

Organoboranes for synthesis—substitution with retention

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Abstract - The facile reaction of olefins, dienes and acetylenes with various hydroborating agents made a vast array of organoboranes readily available. Organoboranes tolerate many functional groups and are often formed in a stereospecific manner. The boron atom in these organoboranes can be readily substituted with a variety of functional groups to give organic compounds under mild conditions such that organoboranes now appear to be among the most versatile intermediates available for organic synthesis. Exploration of these substitution reactions revealed that the organoboranes transfer the alkyl group to essentially most of the other elements of synthetic and biological interest, including carbon, with complete maintenance of stereochemical integrity. Consequently, the organic groups that are formed stereospecifically by the hydroboration reaction can be readily incorporated into organic molecules. A recent development - preparation of optically pure organoborane intermediates - makes possible the synthesis of essentially any compound containing a chiral center in both optical isomers in essentially 100% optical purity. Thus, our research program has taken boranes from an exotic material of little interest to a reagent widely used in organic synthesis, greatly assisting chemists in overcoming synthetic difficulties.

INTRODUCTION

The remarkably facile addition of diborane in ether solvents to alkenes and alkynes was discovered in 1956 (ref. 1). For the next decade a major portion of the research effort of my students and associates was devoted to systematic studies of the scope and characteristics of hydroboration reaction. These established that hydroboration is essentially quantitative, involves a *cis anti*-Markovnikov addition from the less hindered side of the double bond and can tolerate essentially all functional groups (ref. 2). When we were exploring the hydroboration reaction, many individuals expressed skepticism to me as to the wisdom of devoting so much research effort to this reaction. After all, hydroboration produced organoboranes. At the time we started, only three things were really known about organoboranes: (1) they were oxidized by air; (2) they were stable to water; (3) they formed addition compounds with bases. Besides, relatively little new chemistry of organoboranes had appeared since the original classic publication by Frankland in 1862 (ref. 3). Many individuals took the position that the lack of published material in this area meant that there was little of value there.

In this case, it is now clear that this position is not correct. After our exploration of the hydroboration reaction had proceeded to the place where we felt we understood the reaction and could apply it with confidence to new situations, we began a systematic exploration of the chemistry of organoboranes, with emphasis on reactions of synthetic utility. A systematic study of the reactions of organoboranes revealed their exceptional versatility (ref. 2). Our studies have established that these organoboranes transfer the alkyl group to essentially most of the other elements of synthetic and biological interest with complete maintenance of stereochemical integrity. Typical transformations are indicated in Fig. 1. It is not possible here to give more than a taste of the rich chemistry. Consequently, this article is restricted to some of the substitution reactions of organoboranes that proceed with retention of configuration.

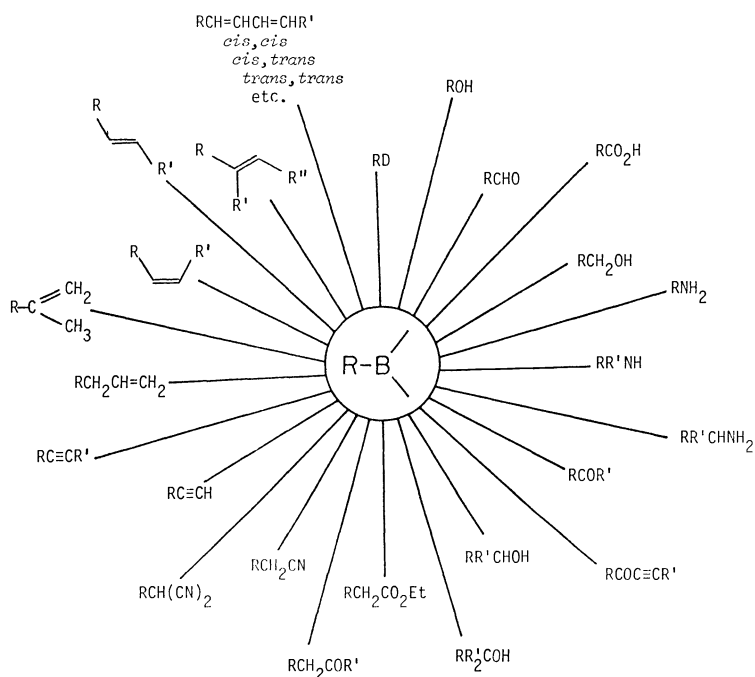
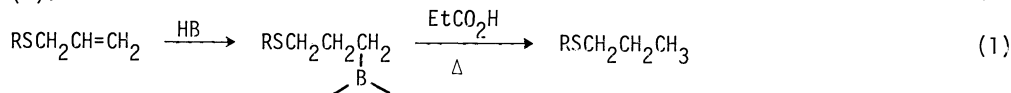


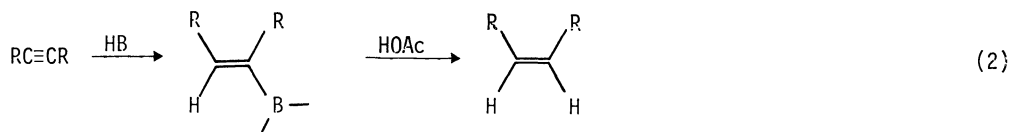
Fig. 1. Chart summarizing representative substitution reactions of organoboranes

PROTONOLYSIS

The organoboranes are remarkably stable to water, aqueous bases, and aqueous mineral acids. However, they are susceptible to protonolysis by carboxylic acids. Trialkylboranes require relatively vigorous conditions. In general, they must be heated under reflux with excess propionic acid in diglyme for 2 to 3 hours (ref. 4). This provides a convenient non-catalytic means of hydrogenating double bonds in compounds where the usual catalytic hydrogenation is difficult (1).



Vinylboranes undergo protonolysis with particular ease, providing a simple route to *cis*-olefins from the corresponding acetylenes (ref. 5) (2).



Protonolysis of organoboranes proceed with retention of configuration (ref. 4). Thus one can take advantage of the unique properties of the hydroboration reaction to achieve stereo-specific hydrogenations (ref. 6, Fig. 2).

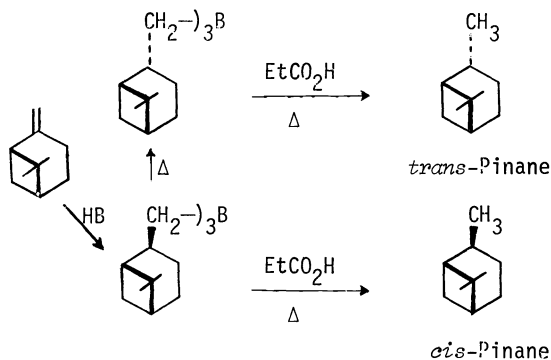


Fig. 2. Hydroboration-protonolysis of β -pinene to provide either *cis*- or *trans*-pinane as desired

Protonolysis also makes possible the stereospecific synthesis of deuterium derivatives (Fig. 3).

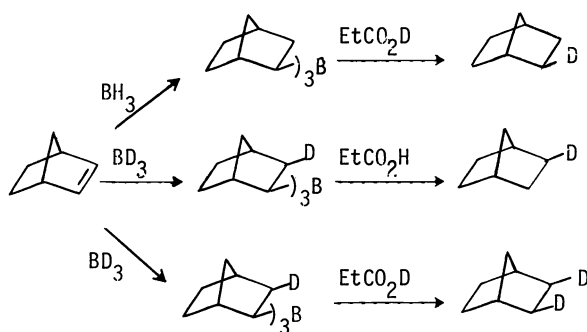
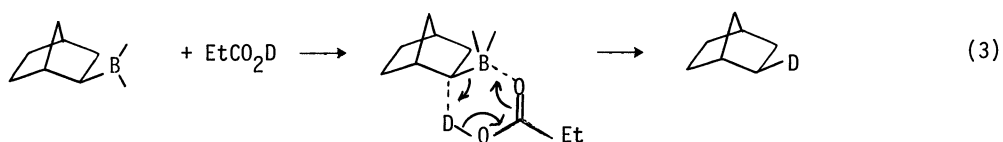


Fig. 3. Hydroboration-protonolysis of norbornene to demonstrate protonolysis with retention

The high reactivity of organoboranes with carboxylic acid is unexpected, although not unreasonable. This reactivity may be ascribed to an initial coordination of the electron-rich carbonyl oxygen of the acid with electron-deficient boron (3).



OXIDATION

The reaction of alkaline hydrogen peroxide with organoboranes is a remarkably clean reaction of wide generality (ref. 7, 8). It is essentially quantitative and takes place readily in the presence of the usual hydroboration media and can accommodate all groups which tolerate hydroboration. Alternative reagents include buffered peroxide, trimethylamine oxide and *m*-chloroperbenzoic acid (ref. 9-11). Hydroboration-oxidation studies with cyclic and bicyclic alkenes led to the generalization that the reaction proceeds with complete retention of configuration (Fig. 4, ref. 12).

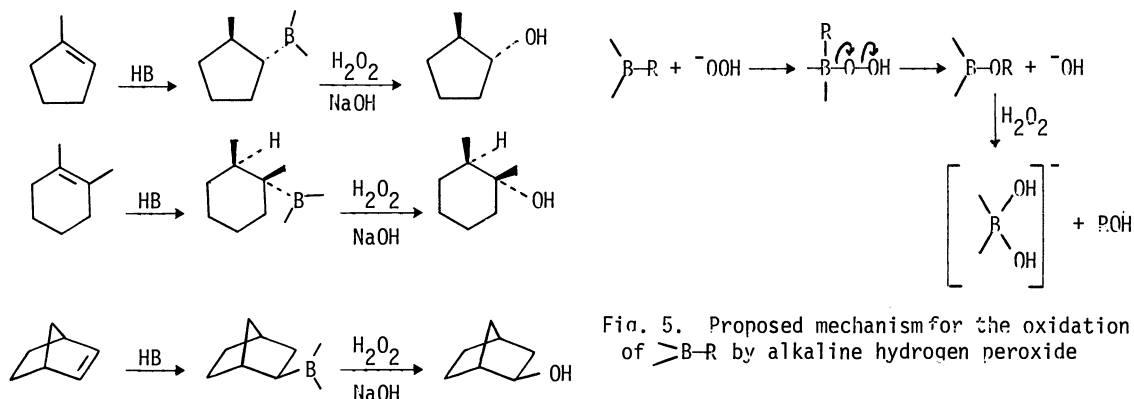


Fig. 4. Representative hydroborations-oxidations which establish retention in the oxidation stage

Consequently, hydroboration, followed by *in situ* oxidation with alkaline hydrogen peroxide, provides a simple, broadly applicable procedure to achieve the *cis*-, *anti*-Markovnikov hydration of double bonds (4).



Fig. 5. Proposed mechanism for the oxidation of >B-R by alkaline hydrogen peroxide

FORMYLATION

Carbonylation to aldehydes

Treatment of organoboranes with carbon monoxide in the presence of certain hydride reagents provides an intermediate which is oxidized to the aldehyde or hydrolyzed to the homologated alcohol derivative. The use of B-alkyl-9-BBN derivatives is especially effective in permitting complete utilization of the alkyl groups (Fig. 6, ref. 15,16).

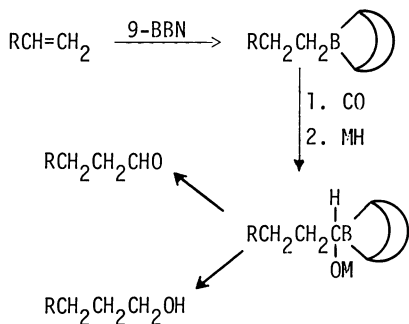


Fig. 6. Conversion of R-B via carbonylation into aldehydes or methylol derivatives

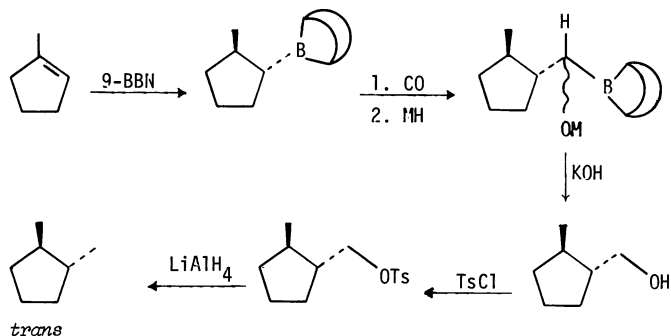


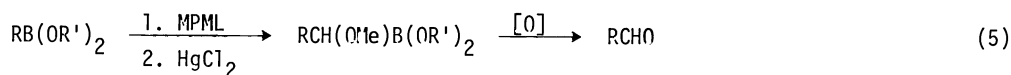
Fig. 7. Proposed mechanism for the carbonylation of organoboranes to aldehydes or methylols with complete retention of configuration

The stereospecificity realized in the hydroboration reaction is retained during the reaction (Fig. 7, ref. 17).

A possible mechanism for this reaction is that the acyldialkylborane, the first alkyl migrated product in the carbonylation reaction of trialkylboranes, is trapped by the hydride reducing agent to provide the α -alkoxy intermediate (Fig. 6).

Aldehydes from boronate esters

Alkylboronate esters are readily converted into the corresponding aldehydes by successive treatment with methoxy(phenylthio)-methyl lithium (MPML), mercuric chloride and buffered hydrogen peroxide (ref. 18) (5).



The reaction proceeds with retention of configuration at the migrating carbon atom, as observed in other related reactions of organoboranes. Thus, the *trans* geometry obtained by hydroboration of 1-methylcyclohexene is retained in the product (Fig. 8).

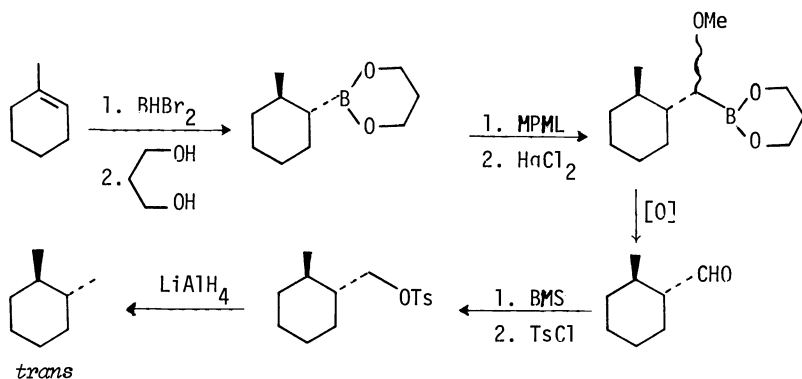


Fig. 8. Transformation of the hydroboration product from 1-methylcyclohexene into *trans*-2-methylcyclohexane carboxaldehyde with complete retention of configuration

The reaction proceeds through the intermediate formation of a stable ate complex. Addition of mercuric chloride induces the alkyl group of migration, presumably by coordinating with the sulfur atom. The α -methoxyboronate ester, upon oxidation, furnishes the aldehyde (Fig. 9).

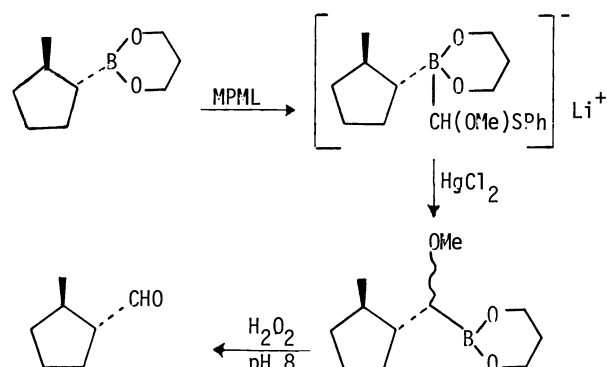


Fig. 9. Intermediates in the conversion of boron intermediates into the aldehyde by the MPML reaction

OXYCARBONYLATION

Treatment of alkylthioboronic esters with trichloromethylithium provides an intermediate which is oxidized to the carboxylic acids or hydrolyzed to the aldehyde thioacetals (Fig. 10, ref. 19).

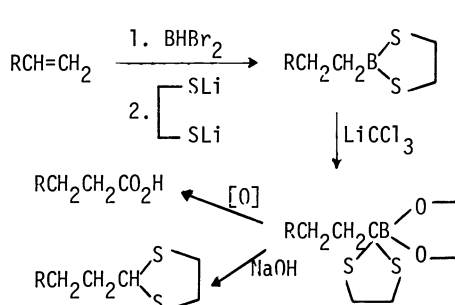


Fig. 10. Conversion of organoboranes into carboxylic acids

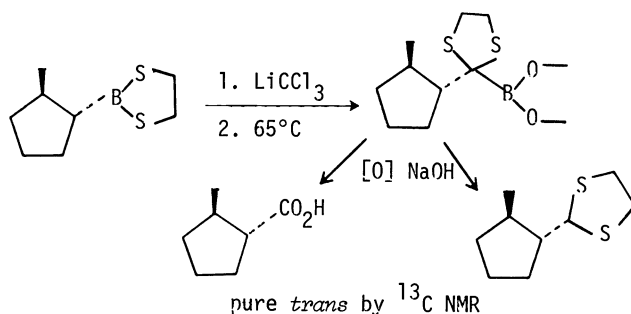


Fig. 11. Evidence that the conversion of organoborane intermediates into carboxylic acids by the MPML reaction proceeds with retention

The configuration attained by hydroboration of 1-methylcyclopentene is retained in the product (Fig. 11).

This reaction apparently proceeds through the following mechanism (Fig. 12).

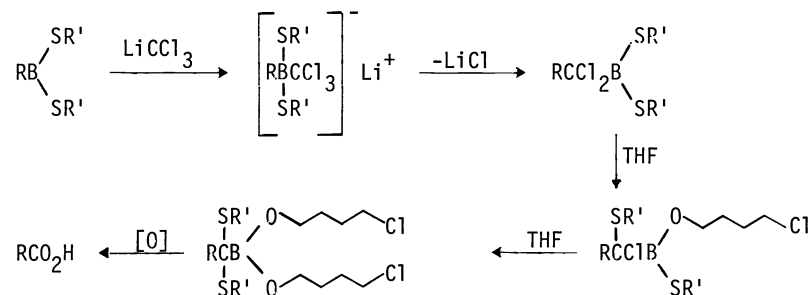
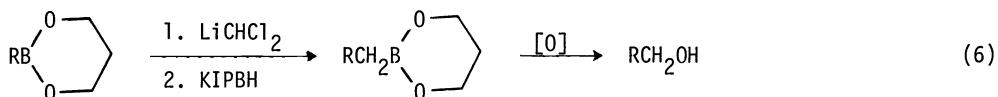


Fig. 12. Proposed mechanism for the conversion of organoborane intermediates into the corresponding carboxylic acids

Alternatively, the aldehydes obtained from the formylation of organoboranes can be easily oxidized by the two-phase chromic acid procedure to furnish carboxylic acids (ref. 20).

HOMOLOGATION TO METHYLOL DERIVATIVES

Reaction of alkylboronic esters with dichloromethyl lithium (the Matteson reaction), followed by reduction of the intermediates with potassium triisopropoxyborohydride (KIPBH), gives the corresponding one-carbon homologated boronic esters. Oxidation provides methylol derivatives (ref. 21) (6).



In this reaction also, the transfer of the alkyl group from boron to carbon proceeds with stereochemical integrity (Fig. 13). The mechanism of the reaction is given in Fig. 14.

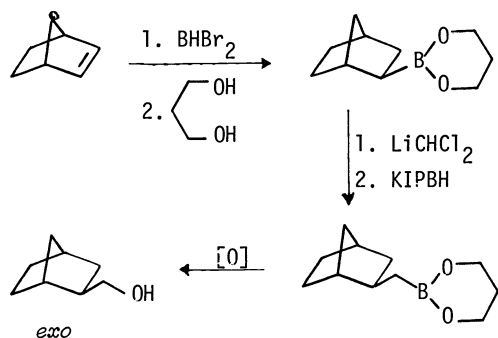


Fig. 13. Homologation of boronic esters into the higher boronic esters with retention

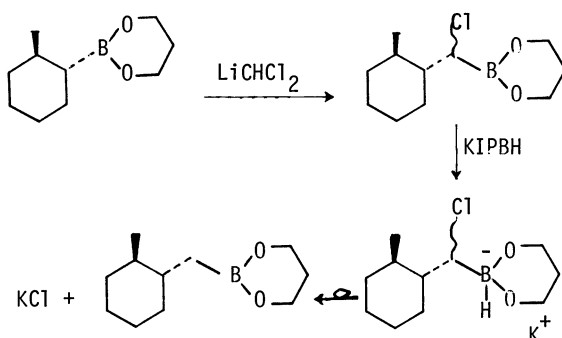


Fig. 14. Proposed mechanism homologation of boronic esters with retention

Alternatively, a one-carbon homologation of organoboranes can be achieved by the reaction with chloromethyl lithium generated *in situ* from either ClCH_2I and $n\text{-BuLi}$ (ref. 22) or ClCH_2Br and $n\text{-BuLi}$ (ref. 23).

AMINATION

Primary amines

Either chloramine or *o*-hydroxylamine sulfonic acid (HSA) can be used to convert organoboranes into the corresponding amines (ref. 24). The use of dimethylalkylboranes is especially effective in permitting essentially complete utilization of the alkyl groups (ref. 25) (7).



The reaction proceeds with retention of configuration, making it possible to retain the remarkable stereospecificity of the hydroboration reaction (Fig. 15). The reaction is believed to involve a mechanism similar to that postulated for oxidation with hydrogen peroxide (Fig. 16).

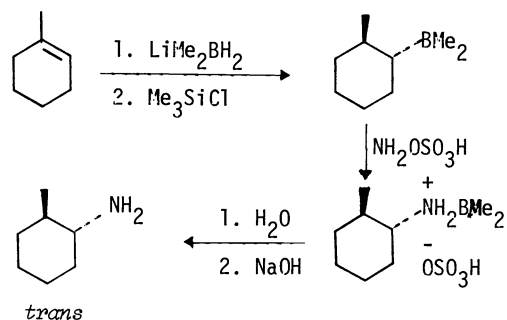


Fig. 15. Amination of organoborane intermediates with retention of configuration

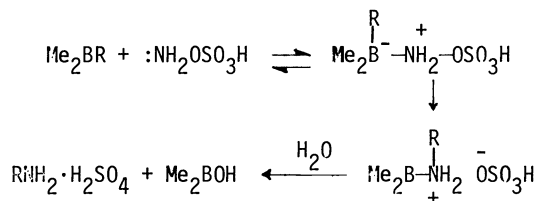
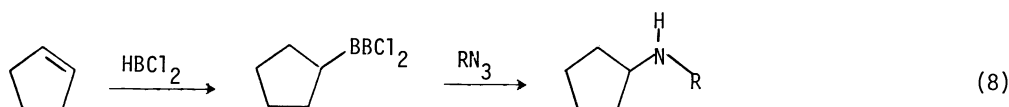


Fig. 16. Proposed mechanism for the amination reaction

Secondary amines

The reaction of organic azides with organoboranes, preferably the monoalkyldichloroboranes, provides a convenient route to secondary amines (ref. 26) (8).



This procedure provides a simple route to pure *N-exo-norbornyl* aniline, corresponding to retention in the reaction of the *exo-norbornyl* boron moiety produced in the hydroboration (Fig. 17). Experimental data for this reaction is consistent with a mechanism involving Lewis acid complexation (Fig. 18).

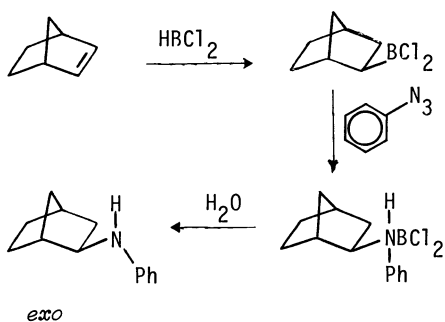


Fig. 17. Synthesis of secondary amines with retention from organoborane intermediates and organic azides

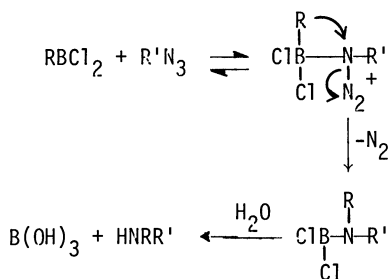
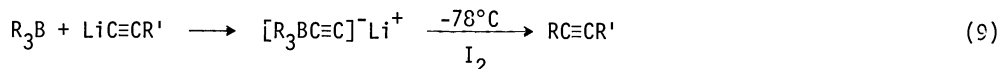


Fig. 18. Mechanism for the synthesis of secondary amines

ACETYLENE SYNTHESIS

The ate complex formed by the reaction of an organoborane with a lithium acetylide reacts readily with iodine at -78°C to give the corresponding acetylene (ref. 27) (9).



The reaction makes possible the ready synthesis of some acetylenes that would otherwise be difficult to prepare (Fig. 19).

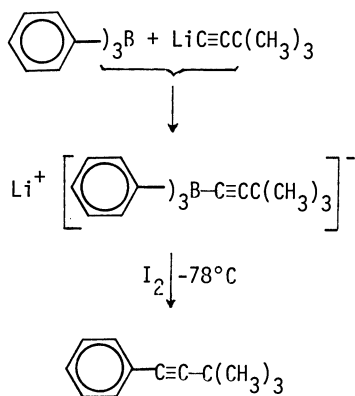


Fig. 19. Simple synthesis of phenyl-*tert*-butyl-acetylene

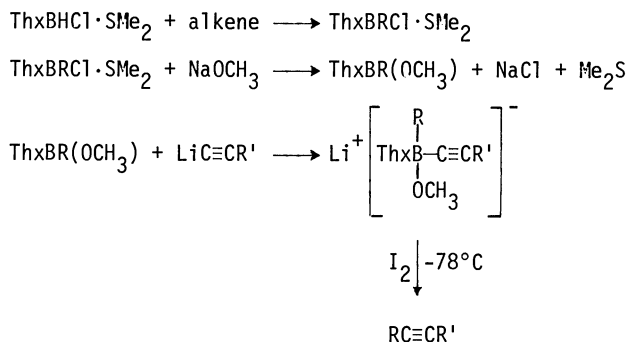


Fig. 20. Improved procedure for the synthesis of acetylenes avoiding the R groups

This procedure involves the loss of two of the three organic groups on boron. Fortunately, a recent development allows one to avoid such loss (Fig. 20, ref. 28).

Use of lithium acetylide-ethylene diamine makes possible the synthesis of simple acetylenes (ref. 27). Application of the reaction to 1-methylcyclopentene established that the reaction proceeds with complete retention of configuration (Fig. 21).

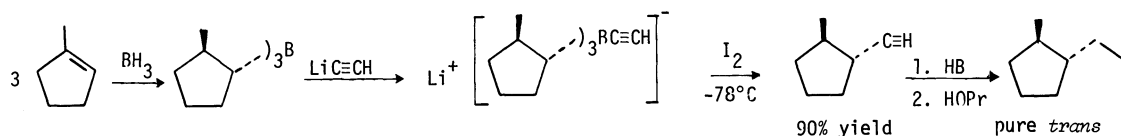


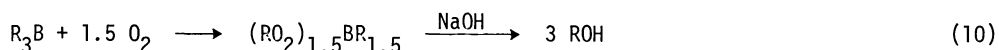
Fig. 21. Acetylene synthesis proceeds with retention

SUBSTITUTION WITHOUT RETENTION

Whereas the great majority of the substitution reactions of organoboranes proceed with complete retention, a few reactions are known which proceed with loss of stereochemical integrity or with inversion.

Oxidation by oxygen

Organoboranes can be quantitatively converted into alcohols by the controlled treatment with air or molecular oxygen (10, ref. 29).



The formation of the peroxy intermediate proceeds through free radical intermediate, resulting in a loss of the stereochemical integrity of the final product (Fig. 22).

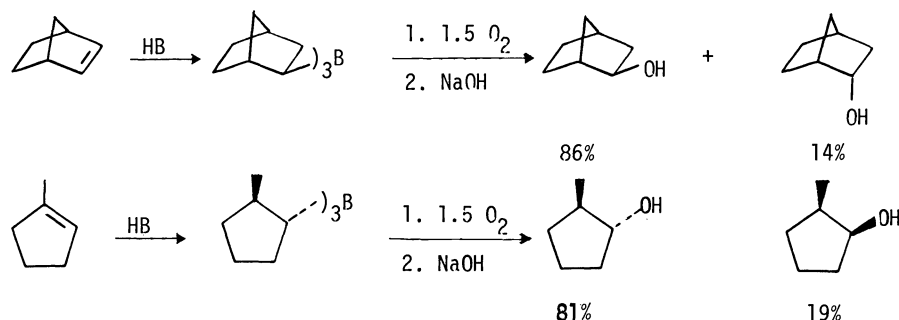
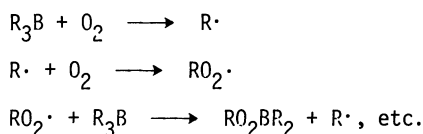


Fig. 22. Oxidation of organoboranes by molecular oxygen proceeds with loss of stereochemical identity

It is important that the oxidation by alkaline hydrogen peroxide, which proceeds with complete retention of configuration (ref. 8) be carried out with complete exclusion of atmospheric oxygen.

REACTION OF R_3B WITH CONJUGATED ALDEHYDES AND KETONES

The treatment of organoboranes with acrolein or other α,β -unsaturated carbonyl compounds likewise proceeds through free radical intermediates (11, ref. 30,31).



The reaction appears to involve an interesting type of chain reaction (Fig. 23).

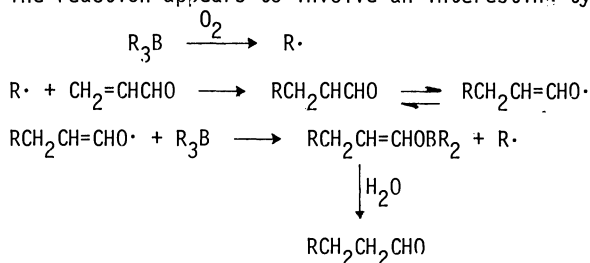
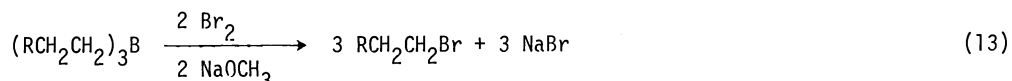
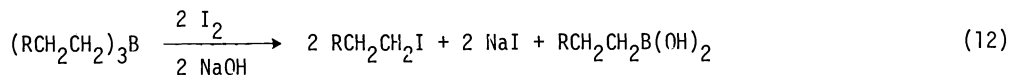


Fig. 23. Proposed mechanism for the reaction of organoboranes with conjugated aldehydes and ketones

Although this point does not appear to have been examined critically, it is probable that the reaction will involve the same kind of loss of stereochemical identity in the alkyl groups as has been established for the reaction of organoboranes with oxygen.

CONVERSION OF ORGANOBORANES TO HALIDES

In the presence of alkali, organoboranes, R_3B , readily react with bromine or iodine to give the corresponding halides, RBr and RI (12,13, ref. 32,33).



The reaction is more sluggish for secondary alkyl groups. Somewhat surprising, the bromination of *exo*-norbornyl boron derivatives proceeds with predominant inversion to yield *endo*-norbornyl bromide, the inverted product (Fig. 24).

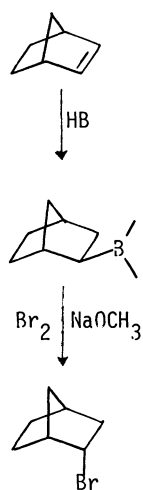


Fig. 24. Inversion in the conversion of *exo*-norbornyl boron intermediate into the norbornyl bromide

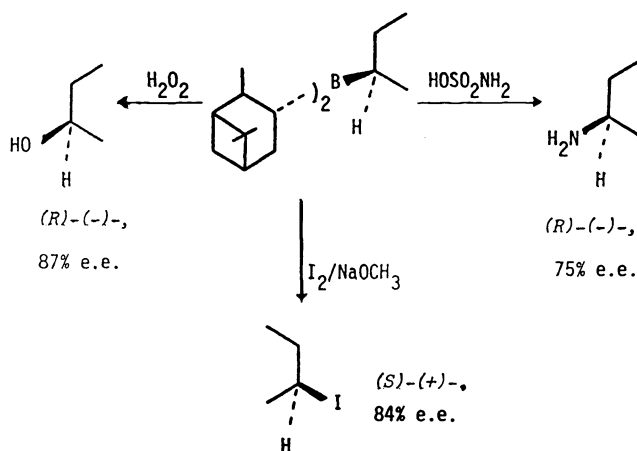


Fig. 25. An example of inversion as contrasted to predominant retention in the substitution reactions of organoboranes

As a final example, it may be mentioned that the observation that the chiral intermediate, 2-butyldiisopinocampheylborane, is readily converted into optically active 2-butanol (ref. 35) and optically active 2-aminobutane (ref. 36), both with complete retention of configuration, but into 2-iodobutane (ref. 37) with complete inversion of configuration (Fig. 25).

A GENERAL ASYMMETRIC SYNTHESIS

The realization that the great majority of the substitution reactions of organoboranes proceed with retention made it evident that if we could learn to achieve the synthesis of optically active groups attached to boron, we could transfer those groups to carbon and other elements to permit a general synthesis of optically pure enantiomers.

Our approach has been to emphasize the synthesis of optically active hydroborating agents by practical hydroboration of appropriate terpenes. These reagents are then used to hydroborate alkenes to produce the desired optically active alkyl group attached to boron (ref. 38). An alternative approach has been utilized by D. S. Matteson and his coworkers (ref. 39). They have synthesized esters of boronic acids, $RB(OH)_2$, with appropriate chiral diols and then treated these esters with lithium dichloromethide. Subsequent treatment of the intermediate with $R'Li$ or $RMgX$ provides the optically active intermediate, $RR'C^*HB(OH)_2$. Since Matteson is presenting his approach at IMEBORON VI, we shall concentrate on the hydroboration approach in the present treatment.

ASYMMETRIC HYDROBORATION— Ipc_2BH

In our original study of hydroborations with optically active Ipc_2BH (ref. 35), we used reagent prepared from commercial α -pinene of relatively low enantiomeric purity ($\sim 93\%$). However, we have now learned to prepare reagent of high enantiomeric purity from such α -pinene. The reagent is equilibrated at 0°C with 15% excess α -pinene. The major isomer becomes incorporated into the crystalline reagent, leaving the minor isomer in solution (Fig. 26, ref. 40).

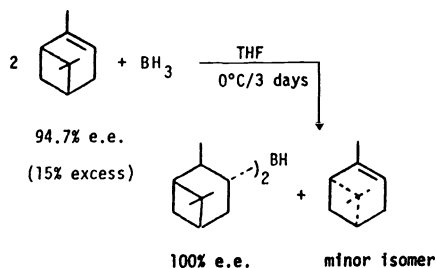


Fig. 26. Preparation of pure diisopinocampheylborane

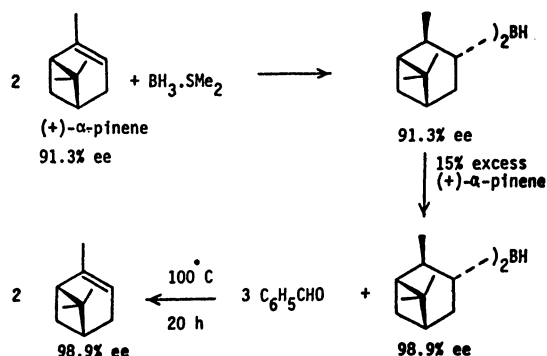


Fig. 27. Preparation of α -pinene of high optical purity

Treatment of Ipc_2BH with benzaldehyde liberates α -pinene of $\sim 100\%$ ee. Thus the two reactions provide a convenient procedure for upgrading commercial α -pinene to an enantiomeric purity of essentially 100% ee (Fig. 27, ref. 41,42).

Improved asymmetric results were realized in the hydroboration of *cis*-alkenes with this improved reagent and a somewhat lower hydroboration temperature (-25°C) (Fig. 28, ref. 43).

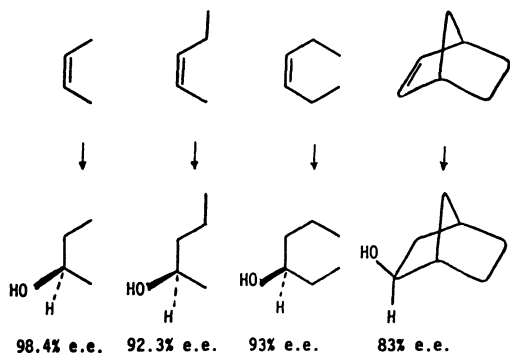


Fig. 28. Asymmetric hydroboration of *cis*-alkenes with Ipc_2BH

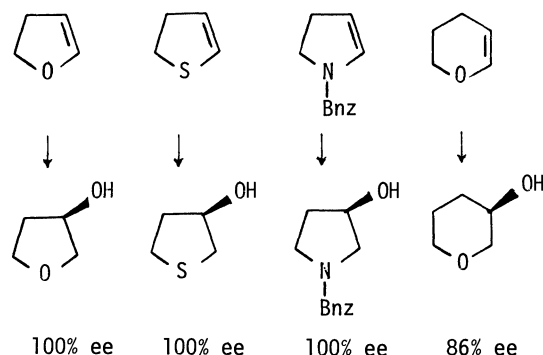


Fig. 29. Asymmetric hydroboration of some heterocyclic alkenes

Hydroboration of heterocyclic olefins with Ipc_2BH is both highly regio- and enantioselective. Thus asymmetric hydroboration of 2,3-dihydrofuran, followed by oxidation of the intermediate, provides 3-hydroxytetrahydrofuran in essentially 100% ee (Fig. 29, ref. 44,45).

Diisopinocampheylborane handles *cis*-alkenes very effectively. However, it is not an effective asymmetric hydroborating agent for 2-methyl-1-alkenes, *trans*-alkenes and trisubstituted alkenes. Evidently the steric requirements of 2-methyl-1-alkenes are too low to provide a good steric fit with the reagent. On the other hand, the steric requirements of *trans*- and trisubstituted alkenes appear too large for the reagent. It appeared that monoisopinocampheylborane, IpcBH_2 , might be more effective for the latter types of alkenes (Fig. 30).

Increasing Steric Requirements	2-METHYL-1-ALKENE	$\sim 20\%$ e.e.
	<i>cis</i> -ALKENES	$\sim 100\%$ e.e.
	<i>trans</i> -ALKENES	$\sim 20\%$ e.e.
	TRISUBSTITUTED ALKENES	$\sim 20\%$ e.e.

Will IpcBH_2 handle more hindered classes?

Fig. 30. Ipc_2BH handles only one class effectively

ASYMMETRIC HYDROBORATION—IpcBH₂

It is difficult to halt the hydroboration of α -pinene at the monoalkylborane stage. Consequently, IpcBH₂ must be prepared by an indirect route. Treatment of Ipc₂BH with one-half molar equivalent of *N,N,N',N'*-tetramethylethylenediamine (TMED) provides 2 IpcBH₂·TMED. The diastereomeric adduct crystallizes out in enantiomerically pure form. The pure reagent, IpcBH₂, is readily liberated by treating the adduct with boron trifluoride etherate (Fig. 31, ref. 46).

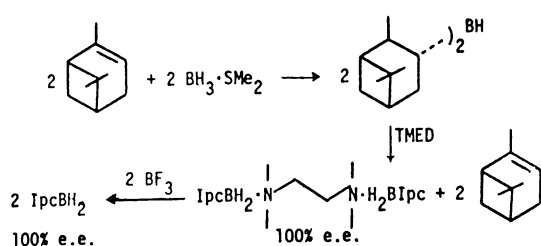


Fig. 31. Synthesis of IpcBH₂ in 100% ee

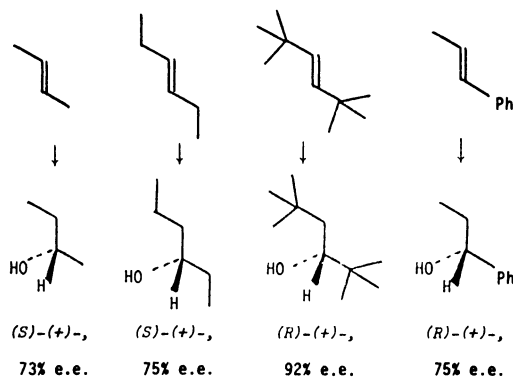


Fig. 32. Asymmetric hydroboration of *trans*-alkenes with IpcBH₂

Monoisopinocampheylborane is very effective for the asymmetric hydroboration of *trans*-alkenes (Fig. 32, ref. 47).

Similarly, the hydroboration of trisubstituted alkenes with IpcBH₂, followed by oxidation of the intermediate organoboranes, provides the corresponding alcohols in 53-72% ee (Fig. 33, ref. 48,49).

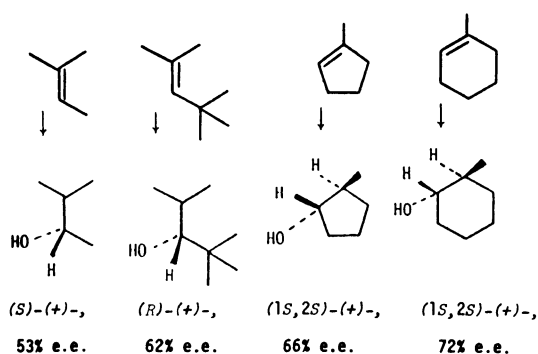


Fig. 33. Asymmetric hydroboration of tri-substituted alkenes with IpcBH₂

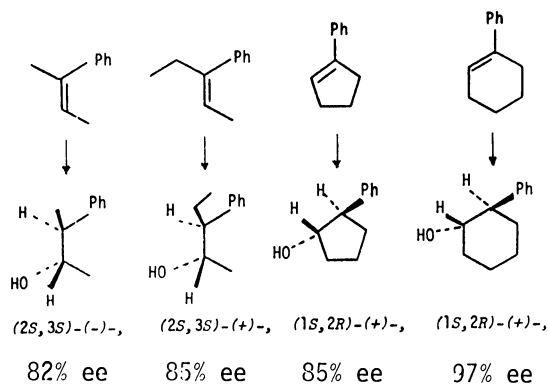


Fig. 34. Asymmetric hydroboration of tri-substituted alkenes with a phenyl substituent by IpcBH₂

For some reason, the asymmetric hydroboration of the phenyl derivatives provides considerably improved asymmetric synthesis. For example, 1-phenylcyclopentene provides the hydroboration product in 85% ee. Possibly the greater steric requirements of the phenyl group or the π -cloud provide a more optimum fit with the reagent (Fig. 34, ref. 50,51).

It appears that Ipc₂BH and IpcBH₂ are complementary to each other. Excellent results are realized in the case of unhindered *cis*-olefins by using a reagent with large steric requirements, Ipc₂BH. On the other hand, hydroboration of olefins with larger steric requirements is more favorable with a reagent of lower steric requirements, IpcBH₂. These two reagents handle three of the four major classes of alkenes. There remains a need for a reagent which will provide access to products of high ee from alkenes of relatively low steric requirements such as the 2-methyl-1-alkenes (Fig. 35). However, as discussed later, we have developed an alternative solution to this problem.

CLASS	Ip _c ₂ BH	Ip _c BH ₂
	2-METHYL-1-ALKENE	~ 20% e.e.
<i>cis</i> -ALKENES	~ 100% e.e.	~ 25%
<i>trans</i> -ALKENES	~ 20% e.e.	70-90% e.e.
TRISUBSTITUTED ALKENES	~ 20% e.e.	60-100% e.e.

Fig. 35. Range of applicability of Ip_c₂BH and Ip_cBH₂

Fig. 35. Range of applicability of Ip_c₂BH and Ip_cBH₂

A NEW ASYMMETRIC HYDROBORATING REAGENT

Recently Masamune and coworkers have reported an alternative approach to asymmetric hydroborating agents (ref. 52). Instead of relying on optically active terpenes to provide the active R₂BH reagents, they undertook to synthesize such a reagent. 2,5-Dibromohexane was converted into the di-Grignard reagent. This was treated with Cl₂BNEt₂ to form the three isomeric *B*-methoxy-2,5-dimethylborinanes. By appropriate use of three complexing agents, *N,N*-dimethylethanolamine, (+)-prolinol and (-)-valinol, these three isomers were separated and resolved (Fig. 36).

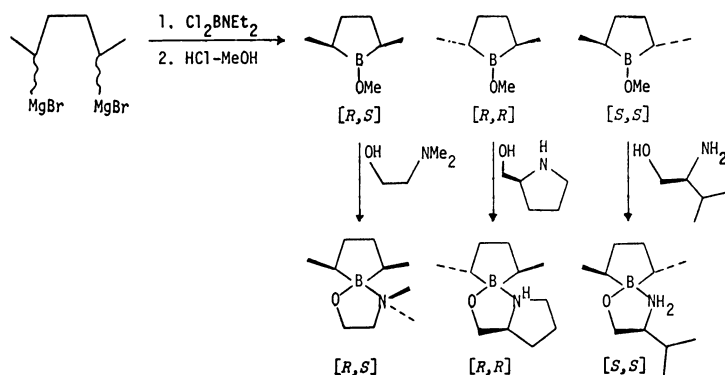
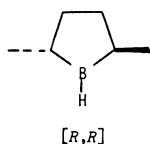


Fig. 36. Synthesis of a new asymmetric hydroborating agent

Utilizing a reaction to be discussed later, they converted the desired isomer into an optically active hydroborating agent.



This reagent yielded excellent results in the hydroboration of three of the four representative classes of olefins. Only 2-methyl-1-alkenes proved resistant (Fig. 37).

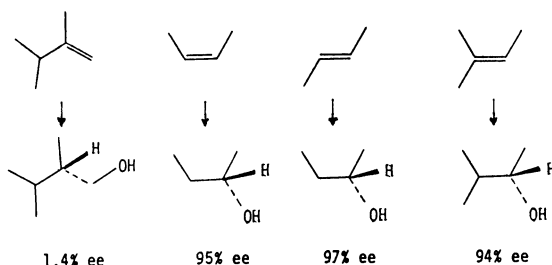


Fig. 37. Asymmetric hydroboration with the Masamune reagent

It has not yet been established whether this new hydroborating agent can be recycled in the manner to be discussed later for diisopinocampheylborane.

ASYMMETRIC BORONIC AND BORINIC ACIDS

Initially, the application of chiral organoboranes was limited primarily to alcohols because of the presence of the isopinocampheyl groups on boron in the product. Recently we discovered that these groups can be selectively eliminated by treatment of the mixed chiral organoboranes with acetaldehyde, regenerating α -pinene, and providing the optically active boronate as the product. In this way, 2-butylidiisopinocampheylborane is readily converted into diethyl 2-butylboronate in 97% ee (Fig. 38, ref. 53).

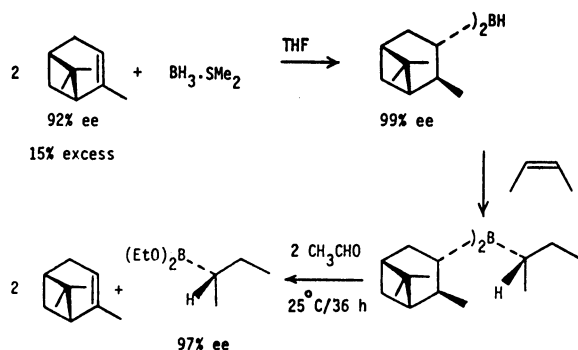


Fig. 38. Asymmetric hydroboration with Ipc_2BH with regeneration of the α -pinene

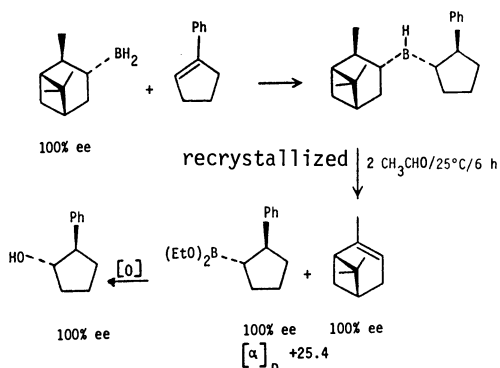


Fig. 39. Asymmetric hydroboration with IpcBH_2 with regeneration of α -pinene

Similarly, diethyl *trans*-2-phenylcyclopentylboronate can be obtained in 100% ee (ref. 51). The elimination of the isopinocampheyl group is highly selective. Indeed, in all cases we have studied thus far, this group is eliminated in preference to the desired chiral group (Fig. 39, ref. 53,51).

It should be noted that in this synthetic approach the chiral auxiliary, α -pinene, is readily recovered and recycled (Fig. 40)

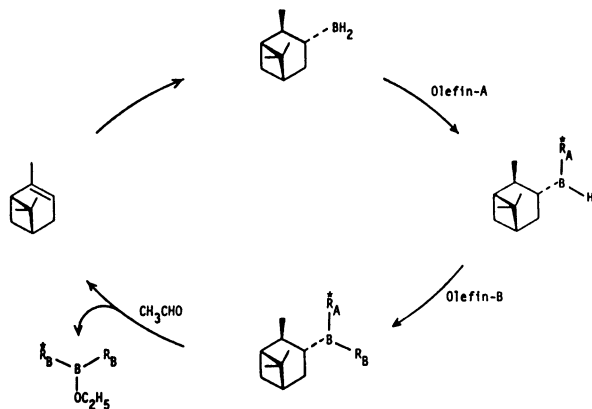


Fig. 40. Easy recycle of the chiral auxiliary

It was apparent that if we could control the hydroboration step to yield boron intermediates of 100% ee this chemistry would provide a major synthetic route to the preparation of optically pure enantiomers.

GENERAL ASYMMETRIC SYNTHESIS

A recent development in our laboratories offers promise of a general synthesis of essentially any organic compound containing an asymmetric center in 100% ee. Either of the two enantiomers can be produced as desired. Consequently, it would appear that for the first time we have within our grasp a rational synthesis of almost any organic compound with an asymmetric center in 100% ee.

As discussed earlier, asymmetric hydroboration of alkenes with either Ipc_2BH or IpcBH_2 as appropriate provides the corresponding chiral organoborane containing the new alkyl group R^* in from 53 to 100% ee. While this is encouraging, it would be more desirable to have the alkyl group R^* available in all cases in 100% ee. Once the group is on boron, it can be transferred to carbon and many other elements of interest with essentially complete retention of activity.

It was noted that the hydroboration products of both Ipc_2BH and IpcBH_2 are often solids. Consequently, instead of oxidizing the entire reaction product, providing us with the total ee achieved, we undertook to separate the crystalline product from the total hydroboration product. We achieved organoboranes containing the R^* group in essentially 100% ee (Fig. 41, ref. 54).

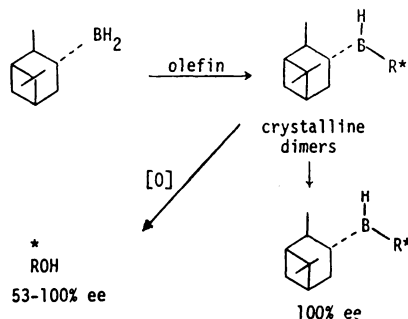


Fig. 41. Major improvement in optical purity afforded by recrystallization of the hydroboration product

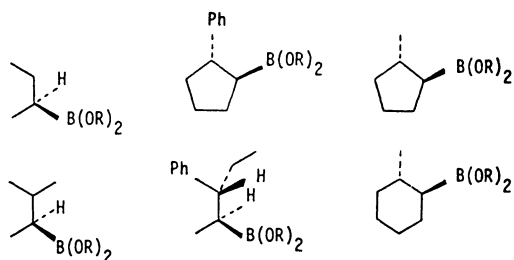


Fig. 42. Optically pure boronic esters

We are now in position to obtain both the initial hydroboration product, IpcR^*BH , and the derived boronic esters in a state of high optical purity, essentially 100% ee (Fig. 42, ref. 54).

It should be noted that we achieve predominant formation of the desired optical isomer by utilizing the appropriate hydroborating agent from either (+)- or (-)- α -pinene. We then bring it to 100% ee by a crystallization of the hydroborating product. Once we obtain the boron intermediate, IpcR^*BH or $\text{Ipc}_2\text{R}^*\text{B}$, optically pure, we can remove the Ipc groups by treatment with an appropriate aldehyde. This provides us with chiral boronic esters in 100% ee (Fig. 42).

Fortunately, there are now a number of reactions which can be applied to boronic esters. Thus they are readily converted into aldehydes, R^*CHO , and these can either be reduced to alcohols, $\text{R}^*\text{CH}_2\text{OH}$, or oxidized to carboxylic acids, $\text{R}^*\text{CO}_2\text{H}$ (Fig. 43, ref. 55). These chiral boronic esters of 100% ee can be converted into chiral ketones of 100% ee (Fig. 44, ref. 56).

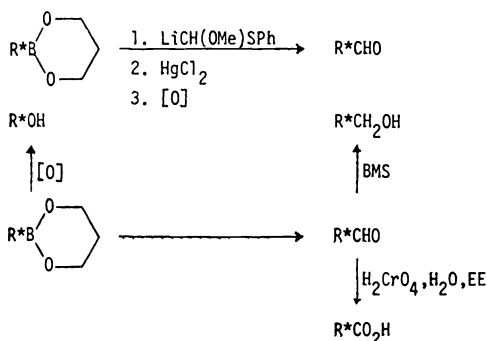


Fig. 43. Conversion of optically active boronic esters into optically active aldehydes, acids and methylol derivatives of essentially 100% ee

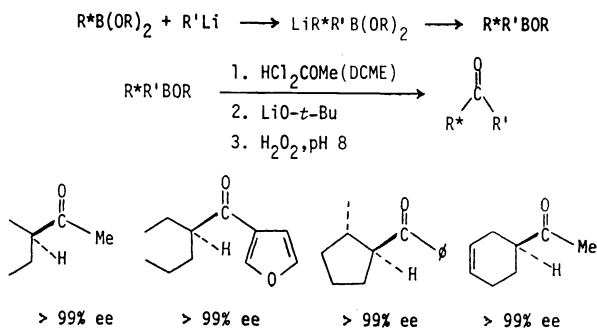


Fig. 44. Synthesis of optically active ketones of essentially 100% ee

We can adopt the Matteson homologation reaction to achieve the synthesis of optically active boronic esters, making available the β -chiral boronic esters (ref. 57). A second operation provides the γ -chiral boronic ester (Fig. 45).

Treatment of boronic esters with lithium aluminum hydride provides the optically active borohydrides, LiR^*BH_3 . By an appropriate choice of the ester group, the aluminum by-product, Al(OR)_2 , readily precipitates from solution (Fig. 46, ref. 58).

We are now in position to make all of the boron reagents we had previously found valuable to achieve syntheses *via* organoboranes without loss of alkyl groups (Fig. 47, ref. 59).

To illustrate, in the past the synthesis of amines from organoboranes invariably resulted in the loss of approximately 50% of the organic groups attached to boron. Such a loss is highly undesirable for 100% ee organic groups. We can avoid any loss by the procedure indicated (Fig. 48, ref. 60).

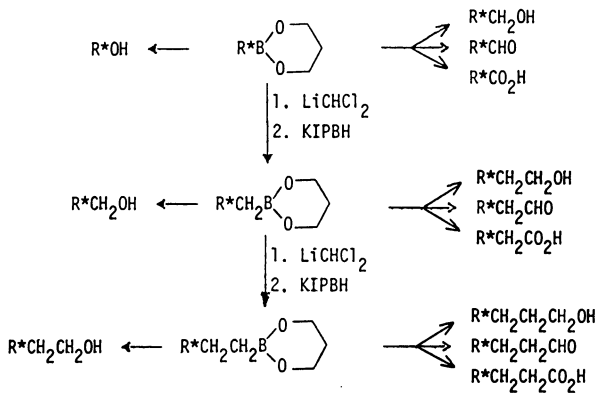


Fig. 45. Synthesis of optically active derivatives *via* successive homologations

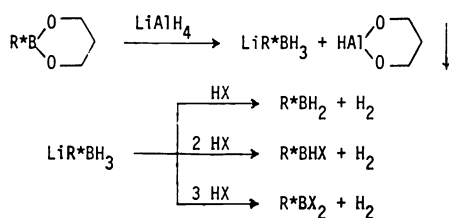


Fig. 46. Conversion of optically active boronic acids into optically active borohydrides and derived boranes

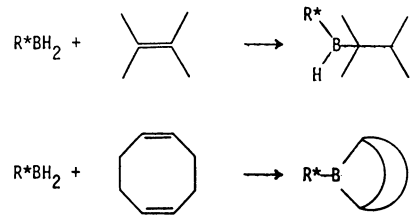


Fig. 47. Synthesis of optically active thexyl and 9-BBN derivatives

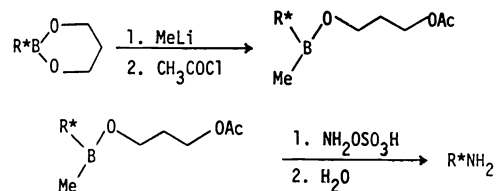


Fig. 48. Procedure for the synthesis of primary amines in high enantiomeric purity

IMPLICATIONS

Now we are in position to obtain by relatively simple procedures a wide variety of organic groups of 100% ee attached to boron, $R^*B\leq$. We have simple procedures to convert these into our common reagents, $R^*B(OR)_2$, LiR^*BH_3 , R^*BH_2 , R^*BHX , R^*BX_2 , $R^*B\text{---}$, $R^*HB\text{---}$, R^*RBOR , LiR^*RBH_2 , R^*RBH and R^*RBX .

An important characteristic of the reactions of organoboranes and of these organoboron reagents is that in almost all reactions the organic group transfers from boron to other elements, including carbon, with complete retention of configuration. Consequently, it should be possible to duplicate Fig. 1 in optically active form, Fig. 49. This is now the main center of our efforts.

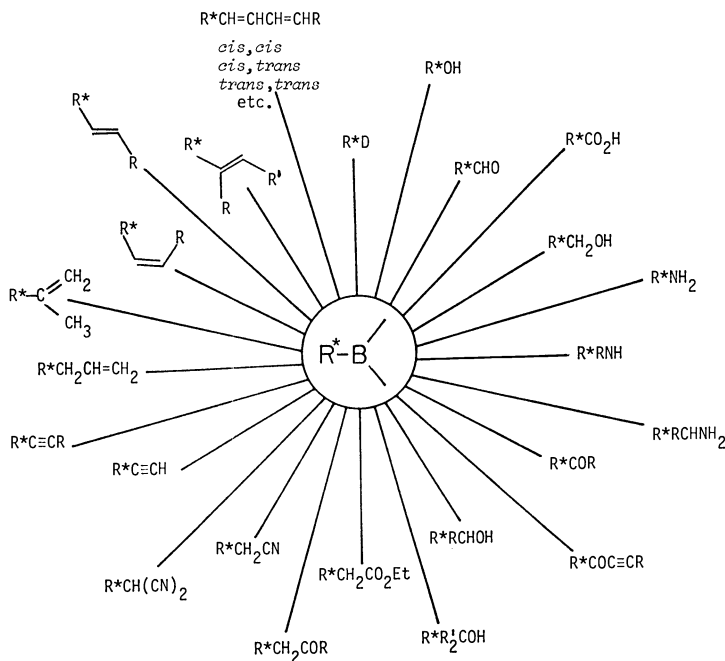


Fig. 49. Borane chemistry makes possible a general synthesis of optically pure enantiomers

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