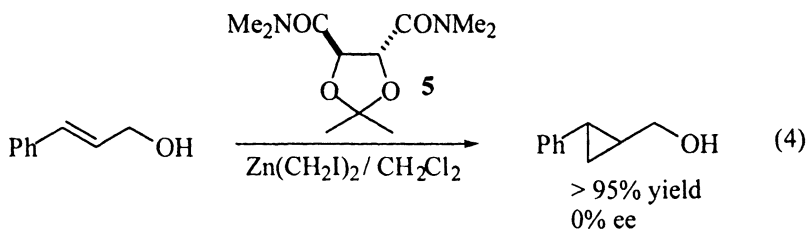
The second site to be altered was the alkyl substituent on the boron center. Initially, it was proposed that the nature of this group should not have a major impact on the level of enantioselection of the cyclopropanation reaction. It is believed that this group simply adopts the pseudoequatorial position of the envelope conformation of the five-membered ring. Several different dioxaborolane ligands were prepared by the same method as that reported earlier. Four novel dioxaborolane additives were prepared with R = Me, Ph, 2-naphthyl and 2,4,6-trimethylphenyl. The enantioselectivities observed for the cyclopropanation reaction are shown in Table I. In all the cases, the enantioselectivities were in the same range as that obtained with R = Bu, except for the 2,4,6-trimethylphenyl substituent. This information suggests that a sterically encumbered substituent on boron may partially prevent the postulated association between the zinc alkoxide and the boron center. In that case, the non-boron-assisted pathway can eventually become competitive.

We finally turned our attention to the nature of the basic groups of the dioxaborolane additive.

Initially, we tested additives in which the basic amides were completely removed and replaced with non-basic groups. The ligand derived from *trans-*

Table I : Variation of the alkyl substituent on dioxaborolane 1.
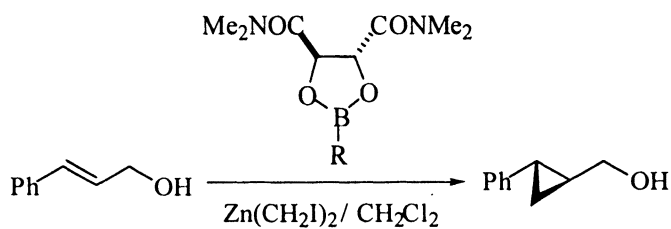
Entry	R	Ee (%)
1	Me	93
2	Bu	93
3	Ph	92
4	2-Naphthyl	92
5		90

dihydroxystilbene was synthesized and tested (entry 1, Table II). As expected, racemic cyclopropane was obtained when this additive was added to the cyclopropanation of cinnamyl alcohol.

By replacing the amide groups with the less basic isopropyl or ethyl esters (entries 2 and 3, Table II), the enantioselectivity was almost completely lost and the other enantiomer of the cyclopropylmethanol was favored. This observation is quite intriguing and it may result from a competitive complexation of the reagent by the dioxaborolane oxygen groups. Conversely, replacement of the dimethylamides with the pyrrolidine amide (or with diethylamide) does not significantly alter the level of enantioselection (entry 6, Table II). However, the enantiomeric excesses are lower if the methylamides that contain potentially acidic protons are used (entry 4, Table II). Interestingly, the removal of one of the dimethylamide groups leads to much lower selectivity (entry 5, Table II). This observation can be explained by the initial formation of a tetracoordinate boron center that may be non-selective and irreversible. One of the two diastereomeric complexes would lead to high enantioselectivities whereas its diastereomer would lead to racemic cyclopropane (Figure 6).
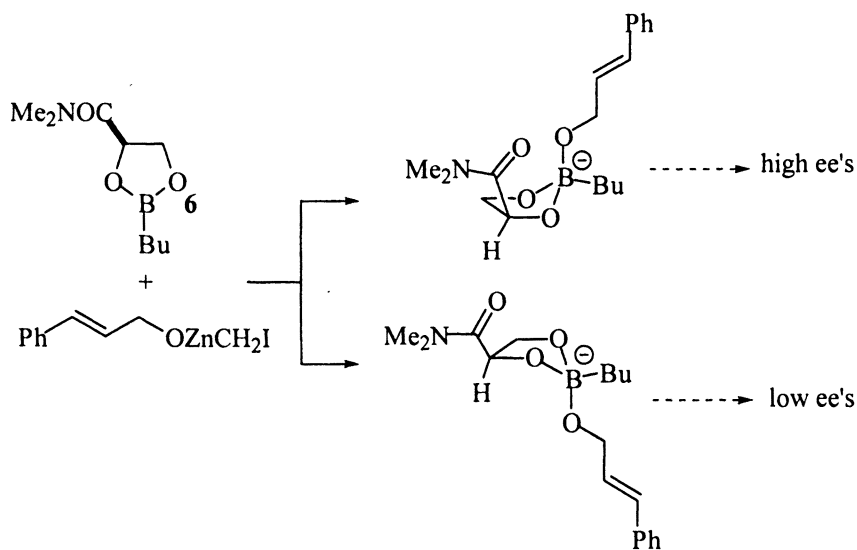
Figure 6 : Diastereomeric complexes proposed when using dioxaborolane 6.

In the last example (entry 7, Table II) a sterically constrained analogue of dioxaborolane of ligand **1** gave similar results as the ester derivatives. This may be explained by the fact that the amide groups in this systems are thought to be less basic than the dimethylamide analogue since the nitrogen lone pair cannot be perfectly delocalized in the carbonyl group.

Table II : Variation of the amides on dioxaborolane 1.

$$\text{Ph}\diagup\diagdown\text{OH} \xrightarrow[\text{Zn(CH}_2\text{I)}_2 \text{ / CH}_2\text{Cl}_2]{\text{Bu}} \text{Ph}\triangleleft\diagup\text{OH}$$
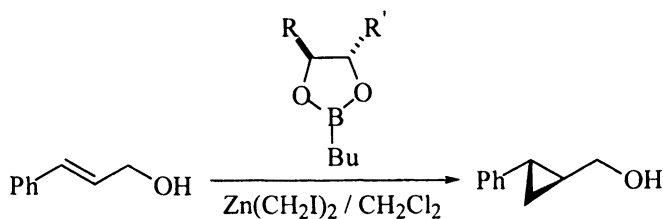
Entry	R	R'	Ee (%)
1	Ph	Ph	0
2	CO$_2$Et	CO$_2$Et	41*
3	CO$_2$i-Pr	CO$_2$i-Pr	29*
4	CONHMe	CONHMe	63
5	CONMe$_2$	H	70*
6			86
7			33*

* other enantiomer

V. Synthetic Applications

The enantioselective cyclopropanation reaction described herein has been used in several syntheses of cyclopropane-containing natural and non-natural products (52-67). Several examples are shown in Figure 7.

VI. Conclusions

An effective, practical and readily available chiral modifier was developed for the effective enantioselective cyclopropanation of several allylic alcohols using bis(iodomethyl)zinc. Several chemical modifications have revealed a unique cooperativity between the boron acidic center and the basic amide groups. These observations and a better understanding of the structure/selectivity relationship of the chiral additive should lead to an improved cyclopropanation system.

Bicyclohumulenone

Curacin A

Halicholactone: X = CH$_2$CH$_2$
Neohalicholactone: X = *cis*-CH=CH

Noranthoplone

Aragusterol A

FR-900848

U-106305
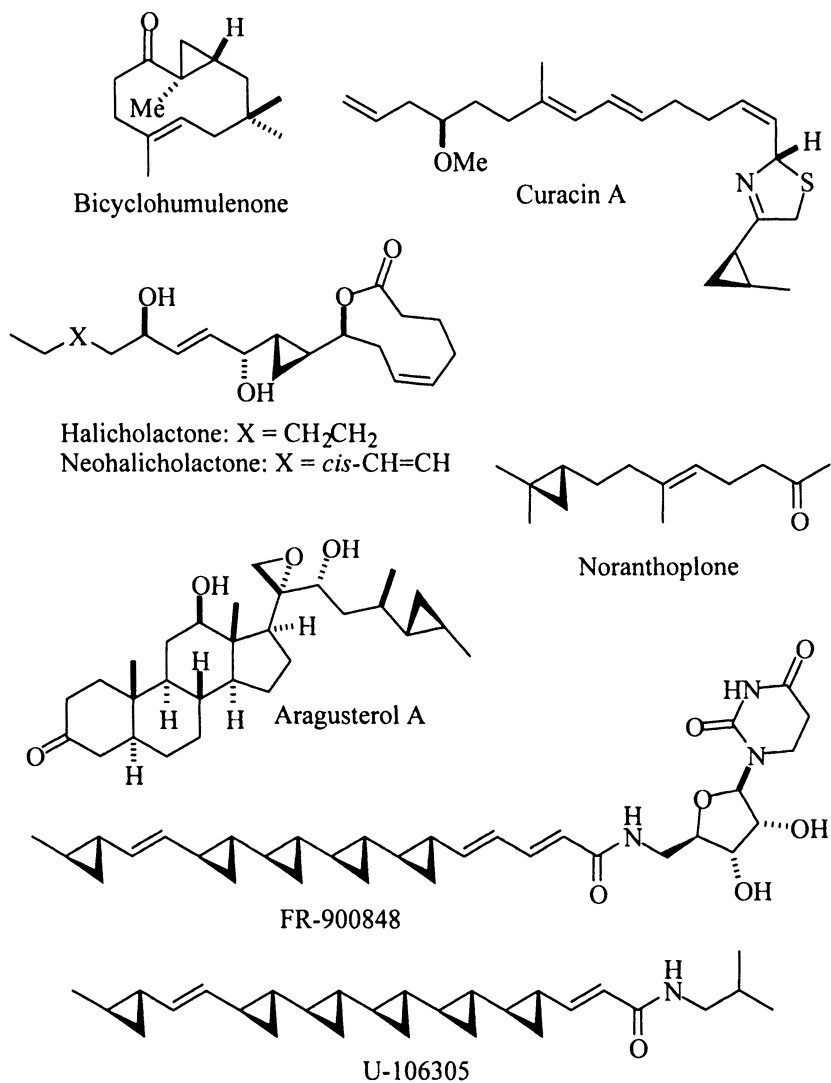
Figure 7 : Examples of cyclopropane-containing natural products where the methodology described herein is used.

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Chapter 11

Organoboron Chemistry on Alumina: The Suzuki Reaction

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A solventless Suzuki coupling reaction has been developed using both thermal and microwave enhancement. A potassium fluoride-alumina mixture is utilized along with palladium powder.

Introduction

The formation of carbon-carbon bonds via the metal-catalyzed coupling of organometallic reagents with organic halides has become an important reaction in modern organic synthesis. In 1972, Kumada (*1,2,3,4,5*) and Corriu (*6*) independently reported that Ni(II) complexes greatly enhanced the rate of reactions of Grignard reagents with aryl and alkenyl halides. Similar results were later reported by Murahashi for palladium catalyzed coupling reactions (*7*). Negishi (*8,9*) and coworkers then reported an alkynyl transfer from 1-alkynyl(trialkyl)borate to iodobenzene through a palladium-catalyzed, addition-elimination sequence analogous to the Heck reaction (*10*). The palladium catalyzed coupling of neutral organoborane derivatives was first reported by Miyaura and Suzuki in 1981 and the reaction has become an integral part of

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modern organic synthesis (*11,12*). The popularity of the Suzuki reaction is a consequence of the ready availability of a wide variety of functionally substituted boron derivatives and the mildness of the coupling reaction itself. Consequently, it is now possible to build rather complex structures from synthons containing reactive functional groups such as carboxylic acids, amides, carbonyl groups, etc. The synthesis of ethyl 3,5-dimethyl-4-phenylpyrrolecarboxylate as a precursor to a tetramethyltetraphenylporphyrin (eq 1) illustrates the utility of the Suzuki reaction (*13*).

$$\text{(1)}$$

$$95\%$$
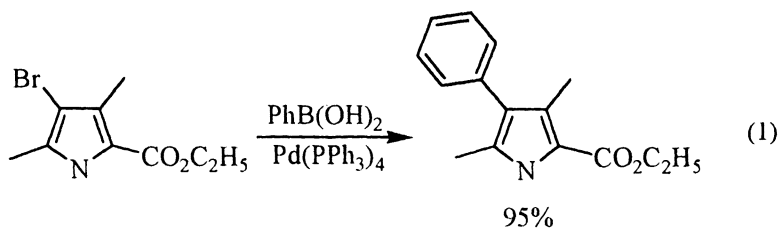
Suzuki reactions generally employ organic solvents such as tetrahydrofuran and ethers as well as palladium complexes which are soluble in these solvents. The palladium reagents tend to be expensive and sometimes difficult to manipulate and recover. The organic solvents also pose recyclability (and waste handling) problems of their own. To counteract the costs related to waste handling and reagent recycling, ecologically friendly chemistry (Green chemistry) has been evolving at a remarkable rate. One aspect of this chemistry is the use of solid-phase reagents in an attempt to minimize the use of solvents (*14,15,16,17,18*). Our efforts in this area have centered on the use of alumina surfaces (*19*).

We have found alumina to be particularly interesting because it can be modified in a variety of ways which enhance its reactivity with organic reagents. What is unusual about alumina is that it can be used as a catalyst, support, or reagent. γ-Alumina is simply a hydrated form of aluminum oxide. It has a very large surface area (>100m/g) and, in its hydrated form, the surface presents a layer of hydroxyl groups which are bonded to a substructure of aluminum ions (*20*). As the hydrated alumina is heated, water is driven from the surface which leaves both oxide ions (basic) and aluminum ions (acidic) exposed on the surface. Thus, depending on the temperature of dehydration, the alumina surface contains mixtures of aluminum ions, oxide ions, and hydroxyl groups and thus individual surface sites can act as an acid, base, or nucleophile. The fact that alumina can contain strongly basic and acidic sites adjacent to each other allows for chemistry that cannot be achieved in solution reactions.

In early studies, we capitalized on the relative ease with which water can be removed and then replenished on an alumina surface. By first dehydrating alumina and then "rehydrating" it with deuterium oxide, we were able to replace active hydrogens in organic molecules with deuterium under very mild conditions, eq 2 (*21,22*). We then found that the surface could be modified to affect a variety

$$\text{(structure)} \xrightarrow{D_2O/Al_2O_3} \text{(structure)} \quad (2)$$
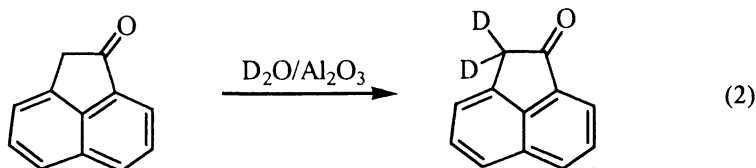
of organic reactions including halogenations, oxidations and reductions; the surface oxides were also capable of acting as nucleophiles. We also found that alumina could be useful in organoborane reactions (*23,24,25*). For example, we were able to carry out halogenation reactions in which boronic acids were attached to the surfaces to form mixed anhydrides, eq 3.

$$R\diagdown B(OH)_2 \xrightarrow[\text{(2) } X_2]{\text{(1) } Al_2O_3} R\diagdown\diagdown X \quad + \quad R\diagdown X \quad (3)$$

$$\qquad\qquad\qquad\qquad\qquad E \qquad\qquad\qquad Z$$
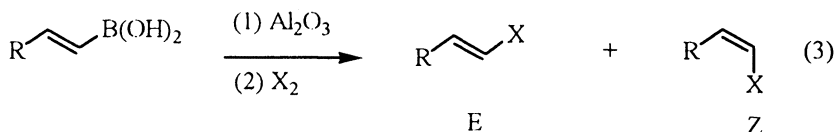
when: $R = Cl(CH_2)_3$, $X = I$; $E{:}Z = 74 : 26$
when: $R = Cl(CH_2)_3$, $X = Br$; $E{:}Z = 20 : 80$

These early results led us to investigate the feasibility of carrying out Suzuki coupling reactions on alumina in the absence of solvents. We investigated both thermal and microwave-assisted reactions, eq 4. Microwave irradiation of organic reactions has gained in popularity in recent years since it was found to accelerate a wide variety of transformations (*26,27*)

$$\text{(structure)}{-}I \quad + \quad \overset{HO}{\underset{HO}{}}B{-}\text{(structure)}{-} \xrightarrow[\text{No solvent}]{\substack{Pd(0) \text{ on} \\ KF/Al_2O_3}} \text{(structure)}{-}\text{(structure)}{-} \quad (4)$$

$$\text{Yield} = 88 - 98\%$$
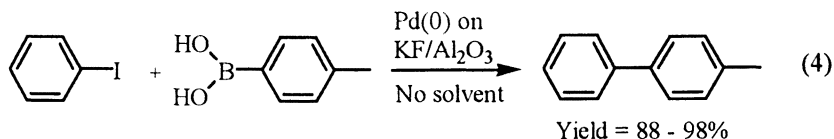
Results and Discussion

The initial studies focused on more traditional thermal reactions. A number of parameters were investigated. An important observation was made early in the study concerning the chemical form of the palladium catalyst. Most palladium catalyzed coupling reactions involving boron reagents utilize complexes of palladium. These tend to be expensive and may also be sensitive to water and oxygen (depending on the ligand.) We discovered that palladium metal (obtained as a submicron powder) worked quite well. Commercially available, palladium powder is simply mixed with the alumina to achieve the desired reactions. The initial studies focused on the addition of bases to the reaction mixtures since the Suzuki reactions require the presence of a base.

Just as in solution, the solid-state reactions do not proceed in the absence of base (Table I). A variety of bases successfully induced the reaction of tolylboronic acid with iodobenzene to form 4-methylbiphenyl but potassium phosphate and potassium fluoride were most effective, Table I.

Table I. Base Survey

$$\text{C}_6\text{H}_5\text{-I} + \text{HO-B(OH)-C}_6\text{H}_4\text{-CH}_3 \xrightarrow[\text{Temp} = 80\ ^\circ\text{C}]{\substack{5\%\ \text{Pd(0)} \\ \text{"ionic base" Al}_2\text{O}_3}} \text{C}_6\text{H}_5\text{-C}_6\text{H}_4\text{-CH}_3$$
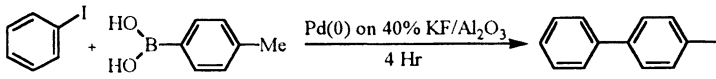
Base[a]	Reaction Time	Yield (%)
NaOH	3 hr	23
K_2CO_3	3 hr	27
K_3PO_4	3 hr	71
KF	3 hr	86
NaF	4 hr	5
Al_2O_3 (basic)	6 hr	0

[a]The base (40% by weight) was added to the alumina prior to reaction.

Since KF/Al_2O_3 is commercially available, we utilized it for the thermal studies. The quantity of palladium required was then investigated. The results are

presented in Table II. For a reaction time of 4 hours, palladium concentrations of 4 - 5 % are most efficient. If time is not an important factor, lower loadings can be utilized. For the remainder of the study, we utilized 5% palladium for convenience. It should be noted that, since the catalyst is a solid, it can be separated from the reaction mixture by simple filtration and recycled. We are currently investigating the efficiency of the recycling process.

Table II. Effect of Palladium Concentration
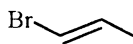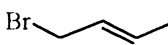
Palladium (%)	Average Yield (%)
1	70.3
2	76.1
3	83.3
4	95.6
5	96.0

Commercially available KF/Al_2O_3 can be used in the solid-state reactions or it can be prepared by simply dissolving potassium fluoride in water or methanol, adding the appropriate quantity of alumina and then allowing the solvent to evaporate under reduced pressure. The percentage of KF added to the alumina is important. From earlier studies, we determined that there are approximately 3.2 mmoles of active sites (hydroxyl groups under normal conditions) per gram of alumina. Since one equivalent of KF presumably reacts with one equivalent of hydroxyl groups, we would assume that no more than 3.2 mmoles of "base" are generated per gram of KF alumina (*28,29,30*). Commercial KF/Al_2O_3 contains approximately 4.5 mmoles of KF per gram which is sufficient to react with all available hydroxyl sites. It is also important to note that the reaction is most efficient if the surface is exposed to moisture in the air. Reactions utilizing freshly prepared KF/Al_2O_3, obtained from commercial sources often produce lower yields than identical reactions carried out with KF/Al_2O_3 that has been opened to the atmosphere. We generally allow a new bottle of KF/Al_2O_3 to stand overnight in

the open air. For samples that we prepare, we remove solvent (water or methanol) only until the powder flows freely.

The reactions were generally complete in a matter of hours but the time, as expected, was inversely proportional to the temperature. For convenience, we carried out the inital reactions at 100 °C. Suzuki reactions are normally very effective when coupling arylboronic acids with aromatic iodides. The reactions are less effective when aromatic bromides and chlorides are utilized. A parallel trend is observed when alumina is utilized in the absence of solvents, Table III.
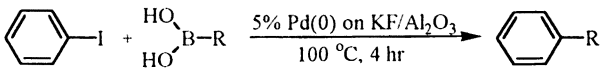
Table III. Halide Survey

$$R-X \ + \ \underset{HO}{\overset{HO}{\text{B}}}-\text{C}_6\text{H}_4- \ \xrightarrow[100\ ^\circ C,\ 4\ Hr]{5\%\ Pd(0)\ on\ KF/Al_2O_3} \ R-\text{C}_6\text{H}_4-$$
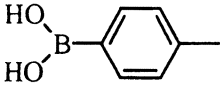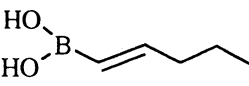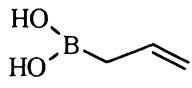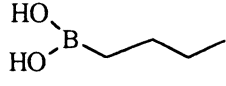
R—X	Yield (%)	Recovered Halide (%)
Iodobenzene	99	<1
Bromobenzene	60	0
Chlorobenzene	5	0
Fluorobenzene	0	0
I (allyl)	39	0
Br (vinyl)	0	0
Br (allyl)	66	0
Alkyl-X	0	0

Overall, the solid-phase Suzuki reactions were successful for coupling arylboronic acids to aromatic halides. The fact that a vinyl bromide did not react is a bit of a puzzle since such reactions do occur in solution in the presence of strong bases. Reactions involving alkyl halides (hexyl iodide, butyl iodide, isopropyl iodide, cyclohexyl iodide and butyl bromide) or vinyl halides were unsuccessful although, as expected, allylic systems did undergo the reaction (Table III).

The reaction can also be used to couple aryl iodides to aryl, vinyl, and alkylboronic acids but the yields are variable (Table IV).

Table IV. Boronic Acid Survey

Boronic Acid	Product Yield (%)	Recovered C_6H_5I (%)
	98	0
	79	0
	0	29
	26	trace

We then examined an energy efficient modification of the new chemistry which enhances the reaction's eco-friendly attributes. The new methodology couples microwave irradiation with a solid-state, solvent free approach and leads to enhanced yields of the desired products, eq 5. Early experiments utilized solvents with high dielectric constants which permitted rapid heating of reaction solutions. In recent years, a number of reports have appeared in which the organic reagents themselves are coated on to surfaces which themselves absorb little or no microwave energy; in these instances, the reactive species absorb the microwave energy but the bulk temperature of the reaction mixtures tend to rise only modestly. This results in a relatively large energy savings as well as making it possible to carry out reactions in relatively simple glassware (open beakers, flasks, etc).

$$5\% \text{ Pd(0)}$$
$$40\% \text{ KF/Al}_2\text{O}_3$$
MW, 2 min.

82% (5)
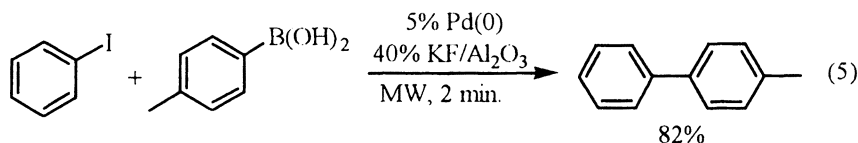
In the thermal studies, the reactants were mixed (in the absence of a solvent) with palladium doped, potassium fluoride treated alumina and the mixture heated for four or more hours at temperatures approaching 100 °C. In this portion of the study, we examined the effectiveness of microwave irradiation for enhancing the rate of the reactions. The feasibility of using microwave irradiation to induce organic reactions on solid surfaces in the absence of solvents has been demonstrated previously. As a probe, we investigated the reaction of tolylboronic acid with iodobenzene for various time periods, Table V. 2-Methylbiphenyl was formed readily under a variety of reaction conditions. For convenience, we found it most efficient to simply heat the mixtures for 2 minutes at 100% power. Under these conditions, a small amount of organic material could be observed condensing on the cooler portions of the reaction vessel.
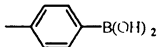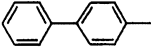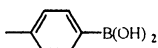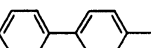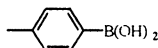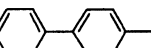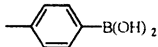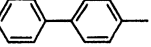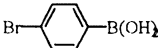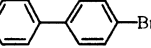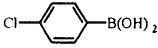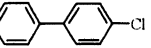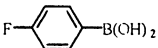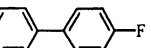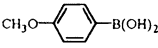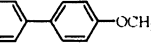
Table V. The Reaction of *o*-Tolyboronic Acid with Iodobenzene to Form 2-Methylbiphenyl

Experiment[a]	Microwave[b] Power (%)	Time (min)[c]	Yield (%)[d]
1	30	5	24
2	30	10	64
3	50	3	34
4	50	6	83
5	100	2	80
6	100	3	78

[a]Reactions were carried out by mixing 1mmole of *o*-tolyboronic acid with 1 mmole of iodobenzene and 1 gram of 5% palladium on KF/alumina. [b]Power setting on commercial microwave unit. [c]Except for experiment 5, reactions were halted at the half way point to allow mixtures to cool. [d]Isolated yield.

We then examined the reactions of a variety of aryl halides with arylboronic acids containing both electron donating and electron attracting substituents, Table VI. As can be seen from the data contained in Table VI, the reaction appears to be insensitive to the substituents on the boronic acid. However, the reaction is most efficient when aryl iodides are used as the co-reactant. In fact the reactivity trend aryl iodide > aryl bromide > aryl chloride > aryl fluoride parallels the trend observed in Suzuki reactions carried out thermally, both in solution and on alumina.

Table VI. Microwave Enhanced Reaction of Aryl Halides (ArX) with
Boronic Acids [RB(OH)₂]

Exp.	ArX[a]	RB(OH)$_2$	Product[b]	Yield (%)[c]
1	⬡—I	—⬡—B(OH)₂	⬡—⬡—	82
2	⬡—Br	—⬡—B(OH)₂	⬡—⬡—	52
3	⬡—Cl	—⬡—B(OH)₂	⬡—⬡—	4
4	⬡—F	—⬡—B(OH)₂	⬡—⬡—	0
5	⬡—I	Br—⬡—B(OH)₂	⬡—⬡—Br	80
6	⬡—I	Cl—⬡—B(OH)₂	⬡—⬡—Cl	87
7	⬡—I	F—⬡—B(OH)₂	⬡—⬡—F	86
8	⬡—I	CH₃O—⬡—B(OH)₂	⬡—⬡—OCH₃	84

[a]Reactions carried out by mixing 1 mmole of aryl halide with 1 mmole of boronic acid and 1 gram of 40% KF/Al$_2$O$_3$ mixed with 5% palladium powder .[b]All products exhibited physical and spectral characteristics in accord with authentic samples. [c]Isolated yields.

Reactions of vinylboronic acids with aryl halides were also successful but no reactions occurred when alkylboronic acids were utilized or when alkyl halides were used eq 6.

$$(6)$$
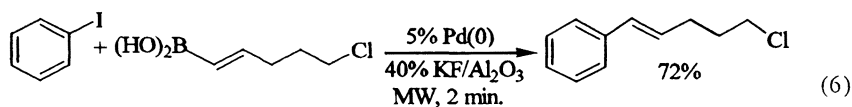
Conclusions

The use of KF/alumina as a solid-phase support for solventless Suzuki reactions(*33*) offers a convenient, environmentally friendly alternative to traditional reactions especially when microwave irradiation is employed. It would appear that KF is the most effective base. The reactivity trends observed in solution reactions are also observed in the solid state syntheses. That is, organic iodides react faster than the bromides and chlorides; aryl moieties are more reactive than alkenyl groups which are themselves more reactive than alkyl. In addition, the solid phase syntheses provide one of the few successful Suzuki methodologies that can be carried out utilizing ligandless palladium reagents. Although our studies are not yet complete, the solid-state methodology offers the opportunity to recycle the reagent (via simple filtration) which has significant commercial appeal.

Acknowledgements

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Chapter 12

Synthesis of Heterocyclic Compounds by Allylboration Reactions

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Abstract: Intramolecular allylboration of ω-oxo-2-alkenylboronates allows the stereoselective formation of 2-vinyl-cycloalkanols. When heteroatoms are present in the chain linking the aldehyde and allylboronate functions a variety of saturated heterocycles with a stereodefined pattern of substituents may be prepared in this manner. Rapid assembly of anellated heterocycles becomes possible by domino-hydroformylation-allylboration-hydroformylation cascade reactions.

Introduction

The synthesis of saturated oxygen- and nitrogen heterocycles is of long term interest, because these are key structural elements in the polyether antibiotics and a large variety of alkaloids.

In particular, it is still a challenge to devise methods which allow to generate polysubstituted tetrahydropyrans and piperidines with a predefined stereochemical arrangement of the substituents. The strive for efficiency in synthesis demands, that those steps that lead to the closure or formation of the heterocyclic ring should at the same time generate the largest possible number

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of stereocenters with high predetermined stereoselectivity. It is for this reason, that we became interested in the allylmetallation approach to heterocycles.

The intramolecular allylmetallation of open chain compounds **1** should give rise to the formation of heterocycles **2** which carry adjacent hydroxy- and vinyl-substituents. The issues to be clarified with such an approach are: (i) The simple diastereoselectivity on formation of the two stereogenic centers bearing the vinyl and hydroxy groups, i.e. the relative configuration of the two new stereogenic centers generated in the ring closure reaction; (ii) the level of asymmetric induction that originates from stereogenic centers in the chain linking the aldehyde and the allylmetal entities.
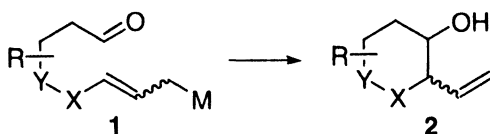
Scheme 1:   Formation of heterocycles by intramolecular
             allylmetallation of aldehydes

There are several mechanistic modes for the allymetallation of aldehydes (*1*) The reaction may proceed via open transition states, this would amount to a monocyclic situation on ring closure of **1**, cf. **3**. Alternatively, the reaction may proceed via cyclic transition states , in which the metal coordinates to the aldehyde function. On cyclization of **1** this would amount to bicyclic transition states **4**.
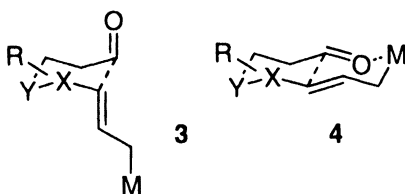
Scheme 2:   Simple diastereoselectivity on intramolecular
             allylmetallation of aldehydes

We expected that the latter situation should give rise to particularly high levels of stereoselectivity.

Intramolecular allylboration reactions

Among the possible intramolecular allylmetallation reactions the intermolecular allylstannation (2) has been most widely studied by the group of Y. Yamamoto. (1) These reactions can be carried out under Lewis acid catalysis to proceed via transition states of the type **3**, thermally via transition states of the type **4**, and under Broensted acid catalysis, a reaction for which the nature of the transition state is not yet clear. In these reactions high to very high stereoselectivity has been attained. But there is not yet a uniform solution to reach predictable stereoselectivity in terms of attaining each of a number of possible stereoisomers selectively. It is for this reason that we wanted to evaluate the scope of the intramolecular allylboration reaction as a route to substituted tetrahydropyrans and piperidines.

Intermolecular allylboration of aldehydes proceeds with high simple diastereoselectivity to give either anti- or syn-ß-methyl homoallylic alcohols **5** and **6**. (3)
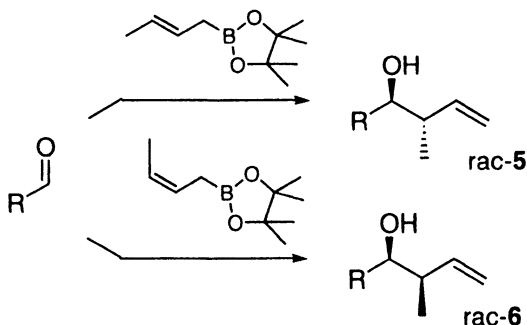
Scheme 3:   Simple diastereoselectivity in allylboration of aldehydes

The high simple diastereoselectivity is maintained on intramolecular allylboration of either **7** or **8** to give the trans- or cis-2-vinylcyclohexanol **9** or **10**. (4)

When methyl or benzyloxy substituents were placed on the chain linking the aldehyde and allylboronate functions, ring closure proceeded with moderate to excellent levels of asymmetric induction. (5, 6)

These results augured well for applying the intramolecular allylboration reaction to the synthesis of multisubstituted tetrahydropyrans and piperidines.

When planning such reactions there is the non-trivial problem to generate the staring material such as **8**. This implies the generation of an aldehyde function in the presence of an acid- and oxidation-labile allylboronate moiety or to generate the allylboronate moiety in the presence of an aldehyde function, which does not tolerate the use of organolithium reagents and the like. In the
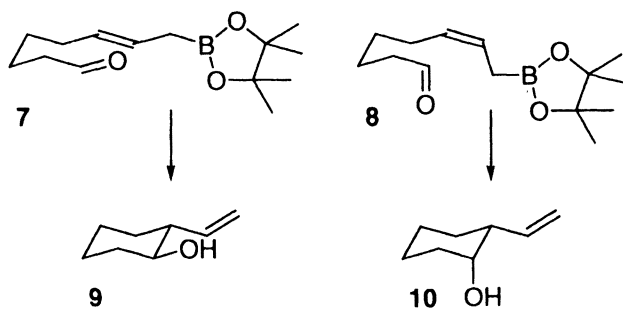
Scheme 4: Simple diastereoselectivity in intramolecular allylboration reactions
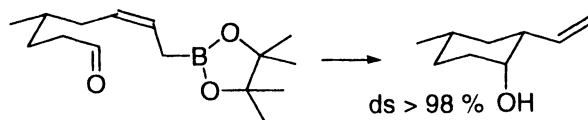
Scheme 5: Asymmetric induction in intramolecular allylboration reactions

carbocyclizations mentioned above the aldehyde function has been generated last, being liberated from a dimethylacetal under the mildest possible conditions such as lithium tetrafluoroborate in moist acetonitrile.(7)

The synthesis of 3-vinyl-tetrahydro-4-pyranols

To explore routes to both trans- and cis-3-vinyl-tetrahydro-4-pyranol a common intermediate, the alkyne 11 was used.
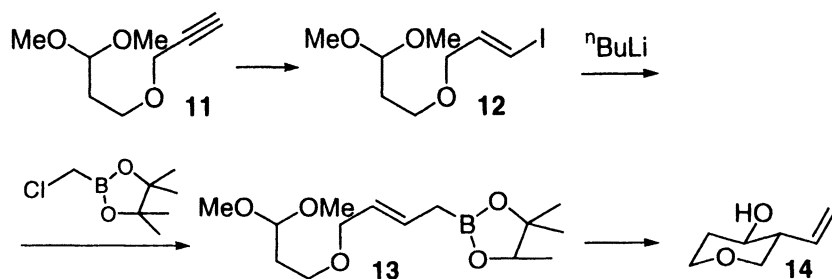
Scheme 6:   Formation of tetrahydro-4-pyranols

11 was converted via a procedure developed by H. C. Brown (8, 9) to the E-vinyl iodide 12. After conversion to the vinyllithium species, the latter was alkylated (10) by chloromethane boronate (11) to give the allylboronate 13 in 71% yield. Treatment of the latter with LiBF$_4$ in moist acetonitrile liberated the aldehyde which underwent intramolecular allylboration to furnish the trans-vinyltetrahydropyranol 14 in 70% yield and 94% diastereoselectivity.(12)

The same alkyne could be converted to the cis-vinyl iodide 15 and carried on in a like manner to the Z-allylboronate 16. Its cyclization to give 17 proceeded with >98% diastereoselectivity. (12)
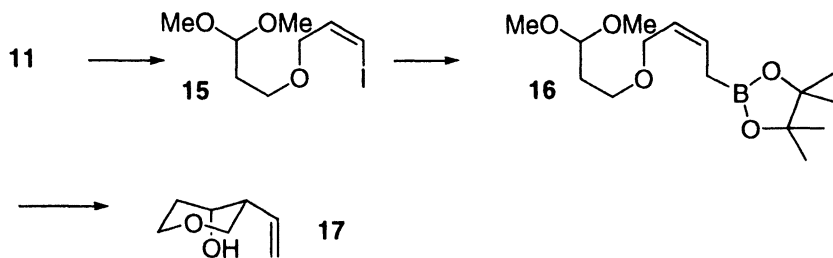
Scheme 7:   Formation of tetrahydro-4-pyranols

The synthesis of 3-vinyl-4-piperidinol

The exploratory experiments again used alkyne precursors **18** and **22** to access both the trans- and the cis-3-vinyl-4-piperidinols **21** and **25**.
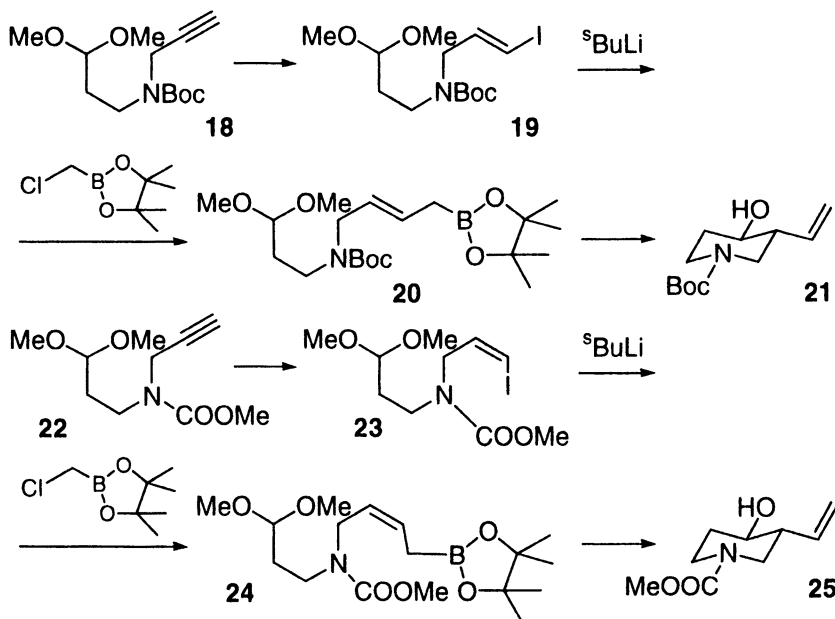
Scheme 8:   Formation of 4-piperidinols

The E-allylboroante **20** was obtained in 53% yield from the vinyl iodide **19** and could be cyclized to the vinyl piperidinol **20** with complete diastereoselectivity (51% based on **19**). For the synthesis of the Z-allylboronate **24** the Boc-protecting group on nitrogen was found to be unsuitable. Change to a methoxycarbonyl group allowed access to the allylboronate **24** in 50% yield. Liberation of the aldehyde function with LiBF$_4$ in moist acetonitrile triggered the cyclization to the cis-vinylpiperidinol **25** which was obtained as a single diastereomer (49% yield based on based on **23**). (*12*)

In the context of a natural product synthesis we explored, whether the cyclization to cis-3-vinyl-piperidinols can be effected under the asymmetric induction of resident stereogenic centers. To this end, the alkyne **27** was generated over 5 steps from homoserine lactone **26**.
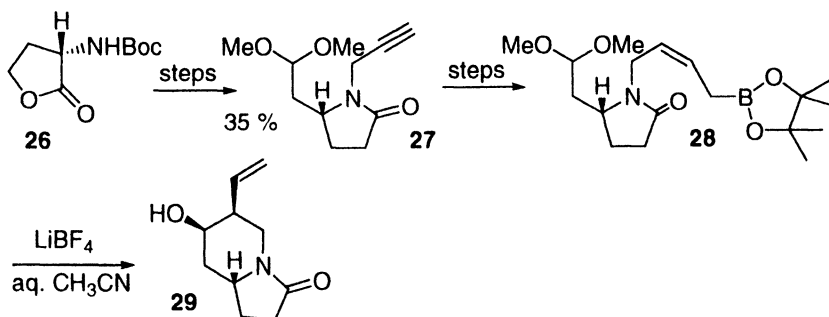
Scheme 9: Asymmetric induction on the formation of 4-piperidinols

The former was converted to the Z-allylboronate **28** in 32% unoptimized yield. Upon treatment of **28** with LiBF$_4$ it was found that the intramolecular allylboration to give **29** (68%) proceeded with complete simple and induced stereoselectivity. (*13*)

The synthesis of 2-vinyl-tetrahydro-3-pyranols

Both cis- and trans-2-vinyl-tetrahydro-3-pyranol are of high current interest as intermediates in the synthesis of polyether antibiotics, the halochondrins, or less common annonins. The inroad to the cis-2-vinyl-tetrahydro-3-pyranol **32** appeared straightforward, as Z-γ-alkoxyallylboronates such as **31** are readily generated from allylethers by metallation with s-butyllithium followed by borylation. This worked nicely (67%) when applied to the allyl ether **30**. (*14*)
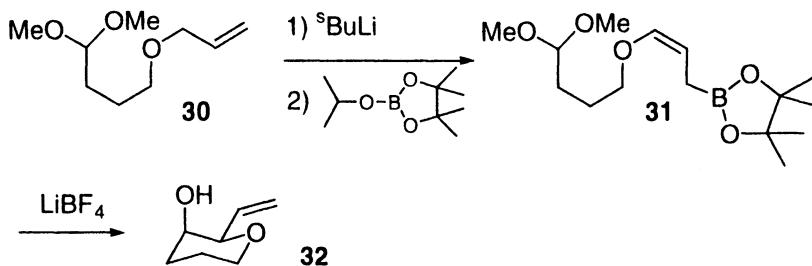
Scheme 10: Formation of tetrahydro-3-pyranols

Liberation of the aldehyde from **31** was followed by cyclization to give **32** as a single stereoisomer in up to 60% yield. However, the yields were compromized by partial decomposition of **31** due to the higher acid lability of the γ-oxyallylboronate moiety. This induced us to develop an alternate route, in which the allylboronate moiety was generated under in situ protection of the aldehyde function. To this end, the N-methoxy-methyl amide was added to the aldehyde **33** followed by metallation with s-butyllithium. Upon addition of the mixed borate ester the intermediate **34** was formed. Hydrolysis of the reaction mixture with a pH7-buffer solution liberated both the aldehyde and the allylboronate function which immediately underwent the intramolecular allylboration reaction. This resulted in a 74% overall yield of the cyclized product **32**. (*14*)
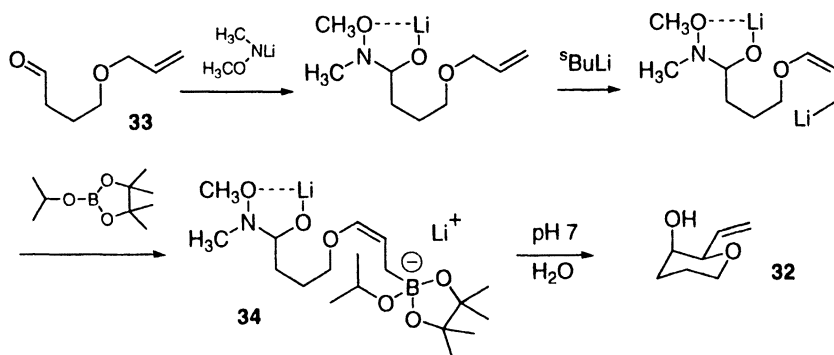
Scheme 11: One pot procedure for the formation of tetrahydro-3-pyranols from allyloxyaldehydes

Since this heterocyclization was very simple and efficient, we explored the scope of this reaction further with respect to asymmetric induction from resident stereogenic centers. To this end, **32** was converted over several steps

into the allylic ether **36**. When this compound was subjected to the one-pot procedure of in situ protection of the aldehyde, allylboronate generation and intramolecular allylboration, the bicyclic product **37** was formed as a single stereoisomer in 51% yield. (*14*)
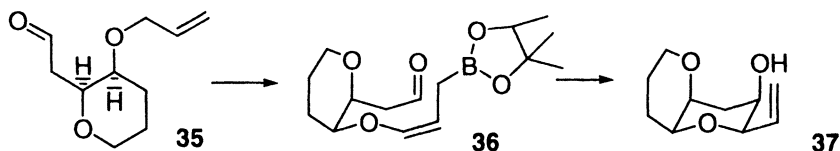
Scheme 12: Synthesis of cis-dioxadecalins

Apparently the cyclization occurs through a single transition state, in which the oxygen functions are placed in axial positions at the newly formed tetrahydropyran ring. This arrangement maintains the preferred gauche conformation between all oxygen atoms in this system.

The high level of induced and simple diastereoselectivity was also maintained on ring closure to a cis-oxocene-ring **39** bearing a hydroxy and vinyl function. This ring closure was the key step in our partial synthesis of (+)-laurencin **40**. This time, the aldehyde function was pregenerated in protected form by reduction of a Weinreb-amide **38**. (*15*)
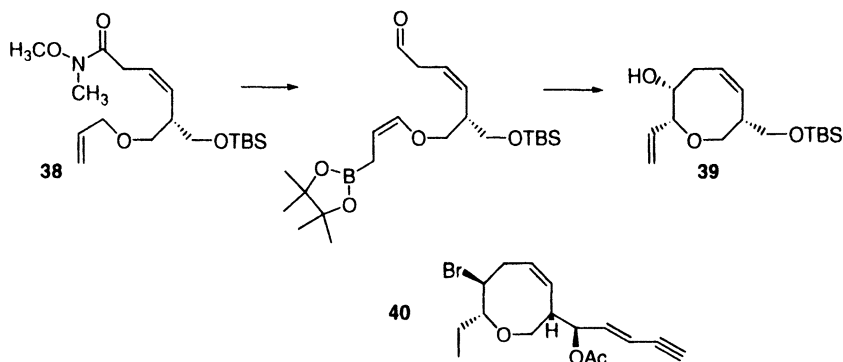
Scheme 13: Stereoselective synthesis of the oxocane ring of (+)-laurencin

While these reactions allowed ready access to oxygen heterocycles having the adjacent hydroxy and vinyl groups in a cis-disposition, access to the corresponding trans-derivatives was more difficult due to a lack of generally applicable routes (*16, 17*) to E-γ-alkoxy allylboronates. We therefore eventually developed a new route to this entity based on a rhodium or zirconium catalysed hydroboration of ynol ethers. (*18*)
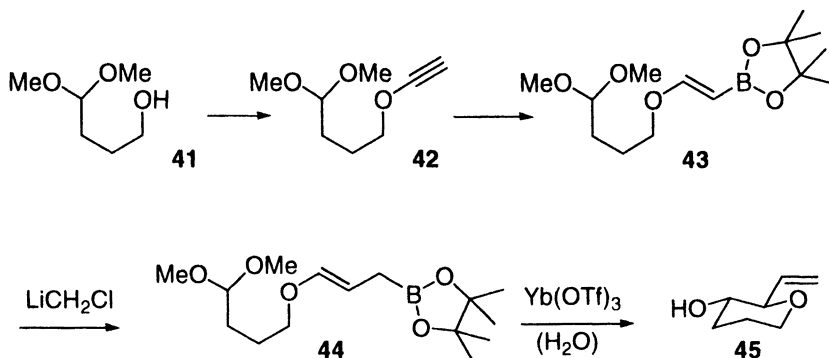
Scheme 14: E-γ-Alkoxyallylboronates from alkoxyalkynes and use in the synthesis of tetrahydro-3-pyranols

The alcohol **41** was converted to the alkoxyalkyne **42** in standard fashion (*19*) (80%). Rhodium-catalyzed hydroboration (*20*) with pinacol borane (*21*) provided the E-vinylboronate **43** (70%). The latter could be homologated following a D. S. Matteson / H. C. Brown procedure (*22, 23*) to give the E-allylboronate **44** (90%). To liberate the aldehyde function we used the less Broensted acidic Yb(OTf)₃ instead of LiBF₄ and succeeded to obtain the trans-2-vinyl-tetrahydro-3-pyranol **45** in 66% yield as a single stereoisomer.

Synthesis of trans-2-vinyl-3-piperidinol derivatives

Following the precedent set above, the logical precursor to trans-2-vinyl-3-piperidinols **46** would be E-γ-amidoallylboronate **47**. Such species being unknown, we set out to study their generation via the aldehydoboronate **48**.
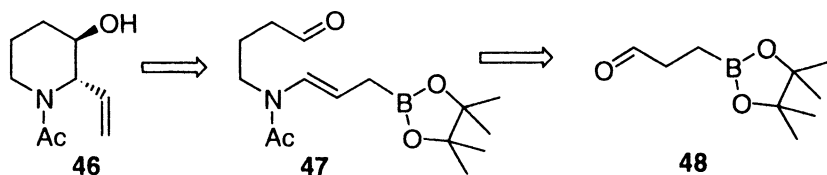
Scheme 15: Synthesis of 3-piperidinol-derivatives

We tested several routes to the aldehyde boronate **48**. The following one turned out to be most reliable: Acrolein-dimethylacetal was subjected to rhodium catalyzed hydroboration to give **49**. Acetal cleavage was achieved with yet another mild reagent, cerium-montmorillonite in moist dichloromethane (*24*) to give 98% of the desired aldehyde **48**. (*25*)
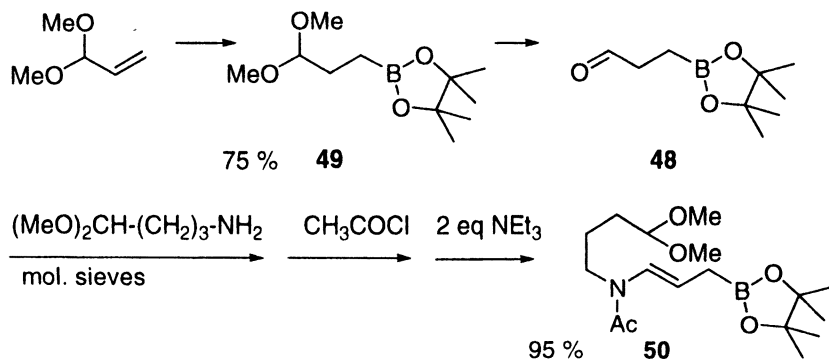
Scheme 16: Synthesis of E-γ-Amido-allylboronates

The aldehyde could readily be converted to the desired γ-amidoallylboronate **50** by the standard enamide formation method (Schiff-base formation, followed by acetylation, followed by deprotonation of the acylimmonium ion to the enamide). Treatment of **50** with either Yb(OTf)$_3$ or LiBF$_4$ in moist dichloromethane or acetonitrile did liberate the desired aldehyde **47** which indeed cyclized as anticipated to the desired trans-2-vinyl-3-piperidinol **46**. Yet the yields remained unsatisfactory (40 - 45%). The main reaction was the acid-catalyzed hydrolysis of the enamide function, which eventually gave rise to the formation of the undesired pyrrolidine derivative **51**. (*25*)
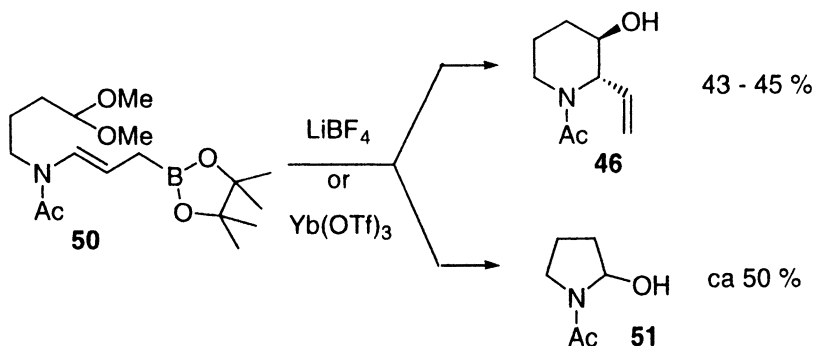
Scheme 17: Reaction modes of E-γ-Amido-allylboronates

This clearly demonstrated the drawbacks connected with the use of an acetal as the latent aldehyde function.

Domino-hydroformylation-allylboration-hydroformylation reaction

The bottomline from the last section is, that better methods are required to generate an aldehyde function in the presence of acid-labile allylboronates. For this reason we got attracted to the rhodium catalyzed hydroformylation of alkenes as a route to aldehydes, the hydroformylation being a reaction that proceeds under completely neutral conditions.
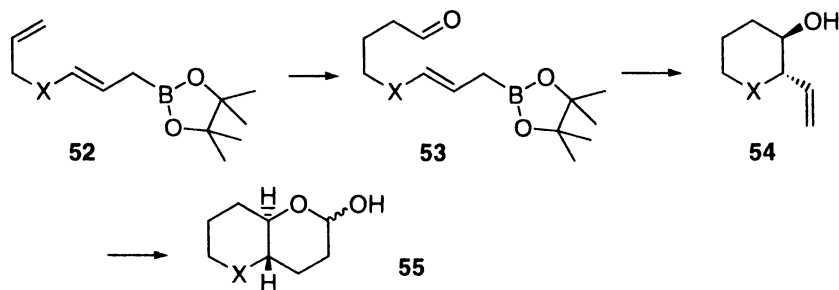
Scheme 18: Domino hydroformylation-allylboration-hydroformylation

We envisaged the hydroformylation of the alkene **52** to give the desired aldehyde **53** which would directly cyclize to **54**. In this case the reaction would not stop at this stage, because in the allylboration reaction another terminal olefin function is generated, which would undergo a second hydroformylation. Therefore a domino hydroformylation-allylboration-hydroformylation reaction sequence of **52** could give rise to the heterocycles **55**. The regioselectivity in the hydroformylation of terminal alkenes may be a problem. (*26, 27*) However, conditions have been worked out (*23*) which result in a high linear (to give **53**) versus branched aldehyde ratio. To test this conjecture we reacted the aldehyde **48** with allylamine followed by carbobenzoxy chloride to give the γ-amidoallylboronate **56** in 90% yield.
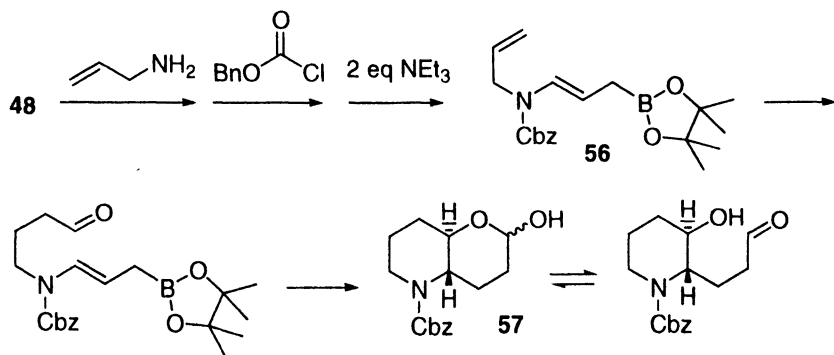
Scheme 19: Domino hydroformylation-allylboration-hydroformylation to give oxa-aza-decalins

We subjected this compound to rhodium catalyzed hydroformylation using the BIPHEPHOS ligand, which guarantees the predominant formation of the unbranched aldehyde. (*28, 29*) Hydroformylation, allylboration and the second hydroformylation proceeded cleanly to furnish the piperidinol derivative **57** in 73% yield. The latter compound was found to exist as a mixture of the lactol and the aldehyde form. (*25*)

The successful completion of this domino reaction encouraged us to check some further hydroformylation-allylboration-hydroformylation sequences. For instance, the homoallylic alcohol **58** was converted to the ynol ether **59**. To convert the latter to the alkenyl boronate (55%) **60** a zirconium catalyst (*30*) had to be chosen for the hydroboration. With rhodium catalysts chemoselectivity between the alkyne and the alkene moieties was unsatisfactory. The alkenyl boronate **60** was homolagated to the E-allylboronate **61** (95%) in standard fashion.

Hydroformylation with the BIPHEPHOS ligand is a slow process requireing 5 days at 65°C to proceed. The domino hydroformylation allylboration hydroformylation sequence resulted in a mixture of anomeric lactols (48%). In order to facilitate product analysis this mixture was directly oxidized to the corresponding lactones **62** and **63** (63%). The diastereomeric lactones were obtained in a 1:1 ratio, (*18*) indicating that the asymmetric induction from the resident stereocenter is low.

58   **59**   **60**

H$_2$/CO

Rh(CO)$_2$acac
BIPHEPHOS

Dess-Martin
oxidation

61

62 + **63**
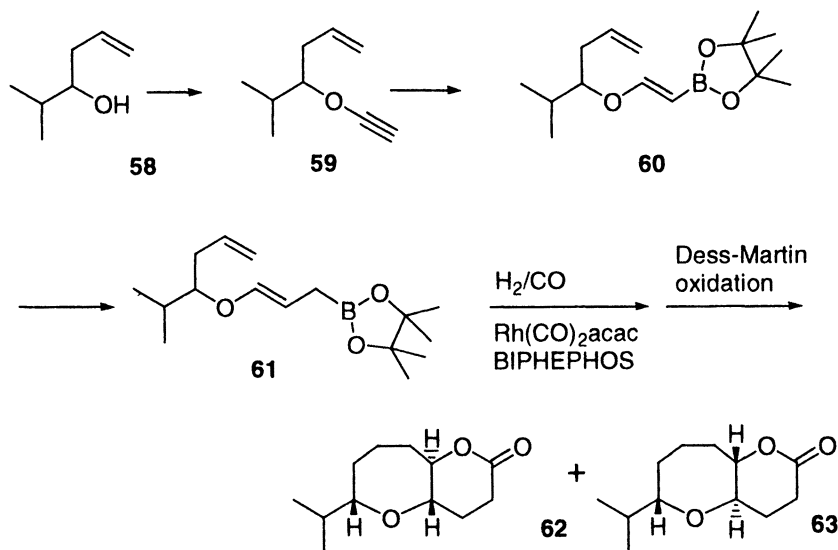
Scheme 20:   Domino hydroformylation-allylboration-hydroformylation to give hydrooxepane-lactones

This may be connected with the formation of a seven-membered ring in the intramolecular allylboration reaction, because this turned out not to be a single event: In a second experiment we subjected the conformationally more preorganized vinyl-tetrahydropyranol **45** to a similar sequence of reactions, cf. scheme 21. The E-allylboronate **64** when subjected to the hydroformylation-allylboration-hydroformylation sequence gave again rise to a 1:1 mixture of stereoisomeric products **65** and **66**. (*18*) In this case the long reaction time (6 days) and high temperature (65°C) resulted in the dehydration of the initially formed lactols to the enol ethers **65** and **66**. This reenforces the conclusion, that asymmetric induction from resident stereocenters on intramolecular allylboration is low, when forming a 7-membered oxepane ring. This contrasts the asymmetric induction witnessed before, when closing 6- or 8-membered rings (cf. the formation of **29**, **37**, and **39**).
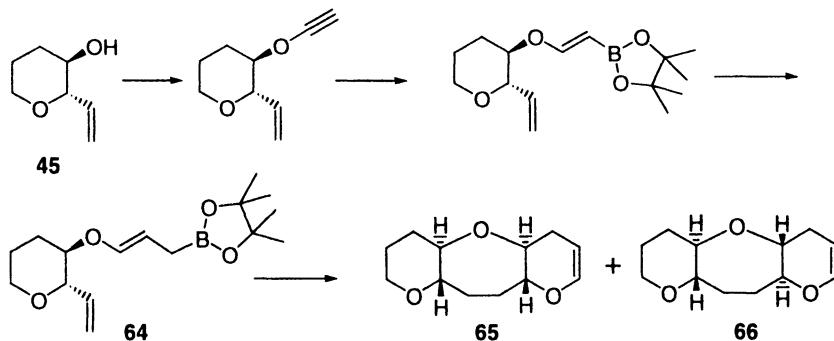
Scheme 21: Domino hydroformylation-allylboration-hydroformylation to give anellated oxygen heterocycles

All in all, we found that intramolecular allylboration of aldehydes proceeds with predictable and reliable stereoselectivity when forming 6-membered tetrahydropyrane or piperidine rings which are adorned with adjacent vinyl and hydroxy substituents.

References and Footnotes

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Chapter 13

Novel Silyl-Mediated 10-TMS-9-BBD Organoborane Reagents for Asymmetric Synthesis

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Novel 10-trimethylsilyl-9-borabicyclo[3.3.2]decanes (10-TMS-9-BBDs), easily prepared from $TMSCHN_2$ and 9-BBNs, are efficiently obtained in either enantiomerically pure form through their crystalline pseudoephedrine complexes (**8**, 40%). These are easily converted to the *B*-H(**3**), *B*-allyl (**9**) or *B*-allenyl (**13**) 10-TMS-9-BBD derivatives through simple procedures. An effective asymmetric hydroborating agent for both *trans*- (96-97% ee) and *cis*-alkenes (82-92% ee), **3** gives *opposite diastereomeric adducts* from these isomeric alkenes, selectivity which also allows deuterated and 2-methyl-1-alkenes to provide useful substrates for asymmetric hydroboration (*e.g.* α-deuterio or methylstyrene (90% and 62% ee, respectively). Both **9** and **13** are also remarkably enantioselective reagents in their reactions with aldehydes providing homoallylic and homopropargylic alcohols in high ee (*i.e.* 96-99% and 93-95 ee, respectively). Both processes permit the clean recovery of **8** (67-85%).

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Organoboranes have proven value in a variety of asymmetric processes[1] including, among others, hydroboration (*1,6,7*), allylboration (*5-7,12-23*), and allenylboration (*9,10*).In the present study, these three (3) important conversions will be studied employing 10-trimethylsilyl-9-borabicyclo[3.3.2]decyl (10-TMS-9-BBDs] systems, a new stable chiral stationary boron ligation. Owing to its rigid bicyclic structure, it will be demonstrated that chirality transfer is particularly effective with the silyl moiety exerting an unusual effect upon the steric environment present during these reactions which leads to unprecedented high selectivities in several cases. Moreover, for the allyl- and allenylboration processes, in contrast to most existing chiral boron reagents, the 10-TMS-9-BBD system can be easily recovered intact and reconverted to the asymmetric reagent through a simple one-step Grignard procedure.

Many asymmetric stationary chiral boron auxiliaries are ligands derived from optically active terpenes, amino alcohols and acids, tartrates, diols, diamines or sugars (*1-11*). With boron forming strong bonds to elements such as carbon, nitrogen and oxygen, chiral organoboranes are normally stable reagents which retain their integrity once they are assembled. When these reagents are used in asymmetric processes, the substrate is normally placed in close proximity to these ligands at the boron center and high diastereofacial selectivity can be achieved. Representative examples (*2,5-10,12-23*) of chiral auxiliaries which have found useful applications in asymmetric synthesis are shown in Figure 1 (*24-35*). Many of these systems are highly effective for the asymmetric allylboration process and the tartrate (**d**) as well as the 1,3,2-diazaborolane (**c**) have been also successfully applied to the analogous allenylboration process (*9-10*).

Relatively few of these ligands have been successfully applied to asymmetric hydroboration, the more important being diisopinocampheylborane (Ipc$_2$BH, *cf* **h**) (*35-40*), monoisopinocampheylborane (IpcBH$_2$, *cf* **o**) (*41-44*), and Masamune's borolane (2,5-DMB, *cf* **f**) (*45*). The greater Lewis acidity of these alkylborane derivatives compared to the analogous alkoxy or amino derivatives permits hydroboration to take place at or below room temperature where effective chirality transfer can occur. Ipc$_2$BH is effective for unhindered *cis*-alkenes (*cis*-2-butene (98.4% ee)) and related cyclo- and heterocyclic alkenes. However, *trans* and trisubstituted alkenes react sufficiently slowly so that the reagent undergoes dehydroboration producing α-pinene and IpcBH$_2$. Since IpcBH$_2$ hydroborates alkenes faster than does Ipc$_2$BH exhibiting the opposite enantiofacial selectivity, low ee's are obtained from these more hindered alkenes. Thus, IpcBH$_2$ is used for the asymmetric hydroboration of these systems providing products in ~70% ee. In some cases, this value can be upgraded to essentially 100% ee by the isolation of the enantiomerically pure mixed dialkylborane dimeric adducts through their selective crystallization (*43*). While not a general process, these optically pure organoboranes have proven value for many subsequent organoborane conversions
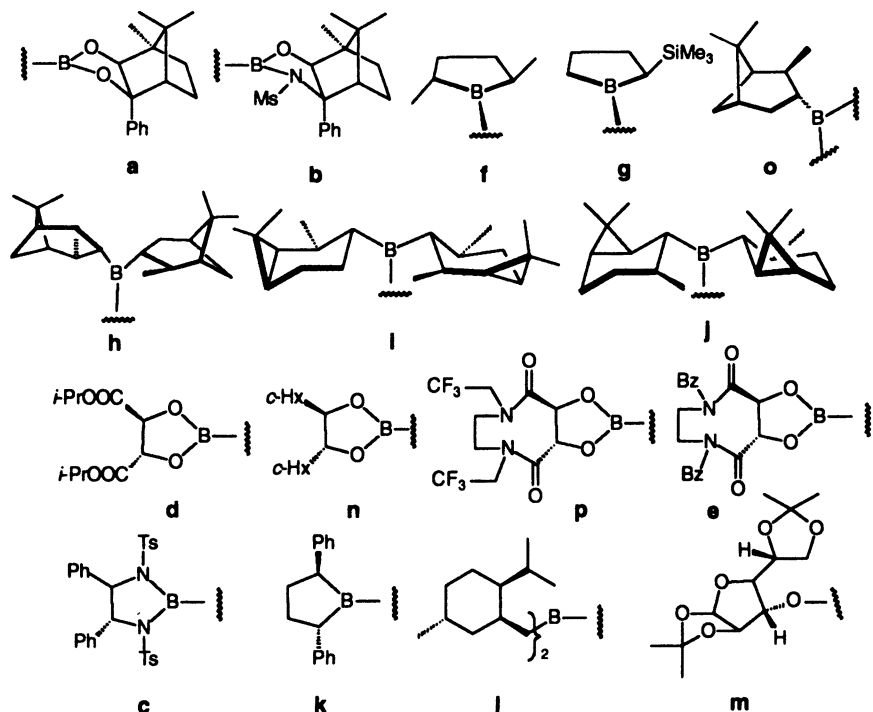
Figure 1. Common chiral ligation for asymmetric organoborane conversions.

(44). The 2,5-DMB reagent is highly selective for *cis*- and *trans*-as well as for tri-substituted alkenes (>97% ee) *(45)*. Unfortunately, these reagents are not readily accessible, being prepared through a multi-step process which requires two separate resolutions. None of the above reagents are effective for 1,1-disubstituted alkenes, with Ipc$_2$BH being the only reagent exhibiting any selectivity (*e.g.* α-methylstyrene (5% ee), 2-methyl-1-butene (21% ee)) *(38)*.

RESULTS AND DISCUSSION

Preparation and Resolution of the 10-TMS-9-BBD ring system

The remarkably stable 9-borabicyclo[3.3.1]nonane (9-BBN-H) is particularly selective hydroborating agent forming trialkylborane adducts which normally are isolable in pure forms owing to their high thermal stabilities *(46-50)*. While the 9-BBN ligation survives many organoborane conversions intact *(46-52)*, it can participate in others, one example being in 1,2-migrations (*c.f.* Scheme 1), such as the oxidation of **2** with trimethylamine *N*-oxide *(53-54)* or related azide
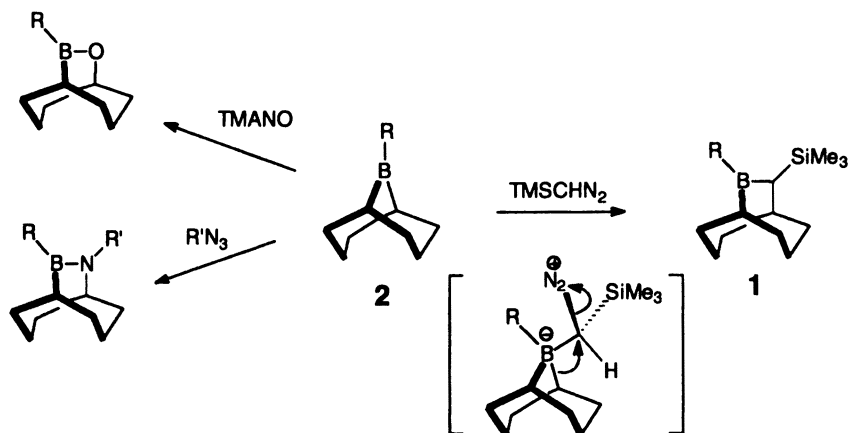
Scheme 1. Ring migrations in the 9-BBN system.

insertions with these organoboranes (*6*). The product borabicyclo[3.3.2]decanes (BBDs) appear to resist such migrations so that their selective formation from 9-BBN precursors are very efficient processes. Recently (*55*), we found that TMSCHN$_2$ inserts cleanly into **2**, forming the 10-TMS-9-BBDs (**1**), behavior suggested by the early work of Hooz, *et al.* with ethyl diazoacetate and 9-BBN systems which give oxidation products consistent with ring B-C insertion (*56*).

The insertion is very clean giving high yields of **1** for R = alkyl, alkenyl after 1-2 h , with the exception of the unreactive R = *t*-Bu derivative, undergo clean insertion in 1-2 h at reflux temperature in hexane solution. Unfortunately, new chiral hydroborating agent (±)-**3** was not directly available by the TMSCHN$_2$ insertion into dimeric 9-BBN-H which undergoes both B-C and B-H insertion. Any (±)-**3** formed undergoes rapid further reaction with the reagent producing **1** (R = CH$_2$TMS). Fortunately, the process is quite efficient for *B*-MeO-9-BBN providing pure **1f** in 90% yield, which permitted us to prepare (±)-**3** in 76% yield from **1f** following the Singaram, Cole, Brown method (*57*). With TMSCl (1.0 equiv), the intermediate borohydride is converted to the free borane which distills as a monomer, but exists in solution as a 3:1 monomer/dimer mixture at 25°C in CDCl$_3$ (Scheme 2). In contrast to 9-BBN-H which forms a strong dimer (*58-60*), (±)-**3** exists largely as the monomer at room temperature. Through variable temperature ^{11}B NMR, the monomer-dimer equilibrium constants were measured and from these data a large entropy factor in the dimerization of (±)-**3** (-47.4 eu (-198 J/mol K)) was determined.

We felt that this operationally simple approach to **3** was well-suited to the preparation of the enantiomerically pure reagent if **1f** could be obtained as a single enantiomer. With this in mind, we chose to examine a modified Masamune
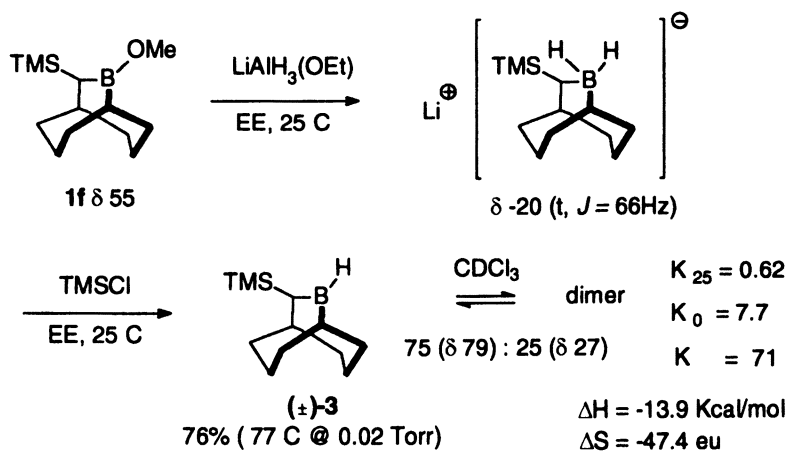
Scheme 2. Formation of racemic 3.
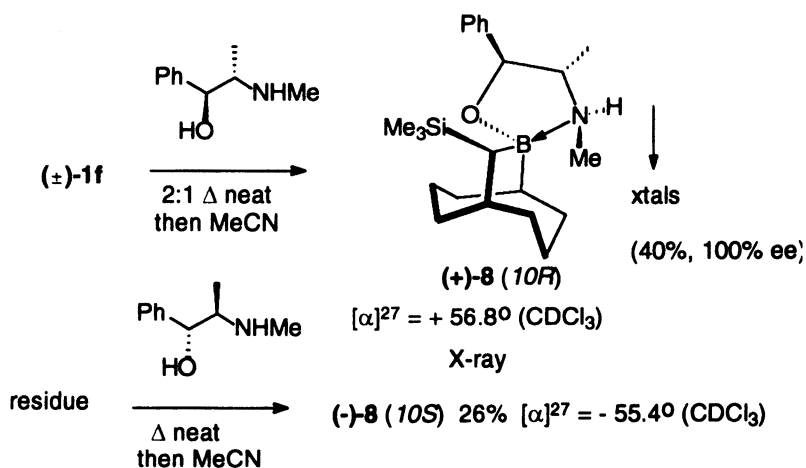
Scheme 3. Resolution of the BBD system.

approach (*19,45*) employing readily available optically active amino alcohols for the selective formation of a stable closed chelate (*e.g.* **8**) from one of the enantiomers present in racemic **1f**. A systematic MMX computational study on the intramolecular *N*-complexation for **8** and related BBD borinates revealed large energy differences for the *10R* vs. *10S* form of the reagent for (*1S, 2S*)-(+)-pseudoephedrine (Scheme 3). Heating (±)-**1f** with this alcohol (0.5 equiv) effects the transesterification and the enantiomerically pure air-stable crystalline complex (+)-**8** is obtained in 38-40% (76-80% of 50%) yield from acetonitrile. In solution
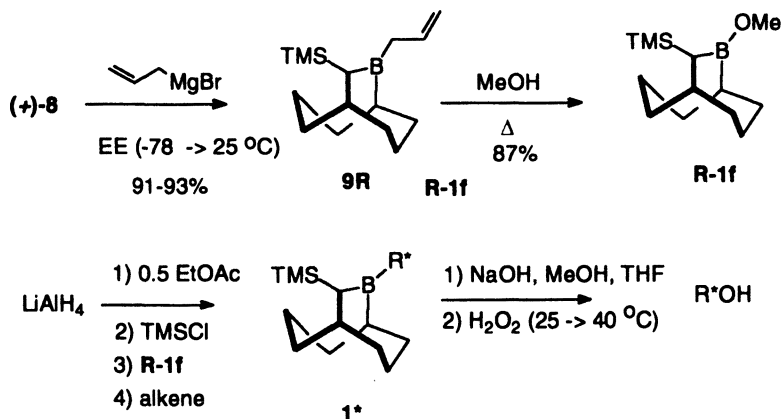
Scheme 4. In situ asymmetric hydroborations with 3.

both the open and closed form of (+)-8 are present (^{11}B-NMR δ 56.3 and 23.7). However, in the solid state, the closed structure and absolute stereochemistry were confirmed by single crystal X-ray analysis (*61*). The (-)-8 isomer was obtained (26%) from the addition of (-)-pseudoephedrine to the concentrated residue, heating and added acetonitrile. Thus, nearly two-thirds of the boron present in racemic **1f** can be isolated as their optically pure chelates, **8**.

The conversion of (+)-8 to **R-1f** was accomplished through the intermediate *B*-allyl derivative **9R** followed by methanolysis (Scheme 4) (*19*). As for the racemic material (Scheme 2), **3R** was readily generated as a monomer-dimer mixture in THF solution. Because this material as well as the racemic **3** were not obtained as crystalline solids, a general protocol was developed (Scheme 4) for the hydroborations with **3**, its being generated *in situ* from **1f** in either racemic or optically pure form.

Hydroboration and Asymmetric Hydroboration with 3

The reactivity and selectivity of (±)-3 was initially examined in the hydroboration of representative alkenes and alkynes (Scheme 5). These results clearly suggest that, like 9-BBN-H (*46-50*), (±)-3 is a very selective hydroborating agent, hydroborating terminal alkenes with excellent regioselectivity. The selectivity of (±)-3 also exceeds that of 9-BBN-H in the 1-hexene *vs.* cyclohexene competitive experiment where the 1-hexene reacts exclusively giving **4** (*c.f.* 9-BBN-H $k_{rel} \sim 13$ (*49*)). However, *trans*-3-hexene does give a minor amount of **6** (4%) in competition with 1-hexene, providing this adduct nearly exclusively (**6/7** = 98:2) in the presence of 1.0 equiv of cyclohexene. Moreover, the low 1-alkyne

4 +

6

4/6 = 96:4

Bu

Bu

Bu

SiMe₃

4

(±)-3

6 +

7

6/7 = 98:2

SiMe₃

Bu

Bu——H

Bu

Bu——H

4/5 = 40:60

Bu

SiMe₃

5
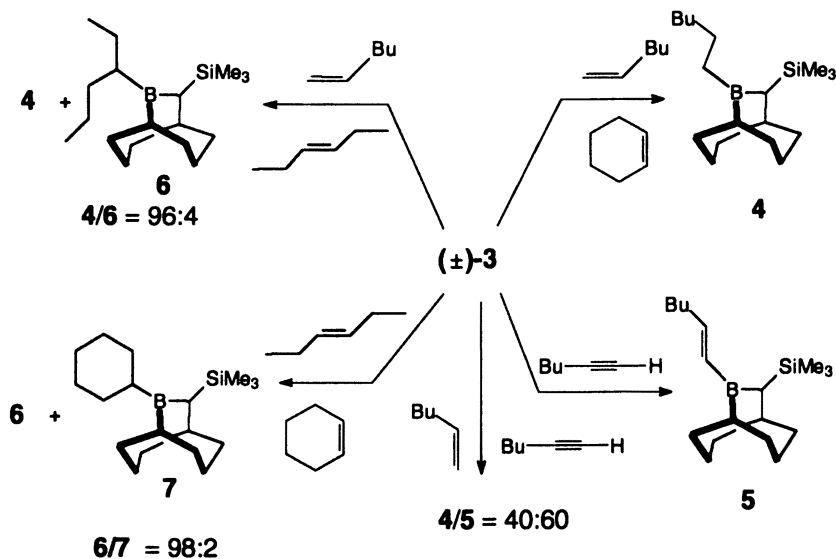
Scheme 5. Reactivity and selectivity of 3.

vs. 1-alkene selectivity (k_{rel} ~ 1.8) of **3** is actually the reverse of the behavior of 9-BBN-H which hydroborates alkynes faster than alkenes (k_{rel} ~6.8) (*49-50*). However, by far the most intriguing feature of the new reagent was revealed in the hydroboration of the 2-butenes. *The cis and trans olefins give the opposite*

(±)-3

13.9
2.3   33.2 13.7
TMS 39.7   B
22.4   34.9   27.8   29.3
25.8
33.7   31.9
26.5   25.0

1g-R*R*

(±)-3

15.2
2.4   32.2 13.8
TMS 38.4   B
22.2   34.9   27.8   29.2
25.3
33.9   31.6
26.7   25.8

1g-R*S*
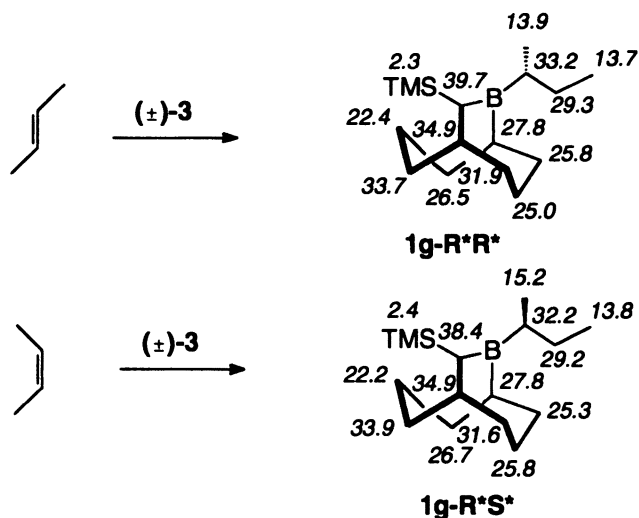
Figure 2. ¹³C NMR assignments for the diastereomeric B-(2-butyl)-10-TMS-9-BBDs.

diastereomers, both in high de (84 and 96 %, respectively)! To the authors' knowledge, this is an un-precedented result for any known chiral hydroborating agent. This result was reconfirmed and cross-checked by an INADEQUATE-based rigorous ^{13}C NMR analysis of each of the diastereomers comparing each to the mixture obtained from the TMSCHN$_2$ insertion into (±)-**2g**. These data are illustrated in Figure 2.

The important point of difference between the behavior of **3** and other known asymmetric hydroborating agents is its greater sensitivity to differences in the substitution pattern at the *beta* rather than *alpha* carbon of the double bond undergoing hydroboration. Thus, the orientation of the α-CHMe (*i. e.* C-2') is reversed in *cis vs. trans* alkenes and the opposite relative configuration is obtained for these isomers after the boron adds to this center. Consistent with this hypothesis, the hydroboration of α-methylstyrene was found to be very slow (*ca* 96 h, 25 °C), but produces the β-boryl adduct in 62% de, a remarkable result! The reaction intermediates were characterized by ^{13}C NMR a technique which provides a direct analysis of the boranes (*58-60*). However, quite clearly the selectivity of optically pure **3** was required to ultimately provide enantiomerically enriched products in asymmetric organoborane conversions.

The **1f→3** conversion was carried out as is outlined in Scheme 4 to give **3R** which adds to *trans*-2-butene to produce the (*1OR, 2'S*) isomer **R-1g** in >98% de. In every case, hydroboration mixture was treated with pentane (equal volume), centrifuged and the supernatant was decanted under nitrogen *via* cannula to a second flask and concentrated *in vacuo*. While we initially employed trimethylamine *N*-oxide as the oxidant which gave (-)-(*2R*)-butanol in >96% ee, we chose to develop an efficient hydrogen peroxide protocol which still avoids loss of optical purity and gives better chemical yields. It should be stressed that the use of methanolic NaOH (10 equiv 5 M), excess H$_2$O$_2$ (10 equiv) and carefully controlled reaction temperatures (addition at 25 °C (water bath) followed by 40 °C (2 h)) produces little or no racemization during oxidation. Representative alkenes were hydroborated at 25 °C with the deuterated styrenes requiring <1 h, *cis*-, 2 h, *trans*-, 1 h, 1,1-di- and trisubstituted alkenes, 3-4 da. The product alcohols were isolated and each was converted to their Mosher esters to determine their ee by NMR analysis. This data is presented in Figure 3.

Armed with direct NMR information on the diastereomeric excess achieved from the hydroboration of several representative alkenes with (±)-**3**, we examined the asymmetric hydroboration of various alkene types. As anticipated, **3** is particularly effective for *trans* alkenes which produce the alcohols in 96-97% ee. This is consistent with the absence of an observable amount of **1g-R*R*** derived from the hydroboration of *trans*-2-butene with (±)-**3**. As expected, the opposite absolute configuration is observed in the alcohols derived from the enantiomeric reagents, **3R** and **3S**. The selectivities observed for the *cis*-alkenes is lower (82-
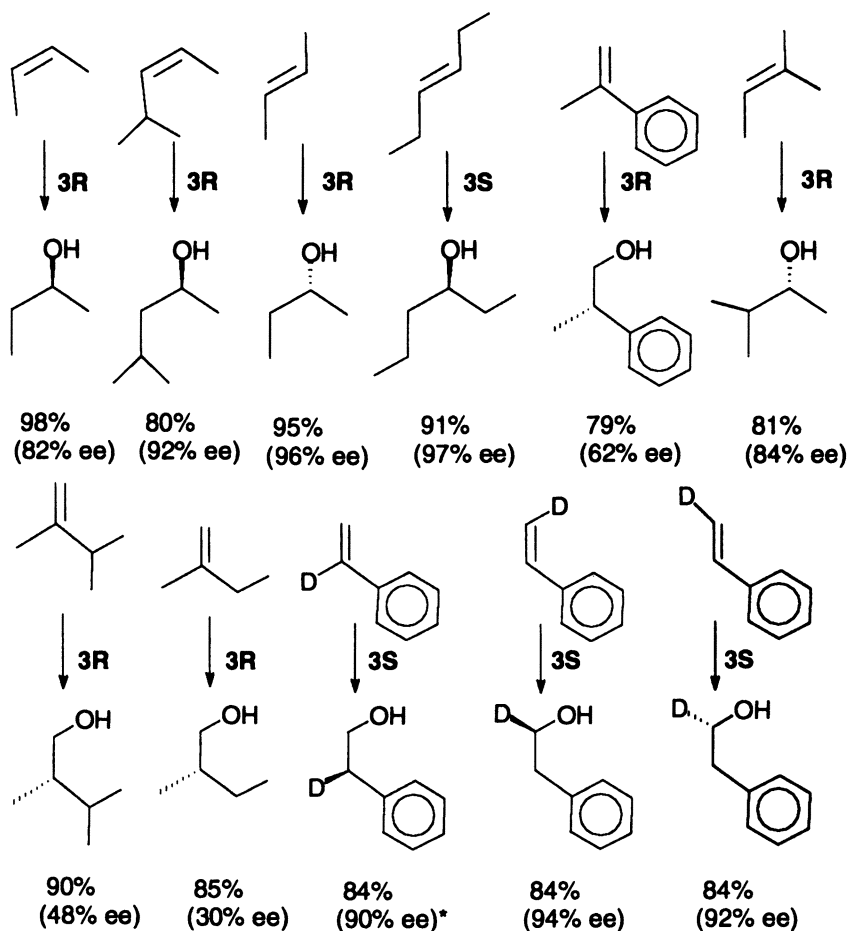
Figure 3. The asymmetric hydroboration of representative alkenes with 3. Chemical yields were determined by GC analysis employing an internal standard. With the exception of the α-deuteriostyrene example (* optical rotation), all product ee determinations were performed by NMR analysis of the Mosher esters through comparisons with authentic samples of each alcohol in both racemic and optically pure forms.

92% ee), a finding also consistent with the formation of ~7-8% of the minor diastereomer **1g-R*S***from (±)-**3** and cis-2-butene. As noted, the hydroboration of 1,1-disubstituted alkenes is slower, but effective enantiofacial selectivities are observed when the substituents differ in their relative sizes (i.e. Ph vs. Me (62%

ee), *i*-Pr *vs.* Me (48% ee), Et *vs.* Me (30% ee). Another remarkable feature of the reagent **3** is seen in its ability to exhibit high enantiofacial selectivity (>90 %) in the hydroboration of D-labeled monosubstituted alkenes such as styrene. The IPC$_2$BH reagent has also been used in this regard, but normally with significantly less selectivity being achieved (42-86%ee), although opposite geometrical isomers do give opposite absolute configurations just as for **3** (*39-40*).

With the general features of the 10-TMS-9-BBD system known from the X-ray data obtained for **8**, we carried out extensive MMX calculations on the possible conformations of the relatively rigid bicyclic reagent **3** concluding that the boat-chair conformations of the ring were much preferred over alternative arrangements. Of the two possible conformers, the more stable is shown in Figure 4. Superimposed upon this structure are representations of the available pockets needed to position an approaching alkene in a four-centered transition state leading to hydroboration. This model fully explains our observations on the reactivities and selectivities observed.

First, it is important to mention that the B-H moiety is held in a rigid chiral environment. The principal reason for the β-group differentiation arises from the TMS group which significantly limits the access of the alkene to the B-H, blocking the *syn* approach completely and with its longer Si-C bonds (18.8 nm) limiting the inward β group on the alkene even on the preferred *anti* side of the ring (see Fig. 4). Moreover, the ring protrudes farther outwardly at the C-4 position than it does in the C-5, C-10 region so than the inward α-group on the alkene actually has more space to reach the transition state than the outward position. Thus, the β,β-disubstituted alkenes react slowly because one of these groups must interact sterically with the bulky TMS group, with the smaller group being preferred on the inward side. With a hydrogen atom on this β position in the alkene, hydroboration
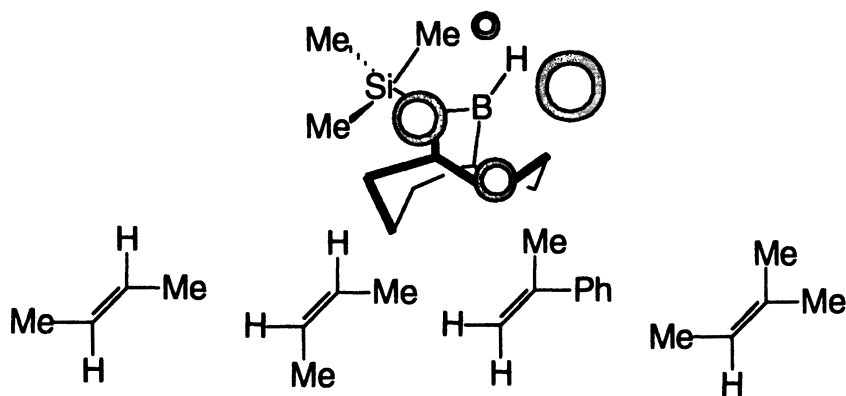
Figure 4. Model for the relevant steric features of 3 which lead to enantiofacial selectivity in the asymmetric hydroboration of alkenes. The preferred orientations are shown for several representative alkene substrates.

is faster with its inward position dominating the selectivity. With *cis*-alkenes exhibiting a somewhat lower selectivity than their *trans* counterpart, the α-alkene substitution also plays a role with the inward substituent being more favorable. These features are amplified by the fact that 2-methyl-2-butene gives a slow reaction and exhibits a major preference for the alkene face which positions the α-methyl group inwardly. To our knowledge the remarkable enantiofacial selectivity achieved for the deuterated styrenes and the 1,1-disubstituted alkenes is unprecedented in the scientific literature (*40,62*). Comparable to Masamune's borolane for *trans*-alkenes , **3** is less selective for *cis*- and trisubstituted alkenes than is this reagent. However, **3** is far easier to prepare. For this reason, Brown's diisopinocampheylborane is still the reagent of choice for unhindered *cis*-alkenes. Moreover, while the selectivity exhibited for 2-methyl-2-butene with **3** (84% ee) exceeds that of monoisopinocampheylborane (53%), the fact that this reagent is more reactive and produces intermediates which, in some cases, can be crystallized to upgrade the optical purities to essentially 100%, preserves its place as a useful asymmetric hydroborating agent. However, the unique selectivity exhibited by **3** represents an exciting new concept in asymmetric organoborane chemistry, two of which are described in the following sections.

Asymmetric Allylboration with the 10-TMS-9-BBD System

Allylboranes are extremely valuable intermediates for carbon-carbon bond formation (*5*), and with chiral boron ligation, these reagents are very effective reagents for the asymmetric synthesis of homoallylic alcohols (**10**) (*12-23*). The reaction can be viewed as the addition of an allyl group to *B*-coordinated aldehydes via a chair-like transition state, with the hydrolysis of the intermediate borane ultimately giving **10** (*5*). Exhibiting high diastereoselectivities in their subsequent conversions (*e.g.* epoxidation, iodocyclizaton) (*63-67*), these alcohols are extremely useful intermediates in asymmetric synthesis (*24-35*). We chose to examine the selectivity of the new chiral organoborane reagent, *B*-allyl-10-(trimethysilyl)-9-borabicyclo[3.3.2]decane (**9**) whose synthesis in either enantiomeric form is particularly simple through the reaction of allylmagnesium bromide with either (+) or (-)-**8** followed by filtration through Celite and concentration. Their remarkable selectivities in this asymmetric organoborane process is described in this Section.

The asymmetric allylboration of representative aldehydes with either **9R** or **9S** was examined in EE (3 h, -78 °C) (Scheme 6). In each case, the homoallylic alcohols **10** were obtained in ≥96% ee. These results are summarized in Table 1. The intermediates **11** were isolated in excellent yields in essentially pure form
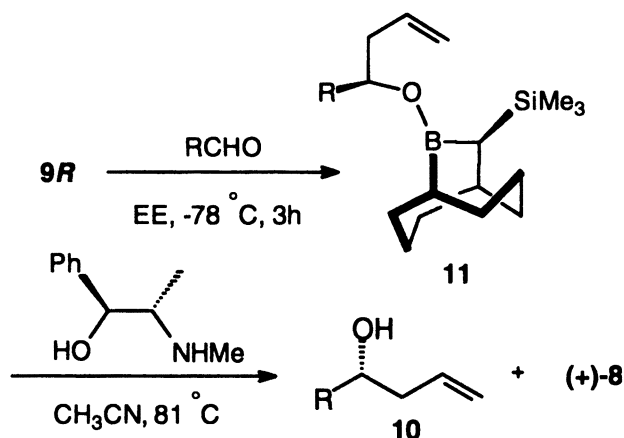
Scheme 6. Asymmetric allylboration with 9.

after solvent removal. For the reactions of **9R**, solutions (~0.5 M) of **5R** and (*1S*, *2S*)- (+)- pseudoephedrine (1.0 equiv) in MeCN were heated at reflux temperature to effect the transesterification with crystalline (+)-**8** being isolable by simple filtration. An analogous procedure was used for the **9S** reactions employing (-)-pseudoephedrine to provide (-)-**8**. The homoallylic alcohols **10** were isolated in good to excellent yields by simple distillation.

Table 1. Allylboration with *B*-Allyl-10-TMS-9-BBD (9).

R in RCHO	9	Series	Yield (%)			%ee
			11	8	10	
Ph	S	a	92	84	80	≥98 (S)[a, c]
Vi	S	b	87	77	71	≥98 (S)[a c]
i-Pr	S	c	91	67	62	≥99 (S)[b]
t-Bu	R	d	94	71	77	≥98 (R)[a]
n-Pr	R	e	100	79	79	≥98 (S)[b]
Me	R	f	99	73	71	96 (S)[a]

[a] Product ee determined by conversion to the Mosher ester and analysis by ^{13}C NMR.
[b] Determined by conversion to the Mosher ester and analysis by ^{1}H NMR and ^{13}C NMR.
[c] Determined by conversion to the Mosher ester and analysis GC chromatography.

Many of the best known chiral boron reagents for asymmetric allylborations (see Fig. 1, **a-j**) have been compared (7,12-23). At -78 °C, the diisocaranylboranes (**i,j**) generally exhibit the best selectivities (87-98% ee) with this value increasing to 98->99% ee at -100 °C. The more accessible diisopinocampheylborane reagent (Fig. 1, **h**) is nearly as selective (-78 °C, 83-94%; -100 °C, 96->99%) as is the silylated borolane **g** (-100 °C , 96-97% ee) for these systems. Comparing our results from **9** to these reagents reveals that this new asymmetric reagent equals or exceeds these selectivities at -78 °C. The new reagent **9** is efficiently prepared in three (3) steps from **1** in either enantiomeric form. Moreover, none of these reagents are so easily recovered and reconverted back to the asymmetric reagent (*i.e.* **9**).

Performing limit-of-detection studies, we were unable to confidently rule out the presence of 1 mol % of the minor diastereomeric Mosher esters through either reported NMR (including ^{13}C satellite methods) or GC techniques except in the case of isobutyraldehyde (*i.e.* **10c**) where, if present, we could detect 0.5 mol %. However, in only the acetaldehyde case were we able to detect any of the minor diastereomer (2 %).

Table 2. Temperature Effects in the Allylboration Reaction with 9.

temp, °C	% ee with 9 (Ipc$_2$BAll)^a	
	PhCHO	MeCHO
25	90.0	93.8
0	93.0^b	93.0 (79.4)
-25	94.0	98.0 (85.4)
-78	≥98.0 (94)	96.0 (93.0)

^{a} From ref. 68.
^{b} For **9S**. ^{13}C NMR analysis of the Mosher esters.

We felt that the bicyclic nature of **9** may provide an unusually well-defined asymmetric environment which would permit high enantiofacial selectivities to be achieved without having to conduct the allylborations at low temperatures. Since a significant loss of selectivity with increasing reaction temperature had been reported (68) for the diisopinocampheylborane reagent (Ipc$_2$BAll), we chose to conduct similar studies with **9**. These results (Table 2) reveal far less temperature dependence for the selectivity of **9** *vs.* Ipc$_2$BAll. In fact, the selectivity of **9** at room temperature is comparable to Ipc$_2$BAll at -78 °C in the case of acetaldehyde. Moreover, for benzaldehyde, only a few reagents (*i.e.* Fig. 1, **c, h, i**) give the

homoallylic alcohol **10a** in higher ee at -78 °C than **9** does at room temperature. We were intrigued by the exceptional behavior of **9**, turning once again to crystallographic data (*i.e.* **8**) and computational models for a possible explanation. What we had observed in the absolute configurations of **10** could only be explained through the formation of the aldehyde complex from the TMS side of the ring system. (Figure 5). While this was not appear intuitively obvious to us initially, the data was clear. However, closer examination of the structural features of **8** and computational data suggests that it is the small size of the oxygen atom in the complexing aldehyde *vs.* the larger $CH_2CH=CH_2$ moiety which minimizes the steric interactions with the TMS group and thus, favors this approach to the transition state. Consequently, we chose to examine the allenylboration process which we anticipated should exhibit related behavior.
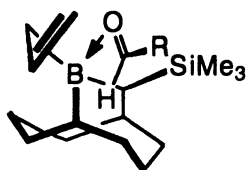
Figure 5. Pre-transition state complexation model for allylborations with 9.

Asymmetric Allenylboration with the 10-TMS-9-BBD System

Closely related to the above asymmetric allylboration process, allenylboration has been demonstrated to provide an effective entry to synthetically versatile homopropargylic alcohols (**12**) (*69,70*). Initial studies by H. Yamamoto, *et al.* (*9*) effectively employed bulky tartrate esters (*cf* Fig. 1, **d**) to prepare allenylboronic esters which produce **12** in high ee (73-99%) for various aldehydes with aromatic derivatives (*e.g.* PhCHO) being less effective substrates than their aliphatic counterparts. The relative complexity and low yields (40-60%) of the procedures required to prepare the starting allenylboronic acid coupled with the requirement that the chiral boronic esters have to be freshly prepared immediately before their use in the allenylboration detract somewhat from the overall value of the process. Other drawbacks to the method include: long reaction times (20 h, -78 °C), the hydrolysis of the chiral boron ligation upon work-up and the relative inefficiency of chirality transfer for aromatic substrates.
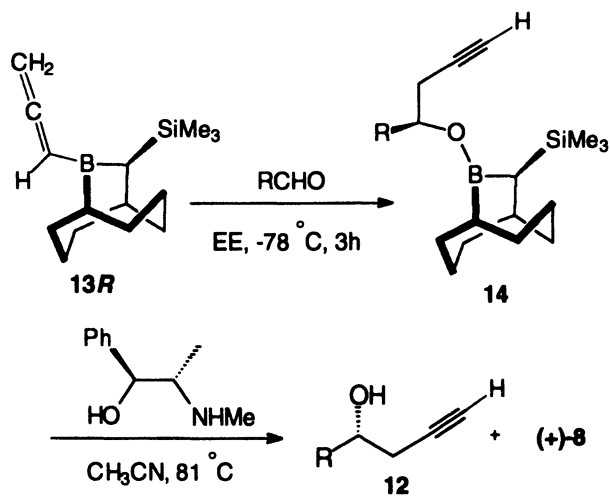
Scheme 7. Asymmetric allenylboration with 13R.

Improvements in this process were reported by Corey, *et al.* (*10*) with his demonstration that chiral *B*-allenyl-1,3,2-diazaborolanes (*cf* Fig. 1, **c**) are effective asymmetric allenylborating agents providing **12** in high yield (74-82%) and ee (91-98%). Generated *in situ* from the reaction of the *bis-p*-toluenesulfonamide of 1,2-diphenyl-1,2-diaminoethane with BBr$_3$ in CH$_2$Cl$_2$, the corresponding *B*-Br boracycle is converted to its *B*-allenyl derivative with propargyltriphenyltin. After allenylboration at -78 °C, the chiral auxiliary is recoverable (90%). The versatility of this process is further enhanced by the fact that allenyltins can also be used to prepare allenyl carbinols by an analogous process.

We felt that an improvement in the overall process would be made through the direct preparation of a stable *B*-allenyl chiral boron reagent from allenylmagnesium bromide thereby circumventing the need to both prepare an additional intermediate precursor to the allenylboron reagent and generate the reagent each time prior to its use. Toward this end, we found as for the above allyl system (*i.e.* **9R**), the pseudoephedrine complex (+)-**8** provided the ideal substrate for the preparation of the allenylborane **13R** (93%) from a Grignard procedure. The stable new reagent can be distilled and stored indefinitely under nitrogen at -20 °C. As for **9**, **13** undergoes clean reaction with representative aldehydes (3 h, -78 °C) producing, after a pseudoephedrine work-up, the homopropargylic alcohols **12** in 74-92% yields and 93-95% ee (Scheme 7, Table 3). In addition, the chiral organoborane complex (+)-**8** is recovered in 80-86% yield by its crystallization from acetonitrile in all cases through this simple procedure.

Table 3. Allenylboration with B-allenyl-10-TMS-9-BBD (13)

R in RCHO	13	Series	Yield (%)		$[\alpha]_D^{28}$, deg (c in MeOH)	%ee (config)[a]
			8	12		
Ph	R	a	84	92	-29.2 (2.2)	93 (R)
Vi	R	b	85	74	-36.79 (2.1)	94 (R)
i-Pr	R	c	80	81	-3.45 (1.2)	93 (R)
t-Bu	R	d	81	75	+45.37 (1.1)	94 (R)
n-Pr	R	e	84	82	-28.18 (2.2)	93 (S)[b]
Furaldehyde	R	f	80	80	-6.61 (2.4)	95 (R)

[a] Product ee determined by conversion to the Mosher ester and analysis by ^{1}H NMR and ^{13}C NMR.
[b] Absolute configuration reversed only because of group priorities (*i.e.* n-Pr *vs.* allyl).

As for **9**, the approach of the aldehyde to **13** occurs principally from the TMS side of the ring with the smaller effective size of the allenyl *vs.* allyl group accounting for a slightly lower selectivity in allenylboration *vs.* allylboration. Comparing very well to the Corey reagent, **13** is equally accessible in either enantiomeric form directly from **8** through a simple Grignard procedures avoiding the addition steps of preparing organotin precursors and handling bromoborane intermediates which are easily hydrolyzed. The fact that **8** is easily recovered from the procedure and reconverted back to **9** also greatly enhances the value of the process by completely circumventing the need to prepare the chiral borane moiety for each new application.

CONCLUSIONS

The 10-TMS-9-BBD system (**1**) is readily prepared from many 9-BBN derivatives through the clean insertion of the stable, commercially available reagent, TMSCHN$_2$. Resolution of the chiral bicyclic system is efficiently accomplished (40%) through its pseudoephedrine complex (**8**) which is readily converted to the B-H (**3**), B-allyl (**9**) or B-allenyl-10-TMS-9-BBD(**13**) derivatives. These new reagents have been demonstrated to function as highly useful

asymmetric hydroborating, allylborating and allenylborating agents, respectively. Studies are currently underway to further develop related reagents in other asymmetric organoborane conversions.

ACKNOWLEDGMENTS

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Chapter 14

Asymmetric Aldol Reactions Using Boron Enolates: Applications to Polyketide Synthesis

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The chiral boron enolates **7-14** add to aldehydes with high levels of stereocontrol in a predictable sense. These enolates are designed specifically for the aldol-based construction of the highly oxygenated and stereochemically challenging structures found in polyketide natural products, as illustrated here by their application to the total synthesis of concanamycin F and discodermolide.

Introduction

The boron-mediated aldol reaction (*1-13*) allows the construction of new carbon-carbon bonds between two carbonyl compounds in a regio-, diastereo-, and enantioselective fashion. The addition of chiral boron enolates to aldehydes to produce β-hydroxy carbonyl compounds is one of the most powerful and dependable methods available for achieving acyclic stereocontrol, with the creation of up to two stereogenic centers. Generally, the geometry of the boron enolate produced by enolisation of a given carbonyl compound with a suitable Lewis acidic boron reagent (L_2BX, usually X = OTf or Cl) is translated faithfully into relative stereochemistry (Figure 1), *i.e.* (*Z*)-enolates (**1**) → *syn* (**2** or **3**) and (*E*)-enolates (**4**) → *anti* aldol adducts (**5** or **6**).

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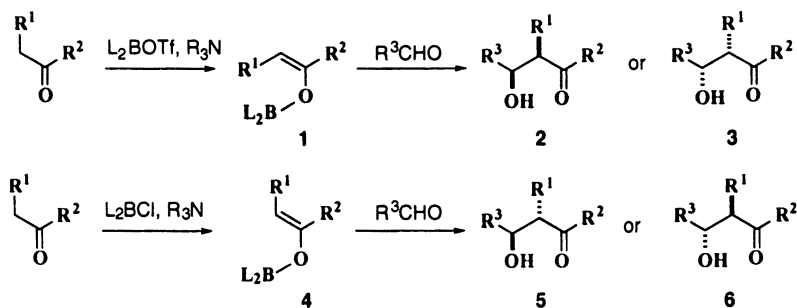
Figure 1. Relationship between boron enolate geometry and aldol adduct stereochemistry.

Asymmetric Aldol Reactions Using Chiral Boron Enolates

Compared to other enolates, the metal-oxygen bond in boron enolates is relatively short which leads to a tight cyclic transition state which is energetically responsive to quite subtle steric and electronic influences (*13*). Variation of the steric demands of the ligands (L) on boron, in combination with the choice of substituents (R^1, R^2, *etc.*) on the enolate, allows discrimination between competing transition structures. High levels of π-facial selectivity may then result under kinetic control. Figure 2 shows a selection of chiral boron enolates **7-14**, as developed in our laboratory (*14-21*), which add to aldehydes with synthetically useful levels of π-facial selectivity in a predictable sense (without the requirement for an auxiliary). These enolates are designed specifically for the construction of the highly oxygenated structures found in polyketide natural products (*22*).

Chiral ligands attached to boron can be employed to produce enantiomerically enriched aldol adducts from simple carbonyl compounds, as well as to reinforce substrate-based stereoinduction arising from the use of chiral carbonyl components (*1*). Of particular note is the use of the readily available α-pinene-derived boron reagents (*14,23*), (+)- and (−)-Ipc$_2$BX (X = Cl or OTf), in association with a tertiary amine base for the enolisation of ketones, giving regio- and stereodefined diisopinocampheyl enol borinates, as in **7** and **8**. Remote 1,4- and 1,5-stereoinduction can be realised using the enolates **12** (*19*) and **13** (*21,24*), prepared from certain structural types of methyl ketone by enolisation with Brown's *c*-Hex$_2$BCl reagent (*25,26*) in the presence of Et$_3$N. This substrate-based asymmetric induction can also be reinforced by using the appropriately matched Ipc$_2$BCl reagent instead.

Syn–Selective Enolates

Anti–Selective Enolates

Remote Stereoinduction

1,4-   1,5-   1,n-
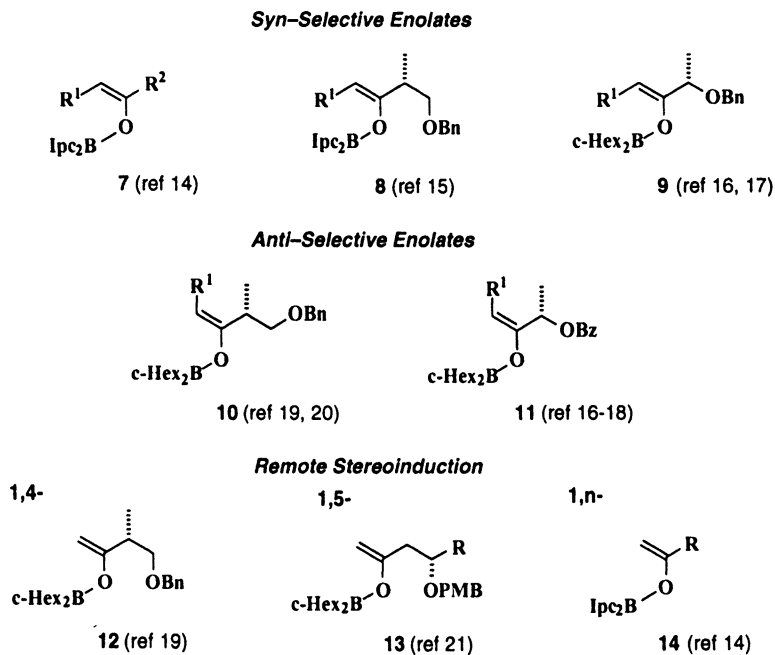
Figure 2. Chiral boron enolates for asymmetric aldol reactions.

Applications to Polyketide Synthesis

The ability to achieve such highly controlled aldol bond assemblies using boron enolates enables their application to the synthesis of the carbon and oxygen skeleton of stereochemically rich, polyol-containing, natural products. In particular, the polyketides represent a diverse array of structurally complex natural products having a wide range of important biological activities. Asymmetric aldol reactions using the ketone-derived enolates **7-14** (or their enantiomers) with a wide variety of aldehydes (prochiral or chiral) give ready access to elaborate segments of polyketide natural products in an efficient manner. Subsequent elaboration of the corresponding β-hydroxy ketone adducts can then be performed with a high level of overall diastereoselectivity. For example, carbonyl reduction can be realised by appropriate choice of reagent to produce 1,3-*syn* or 1,3-*anti* diols selectively. Recent examples of some of these asymmetric boron aldol reactions are now given in the context of two polyketide total synthesis projects performed in our laboratory.

Concanamycin F

The concanamycins are a group of 18-membered macrolides produced by *Streptomyces* microorganisms (*27-32*), which have generated considerable interest due to their potent and relatively specific inhibition of vacuolar ATPases (*33,34*). By using stereodefined boron enolates derived from chiral ketones, we have devised a concise aldol-based synthesis (*35-37*) of the highly oxygenated and stereochemically challenging concanamycin F (**15**) (*38,39*). Figure 3 shows the three subunits selected, *i.e.* **16- 18**, based on the identification of five strategic aldol disconnections, #1-5. This analysis leads back to the use of the appropriate (*E*)-enolates derived from the chiral ketones **19-22**.
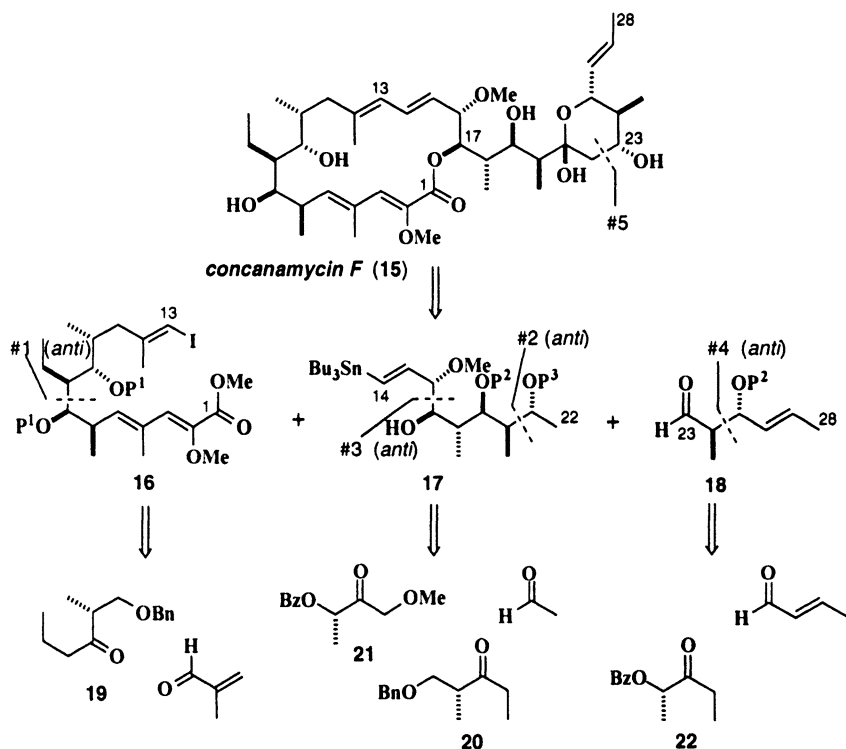
Figure 3. Retrosynthetic analysis for concanamycin F.

Using our standard conditions (*19,20*), the *anti* aldol reaction (#1) of the propyl ketone **19** (available in 3 steps from methyl (*R*)-3-hydroxy-2-methylpropionate) with methacrolein proceeded *via* the preferred chair TS **23** (Figure 4). The *in situ* reduction (*40*) of the resulting boron aldolate **24** with LiBH$_4$ proceeds by axial delivery of hydride through the TS **25** to produce the 1,3-*syn* diol **26** (>95% ds for the introduction of 3 stereocenters). Protection of the hydroxyl groups in **26** followed by diastereoselective hydroboration of the

alkene introduced the C6-stereocenter. Further elaboration to install the vinyl iodide and dienoate functionality was then achieved to reach the required C1-C13 subunit 16.
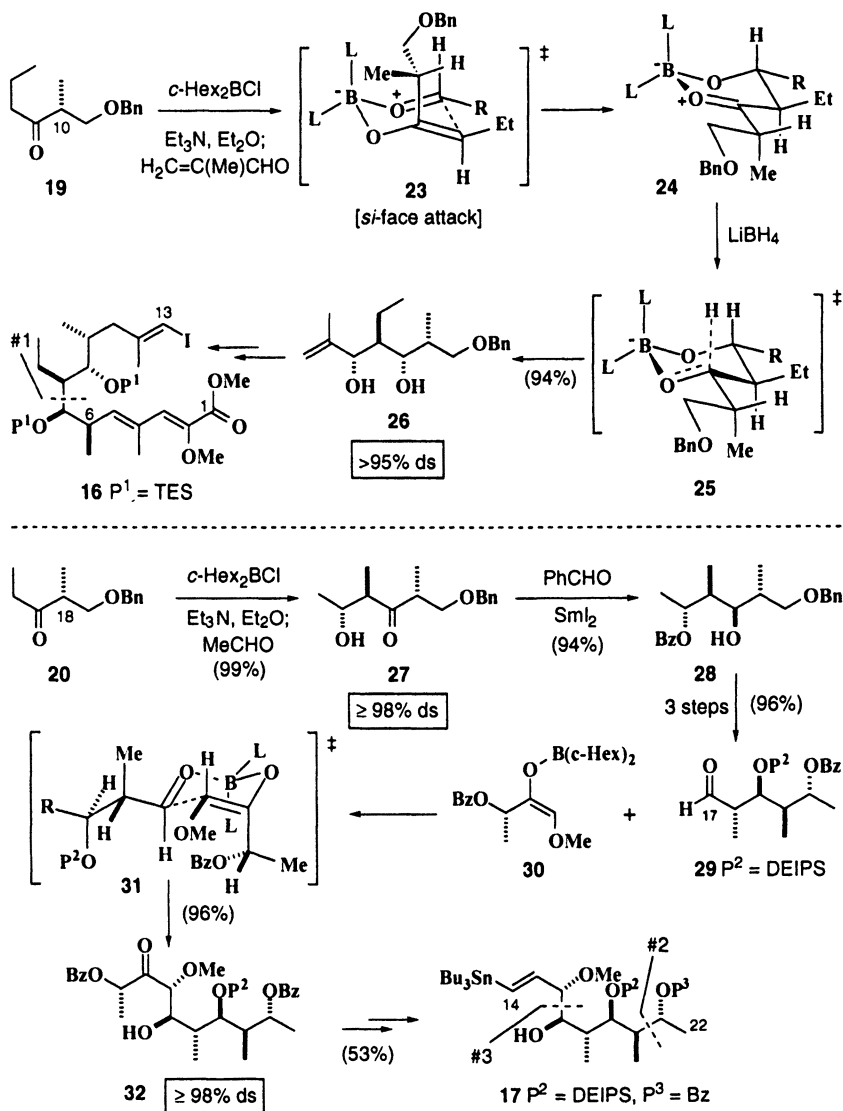
Figure 4. Synthesis of the C1–C13 subunit 16 and the C14–C22 subunit 17.

For the synthesis of the corresponding C14-C22 subunit, vinyl stannane 17, the aldol adduct 27 (#2; >98% ds) obtained in a similar manner from ethyl ketone 20 and acetaldehyde required reduction in a 1,3-*anti* sense. Thus, an

Evans-Tishchenko reaction (*41*) gave the benzoate **28**. Functional group manipulation then gave the aldehyde **29**. A matched aldol reaction (#3) between aldehyde **29** and the (*E*)-enolate **30** (derived from ketone **21**), which presumably proceeds *via* TS **31**, provided the *anti* adduct **32** (≥98% ds). This was then elaborated into the stannane **17**. In this way, the introduction of the 6 contiguous stereocenters was achieved with essentially complete control.

As shown in Figure 5, a Cu(I)-promoted, Liebeskind-Stille coupling (*42*) between the stannane **17** and the iodide **16** produced the methyl ester **33** in high yield. After chemoselective ester hydrolysis, the resulting seco acid derivative was macrolactonised using the Yamaguchi procedure (*43*) and taken on to give the 18-membered macrolide **34**. The completion of our synthesis of concanamycin F required a final aldol coupling (#5) between the macrocyclic methyl ketone **34** and the aldehyde **18** – itself derived from a boron-mediated *anti* aldol reaction (#4) between the ethyl ketone **22** and crotonaldehyde. This coupling step was best achieved using a Mukaiyama aldol reaction to form **35**, thereby maximising Felkin-Anh stereoinduction from the α-chiral aldehyde **18**. Appropriate deprotection conditions led to concomitant hemiacetalisation and gave concanamycin F (**15**).

Altogether, four asymmetric, *anti*-selective, boron aldol reactions were employed in this highly convergent synthesis (26 steps longest linear sequence, 5.3% overall yield), which ensured a high level of stereocontrol throughout.
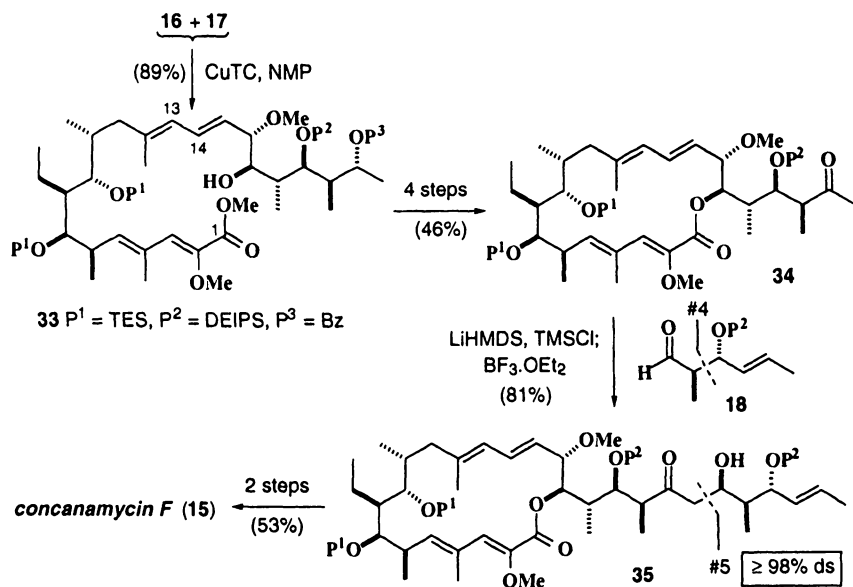
Figure 5. Completion of the total synthesis of concanamycin F.

Discodermolide

Discodermolide (**36**) is a cytotoxic polyketide isolated in low yield from the Caribbean sponge *Discodermia dissoluta* (*44*). The recent discovery that discodermolide shares the same microtubule-stabilising mechanism of antimitotic action as the clinically important anticancer drug, Taxol®(paclitaxel), and retains activity against Taxol®-resistant cancer cells has stimulated considerable interest (*45,46*). Due to the scarce supply of the natural material, the development of an efficient total synthesis (*47-52*) of (+)-discodermolide is needed to provide useful quantities for further testing, as well as enabling access to structurally simplified analogues.

This proved to be an excellent opportunity (*52*) to demonstrate the utility of our boron enolate methodology for the introduction of most of the 13 stereocenters, which entailed the preparation of the 3 subunits **37-39** on a multigram scale (Figure 6). Here, five strategic aldol disconnections, #1-5, were identified. Most notable is the final aldol coupling proposed with the (*Z*)-enal **40**. This analysis leads back to the use of the appropriate boron enolates derived from chiral ketones *ent*-**20**, **22**, **37** and **41**.
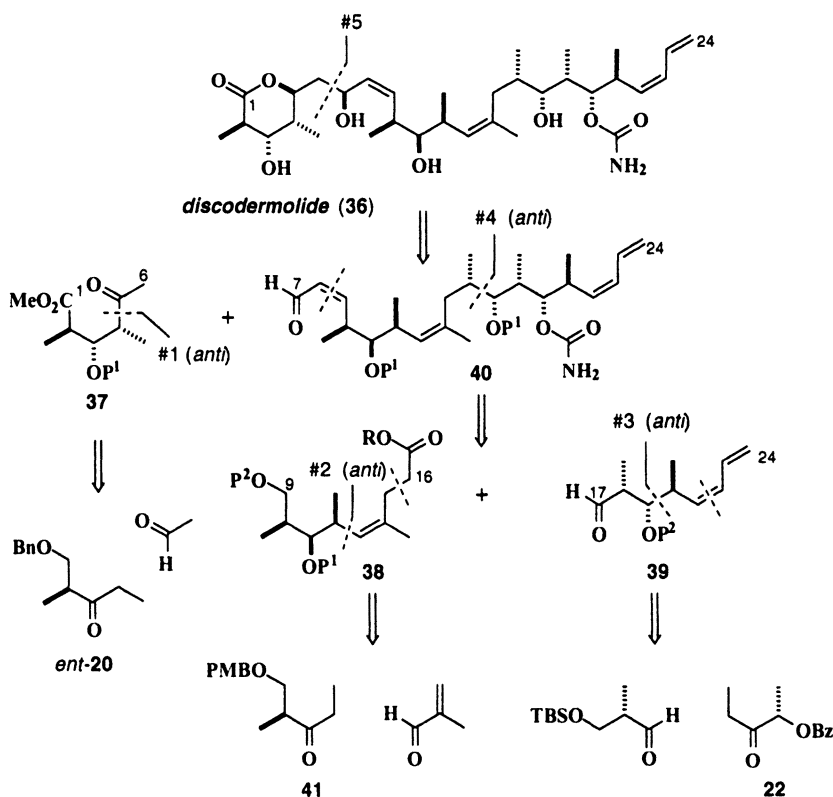
Figure 6. Retrosynthetic analysis for discodermolide.

As outlined in Figure 7, the C1-C6 subunit **37** was readily prepared using a boron-mediated, *anti* aldol reaction (*19,20*) between the ethyl ketone *ent*-**20** (obtained from methyl (*S*)-3-hydroxy-2-methylpropionate) and acetaldehyde. An *in situ* reduction (*40*) of the intermediate aldolate with LiBH$_4$ gave the 1,3-*syn* diol **40** (≥97% ds). A similar reaction sequence was used earlier for concanamycin F (see Figure 4). Protecting group adjustment and oxidation then gave the methyl ketone **37**.
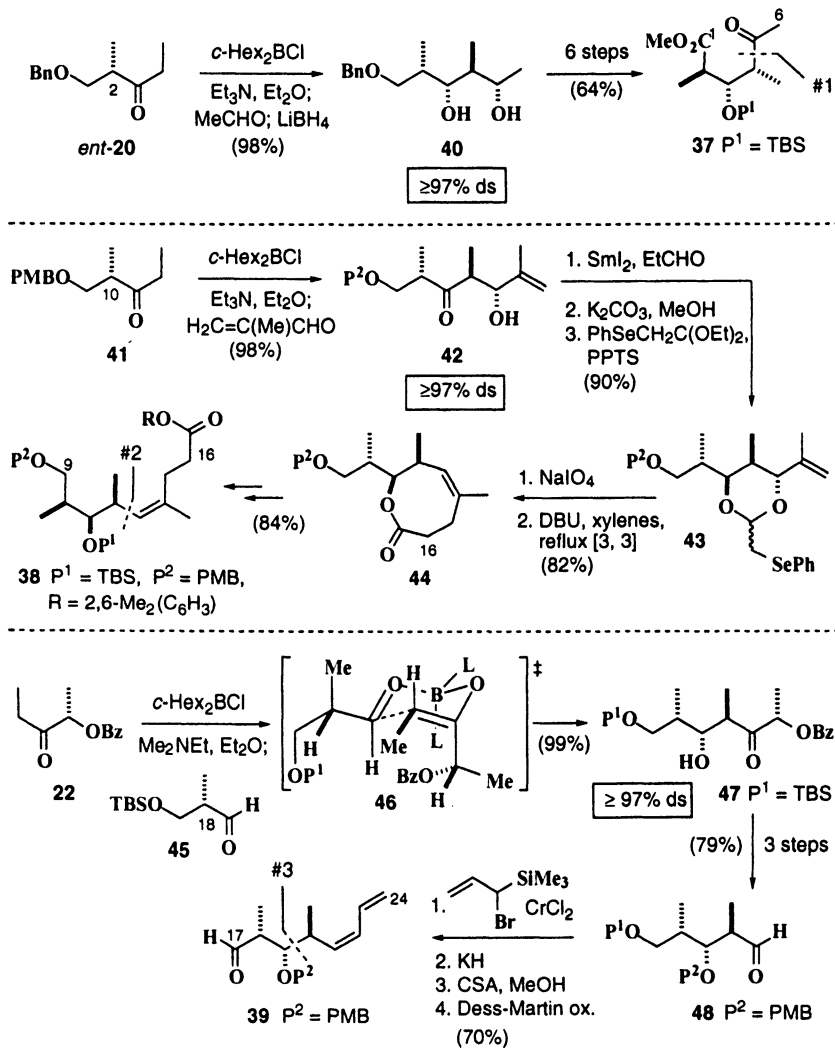
Figure 7. Synthesis of the subunits 37, 38 and 39.

The synthesis of the C9-C16 subunit **38** was based on an analogous boron-mediated aldol reaction between the ethyl ketone **41** and methacrolein to give the *anti* adduct **42** (≥97% ds). After reduction to the corresponding 1,3-*anti* diol, the Holmes-Petrzilka protocol (*53-55*) for Claisen [3,3] rearrangement was used to generate the 8-membered lactone, as in **43** → **44**. This resulted in perfect control of the (*Z*)-alkene geometry, together with introduction of a strategically placed carbonyl group to enable a later aldol coupling, which followed transformation of **44** into the Heathcock-type (*56*) aryl ester **38**. The remaining C17-C24 subunit **39** was obtained using a further boron-mediated asymmetric aldol reaction; this time between the ketone **22** (prepared in 3 steps from ethyl (*S*)-lactate) and aldehyde **45** *via* TS **46** to give the *anti* adduct **47** (≥97% ds). By using a Nozaki-Hiyama reaction in tandem with a Peterson elimination on the derived aldehyde **48**, the (*Z*)-diene-containing aldehyde **39** was obtained.
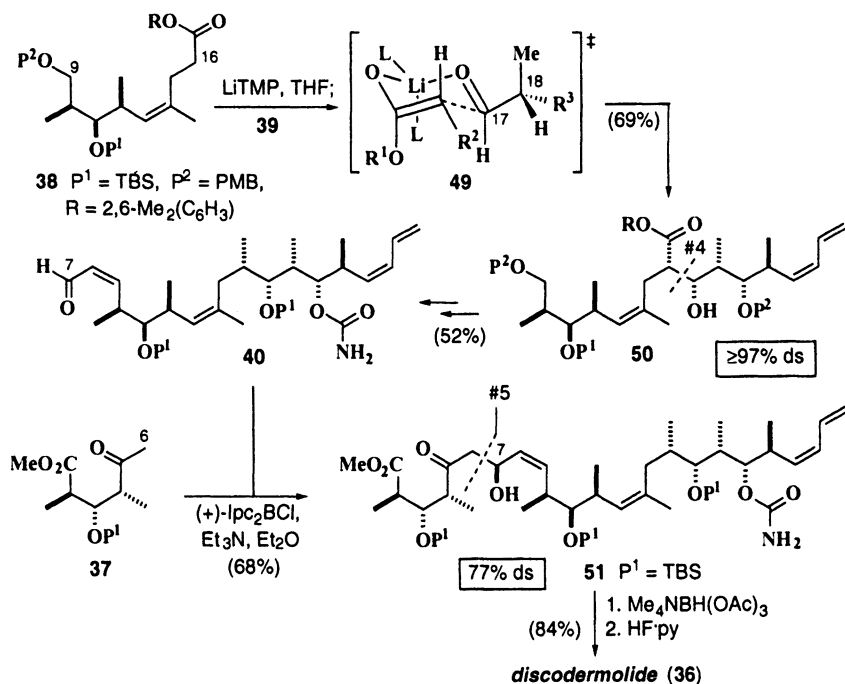
Figure 8. Completion of the total synthesis of discodermolide.

As shown in Figure 8, the *anti*-selective aldol coupling at C16-C17 employed the addition of the lithium (*E*)-enolate of the aryl ester **38** to the aldehyde **39**. This proceeded preferentially *via* TS **49** to generate the Felkin-Anh adduct **50** (≥97% ds). After appropriate deoxygenation to introduce the C16-methyl group, this was transformed into the (*Z*)-enal **40**. In the final boron aldol coupling step, the undesired inherent facial bias of the γ-chiral (*Z*)-enal **40** was overturned by using (+)-Ipc$_2$BCl and Et$_3$N to generate the enolate from

methyl ketone **37**, giving 77% ds in favour of the required (7*S*)-adduct **51**. This is the first case that this reagent system (*1,14*) has been exploited successfully in a challenging triple asymmetric induction situation to overturn substrate-based π-facial selectivity. Stereocontrolled reduction of the β-hydroxy ketone **51** and deprotection with concomitant lactonisation then gave (+)-discodermolide (**36**).

Altogether, our total synthesis of (+)-discodermolide uses four asymmetric boron aldol reactions and proceeds in 27 steps and 7.7% overall yield (for the longest linear sequence starting from commercial methyl (*S*)-3-hydroxy-2-methylpropionate).

Acknowledgements

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Chapter 15

Recent Progress in Asymmetric Synthesis with Boronic Esters

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Asymmetric 1,3,2-dioxaborolanes (cyclic boronic esters) react with (dichloromethyl)lithium to form the homologous α-chloro boronic esters with exceptionally precise stereocontrol. The range of potential synthetic applicability is very broad. Recent approaches to synthetic strategy and functional group protection are discussed, together with new developments in the applicability of the method.

Introduction

The general reaction of a 2-alkyl-1,3,2-dioxaborolane (cyclic boronic ester) (**1**) with (dichloromethyl)lithium followed by zinc chloride promoted rearrangement inserts a chloromethyl group into the carbon-boron bond to form the homologous α-chloro boronic ester (**2**). Further reaction with a nucleophilic reagent M^+Y^- produces substitution product **3** in very high stereopurity (*1,2,3*). Known M^+Y^- include Grignard and lithium reagents, alkali metal alkoxides, lithium enolates, and lithiohexamethyldisilazane. The products (**3**) are boronic esters, and can undergo similar chain extension with (dichloromethyl)lithium to introduce additional stereogenic centers (Scheme 1). This chemistry can provide precise stereocontrol for a wide variety of synthesis problems. Several recent developments are reviewed in this article.

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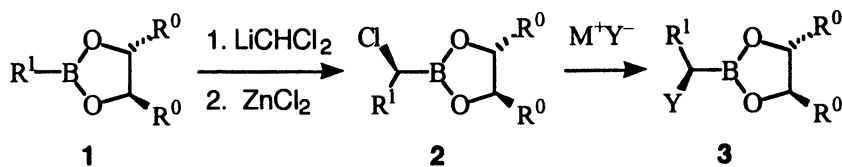
Scheme 1. *General route for controlled introduction of stereogenic centers into boronic esters.*

This general scheme has been used to solve a variety of synthetic problems (*2*). Insect pheromone targets have been among the most notable successes (Scheme 2). The isomeric 4-methyl-3-heptanols **4** and **5**, pheromones of the elm bark beetle and an Asian ant, respectively, were obtained in 99.8% diastereopurity and similar or higher enantiopurity (*3*). Stegobinone (**6**), the stereolabile pheromone of the drugstore beetle, *Stegobium paniceum*, as well as the furniture beetle, *Anobium punctatum*, was also prepared in very high stereopurity (*4*).
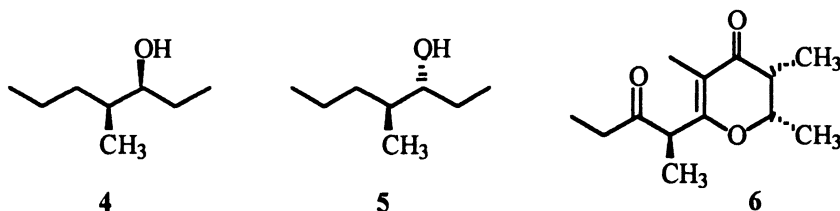
Scheme 2. *Some insect pheromones synthesized via boronic ester chemistry.*

Chiral Direction Strategy

Though the first chiral director used in this work, pinanediol (*2*), is still the simplest to prepare and there are uses for which it works best, the highest stereoselectivity, up to 1000:1, has been achieved with 1,2-diols of C_2 symmetry (*3*). We now favor (*R,R*)- or (*S,S*)-1,2-dicyclohexyl-1,2-ethanediol [(*R*)- or (*S*)-DICHED] for routine use. This diol was introduced by Hoffmann (*5*), and is easily made via a Sharpless dihydroxylation of *trans*-stilbene (*6*) followed by hydrogenation of the benzene rings over rhodium (*7*).

Our recent synthesis of serricornin (**17**) (*8*), the pheromone of the cigarette beetle, *Lasioderma serricorne*, illustrates the efficiency of the method when an optimized stereodirector strategy is employed and all of the substituents are nonpolar (Scheme 3). Because the synthetic method connects a single stereogenic carbon in each chain extension step, the required sequence of linear

steps is lengthy. Even so, the estimated overall yield of **17** from 1-butyne was ~35%. From the first asymmetric intermediate, the 2-methyl-1,3,2-dioxaborolane **10**, the calculated yield was ~59% (*8*).

To achieve such a high overall yield with so many individual steps requires a very efficient process at each step. Chromatography of intermediates proved unnecessary until the last boronic ester intermediate (**15**) was reached. Several problems in synthetic strategy are worth mentioning.
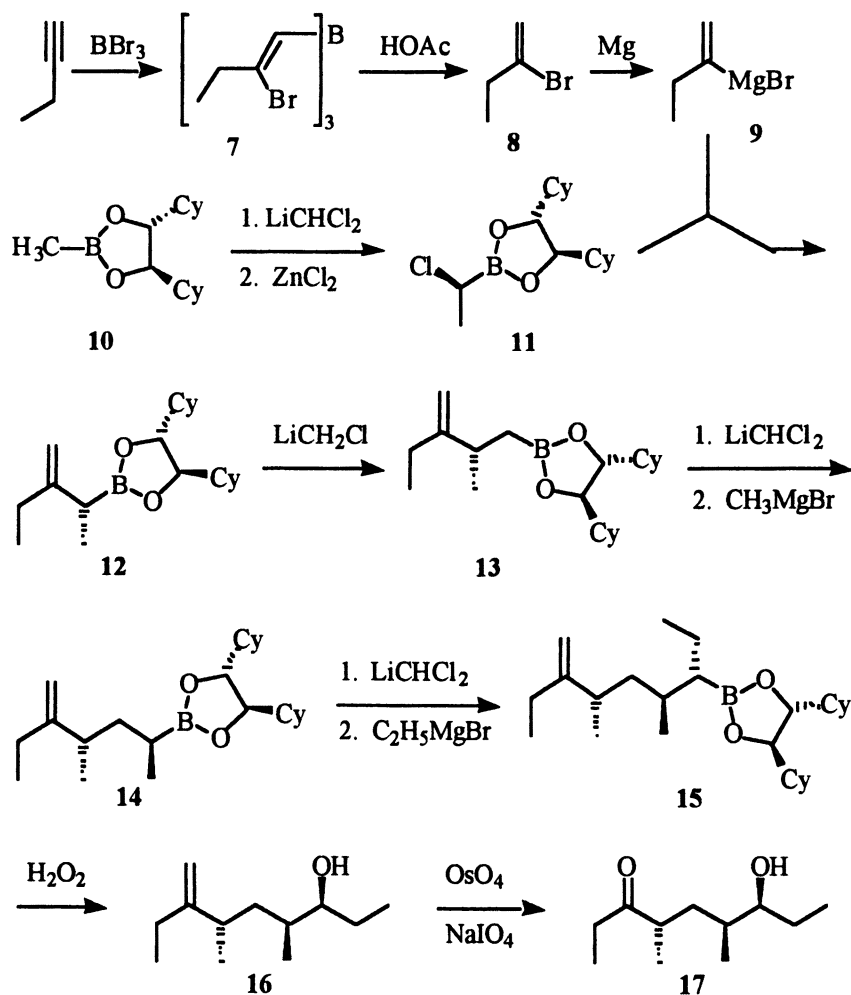
Scheme 3. *Synthesis of serricornin via boronic esters.*

It would have been possible to introduce the ketone functionality of serricornin (**17**) as a protected hydroxyl group in the manner previously described in the stegobinone synthesis (*4*). However, proceeding in linear fashion along the carbon chain would then require a change of chiral directors, because the methyl substituents at positions 4 and 6 of serricornin have opposite orientations. Removal of the chiral director *R*)-DICHED and replacement by its enantiomer (*S*)-DICHED has been accomplished (*9*), but thermodynamics disfavors hydrolysis of chiral 1,3,2-dioxaborolanes, and the inherent inefficiency of using two different chiral directors is compounded by the difficulty of removal and replacement.

An α-lithioether could combine with 2-(1-chloroethyl)-1,3,2-dioxaborolane **11** in order to accomplish the assembly of all three stereogenic centers of **17** with a single chiral director. However, use of a racemic lithioether would result in a diastereomeric mixture at the alkoxy substituent, which would complicate purification and NMR identification of the boronic ester intermediates. An enantiopure α-lithioether, whether prepared via our own route (*10*) or others, would be extra effort.

In view of the foregoing considerations, the use of an ethylenic double bond as the masked carbonyl function was selected. We had expected that hydroboration of 3-hexyne with catecholborane would yield a single stereoisomer of alkenylboronic ester **18** (X_2 = catechol) (*11*), which could be converted to pure (*Z*)-3-bromohexene via long established bromination and elimination (*12*). Much to our surprise, a gross mixture of isomers was obtained, with **19** predominating (Scheme 4). It was shown that the isomerization was caused by free radicals, but we were unable to suppress it completely. Attempted hydroboration with boron trichloride and triethylsilane (*13*) appeared to result only in addition of boron trichloride to the triple bond, but with the more reactive diethylsilane isomerically pure **18** (X = Cl, OMe) was apparently obtained. However, the boronic ester **18** (R = OMe) partially isomerized to **19** during distillation.
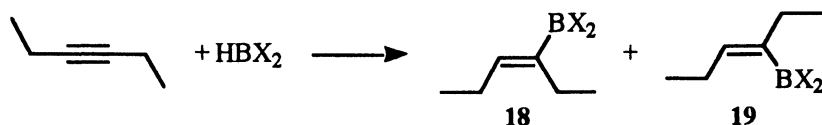
Scheme 4.*Isomerization of alkenylboranes.*

Since it would be difficult to deal with a series of pairs of geometric isomers throughout the synthesis of **17**, we turned to 2-bromo-1-butene (**8**) and the derived Grignard reagent (**9**) as the means for introducing the masked ketone functionality. No good route to pure **8** was found in the literature, and we turned to bromoboration of 1-butyne to **7** and subsequent protolysis to **8**, which proved satisfactory (Scheme 3).

Cleavage of 1,3,2-Dioxaborolanes to Boronic Acids

Hydrolysis of 1,3,2-dioxaborolanes is thermodynamically disfavored, no doubt as a result of the same kinds of entropic factors that favor formation of cyclic acetals in preference to acyclic acetals. Hydrolysis of a 1,3,2-dioxaborolane (1) converts three molecules to two, but hydrolysis of a boronic acid dimethyl ester keeps the total number of molecules at three (Scheme 5). (It may be noted that hydrolysis of a cyclic acetal with one molecule of water keeps the number of reactant and product molecules equal at two, and hydrolysis of an acyclic acetal converts two molecules to three.) Adding base does almost nothing to the equilibrium, since hydroxide ion coordinates to the boronic ester 1 as well as to the boronic acid product. Furthermore, it appears that the *trans* R^0 substituents in 1 further stabilize the structure. Chiral boronic esters of this series are harder to hydrolyze than pinacol boronic esters, and treatment of pinacol boronic esters with DICHED results in liberation of the pinacol and formation of the DICHED boronic ester.
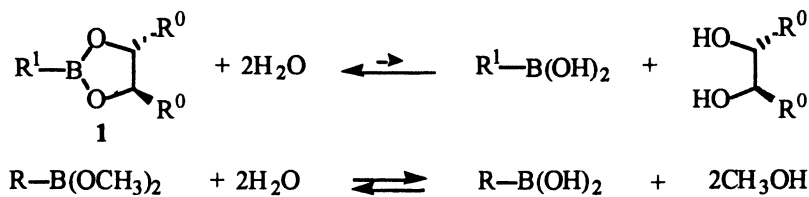
Scheme 5. *Hydrolysis of cyclic and acyclic boronic esters.*

There are several situations where cleavage of a 1,3,2-dioxaborolane to the boronic acid and diol is useful. One of these is for removal of a chiral director and replacement by its enantiomer. The first time we encountered this problem, a pinanediol ester was converted to the boronic acid via destructive cleavage of the pinanediol with boron trichloride (*14*). More recently, it has proved possible to convert an (*R*)-DICHED α-benzyloxy boronate (20) to the free boronic acid (23) with the aid of sodium hydroxide and a tris(hydroxymethyl)methane to form water soluble derivative 21 (R = CH_2OH or $NH(CH_2)_3SO_3^-$) plus water insoluble (*R*)-DICHED (22). Treatment of 23 with (*S*)-DICHED (24) then yielded diastereomer 25 (76%, 97-98% diastereomeric purity). Further chain extension and alkylation led to 26 and 27, and deboronation yielded 28, all of which are stereoisomers that could not be accessed directly with a single chiral director (Scheme 6).
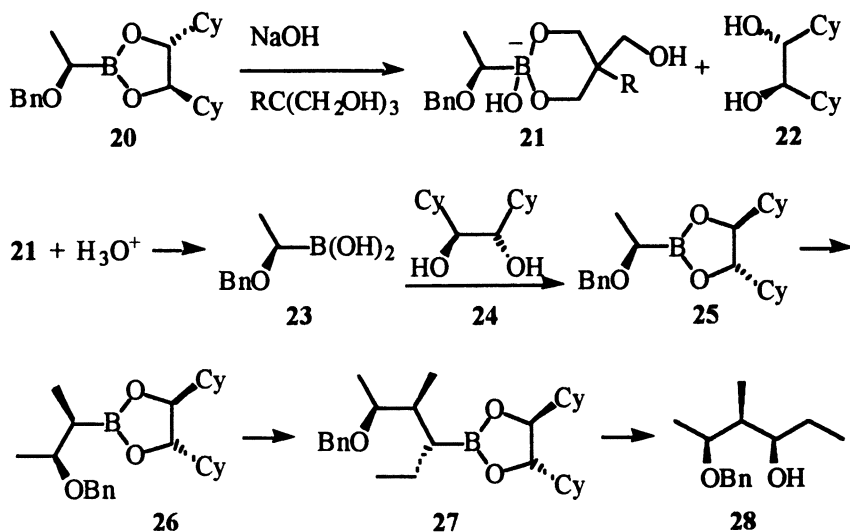
Scheme 6. *Cleavage of one enantiomer of a chiral director and replacement by its enantiomer.*

In view of the inherent inefficiency of preparing both enantiomers of a chiral director as well as the roundabout removal and replacement process, it is unlikely that changing chiral directors will prove useful for synthesizing purely organic compounds. An alternative approach to **26-28** or analogous stereoisomers is probably possible via the reaction of an asymmetric α-lithio ether with (S)-DICHED (R)-(1-chloroethyl)boronate (*10*), which would set up the relative steric relationship of **26**, though this route would not be more efficient. However, there is a potential practical application in the synthesis of boronic acid analogs of biologically significant compounds. Certain α-amido boronic acids have been found to be potent inhibitors of serine proteases such as elastase (*15*) or thrombin (*16*), and the ability to make any desired stereoisomer of a chiral boronic acid is potentially useful for making boronic acids of biological interest.

For any asymmetric boronic acid of biological interest that is synthesized via 1,3,2-dioxaborolanes, it is of course necessary to be able to remove the chiral director in order to complete the synthesis. The exchange reaction described above is useful for liberating boronic acids that are not water soluble, though it has only been proved to work with an α-alkoxy boronic ester (**20**). If the boronic acid product is water soluble, the best method for cleaving its cyclic esters is ester interchange with phenylboronic acid (*17*). This has been used for the liberation of the thrombin inhibitor DuP 714 from its pinanediol ester, illustrated in general form by the conversion of **29** to **30** (Scheme 7). The reaction is driven to completion by the extraction of the pinanediol phenylboronate into a separate

phase. This conversion is particularly noteworthy because pinanediol esters are the hardest to cleave, and the method used to convert **20** to **23** did not result in complete conversion of a pinanediol ester to the boronic acid.
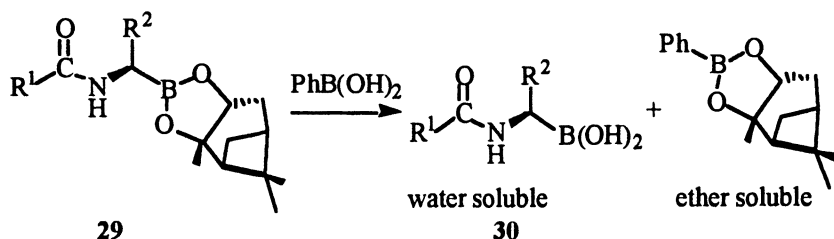
Scheme 7. Cleavage of an amido boronic ester by transesterification.

Nitrogen Functionality

The reaction of 1,3,2-dioxaborolanes with (dichloromethyl)lithium has worked best when all substituents are nonpolar and nonbasic. It is probably the zinc chloride promoted rearrangement step that is most affected, since coordination of the zinc chloride with a nucleophilic site results in a sterically bulky complex that can inhibit the rearrangement of the intermediate borate anion. This coordination was noted early in our work, as increasing amounts of zinc chloride were required as the number of benzyloxy groups increased during a synthesis of L-ribose (*18*).

During investigation of means of introducing nitrogen functionality into synthetic schemes, some of the limits of polar functionality have been encountered (*19*). Bis(trimethylsilyl)amino boronic esters are easily prepared but very labile to water and consequently difficult to purify. We did succeed in preparing the cyclic silylated (aminomethyl)boronic ester **31** in impure form, and it did undergo chain extension to **32** with (dichloromethyl)lithium (Scheme 8). Substitution of the chloride by sodiomethanethiol or lithiodimethylamine was successful, but lithium benzyl oxide failed to yield the benzyloxy derivative.
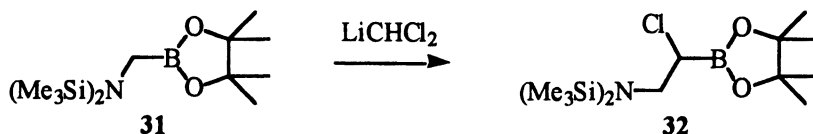
Scheme 8. Chain extension of a silylated amino boronic ester.

More hindered silylamino boronic esters such as **33** failed to undergo useful amounts of CHCl insertion with (dichloromethyl)lithium. The *O*-silylated and *N*-benzylated formamido compounds **34** and **35** likewise appeared to undergo no more than ~30% chain extension with (dichloromethyl)lithium (Scheme 9). The major difference between **31** and **33** is presumably steric, and these results are in accord with the hypothesis that the major interference to these chain extensions is steric hindrance resulting from complexation of zinc chloride with nucleophilic oxygen or nitrogen.
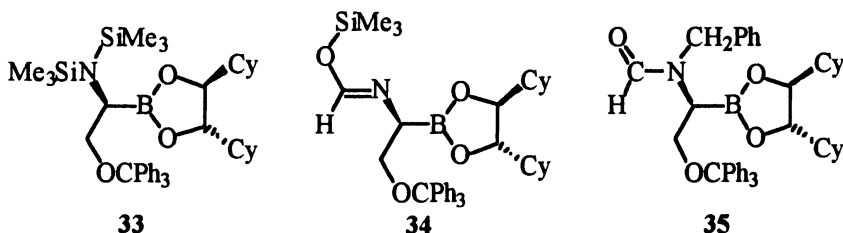
Scheme 9. *Structures which do not undergo useful reaction with LiCHCl₂.*

A somewhat less hindered amido boronic ester (**40**) has given a very low yield of homologation product, which was oxidized directly to the corresponding aldehyde **42** in an unsuccessful attempt to synthesize kainic acid (*20*) (Scheme 10). Preparation of **40** required the chain extension of the cyano substituted boronic ester **36** to **37**, which with lithiohexamethyldisilazane yielded **38**. Conversion of **38** to the acetamido derivative was followed by detritylation, methanesulfonylation, and treatment with base to form **37**, which appeared to undergo very sluggish reaction with (dichloromethyl)lithium. Conversion of **37** to the boronic acid was accomplished by the exchange with phenylboronic acid (*17*) noted in the preceding section, and the boronic acid was esterified with ethylene glycol to form **40**. The estimated yield of **42** from LiCHCl insertion was only ~6%, with the major product of the reaction sequence being **41**, the direct oxidation product of **40** (Scheme 10).

In earlier work, we had shown that α-azido boronic esters are surprisingly stable and will undergo the reaction with (dichloromethyl)lithium, albeit with some complications caused by azide reactivity (*1*). We have also used azido boronic esters as intermediates in an asymmetric amino acid synthesis (*21*). It now appears that azido boronic esters may be the best general protected amine functionality for synthetic purposes, and we will report new findings in this area shortly (*22*). Older findings with azido boronic esters as well as the compatibility or incompatibility of other polar functionality with boronic ester chemistry have been reviewed elsewhere recently in considerable detail (*23*).
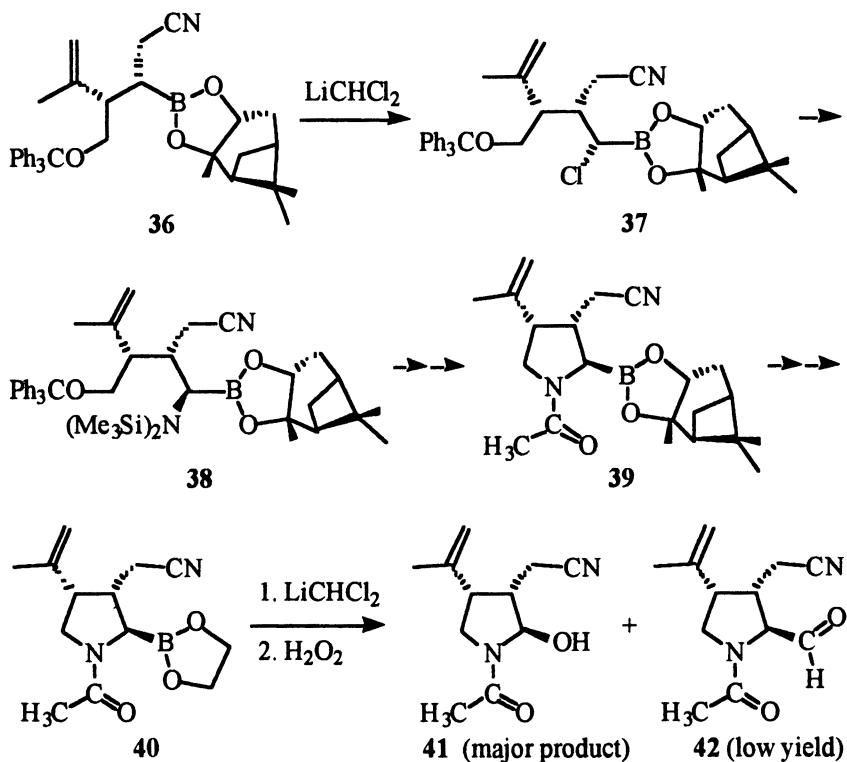
Scheme 10. *Attempted synthesis of kainic acid and failure of final carbon connection.*

An Asymmetric Cyclobutane Synthesis

As is evident from the preceding section, a cyano substituent does not interfere with the reaction of (dichloromethyl)lithium with boronic esters. However, the proton α to the cyano group can be removed by a sterically hindered strong base such as lithium diisopropylamide (LDA), and the resulting carbanion can react with the α-halo boronic ester, which provides the basis for a new ring closure process (*24*).

In earlier work, we had shown that lithium enolates of esters react with α-bromo boronic esters in a highly diastereoselective manner (*25*). A similarly high level of diastereocontrol prevails in the cyclization of cyano substituted boronic esters (*24*). We chose to concentrate first on closure of cyclobutanes,

since four-membered rings are perhaps the hardest to make by other methods in a fully stereocontrolled manner.

The route chosen to make starting materials depends on how many substituents are desired on the final product. If there are no substituents other than the cyano group and the boronic ester, or if there is only one alkyl substituent on the carbon α to the cyano group, the shortest route we found involves hydroboration of allyl bromide, for which the boron trichloride and triethylsilane method (*13*) works very efficiently. Treatment of the resulting (bromopropyl)boron dichloride with pinacol yields the boronic ester **43**.

Treatment with sodium cyanide in DMSO converts **43** to the cyano derivative. If an R group other than H α to the cyano group is desired, the cyano compound can be alkylated by treatment with LDA and an alkyl halide. Only monoalkylation was observed with either CH₃I or ICH₂CH₂OSiMe₂*t*-Bu. Transesterification with (*R*)-DICHED yields the diastereomeric mixture of cyano substituted boronic esters **44**, which with (dichloromethyl)lithium leads to the α-chloro boronic esters **45**. The absolute configuration of the stereogenic center next to the boron atom in **45** is well defined by the stereoselective CHCl insertion, and the stereogenic center adjacent to the cyano group is deprotonated and closes to postulated borate intermediate **46** (Scheme 11).
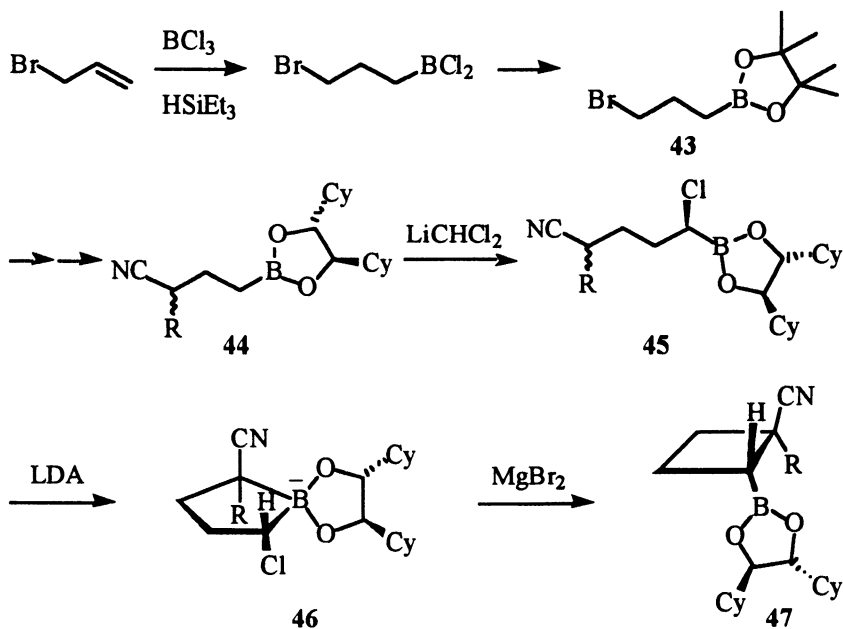
Scheme 11. Synthesis of cyclobutanes via boronic esters.

At first, yields of cyclobutanes were erratic and seemed dependent on precise adherence to arbitrary conditions as well as particular batches of commercial LDA. Ratios of cyclobutane **47** to its diastereomer were ~20:1. Freshly prepared LDA failed altogether. Addition of zinc chloride resulted in zero yield. It was then noted that the purchased LDA contained a few percent of magnesium diisopropylamide as a preservative, and that a precipitate formed in older samples of LDA. Addition of 0.1-1 equivalent of anhydrous magnesium bromide in THF after the LDA treatment was then found to result in reliable ring contraction of **46** to the (cyclobutyl)boronic ester **47**. The amount of diastereomer of **47** was too small to be detected by NMR (Scheme 11).

The potential synthetic utility of cyclobutanes of the class **47** was demonstrated by the conversion of **48** to the isopropenylcyclobutane **49** by means of the Zweifel coupling process (Scheme 12).
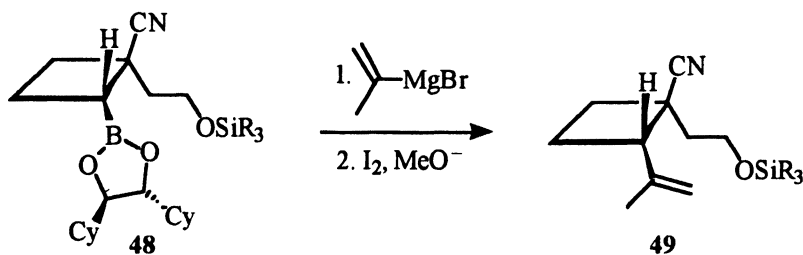
Scheme 12. Replacement of a boronic ester group by alkenyl.

If more substituents are desired, the precursor to the cyclobutane can be assembled with more chain extensions with (dichloromethyl)lithium. For example, the (bromomethyl)boronic ester **50** is easily prepared in lots >300 g (*26*). Alkylation with lithiopropionitrile yielded **51**, which was transesterified to diastereomeric mixture **52**, converted via **53** to **54** in the usual manner, and again treated with (dichloromethyl)lithium to form **55**. An analogous series without the methyl substituent was also prepared from lithioacetonitrile. Treatment with LDA led via **56** to cyclobutanes **57**. This work was done before the role of magnesium salts in the ring closure was understood, and yields of **57** were consequently not optimized (Scheme 13).

Because the conditions were not optimized by the addition of magnesium bromide, **57** were obtained together with a few percent of their diastereomers having the cyano group *cis* to the boronic ester function, and it proved possible to separate the diastereomers. The assignment of stereochemistry to **57** was aided by comparison of NOE spectra of **57** (R = OCH_2Ph) and its minor diastereomer. Comparison of the NOE spectra of a boronic ester lacking the methyl substituent α to the nitrile group, but otherwise analogous to **57** (R = CH_3), and its diastereomer also supported the assignment of a *trans* relationship between the cyano and boronic ester groups in the major isomer.
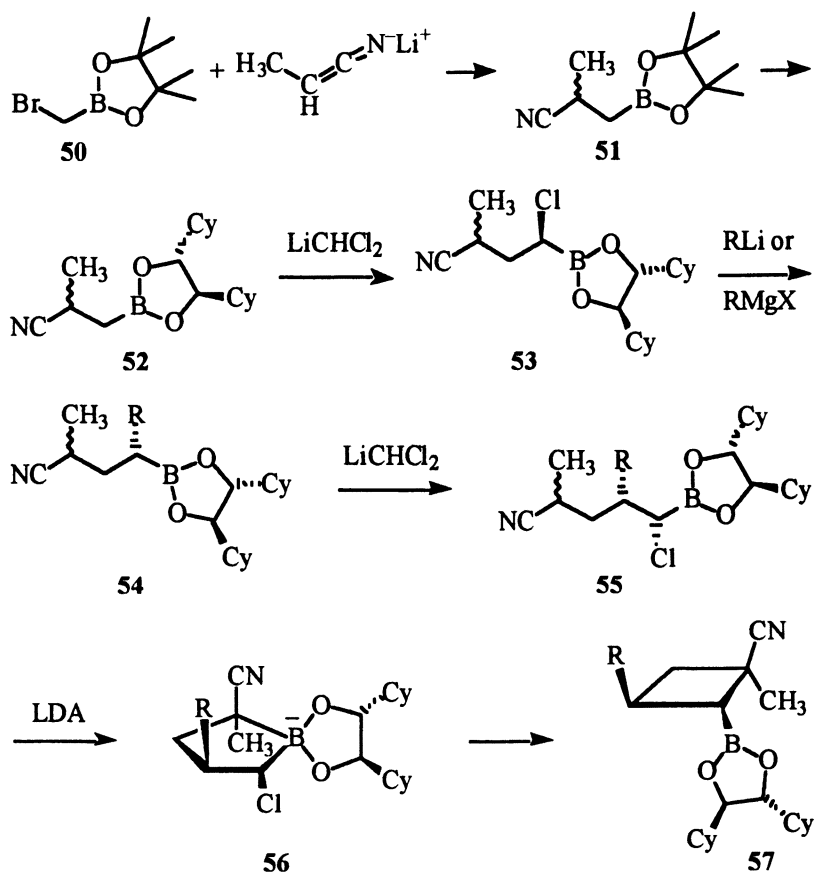
Scheme 13. *Synthesis of tetrasubstitued cyclobutanes.*

Acknowledgment

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Chapter 16

Syntheses of Chiral Lactones via Asymmetric Allylboration

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The syntheses of lactenones and lactones of different ring sizes in high enantiomeric excesses involving asymmetric allylboration with *B*-allyldiisopinocampheylborane have been described (*1*). γ-Substituted γ-butyrolactones have been synthesized from homoallyl alcohols via a protection-hydroboration-oxidation-deprotection-cyclization sequence. The unique nature of α-perfluoroalkyl homoallyl alcohols has been exploited for the synthesis of γ-perfluoroalkyl γ-butyrolactones without protecting the alcohols. Allylboration of formyl esters provide a general route to prepare ω-allyl and ω-propyllactones. The ring-closing metathesis of homoallyl enoates provides a methodology to prepare a variety of α-pyranone-containing natural products.

Introduction

Lactones are important synthons in organic chemistry (2). Scheme 1 represents some of the transformations that can be achieved via lactones. They

are also present in a large number of natural products (*3*). Accordingly, the synthesis of lactones has attracted the attention of organic chemists. Until recently, the most commonly used methodology for the preparation of chiral lactones was asymmetric reduction of keto esters (*4*) or enzymatic esterification of hydroxy esters (*5*), followed by cyclization.

(i) Dibal-H

(ii) MsCl, Et$_3$N

(i) LDA, TMSCl

(ii) PhSCH$_2$X, ZnBr$_2$

(iii) NaIO$_4$, Δ

(i) LDA, (ii) PhSeBr

(iii) H$_2$O$_2$

(i) LDA, (ii) R'X
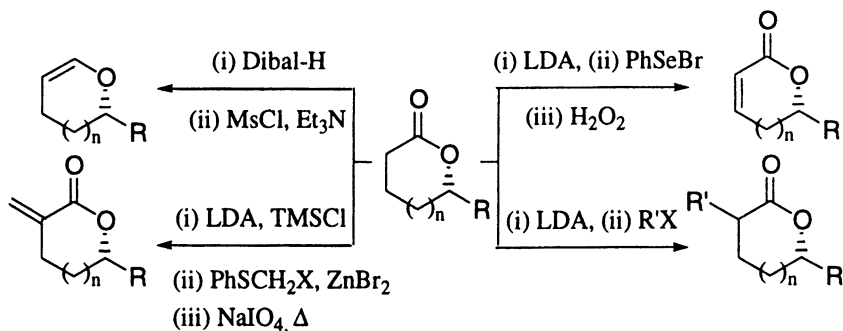
Scheme 1. Applications of lactones in organic syntheses

Recently we undertook the preparation of chiral lactones of different ring sizes utilizing chiral homoallylic alchols derived from the asymmetric allylboration of appropriate aldehydes as the starting materials (*6-8*). Our procedures are reviewed here. The application of our allylboration-esterification-ring closing metathesis reaction sequence for the synthesis of biologically active natural products (*8-11*) are also summarized.

Asymmetric Allylboration

Asymmetric allyl- and crotylboration and related reactions of aldehydes provide an excellent route for the synthesis of various types of homoallylic alcohols. During the course of our research involving pinane-based versatile reagents (PVR) for asymmetric syntheses (*12*), we have developed various allylborating agents (**1-8, 11**) (*13-20*). Several others also have contributed to the development of asymmetric allylborating agents (**9-10**) using α-pinene as the chiral auxiliary (Figure 1) (*21-22*).

1: X, Y, Z = H

2: X, Z = H, Y = Me

3: X, Y = H, Z = Me

4: X = Me, Y, Z = H

5: X = H, Y, Z = Me

6: X = vinyl, Y, Z = H

7: X, Z = H, Y = OMe

8: X, Y = H, Z = B(OR)$_2$

9: X, Y = H, Z = NPh$_2$

10: X, Y = H, Z = Cl
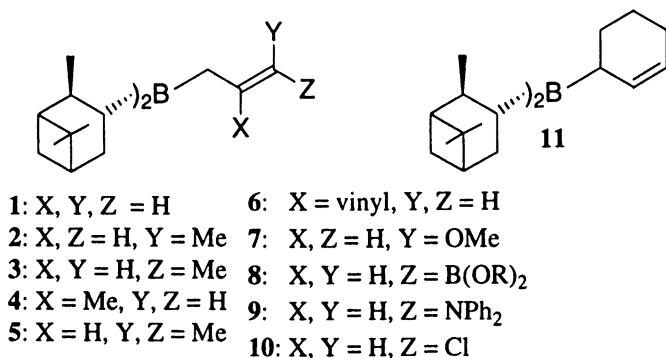
Figure 1. Pinane-based versatile reagents for allylboration

Many other allylborating agents (**12-21**) utilizing chiral auxiliaries derived from carenes, camphor, tartaric acid, stein, etc. are also known (Figure 2) (*23-33*). Recently Villieras described an ester-containing chiral allylborating agent which could be used directly for the synthesis of α-methylene-γ-butyrolactones (*32*). In this review, we have restricted our discussions to the synthesis of lactones via homoallylic alcohols derived from *B*-allyldiisopinocampheyl-borane, **1**.

14: X = O, Z = H
15: X = NSO$_2$Me, Z = H
16: X = O, Z = COOEt

20: R$_1$ = R$_2$ = Me
21: R$_1$ = H, R$_2$ = SiMe$_3$
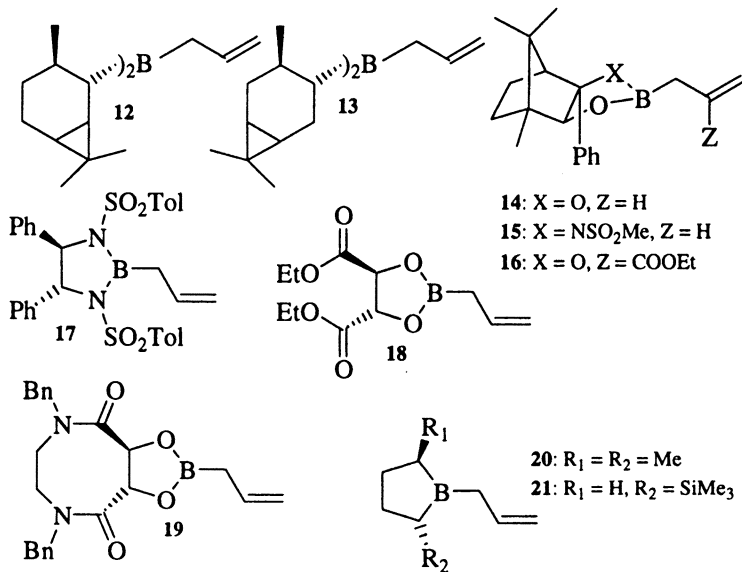
Figure 2. Reagents for asymmetric allylboration

Allylboration with *B*-Allyldiisopinocampheylborane.

Since the introduction of this reagent in 1983 (*12*), it has been utilized in key steps in several syntheses. The reagent can be prepared by the treatment of allyl Grignard reagent with either *B*-chlorodiisopinocampheylborane (DIP-Chloride™) (*34, 35*) or *B*-methoxydiisopinocampheylborane (*12*). A variety of aldehydes, including perfluoroalkyl (*36*) and heterocyclic aldehydes (*37*) have been tested with this reagent to demonstrate its capability. In all of the cases examined thus far the product homoallyl alcohols were obtained in >92% ee (Scheme 2). It has been established that in the case of chiral aldehydes, the reagent controls the diastereoselectivity (*38*).
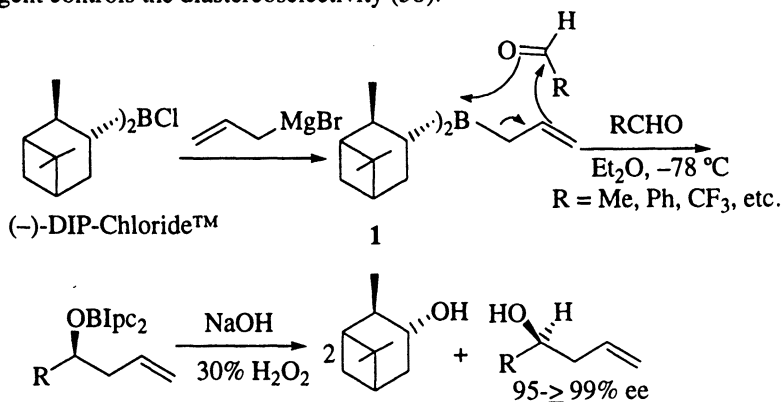
Scheme 2. Preparation and reactions of B-allyldiisopinocampheylborane

γ-Substituted-γ-lactones

Our first synthesis of lactones via allylboration involved the protection of homoallylic alcohols as a *p*-nitrobenzoate ester, followed by hydroboration with chloroborane and oxidation of the intermediate with CrO_3 in acetic acid. Deprotection under basic conditions provided the lactones in very high yields with the same enantiomeric excesses as the starting homoallyl alcohols (Scheme 3) (*6*).

Fluorinated Lactones

Due to the importance of fluorinated organic molecules in agro-, bio-, materials, and medicinal chemistry we subjected a series of fluorinated
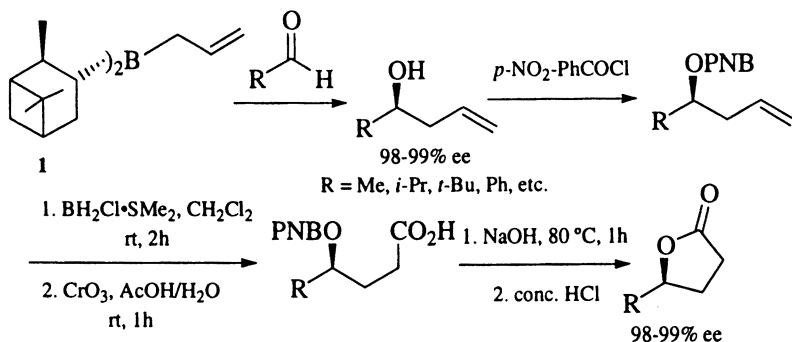
Scheme 3. Synthesis of γ-substituted γ-butyrolactones

aldehydes to the allylboration-lactonization reaction sequence. Initially, we applied the same sequence in Scheme 3 to prepare γ-perfluoroalkyl(aryl) γ-lactones. Later we modified our synthesis. The inertness of perfluorinated 2°-alcohols to Cr(VI) oxidation (39) allowed elimination of the protection-deprotection sequence. Thus, hydroboration of the homoallyl alcohols with two equiv of dichloroborane provided the corresponding intermediate, which upon Jones oxidation in the same pot afforded the lactones in 60-70% yields (Scheme 4). This one-pot procedure is not applicable to non-fluorinated alcohols.
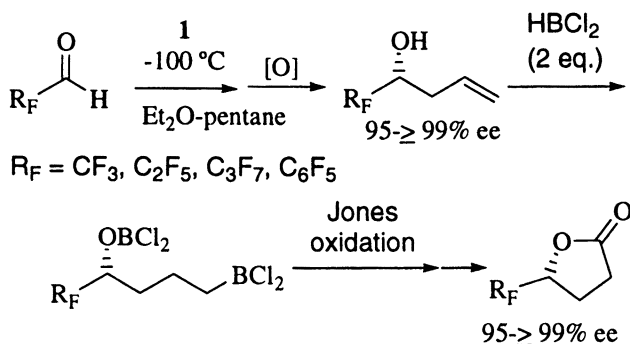
Scheme 4. Synthesis of γ-fluoroalkyl γ-butyrolactones

ω-Allyl- and ω-Propyllactones.

Asymmetric allylboration of aldehydes containing an adjacent ester group with *B*-allyldiisopinocampheylborane, followed by hydrolysis and cyclization, provides the corresponding ω-allyllactones in high yields and ≥ 92% enantiomeric excess. Hydrogenation of these lactones provides the corresponding *n*-propyllactones without any loss of optical purity (Scheme 5) (*7*).
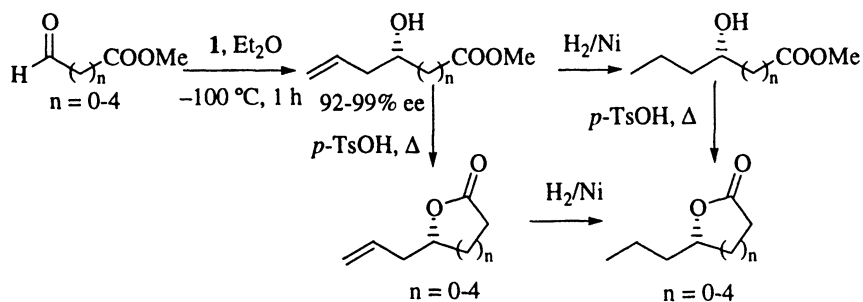
Scheme 5. Synthesis of ω-allyl and ω-propyllactones

Synthesis of α-Pyrones

Optically pure α-pyrones (5,6-dihydro-2*H*-pyran-2-ones) can be found in several biologically active natural products. Their wide range of applications include plant growth inhibitors, anti-feedal, anti-fungal and anti-tumor agents (*40-43*).

Our scheme of α-pyrone synthesis involves the esterification of homoallylic alcohols with acryloyl chloride, followed by ring-closing metathesis (RCM) using Grubbs' ruthenium catalyst (Scheme 6) (*44*). We have identified a large number of such pyrone-containing natural products that can be readily synthesized via our allylboration strategy. Representative examples of our syntheses are described below.
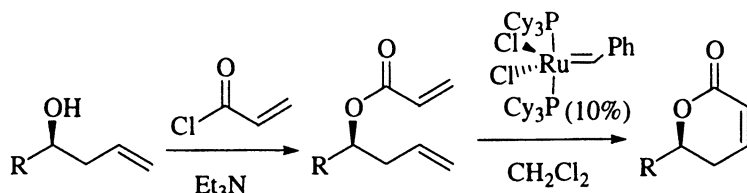
Scheme 6. Synthesis of lactenones via ring-closing metathesis

Synthesis of goniothalamin, massoia lactone, and parasorbic acid

Parasorbic acid [(S)-(+)-5,6-dihydro-6-methyl-2H-pyran-2-one, **22**] has been isolated from mountain ash berries (*sorbus aucuparia*) (*45*). Similarly, massoia lactone [(R)-(−)-5,6-dihydro-6-pentyl-2H-pyran-2-one, **23**] has been isolated from bark oil of *criptocarya massoia* (*46*), jasmine flowers (*47*), and the defense secretion of two species of formicin ants of the genus *camponotus* (*48*). Goniothalamin [(6R, 2'E)-(+)-6-(2'-Phenylvinyl)-5,6-dihydro-2H-pyran-2-one, **24**] has been isolated from several sources (*49-53*), Hexadecanolide [(S)-(−)-6-Undecyltetráhydropyran-2-one, **25**] has been isolated from the mandibular glands of the oriental hornet *vespa orientalis* (*54*). We synthesized lactenones **22-24** (Figure 3) via allylboration, as shown in Scheme 6. Hexadecanolide (**25**) was prepared by hydrogenating the corresponding lactone (Scheme 7) (*8*).

Parasorbic acid, **22**   Masoia lactone, **23**   Goniothalamin, **24**

Figure 3. α-Pyrone-containing natural products
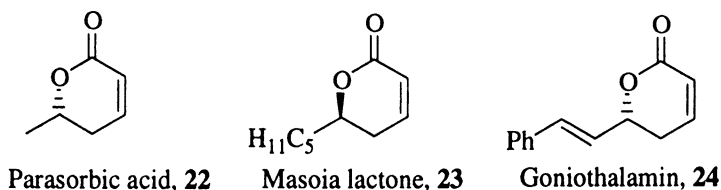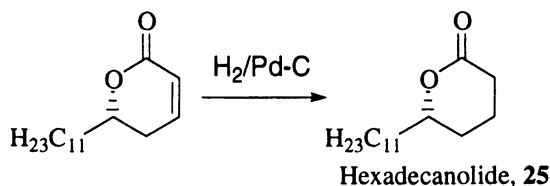
Hexadecanolide, **25**

Scheme 7. Preparation of hexadecanolide

Argentilactone

(-)-(5*R*)-5-Hydroxydodeca-*Z*,*Z*-2,6-dienoic acid lactone (argentilactone, **26**) is a major constituent of the extract of the rhizomes, *Aristolochia argentina* and the roots of a liana from French Guyana (*55*), *Annona haematantha* Miq (*56*). This compound, orginially reported as a skin irritant, has been shown to possess *in vitro* activity against various strains of *Leishmania* specie, such as *L. donovani, L. major*, and *L. amazonensis*, exhibiting a potency similar to that of N-methylglucamine antimonate (*56*).

Our synthesis of (*R*)-(-)-Argentilactone began with asymmetric allylboration of 2-octynal with (+)-*B*-allyldiisopinocampheylborane, followed by the stereoselective hydrogenation of the alkynenol in the presence of Lindlar catalyst. This was then converted to the corresponding acrylic ester, and cyclized by refluxing in dichloromethane in the presence of 10 mol% of Grubbs' catalyst to provide the natural enantiomer in 44% overall yield (Scheme 8) (*9*).
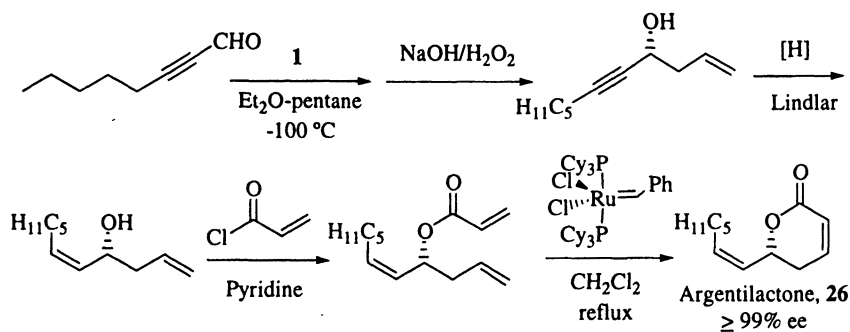
Scheme 8. Synthesis of argentilactone

Tarchonanthuslactone

Tarchonanthuslactone (**27**) has been isolated from a compositae, *tarchonanthus trilobus* (*57*). All of the known syntheses of optically active **27** reported thus far involve substrate-control and >14 steps (*58-61*). Our 7-step reagent-controlled asymmetric synthesis begins with the allylboration of acetaldehyde, followed by osmylation, periodate cleavage, a second allylboration, esterification, and ring-closing metathesis reaction sequence (Scheme 9).
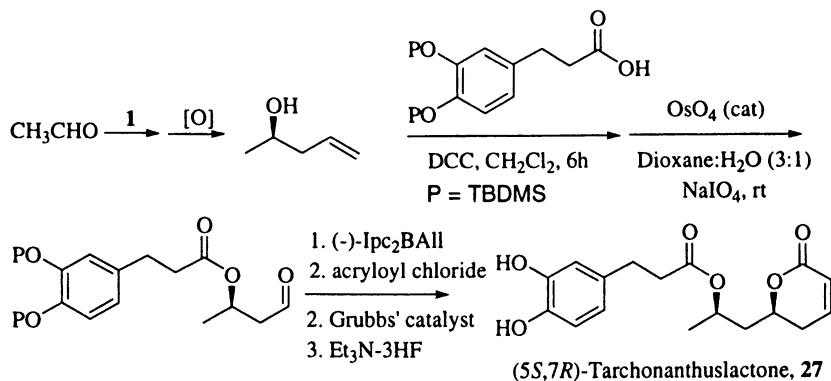
Scheme 9. Synthesis of tarchonanthuslactone

Umuravumbolide

Umuravumbolide (**28**) and desacetylumuravumbolide (**28a**) are α-pyrone containing natural products isolated from *Tetradenia* riparia found in Rwanda (Central Africa) (*62*). So far, no synthesis has been reported for this molecule. Our synthesis of this molecule involves Alpine-Borane mediated asymmetric reduction of heptyn-3-one, followed by formylation, Lindlar reduction, allylboration with **1**, and ring-closing metathesis using Grubbs' catalyst as key steps (Scheme 10) (*11*).

HMG-CoA Reductase Inhibitor Analogs

The discovery of compactin (**29a**) (*63, 64*) and mevinolin (**29b**) (Figure 4) (*65*) two decades ago as inhibitors of hydroxymethylglutaryl coenzyme A reductase revolutionized research toward the treatment of hypercholesterolemia. During this period several analogs of mevinolin and compactin, popularly known as statin drugs, have been examined, approved and marketed as cholesterol lowering pharmaceuticals (*66*).
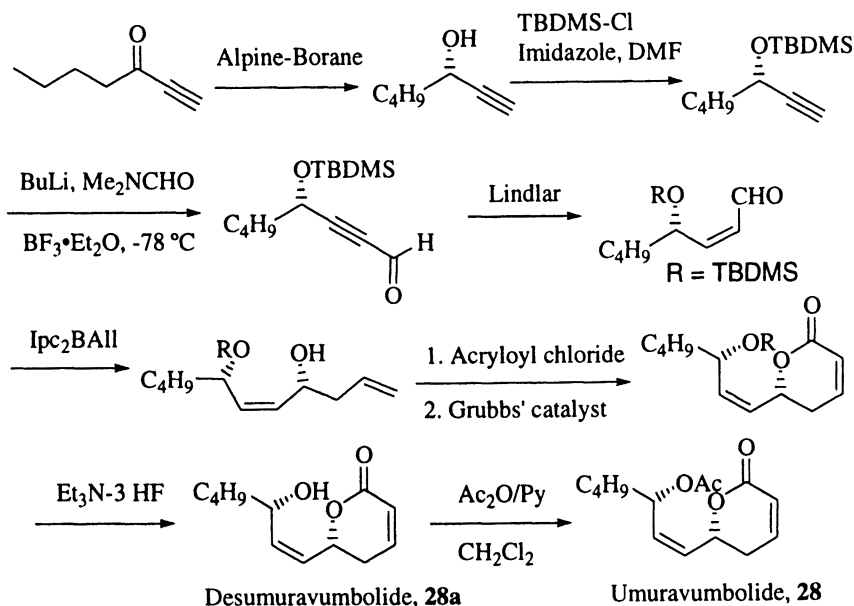
Scheme 10. Synthesis of umuravumbolide
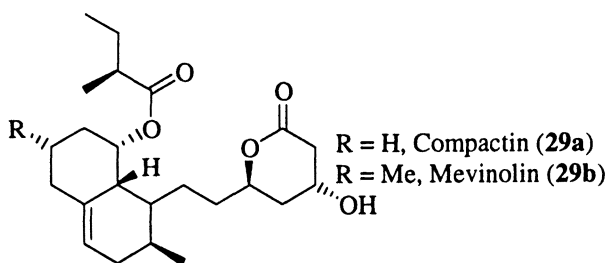
Figure 4. HMG-CoA reductase inhibitors

Systematic studies of the analogs of mevinolin have revealed that the key pharmacophore necessary for the drug action is the β-hydroxy-δ-lactone unit (67,68). Accordingly, several syntheses of this lactone unit has been reported in the literature (69-79) Our synthesis of mevinolin analogs began with allylboration of appropriate aldehydes with 1. Acrylic esters of the product homoallylic alcohols upon ring-closing metathesis in the presence of 10 mol% of Grubbs' catalyst provided the corresponding 6-substituted dihydropyran-2-ones. These were diastereoselectively epoxidized using H_2O_2 and reduced with

phenylselenium hydride to furnish products that were crystallized to yield optically pure compounds (Scheme 11).
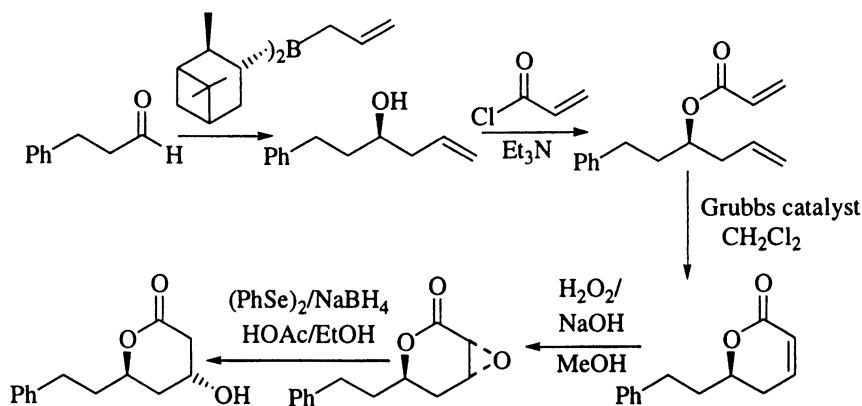
Scheme 11. Synthesis of mevinolin analogs

Synthesis of Macrolactones

We have utlized our allylboration-ring-closing metathesis strategy for the the synthesis of macrolactones, such as ricinelaidic acid lactone (scheme 12) and gloeosporone (scheme 13) (*80, 11*). These syntheses highlight the fact that allylboration-esterification with alkenoyl chloride-ring closing metathesis reaction sequences can be utilized to prepare lactones of various ring sizes.
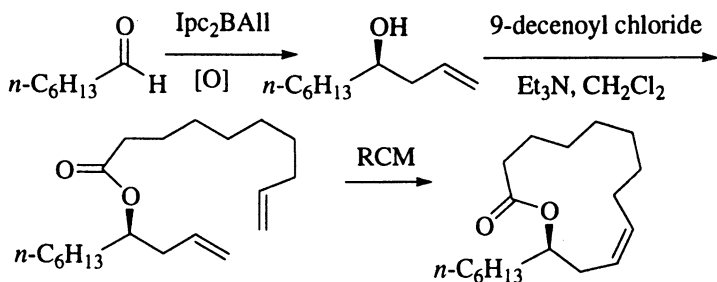
Ricinelaidic acid lactone

Scheme 12. Synthesis of ricinelaidic acid lactone.
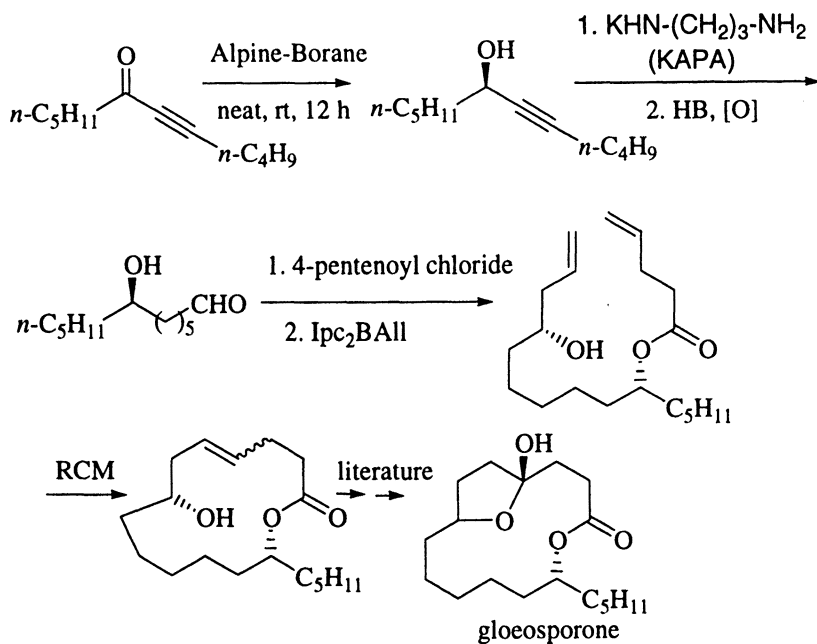
Scheme 13. Synthesis of gloeosporone

Conclusion

In conclusion, we have reviewed the utility of the products from allylboration of aldehydes with *B*-allyldiisopinocampheylborane for the synthesis of lactones of varying ring sizes. This is yet another example of the versatility of organoboranes in asymmetric syntheses.

Acknowledgment

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