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Recent advances in the boron route to asymmetric synthesis

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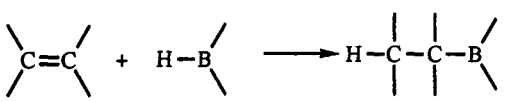
Abstract: Chiral organoboranes, readily available *via* asymmetric hydroboration or the Matteson asymmetric homologation reaction, have been successfully utilized for a general asymmetric synthesis of pure enantiomers. The recent continued successes achieved in our three-pronged approach to asymmetric synthesis – (1) asymmetric hydroboration, (2) asymmetric reduction, and (3) asymmetric allyl- and crotylboration, coupled with developments in asymmetric homologation, reveal the broad scope of these methodologies for the synthesis of stereoisomers in purities approaching 100 % ee.

INTRODUCTION

It was serendipity that we discovered the hydroboration reaction (1), the remarkably facile addition of diborane in ether solvents to alkenes and alkynes (eq 1).



(1)

This reaction was initially received without enthusiasm. Little was known about the chemistry of organoboranes. But, we studied the characteristics of hydroboration systematically (2). These studies gave birth to several new reagents. Systematic study of the organoborane products made available by hydroboration revealed their remarkable versatility (3) (Fig. 1). An unexpected feature revealed by these studies was the fact that the 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 (Fig 2).

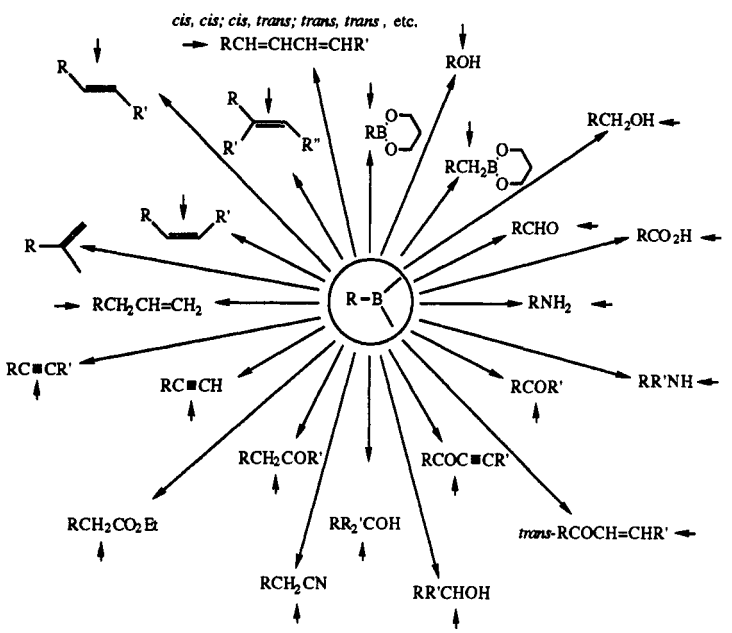


Fig. 1. Chart showing representative transformations of organoboranes.

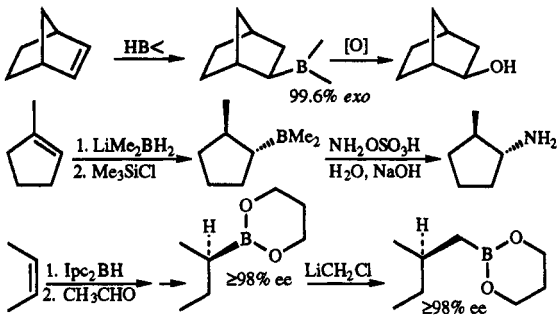


Fig. 2. Substitution reactions of organoboranes proceed with retention in configuration.

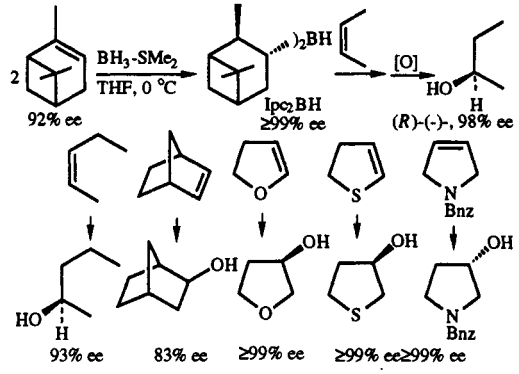


Fig. 3. Asymmetric hydroboration-oxidation of *cis*-alkenes including heterocyclics with optically pure Ipc_2BH.

ASYMMETRIC HYDROBORATION

The discovery of asymmetric hydroboration marked the beginning of practical asymmetric synthesis and a new era in organic chemistry. It began with a study of the hydroboration of α-pinene, a reaction carried out to test for possible rearrangements during the hydroboration of sensitive olefins. This experiment led to diisopinocampheylborane, Ipc_2BH, which hydroborated *cis*-2-butene to provide 2-butanol (after oxidation) in 87% ee, the highest asymmetric yield ever achieved at the time (4a). This result was even better than it appeared since the α-pinene used to prepare the reagent was only 92% ee. Later we developed procedures for preparing Ipc_2BH of ≥99% ee (4b), which provided 2-butanol of 98% ee (4c) (Fig. 3). The reaction is general for most types of *cis*-olefins, including heterocyclic olefins (4d) (Fig. 3).

However, Ipc_2BH failed for the asymmetric hydroboration of other more hindered classes of olefins. Evidently, the effectiveness of the asymmetric hydroboration depends upon a fit between the steric requirements of the alkyl groups of the olefin and the hydroborating agent. This led to monoisopinocampheylborane, $IpcBH_2$, as a useful reagent for the asymmetric hydroboration of more hindered *trans*- and trisubstituted olefins (5) (Fig. 4).

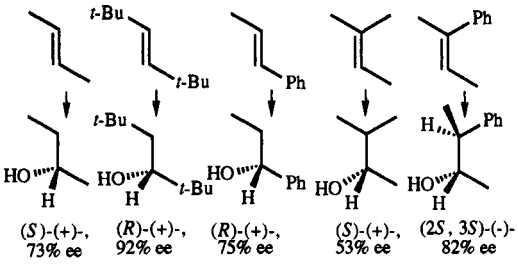


Fig. 4. Asymmetric hydroboration of *trans*- and trisubstituted olefins with $IpcBH_2$.

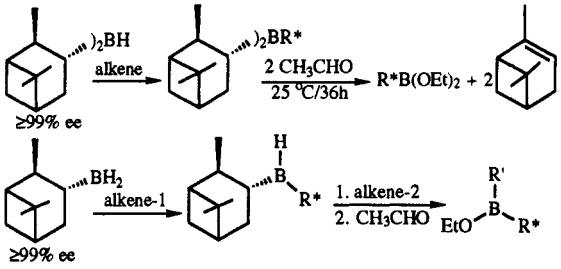


Fig. 5. Synthesis of optically pure boronates and borinates. Recovery of the chiral auxiliary, α-pinene.

A GENERAL ASYMMETRIC SYNTHESIS

Initially, the application of chiral organoboranes was limited to the synthesis of alcohols. It was desirable to recycle the chiral auxiliary (α-pinene) and to use the R*B<, free of the chiral auxiliary for further modification. We successfully achieved both of these aims and developed procedures to convert the trialkylboranes Ipc_2BR^* and IpcBR*R' to $R^*B(OR)_2$ and R*R'BOR, optically active boronates and borinates, respectively, by treatment with an aldehyde (6) (Fig. 5). A bonus in this reaction was the easy recovery of the chiral auxiliary, α-pinene, without loss of optical activity. These boronates and borinates could be easily converted into optically active mono- or dialkylboron intermediates readily utilized in our program on general asymmetric synthesis via chiral organoboranes (Fig. 6). The small arrows in the chart indicate the syntheses that have already been demonstrated.

Recent applications in asymmetric synthesis: Around Figure 6.
A decade ago, we began our systematic program of transforming the chiral boron intermediates into the desired optically active molecules. Several representative reactions from Fig. 6 have been discussed earlier (7). In this lecture, we report the more recent developments in asymmetric synthesis as part of the program to confirm all of the reactions shown on the chart in Fig. 6.

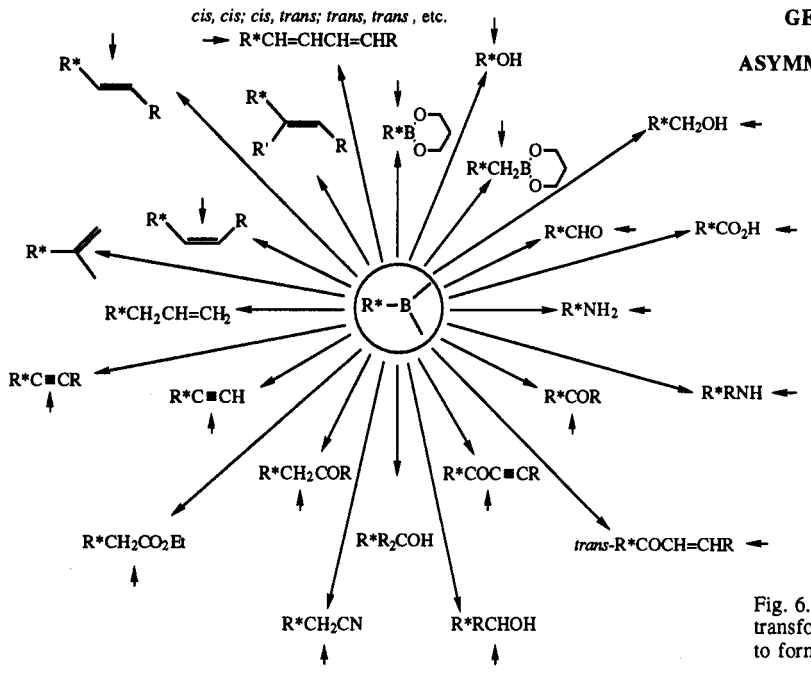


Fig. 6. Chart showing representative transformations of chiral organoboranes to form pure enantiomers.

Upgradation of boronic and borinic esters

Since the alkyl group on boron is most efficiently utilized in transformations with boronic esters, these esters have emerged as important organoborane intermediates for asymmetric synthesis. We have achieved continued success in demonstrating the utility of these esters for the synthesis of optically active compounds. Unfortunately, all of the hydroboration reactions do not yield optically pure organoboranes. We have overcome this difficulty by developing simple upgradation procedures whereby the initial hydroboration product of lower ee is upgraded by one of the following three methods.

Optically pure borinates can be synthesized by successive hydroboration of two appropriate alkenes with $IpcBH_2$, with crystallization of the initially formed IpcR*BH (8). Treatment with aldehyde eliminates α-pinene to provide a single enantiomer of the product (Fig. 7).

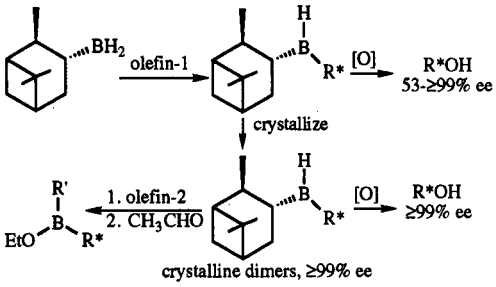


Fig. 7. Optical upgradation by crystallization of borane intermediates.

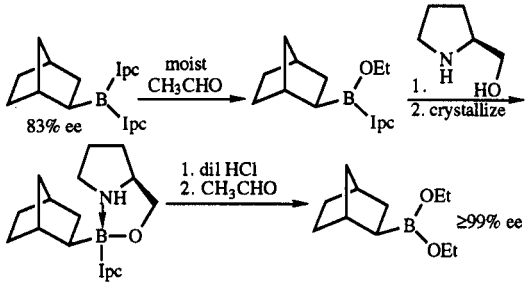


Fig. 8. Optical upgradation of borinates *via* chelation of the intermeidate.

An alternate approach for obtaining optically pure boronic esters *via* asymmetric hydroboration consists of treatment of the initial boronates with a chelating agent to furnish a crystalline material. This is then recrystallized to yield the boronic ester derivatives in essentially optically pure form (9). This method of optical upgrading can also be applied to borinic esters (Fig. 8).

Optical enrichment of the initial hydroboration product can also be achieved by a kinetic resolution with less than one equivalent of benzaldehyde. This controlled treatment liberates α-pinene selectively from one isomer thus providing the boronate ester in essentially 100% ee (10) (Fig. 9).

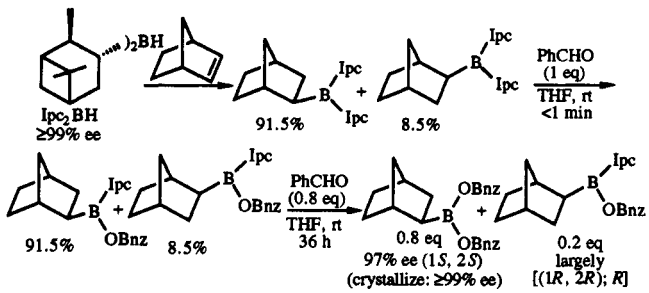


Fig. 9. Optical upgradation by kinetic resolution of borane intermediates.

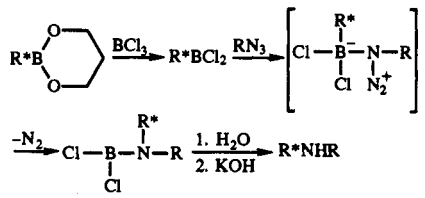


Fig. 10. Synthesis of α-chiral *sec*-amines.

Synthesis of α-chiral *sec*-amines

The synthesis of α-chiral primary amines was reported earlier (11a). We have now achieved an excellent route for the synthesis of α-chiral *sec*-amines (11b, Fig. 10).

α-Chiral alkenones

Our established procedures for the synthesis of α-chiral ketones was applied for the synthesis of α-chiral-α'-*trans*-alkenyl ketones as shown in Fig. 11 (12).

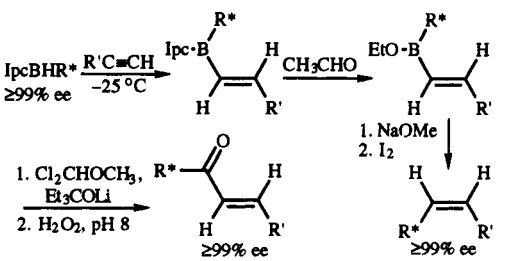


Fig. 11. Synthesis of optically pure α-chiral [*Z*]-olefins and α-chiral-α'-*trans*-alkenyl ketones.

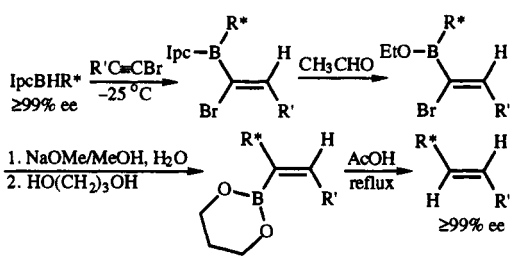


Fig. 12. Synthesis of optically pure α-chiral [*E*]-olefins.

α-Chiral olefins

The synthesis of both [*E*] and [*Z*]-olefins were achieved from chiral boronates using procedures established during our organoborane program. The borinate from the above reaction is treated with iodine in the presence of sodium methoxide to provide [*Z*]-alkenes in high yields and ee (Fig. 11) (13). α-Chiral [*E*]-alkenyl boronates can be prepared by treating IpcR*BH with 1-bromoalkyne followed by, in steps, (1) acetaldehyde, (2) aqueous sodium hydroxide, and trimethylene glycol. This boronate on protonolysis with acetic acid yields optically pure [*E*]-olefins (Fig. 12) (13). This procedure is superior to our earlier multistep procedure for the preparation of α-chiral [*E*]-alkenes starting from R*B(Thx)H (14).

α-Chiral acetylenes

Earlier we had established procedures for the synthesis of chiral internal acetylenes. We extended this for the synthesis of terminal acetylenes *via* the silyl acetylenes as shown in Fig. 13 (15).

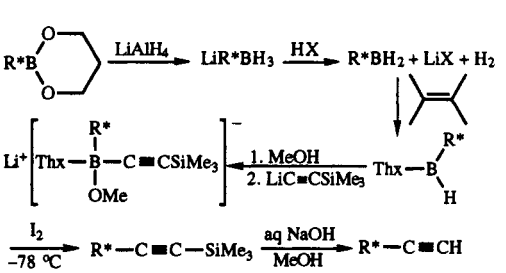


Fig. 13. Synthesis of optically pure terminal acetylenes.

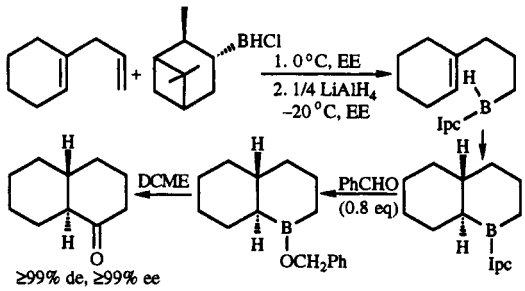


Fig. 14. Asymmetric cyclic hydroboration.

Asymmetric cyclic hydroboration

Application of the asymmetric hydroboration procedure to appropriate dienes, followed by high pressure carbonylation, provides a general method for the synthesis of optically active *trans*-fused bicyclic ketones. $IpcBH_2$ provides the ketones in low ee. Utilization of IpcBHCl for the initial hydroboration (16), followed by the before-mentioned upgradation by kinetic resolution (10) during the preparation of the borinate ester, increases the ee to ≥99% (17) (Fig. 14). This procedure is currently being applied in the hydroboration of acyclic skipped dienes to synthesize a series of optically active cyclic ketones (17).

ASYMMETRIC HOMOLOGATION

Original Matteson procedure

Matteson and his co-workers developed an ingenious and elegant procedure for the preparation of α-chiral boronate esters *via* an asymmetric homologation (18). Thus the reaction of cyclic boronate esters derived from pinanediol with pre-formed dichloromethyllithium, $LiCHCl_2$, at −100 °C, followed by transfer of the organic group from boron to carbon, induced by anhydrous $ZnCl_2$, provides the chiral boronate ester with ≥99% enantioselectivity (Fig. 15).

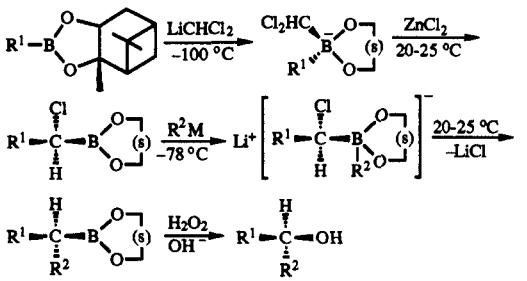


Fig. 15. Matteson's asymmetric homologation procedure for the synthesis of chiral boronic esters.

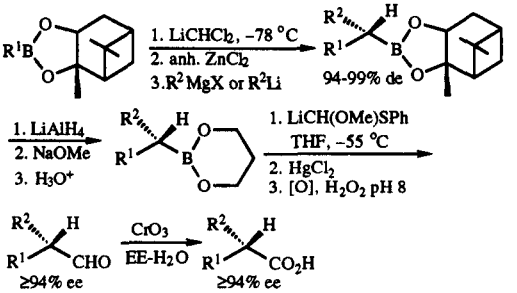


Fig. 16. Synthesis of α-chiral aldehydes and acids *via* asymmetric homologation procedure.

Improved procedure

While the Matteson procedure provides a method for the synthesis of many optically pure compounds that cannot be achieved *via* direct hydroboration, it has certain drawbacks. The rigorous requirement for inconvenient temperatures, such as −100 °C, for the preformation of $LiCHCl_2$ and the difficulty in recycling the chiral auxiliary, pinanediol, limited the scaling-up of this procedure. We overcame these limitations by utilizing $LiCHCl_2$ prepared *in situ* and carrying out the reaction at −78 °C. Procedures were also developed for recycling the pinanediol chiral auxiliary without loss of optical activity. We applied the chiral boronates derived by the modified procedure to the synthesis of aldehydes, acids, amines, ketones etc. using our established procedures (19) (Fig. 16 and 17).

Thus, our established synthetic schemes can also be applied to the boronates prepared *via* Matteson's homologation procedure, the synthesis of which are difficult to realize *via* asymmetric hydroboration (Fig. 18). (The small arrows in the chart indicate completed work).

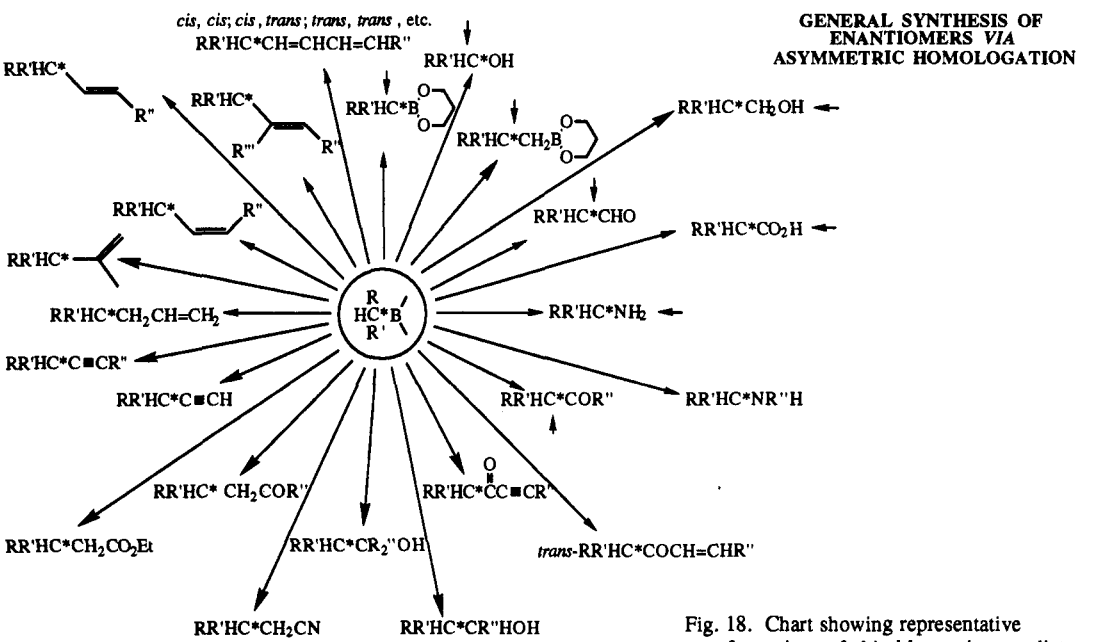


Fig. 18. Chart showing representative transformations of chiral boron intermediates prepared *via* asymmetric homologation.

Alternatives for asymmetric hydroboration of 2-substituted-1-alkenes.
Matteson's homologation procedure helped to circumvent a major deficiency in our asymmetric hydroboration procedure. Using a one-carbon homologation of α-chiral boronates we are now in a position to synthesize the boronates that cannot be obtained in high ee *via* the direct hydroboration of 2-substituted-1-alkenes . We applied this homologation procedure to our α-chiral boronates prepared from asymmetric hydroboration and succeeded in the synthesis of β-chiral boronate esters (20) (Fig. 19).

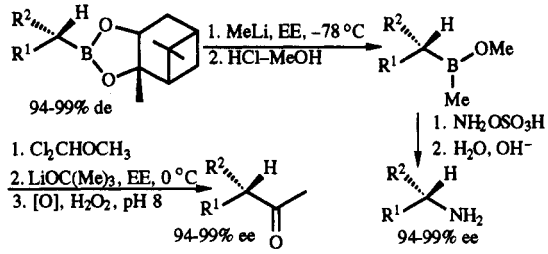


Fig.17. Synthesis of optically pure α-chiral ketones and amines *via* asymmetric homologation.

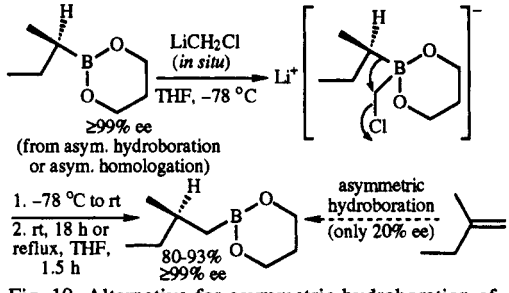


Fig. 19. Alternative for asymmetric hydroboration of 2-substituted-1-alkenes *via* one-carbon homologation.

The above β-chiral boronates can now be utilized in all the usual reactions of organoboranes to prepare β-chiral molecules. Another homologation of the β-chiral boronates provides γ-chiral boronates; and a third homologation, δ-chiral boronates (Fig. 20). These β-, γ- and δ-chiral boronates can be used for the general asymmetric synthesis shown in Fig. 18.

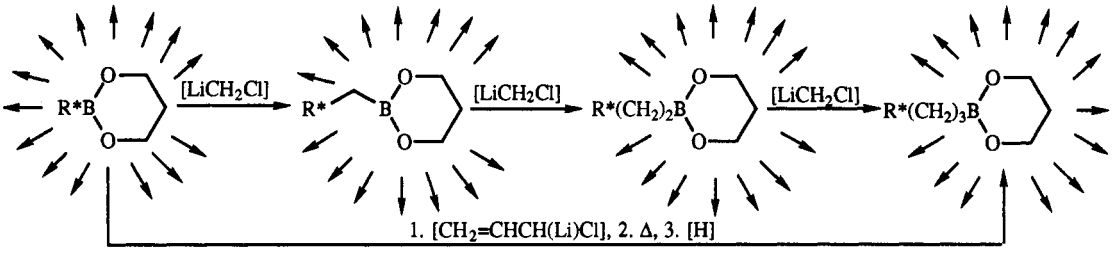


Fig. 20. The scope of our asymmetric synthesis enhanced by one-carbon or three-carbon homologations.

Three-carbon homologation
The utility of the Matteson homologation procedure for the synthesis of medium ring boracyclanes has been established. We synthesized up to the 12-membered boracyclanes starting from borinane, increasing the ring size one carbon at a time (21a). Recently we have developed a three-carbon homologation process utilizing (α-chloro)allyllithium generated *in situ* from allyl chloride and LDA at –78 °C (21b,c) (Fig. 21).

We are currently applying this three-carbon homologation procedure for a general synthesis of optically active allylic alcohols (22) (Fig. 22).

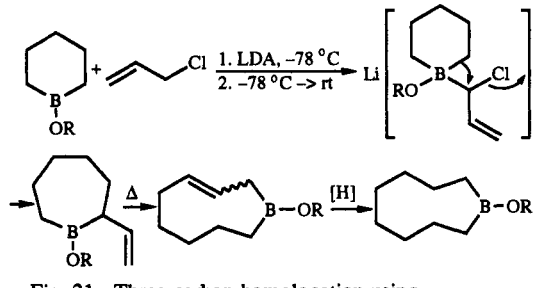


Fig. 21. Three-carbon homologation using (α-chloro)allyllithium.

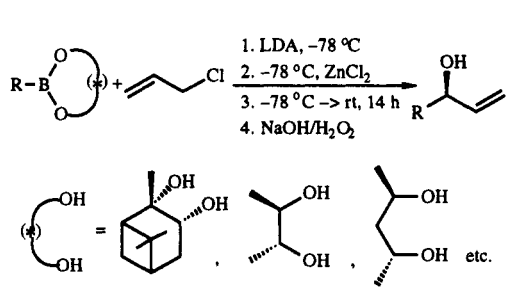


Fig. 22. Synthesis of optically active allylic alcohols.

Broad scope of organoborane chemistry

The easy synthesis of chiral boronate esters by hydroboration with Ipc_2BH or $IpcBH_2$, or by Matteson's homologation procedure, has expanded the scope of this asymmetric synthesis to an unimaginable extent. We have now achieved the synthesis of 34 optically pure boronates *via* hydroboration. Since both enantiomers of α-pinene are readily available, we can synthesize 68 pure enantiomers. A comparable number should be easily synthesized *via* asymmetric homologation. This doubles the number of optically active boron intermediates to 136. A simple one-carbon homologation doubles the number of compounds to 272. A second homologation triples the original number (408). A third sequence makes a total of 544 pure enantiomers.

We have shown 24 major reactions in Figs. 6 and 18 (other, less important reactions are also known). Each of the above boronates can undergo the 24 major reactions in the chart. This makes a total of 13,056 optically pure compounds. Many of the functional groups contained in some of these 13,056 compounds can be transformed to new functional groups. Thus we are now capable of synthesizing more than 100,000 pure enantiomers using simple organoborane chemistry! Based on our successes in a relatively short period of time, we believe that greater success awaits those willing to undertake new applications of this chemistry. Needless to say, this chemistry is still very young.

ASYMMETRIC REDUCTION

The capability of synthesizing optically active organoboranes by hydroborating suitable optically active terpenes led to the possibility of achieving asymmetric reduction of prochiral ketones, another boron based synthesis of pure enantiomers.

B-Isopinocampheyl-9-borabicyclo[3.3.1]nonane (Alpine-Borane®)

M. M. Midland and coworkers developed *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane (Aldrich: Alpine-Borane®) as the first successful chiral organoborane reducing agent. He utilized it to prepare a number of optically pure primary 1-deuteroalcohols by reduction of the deuteroaldehydes, RCDO (23a) (Fig. 23). However, Alpine-Borane fails to reduce simple prochiral ketones, such as acetophenone and 3-methyl-2-butanone. Yet certain reactive

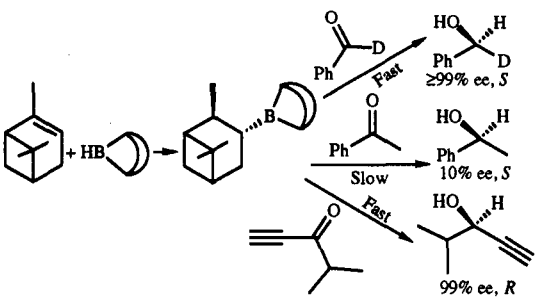


Fig. 23. Synthesis and asymmetric reductions with Alpine-Borane in THF (0.5 *M*) at rt.

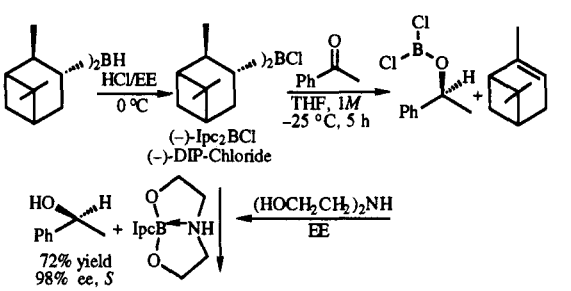


Fig. 24. Synthesis and reactions of DIP-Chloride.

carbonyls, such as α,β-acetylenic ketones, α-keto esters, and α-halo ketones, can be converted to the corresponding alcohols in very high ee with Alpine-Borane (23b) (Fig. 23). The poor selectivity in the reduction of simple ketones with Alpine-Borane is presumed to be due to a concurrent dehydroboration of the reagent in slow reductions, followed by an achiral reduction of the carbonyl group by the 9-BBN produced in this stage (24). This problem can be overcome by minimizing the dissociation either by conducting the reductions in high concentrations (25) at room temperature, or at greatly elevated pressures (26). However these modifications are still incapable of achieving the chiral reduction of unactivated ketones in high ee.

B-Chlorodiisopinocampheylborane (Ipc_2BCl, DIP-Chloride™)

Another method examined for increasing the rate of reduction was a change in the electronic environment of the boron atom. Our investigations had indicated that sterically hindered R_2BCl derivatives are more stable toward dissociation than R_3B. Accordingly, we synthesized *B*-chlorodiisopinocampheylborane (Aldrich: DIP-Chloride™) which consistently reduced aralkyl ketones extremely efficiently with predictable stereochemistry (27) (Fig. 24). Testing the reagent for a series of aralkyl ketones substituted with representative functional groups showed that most substituents do not affect the chiral outcome (28). DIP-Chloride has found many applications in syntheses involving the reduction of aralkyl ketones as a key step (29).

Modified workup procedure

The original workup procedure for DIP-Chloride reductions involved a non-oxidative removal of the boron byproduct as the diethanolamine complex. However, the presence of this complex caused difficulty in scaling up of the reactions and the disposal of the voluminous precipitate may cause environmental problems. We have since developed a considerably improved workup procedure for the isolation of product alcohols after reduction (Fig. 25). This achieves the complete recovery of α-pinene from the reagent for recycle (30).

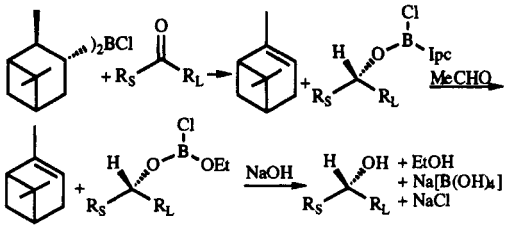


Fig. 25. Improved workup procedure for DIp-Chloride reductions.

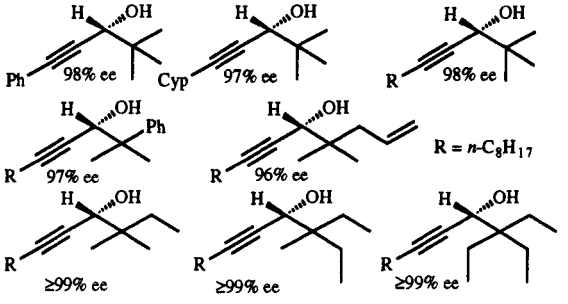


Fig. 26. Asymmetric reduction of hindered acetylenic ketones.

α-Hindered ketones

Though Alpine-Borane reduces acetylenic ketones in very high ee it fails to chirally reduce hindered acetylenic ketones, which on occasion constitute a key step in certain syntheses. Accordingly, the capability of DIP-Chloride to reduce highly reactive hindered ketones, such as hindered α,β-acetylenic ketones, was tested. The asymmetric reduction proceeds with gratifying success (30) (Fig 26).

Perfluoroalkyl ketones

Fluorinated compounds are gaining importance in organic, medicinal, biological, and agricultural chemistry (31). Application of DIP-Chloride for the reduction of perfluoroalkyl ketones provide the products in very high ee (32). Both aromatic and aliphatic ketones are reduced with equal efficiency. One significant feature in the reduction of fluoroalkyl ketones is the fact that the products are of the opposite configuration, compared to the hydrogen analogs. Apparently, the electronic and steric effects of the fluorine atoms alter the course of the reduction (Fig. 27).

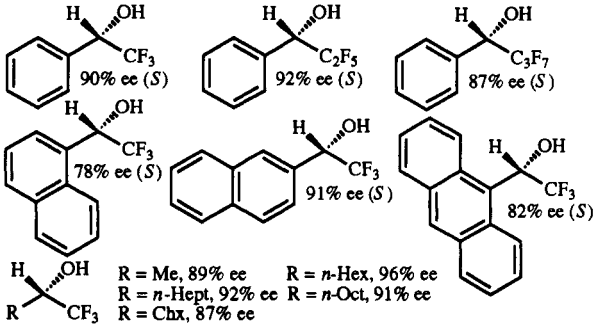


Fig. 27. Asymmetric reduction of trifluoromethyl ketones.

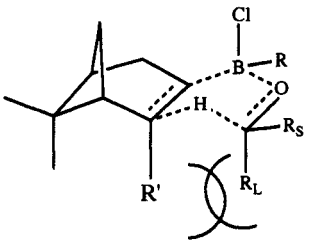


Fig. 28. Transition state model for modified chiral reducing agents.

Modified reagents

The effectiveness of DIP-Chloride for the reduction of hindered ketones persuaded us to consider carefully the proposed transition state for the reaction. It appeared that an increase in the steric requirement of the group at the 2-position of the apopinene moiety might increase the ee achieved in the chiral reduction (Fig. 28).

This hypothesis was tested with *B*-iso-2-ethylapopinocampheyl-9-BBN (Eapine-Borane) (33) and the corresponding lithium borohydride (Eapine-Hydride) (34). Considerable improvement over the parent compounds (R' = Me) was realized. Even better results supporting of this hypothesis were noted with *B*-chlorodiiso-2-ethylapopinocampheylborane, Eap_2BCl (35). This reagent is excellent for the chiral reduction of all those ketones that are handled very effectively by DIP-Chloride. In addition, it also handles aliphatic ketones of intermediate steric requirements, such as 3-methyl-2-butanone (95% ee) and acetylcyclohexane (97% ee).

The success of Eap_2BCl prompted us to examine 2-β-chloroethylapopinene, a precursor in the synthesis of 2-ethylapopinene, for the preparation of a new chiral reducing agent. We were interested in observing the influence that the chlorine atom in the R' group might have in the reduction of ketones, particularly those with strong electronic environments, such as α,β-acetylenic ketones and α-keto esters. Indeed, diiso-2-β-chloroethylapopinocampheylborane ($Cleap_2BCl$), synthesized from 2-β-chloroethylapopinene and chloroborane-methyl sulfide complex proved highly favorable for the chiral reduction of the above two classes of ketones (36) (Table 1, Fig. 29).

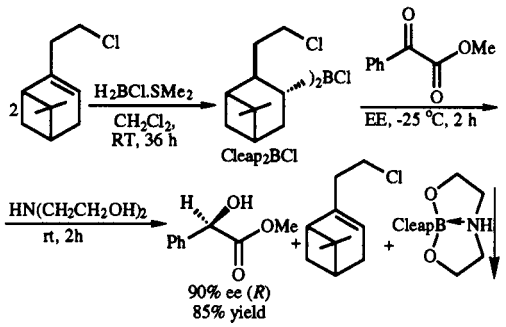


Fig. 29. Synthesis and reaction of $Cleap_2BCl$.

TABLE 1. Asymmetric reduction of ketones with R^*_2BCl at -25 °C.

class of ketone	ketone	%ee		
		Ipc_2BCl	Eap_2BCl	$Cleap_2BCl$
1	acetylcyclohexane	26	97	≥99
2	2,2-dimethylcyclopentanone	98[a]	≥99[a]	≥99[a]
3	acetophenone	98	≥99	≥99
4	acetylpyridine	92	≥99	≥99[b]
5	2-chloroacetophenone	95	≥99	95[b]
6	methyl benzoylformate	50	70	90
7	ethyl benzoylacetate	no reduction		
8	*trans*-4-phenyl-3-buten-2-one	81	82	
9	2-cyclohexen-1-one	36	74	80[b]
10	4-phenyl-3-butyn-2-one	21	33	66

[a]For a reaction at rt. [b]For a reaction at 0-10 °C

We now have a reagent in hand that reduces more classes of ketones in very high ee than any other reagent. Indeed, $Cleap_2BCl$ can handle eight of the ten classes of ketones (37) in high ee and a ninth class in moderate ee. We do not forsee any major difficulty in synthesizing reagents with increased steric requirement at the 2-position of apopinene that can handle all classes of ketones.

ASYMMETRIC ALLYL- AND CROTYLBORATION

The art of asymmetric synthesis has become highly sophisticated in conformationally non-rigid systems such as macrolide and ionophore antibiotics with a plethora of stereodefined *vic*-diols or β-methyl alcohols (38). Here, not only the enantioselectivity, but the diastereoselectivity of the reaction are highly important. Accordingly, numerous searches for the most efficient reagent that can achieve both these selectivities in a single step have been made. Chiral organoboranes have also revealed their uniqueness and advantages for these desired transformations.

B-Allyldiisopinocampheylborane

The allylboration reaction was introduced by Mikhailov in 1972 (39). The chiral version of this reaction was first carried out by Hoffmann with moderate success using a chiral auxiliary derived from camphor (40). Based on our successes in asymmetric hydroboration with Ipc_2BH, we envisaged that *B*-allyldiisopinocampheylborane, Ipc_2BAll, might also be successful. The synthesis of the reagent from Ipc_2BH was simple and the reaction with aldehydes at –78 °C, followed by either alkaline hydrogen peroxide or ethanolamine work-up, provided very good yields of the homoallylic alcohols in very high ee (41) (Fig. 30).

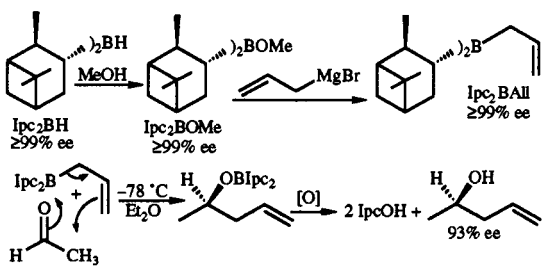


Fig. 30. Ipc_2BAll achieves excellent asymmetric allylborations.

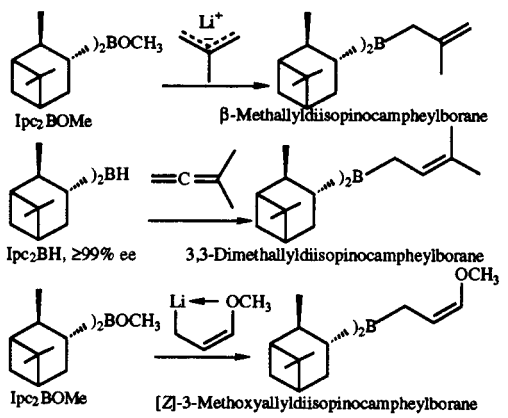


Fig. 31. Synthesis of derivatives of Ipc_2BAll.

The success of Ipc_2BAll led to several other derivatives, such as *B*-methallyldiisopinocampheylborane, 3,3-dimethylallyldiisopinocampheylborane, [Z]-3-methoxyallyldiisopinocampheylborane, etc. (Fig. 31) and all of them proved highly successful. For a discussion of these derivatives see the lecture at IMEBORON VII (7a).

B-[*E*]- and [*Z*]-Crotyldiisopinocampheylborane

Based on our successes with various allylborating agents, there was no reason for us not to believe that crotylborations will also be highly successful with our reliable chiral auxiliary, α-pinene. However, the fast equilibrium of pure *E* and *Z*-crotylboron derivatives *via* a borotropic rearrangement involving the 1-methallyl compound as an intermediate offered possible problems for the synthesis of pure isomers of the crotyl derivatives. Fortunately, the timely publication of a procedure by Schlosser to prepare *t*-butylpotassium aided in the synthesis of isomerically pure crotylpotassium (42). Practical procedures were developed for the synthesis of pure Ipc_2BCrt^E and Ipc_2BCrt^Z. Asymmetric crotylboration of aldehydes with these derivatives proceeded with remarkable optical and geometric efficiencies. Consequently, it is now possible to synthesize, at will, each of the four possible isomers of β-methylhomoallylic alcohols (43) (Fig. 32).

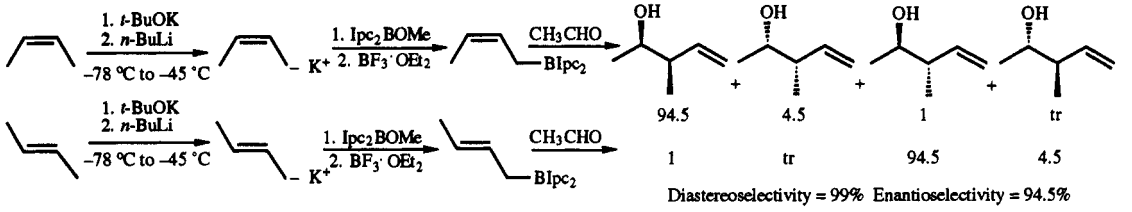


Fig. 32. Synthesis of [Z]- and [E]-crotyldiisopinocampheylboranes and asymmetric crotylboration.

B-2'-Isoprenyldiisopinocampheylborane

Our success with crotylpotassium persuaded us to prepare the *B*-2'-isoprenyldiisopinocampheylborane from isoprenylpotassium and *B*-methoxydiisopinocampheylborane. Condensation of this reagent with aldehydes provided isoprenylated chiral alcohols. This methodology was applied for an efficient one-pot synthesis of both enantiomers of the bark beetle *Ips paraconfusus* Lanier, ipsenol and ipsdienol (44) (Fig. 33). This simple synthesis is the sharp contrast to multistep syntheses (13 and 17 steps) by Mori (45).

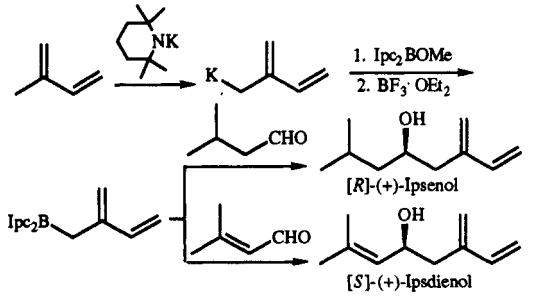


Fig. 33. Asymmetric isoprenylation. Synthesis of Ipsenol and Ipsdienol.

Table 2. Allylboration of aldehydes using Ter_2BAll at −100 °C.

aldehyde	%ee					
	Ipc_2BAll		4-Icr_2BAll		2-Icr_2BAll	
	−78 °C	−100 °C	−78 °C	−100 °C	−78 °C	−100 °C
acetaldehyde	92 (*R*)	≥99	94 (*R*)	≥99	98 (*S*)	≥99
n-butyraldehyde	86 (*R*)	96	88 (*R*)	98	94 (*S*)	≥99
i-butyraldehyde	88 (*S*)	96	95 (*S*)	98	94 (*R*)	≥99
pivalaldehyde	83 (*S*)	≥99	88 (*S*)	≥99	99 (*R*)	≥99
acrolein	92 (*S*)	96	93 (*S*)	98	95 (*R*)	≥99
benzaldehyde	94 (*S*)	96	87 (*S*)	98	95 (*R*)	≥99

Improved reagents

Though we did not have much success with chiral hydroborating agents derived from other terpenes, such as 2-carene, 3-carene, limonene, and longifolene, the allylboration reagents synthesized from 2-carene and 3-carene are proving to be even more efficient than that from α-pinene (46) (Table 2).

Synthesis of γ-butyrolactones

The optically active homoallylic alcohols readily available *via* asymmetric allylborations were protected as the *p*-nitrobenzoate esters and subjected to hydroboration followed by oxidation with CrO_3 in acetic acid (10% H_2O) to give the corresponding carboxylic acids with the same number of carbon atoms. These were hydrolyzed and lactonized to γ-substituted-γ-butyrolactones without loss of optical activity (47) (Fig. 34).

ASYMMETRIC CLEAVAGE OF MESO-EPOXIDES

The use of mono- and dialkylhaloboranes in a selective cleavage of C–O bonds is known (48). We carried out a systematic study of the asymmetric version of this reaction for the ring cleavage of *meso*-epoxides using mono- and diisopinocampheylhaloboranes and succesfully accomplished the preparation of 1,2-halohydrins in good to excellent ee (49). We found that diisopinocampheyliodoborane is the best suited

reagent (95-≥99% ee) to achieve the cleavage in an anti-periplanar manner, with an S_N2 type reaction pathway (Fig. 35). This reaction sequence provides highly valuable optically active difunctionalized compounds for asymmetric synthesis.

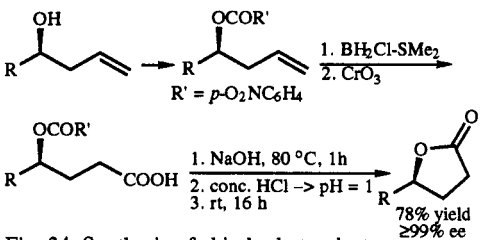


Fig. 34. Synthesis of chiral γ-butyrolactones.

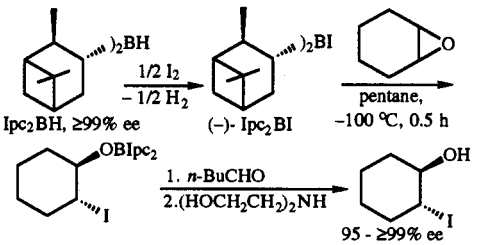


Fig. 35. Asymmetric ring opening of *meso*-epoxides.

CONCLUSIONS

The reaction of α-pinene with borane, just another routine reaction during the study of the characteristics of hydroboration, turned out to be one of those grandiose reactions that is a researcher's dream. α-Pinene proved to be a very fortuitous choice as a chiral auxiliary for asymmetric synthesis. It satisfies most of the conditions that are tests for an excellent chiral auxiliary, such as (1) both isomers of α-pinene are readily available in high ee. (2) Optical upgradation of the commercial material is easily attained during hydroboration. (3) The preparation of the reagents and the reaction conditions in most of the reactions are very simple and convenient. (4) The workup is easy. (5) The chiral auxiliary is readily recovered in all of the reactions without loss of any optical activity in an easily recyclable form. (6) A tentative mechanism is known for all of the reactions which helps in modification, wherever necessary. (7) The configuration of the products can be predicted based on the mechansim, with rare exceptions. (8) The scaling up of the reactions are easy, and most important of all, (9) the enantiomeric excesses achieved in most reactions are very high.

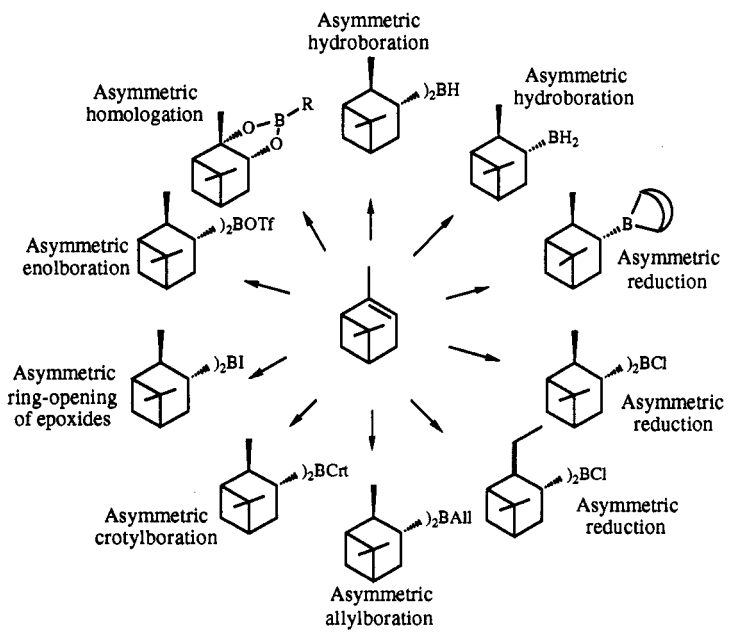


Fig. 36. α-Pinene, the super chiral auxiliary

Enantiomeric excesses in the range of >95% are obtained for the following established procedures: (1) the asymmetric hydroboration of three of the four classes of olefins (the product from the fourth (Class I olefin) can be obtained indirectly *via* asymmetric homologation); (2) in the general asymmetric synthesis *via* boronates and borinates obtained from hydroboration and homologation; (3) in asymmetric homologation; (4) in asymmetric allyl- and crotylboration; (5) in asymmetric reductions; (6) in asymmetric enolboration-aldol reactions, and (7) in the cleavage of epoxides. To our knowledge, there is no other chiral auxiliary and reaction comparable to α-pinene and its hydroboration leading to chiral organoboranes that are capable of achieving so many different types of asymmetric reactions in such high efficiency (Fig. 36). This asymmetric synthesis *via* chiral organoboranes is truly general.

Acknowledgements
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REFERENCES

1. H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.* **78**, 5694 (1956).
2. H. C. Brown, *Hydroboration*, Benjamin, New York (1962).
3. (a) H. C. Brown, *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, New York (1972). (b) H. C. Brown, *Pure & Appl. Chem.* **47**, 49 (1976). (c) H. C. Brown, G. W. Kramer, A. B. Levy and M. M. Midland, *Organic Synthesis via Boranes*, Wiley-Interscience, New York (1975).
4. (a) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.* **83**, 486 (1961). (b) H. C. Brown and N. M. Yoon, *Isr. J. Chem.* **15**, 12 (1977). (c) H. C. Brown, P. K. Jadhav and M. C. Desai, *J. Org. Chem.* **47**, 5065 (1982). (d) H. C. Brown and J. V. N. Vara Prasad, *Heterocycles* **25**, 641 (1987).
5. (a) H. C. Brown, and P. K. Jadhav, *J. Org. Chem.* **46**, 5047 (1981); (b) *ibid.* **47**, 5074 (1982).
6. H. C. Brown, P. K. Jadhav and M. C. Desai, *J. Am. Chem. Soc.* **104**, 4303 (1982).
7. (a) H. C. Brown and P. V. Ramachandran, *Pure & Appl. Chem.* **63**, 307 (1991). (b) H. C. Brown and B. Singaram, *ibid.* **59**, 879 (1987).
8. H. C. Brown and B. Singaram, *J. Am. Chem. Soc.* **106**, 1797 (1984).
9. H. C. Brown and J. V. N. V. Prasad, *J. Org. Chem.* **51**, 4526 (1986).
10. N. N. Joshi, C. Pyun, V. K. Mahindroo, B. Singaram and H. C. Brown, *J. Org. Chem.* **57**, 504 (1992).
11. (a) H. C. Brown, K. W. Kim, T. E. Cole and B. Singaram, *J. Am. Chem. Soc.* **108**, 6761 (1986). (b) H. C. Brown, A. M. Salunkhe and B. Singaram, *J. Org. Chem.* **56**, 3286 (1991).
12. H. C. Brown and V. K. Mahindroo, *Synlett* 626 (1992).
13. H. C. Brown, R. R. Iyer, V. K. Mahindroo and N. G. Bhat, *Tetrahedron: Asym.* **2**, 277 (1991).
14. H. C. Brown, R. K. Bakshi and B. Singaram *J. Am. Chem. Soc.* **110**, 1529 (1988).
15. H. C. Brown, V. K. Mahindroo, N. G. Bhat, B. Singaram *J. Org. Chem.* **56**, 1500 (1991).
16. M. Egger and R. Keese, *Helv. Chim. Acta* **70**, 1843 (1987).
17. H. C. Brown, Pathare, P. M.; V. K. Mahindroo, Unpublished results.
18. (a) D. S. Matteson, K. M. Sadhu and M. L. Peterson, *J. Am. Chem. Soc.* **108**, 810 (1986). (b) D. S. Matteson, *Acc. Chem. Res.* **21**, 294 (1988).
19. M. V. Rangaishenvi, B. Singaram and H. C. Brown, *J. Org. Chem.* **56**, 3286 (1991).
20. H. C. Brown, S. M. Singh, M. V. Rangaishenvi, *J. Org. Chem.* **51**, 3150 (1986).
21. (a) H. C. Brown, A. S. Phadke, and M. V. Rangaishenvi, *J. Am. Chem. Soc.* **110**, 6263 (1988). (b) M. V. Rangaishenvi and H. C. Brown, *Tetrahedron Lett.*, **31**, 7115 (1990). (c) H. C. Brown and S. Jayaraman *ibid.* **34**, 3997 (1993).
22. H. C. Brown, M. M. Qureshi and S. Jayaraman, Unpublished results.
23. (a) M. M. Midland, S. Greer, A. Tramontano, S. A. Zderic, *J. Am. Chem. Soc.* **101**, 2352 (1979). (b) M. M. Midland, D. C. McDowell, R. L Hatch and A. Tramontano, *J. Am. Chem. Soc.* **102**, 867 (1980).
24. M. M. Midland, J. E. Petre, S. A. Zderic, A. Kazubski, *J. Am. Chem. Soc.* **104**, 528 (1982).
25. H. C. Brown and G. G. Pai, *J. Org. Chem.* 50, 1384 (1985).
26. M. M. Midland, J. I. McLoughlin and J. Gabriel, *J. Org. Chem.* **54**, 159 (1989).
27. H. C. Brown, J. Chandrasekharan and P. V. Ramachandran, *J. Am. Chem. Soc.* **110**, 1539 (1988).
28. P. V. Ramachandran, B. Q. Gong and H. C. Brown, Unpublished results.
29. H. C. Brown and P. V. Ramachandran, *Acc. Chem. Res.* **25**, 16 (1992).
30. P. V. Ramachandran, A. V. Teodorovic, M. V. Rangaishenvi and H. C. Brown, *J. Org. Chem.* **57**, 2379 (1992).
31. P. Bravo and G. Resnati, *Tetrahedron: Asym.* **1**, 661 (1990).
32. P. V. Ramachandran, A. V. Teodorovic and H. C. Brown, *Tetrahedron* **49**, 1725 (1993).
33. H. C. Brown, P. V. Ramachandran, S. A. Weissman and S. Swaminathan *J. Org. Chem.* **55**, 6328 (1990).
34. P. V. Ramachandran, H. C. Brown and S. Swaminathan, *Tetrahedron: Asym.* **1**, 433 (1990).
35. H. C. Brown, P. V. Ramachandran and S. Swaminathan, *Tetrahedron Lett.* **32**, 6691 (1991).
36. P. V. Ramachandran and H. C. Brown, Unpublished results.
37. H. C. Brown, W. S. Park, B. T. Cho and P. V. Ramachandran, *J. Org. Chem.* **52**, 5406 (1987).
38. Hoffmann, R. W. *Angew. Chem. Int. Ed. Engl.* **31**, 1124 (1992).
39. B. M. Mikhailov, *Organometal. Chem. Rev. A.* **8**, 1 (1972).
40. R. W. Hoffmann and T. Herold, *Chem. Ber.* **114**, 375 (1981).
41. H. C. Brown and P. K. Jadhav, *J. Am. Chem. Soc.* **105**, 2092 (1983).
42. K. Fujita and M. Schlosser, *Helv. Chim. Acta* **65**, 1258 (1982).
43. (a) H. C. Brown and K. S. Bhat, *J. Am. Chem. Soc.* **108**, 293, (1986). (b) *idem. ibid.* 5919.
44. H. C. Brown and R. S. Randad, *Tetrahedron* **46**, 4463 (1990).
45. (a) K. Mori, *Tetrahedron* **32**, 1101 (1976). (b) K. Mori, *Tetrahedron Lett.* 1609 (1976).
46. H. C. Brown, R. S. Randad, K. S. Bhat, M. Zaidlewicz and U. S. Racherla, *J. Am. Chem. Soc.* **112**, 2389 (1990).
47. H. C. Brown, S. V. Kulkarni and U. S. Racherla, Unpublished results.
48. Y. Guindon, M. Therien, Y. Girard and C. Yoakim, *J. Org. Chem.* **52**, 1680 (1988).
49. H. C. Brown, N. N. Joshi, M. Srebnik, *Isr. J. Chem.* **29**, 229 (1989).