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Development of a Simple General Procedure for Synthesis of Pure Enantiomers via Chiral Organoboranes

HERBERT C. BROWN* and BAKTHAN SINGARAM

H. C. Brown and R. B. Wetherill Laboratories of Chemistry, Purdue University, West Lafayette, Indiana 47907

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Organoboranes, readily available via the hydroboration of unsaturated organic compounds, exhibit a remarkable versatility in their reactions. The boron atom in these organoboranes can be readily converted into a wide variety of organic groups under mild conditions, providing simple versatile syntheses of organic compounds. Exploration of these substitution reactions reveals that, with rare exceptions, the organoboranes transfer the alkyl group to other elements of synthetic interest with complete retention of sterochemistry. An unexpected result of the systematic study of hydroboration and the chemistry of organoboranes has been the discovery of a remarkably simple, exceptionally general synthesis of enantiomerically pure organoborane intermediates. The chiral organic groups attached to boron in these optically active organoborane intermediates can also be transferred with complete retention of configuration. Consequently, it is now possible to achieve, by a rational synthesis, the preparation of any optically active compound containing one chiral center, either *R* or *S*, in enantiomerically pure form. This development promises to have a revolutionary impact on synthetic organic chemistry.

The ether-catalyzed addition of diborane to unsaturated organic molecules—the hydroboration reaction—made organoboranes readily available.[1,2] Systematic study of these organoboranes has revealed that they are among the most versatile intermediates available to the organic chemist.[2,3] Indeed, it is possible to utilize organoboranes to synthesize essentially all structural types of organic compounds of interest to the organic chemist (Figure 1).

With remarkably few exceptions, these reactions proceed with complete retention of configuration.[4] Consequently, it became evident that if we could learn to achieve the synthesis of chiral organic groups attached to boron, we could transfer those groups to carbon and other elements to permit a general synthesis of enantiomerically pure compounds.

Asymmetric Hydroboration with Diisopinocampheylborane. Originally we examined the hydroboration of α-pinene primarily to test the mildness of the hydroboration reaction. α-Pinene was known to be an especially labile alkene, remarkably susceptible to rearrangement when attacked by electrophilic reagents. However, hydroboration proceeded readily to form diisopinocampheylborane (Ipc_2BH)[5] without any detectable rearrangement. The product was the first asymmetric hydroborating agent produced, and it occurred to us to ascertain the degree of asymmetric induction achieved in the hydroboration of those alkenes that would react with this reagent.

Herbert C. Brown was born in London, England, on May 22, 1912. He received a B.S. degree in 1936 and a Ph.D. degree in 1938, both from the University of Chicago. In 1943 he went to Wayne University and in 1947 he transferred to Purdue University. He presently holds the title of Wetherill Research Professor Emeritus. His contributions to chemistry have been recognized by many awards and medals. Among these are the National Medal of Science (1969), the Roger Adams Medal (1973), the Nobel Prize (1979), the "Triple Crown of American Chemistry"—the Priestly Medal of the American Chemical Society (1981), the Perkin Medal from the Society of Chemical Industry (1982), and the Gold Medal of the American Institute of Chemists (1985)—and the Chemical Sciences Award of the National Academy of Sciences (1987).

Bakthan Singaram was born in Madanapali, India, on May 20, 1950. He received a B.S. degree in 1969, a M.S. degree in 1971, and a Ph.D with Professor James Verghese in 1977, all from the University of Madras, India. He did his postdoctoral studies first at Purdue University with H. C. Brown and later at the University College of Swansea, Wales, with Andrew Pelter. He returned to Purdue University in 1982 as the Assistant Research Scientist to H. C. Brown. In 1987 he was promoted to Associate Research Scientist.

(1) Brown, H. C.; Subba Rao, B. C. *J. Org. Chem.* **1957**, *22*, 1139.
(2) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Middland, M. M. *Organic Synthesis via Boranes*; Wiley-Interscience: New York, 1975.
(3) Brown, H. C. *Hydroboration*; W. A. Benjamin: New York, 1963.
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(5) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 486.

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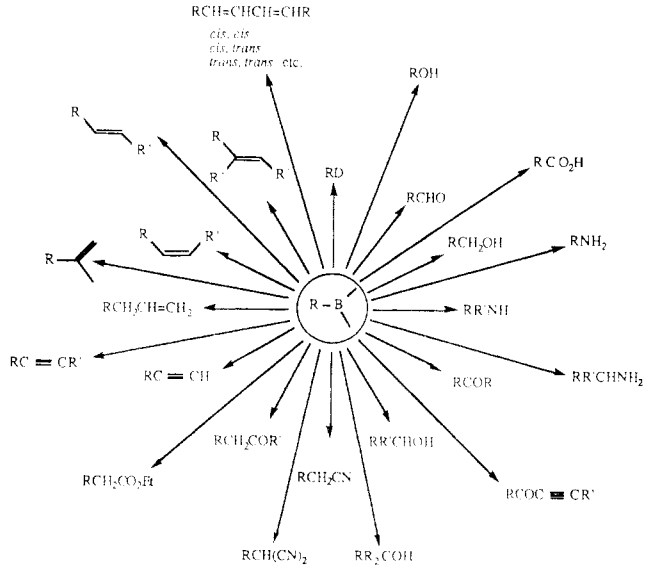


Figure 1. Chart summarizing representative substitution reactions of organoboranes.

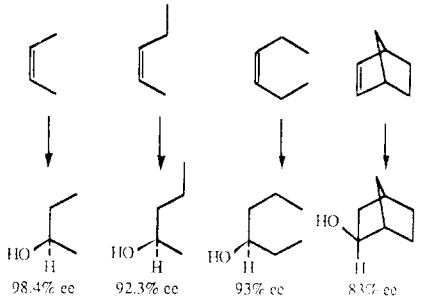
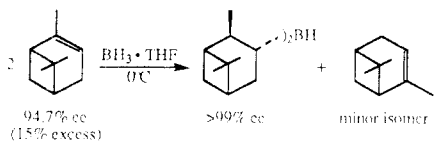


Figure 2. Asymmetric hydroboration or *cis*-alkenes with Ipc_2BH.

We were pleasantly surprised when the hydroboration–oxidation of *cis*-2-butene with Ipc_2BH (from (+)-α-pinene of 93% ee) provided (*R*)-(−)-2-butanol of 87% optical purity.[6] Accordingly, we had achieved the first truly successful, nonenzymatic, asymmetric synthesis. Another major advantage of Ipc_2BH is the ready availability of both (+)- and (−)-α-pinenes. Consequently, chiral centers of opposite configuration can be generated by using Ipc_2BH derived from the appropriate enantiomers of α-pinene.

Commercial α-pinene is only 92% optically pure. However, we have learned to prepare Ipc_2BH of high enantiomeric purity from such α-pinene. The crystalline Ipc_2BH formed on hydroboration of α-pinene (92% ee) is allowed to stand at 0 °C in the presence of a slight excess of α-pinene. The major isomer becomes incorporated into the crystalline reagent, leaving the undesired isomer in solution (eq 1).[7]



(1)

Excellent asymmetric inductions were realized in the hydroboration–oxidation of *cis*-olefins with Ipc_2BH of high enantiomeric purity (Figure 2).[8,9]

(6) Zweifel, G.; Brown, H. C. *J. Am. Chem. Soc.* **1964**, *86*, 393.
(7) (a) Brown, H. C.; Yoon, N. M. *Isr. J. Chem.* **1977**, *15*, 12. (b) Brown, H. C.; Singaram, B. *J. Org. Chem.* **1984**, *49*, 945.
(8) Brown, H. C.; Jadhav, P. K.; Desai, M. C. *J. Org. Chem.* **1982**, *47*, 5065.

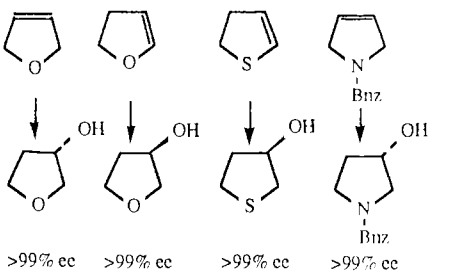


Figure 3. Asymmetric hydroboration of some heterocyclic alkenes.

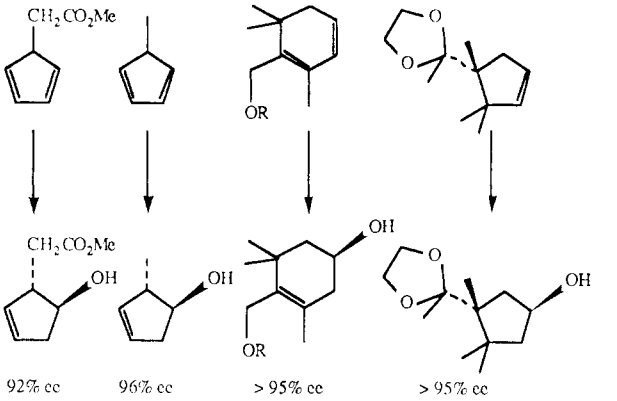


Figure 4. Preparation of synthetic intermediates by the asymmetric hydroboration–oxidation procedure.

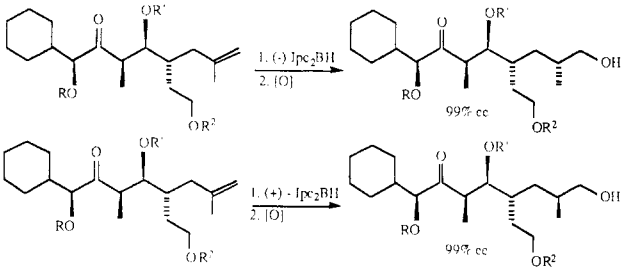


Figure 5. Synthesis of tylonolide precursor by the asymmetric hydroboration–oxidation method.

Similarly, the asymmetric hydroboration of heterocyclic olefins is both highly regio- and enantioselective. Thus, hydroboration of 2,3-dihydrofuran with Ipc_2BH, followed by oxidation, provides 3-hydroxyfuran in essentially 100% ee (Figure 3).[10]

Several synthetic intermediates have been made by using asymmetric hydroboration with Ipc_2BH, followed by oxidation. An example is the prostaglandin precursor obtained from the asymmetric hydroboration–oxidation reaction of methyl cyclopentadiene-5-acetate (Figure 4).[11] Useful intermediates for the synthesis of loganin and zeaxanthin have been obtained by asymmetric hydroboration–oxidation of 5-methylcyclopentadiene[12] and safranol ether,[13] respectively (Figure 4). Similarly, the capsorubin precursor was obtained from the asymmetric hydroboration–oxidation reaction of the acetal of (3*R*)-2,2,3-trimethyl-3-acetylcyclopentene (Figure 4).[14]

(9) All results discussed in this article are for Ipc_2BH and $IpcBH_2$ derived from (+)-α-pinene.
(10) Brown, H. C.; Vara Prasad, J. V. N. *J. Am. Chem. Soc.* **1986**, *108*, 2049.
(11) Patridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 7171.
(12) Patridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 532.
(13) Rüttimann, A.; Mayer, H. *Helv. Chim. Acta* **1980**, *63*, 1456.

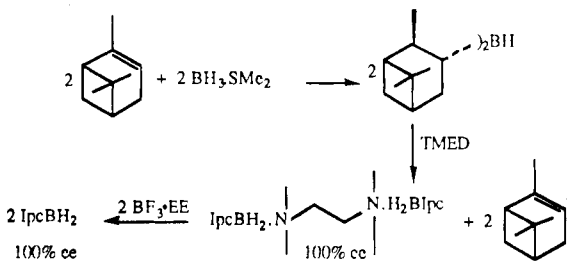


Figure 6. Synthesis of $IpcBH_2$ in 100% ee.

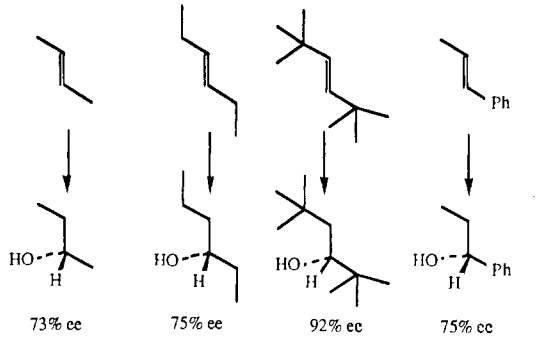


Figure 7. Asymmetric hydroboration or *trans*-alkenes with $IpcBH_2$.

Diisopinocampheylborane handles *cis*-alkenes very effectively. However, it is not an effective asymmetric hydroborating agent for 2-substituted 1-alkenes. Although simple 2-methyl-1-alkenes yield alcohols of ≤30% ee, very high selectivities have been achieved when one of the two substituents is very bulky. Thus, the tylonolide precursor was obtained from the asymmetric hydroboration–oxidation reaction of the complex 2-methyl-1-olefinic compound with (−)-Ipc_2BH, and the epimeric alcohol was obtained with (+)-Ipc_2BH (Figure 5).[15] In both the cases the isomeric ratio was at least 50:1.

Diisopinocampheylborane is also not an effective asymmetric hydroborating agent for *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*-alkenes and trisubstituted alkenes must be too large for the reagent. This problem was partially solved by the synthesis and application of monoisopinocampheylborane ($IpcBH_2$) for the asymmetric hydroboration of *trans*-alkenes and trisubstituted alkenes.

Asymmetric Hydroboration with Monoisopinocampheylborane. Hydroboration of α-pinene cannot be controlled to yield $IpcBH_2$. The reaction generally proceeds rapidly past the $IpcBH_2$ stage to give Ipc_2BH. However, treatment of Ipc_2BH with 0.5 equiv of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMED) provides the 1:2 adduct, TMED·$2BH_2Ipc$, with the liberation of 1 equiv of α-pinene. The adduct crystallizes out in enantiomerically and diastereomerically pure form. The reagent, $IpcBH_2$, is readily liberated by treating the adduct with boron trifluoride etherate (TMED·$2BF_3$ precipitates as a highly insoluble product) (Figure 6).[16]

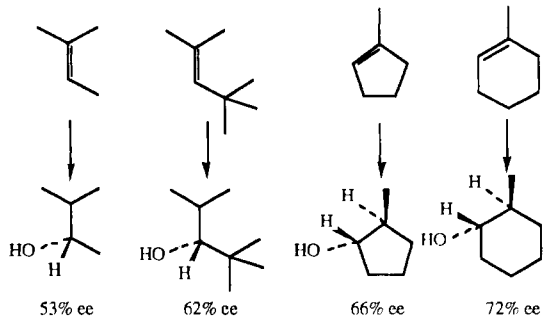


Figure 8. Asymmetric hydroboration of trisubstituted alkenes with $IpcBH_2$.

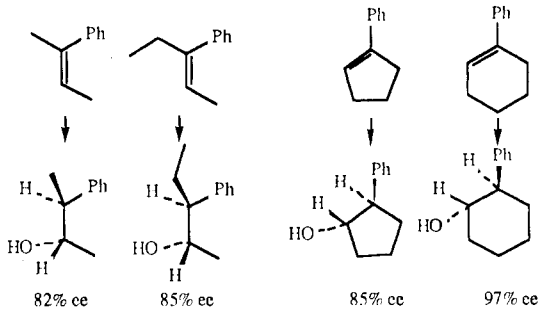


Figure 9. Asymmetric hydroboration of trisubstituted alkenes with a phenyl substituent by $IpcBH_2$.

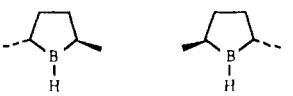
Asymmetric hydroboration–oxidation of *trans*-olefins with monoisopinocampheylborane is very effective (Figure 7).[17]

It is also now possible to achieve the hydroboration–oxidation of trisubstituted olefins to form the corresponding alcohols in reasonable enantiomeric purities (Figure 8).[17]

Considerably improved asymmetric inductions are realized in the hydroboration–oxidation of the phenyl derivatives of the trisubstituted alkenes with $IpcBH_2$. Thus, 1-phenylcyclohexene provides the hydroboration–oxidation product in 97% ee (Figure 9).[17,18]

Apparently, Ipc_2BH and $IpcBH_2$ are complementary to each other. These two reagents handle three of the four major classes of alkenes. There remains a need for a reagent that will provide access to products of high enantiomeric purity from alkenes of relatively low steric requirements such as the 2-methyl-1-alkenes. However, as discussed later, we have developed an alternative solution to this problem.

A fascinating development has recently been reported by Masamune and his co-workers. They have achieved the synthesis and resolution of a new asymmetric hydroborating agent, *trans*-2,5-dimethylboralane.[19] The C_2 symmetry, which makes both faces of the boron atom equivalent, is an important feature of this reagent.



This reagent yielded excellent results in the asymmetric hydroboration of three of the four representative classes of olefins. However, the 2-substituted 1-alkenes

(14) Rüttimann, A.; Englert, G.; Mayer, H.; Moss, G. P.; Weedon, B. C. L. *Helv. Chim. Acta* **1983**, *66*, 1939.
(15) Masamune, S.; Lu, D.-L. L.; Jackson, W. P.; Kaiho, T.; Toyoda, T. *J. Am. Chem. Soc.* **1982**, *104*, 5523.
(16) Brown, H. C.; Schwier, J. R.; Singaram, B. *J. Org. Chem.* **1978**, *43*, 4395.
(17) Brown, H. C.; Jadhav, P. K.; Mandal, A. K. *J. Org. Chem.* **1982**, *47*, 5074.
(18) Brown, H. C.; Vara Prasad, J. V. N.; Gupta, A.; Bakshi, R. K. *J. Org. Chem.* **1987**, *52*, 310.
(19) Masamune, S.; Kim, B. M.; Peterson, J. S.; Sato, T.; Veenstra, S. J.; Imai, T. *J. Am. Chem. Soc.* **1985**, *107*, 4549.

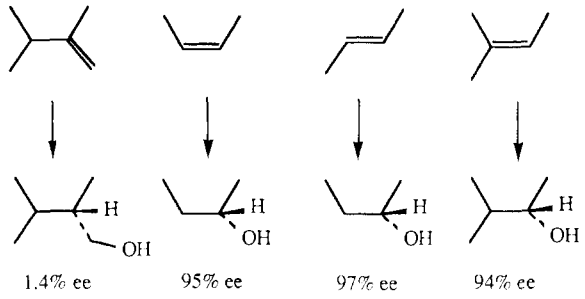


Figure 10. Asymmetric hydroboration with the Masamune reagent.

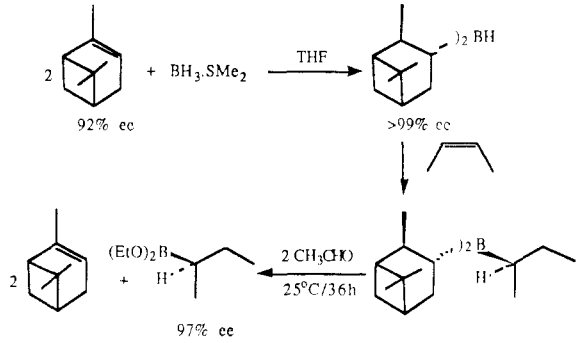


Figure 11. Asymmetric hydroboration with Ipc_2BH with regeneration of the α-pinene.

proved resistant and gave nearly racemic product (Figure 10).[19]

Unfortunately, the synthesis of this asymmetric hydroborating agent is not simple. Moreover, there is no indication as to whether it can be recycled. Consequently, until it becomes commercially available at a reasonable cost, its use will involve considerable effort.

A General Asymmetric Synthesis. As pointed out earlier, our studies have established that organoboranes transfer the alkyl group to essentially most of the other elements of synthetic and biological interest with complete maintenance of stereochemical integrity. Consequently, organoboranes derived from α-pinene exhibit great potential in converting commercially available olefins into various optically active derivatives. Initially, the application of asymmetric hydroboration was limited primarily to the synthesis of optically active alcohols.[20] Recently, chiral organoboranes obtained by asymmetric hydroboration have been utilized to synthesize optically active amines, halides, ketones, and hydrocarbons.[20,21] However, the optical purities of these compounds were less satisfactory, only in the range of 60–90%. One reason for this was the fact that chiral organoboranes were difficult to prepare in an optically pure form. Additionally, the optically active compounds obtained from the Ipc_2BR^* and $IpcBR^*H$ reagents were contaminated with isopinocampheyl migrated product, making further purification necessary.[22]

The chiral organoborane chemistry experienced a major renaissance in the past few years. Three recent developments have proven of major importance and offer promise of a general synthesis of enantiomerically

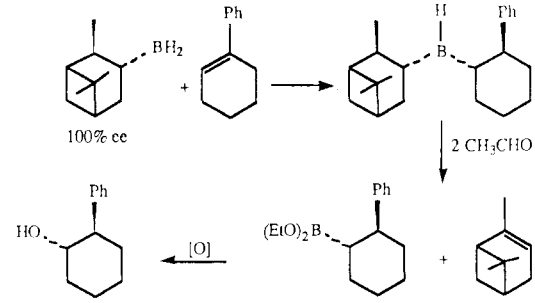


Figure 12. Asymmetric hydroboration with $IpcBH_2$ with regeneration of α-pinene.

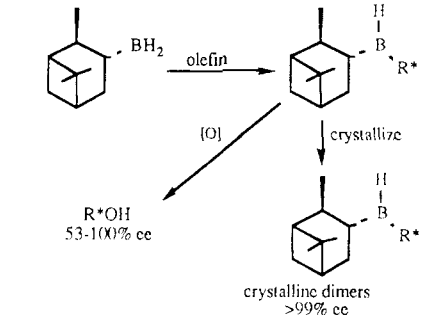


Figure 13. Major improvement in optical purity afforded by recrystallization of the hydroboration product.

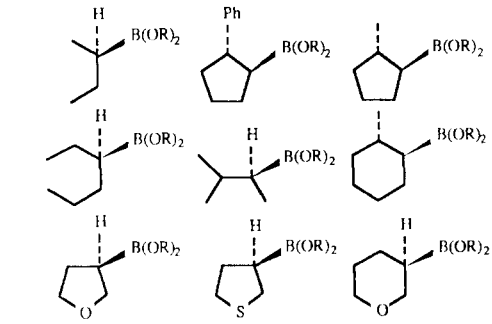


Figure 14. Representative boronic esters of > 99% ee.

pure organic compounds. Either of the two enantiomers can be produced at will. Consequently, for the first time we have within our grasp a rational synthesis of almost any organic compound with one chiral center in essentially 100% ee.

First, we discovered that treatment of the asymmetric hydroboration products with acetaldehyde removes the isopinocampheyl group as α-pinene, yielding the optically active boronic esters. In this way, 2-butyldiisopinocampheylborane is readily converted into diethyl 2-butylboronate in 97% ee (Figure 11).[23]

Similarly, diethyl *trans*-2-phenylcyclohexylboronate can be obtained in 97% ee.[18] The elimination of the isopinocampheyl group is highly selective and in all cases we have studied thus far this group is eliminated in preference to the chiral organic group. The α-pinene displaced could be readily recovered for recycling (Figure 12).

Second, it has proven possible to upgrade the hydroboration products from $IpcBH_2$ to materials approaching 100% ee. The reaction products from $IpcBH_2$ and olefins, IpcR*BH, are often crystalline dimers and readily crystallize from the reaction mixture. We have now discovered that such simple crystallization

(20) Brown, H. C.; Jadhav, P. K.; Mandal, A. K. *Tetrahedron* **1981**, *37*, 3547.
(21) Brown, H. C.; Jadhav, P. K.; Desai, M. C. *Tetrahedron* **1984**, *40*, 1325.
(22) Brown, C. A; Desai, M. C.; Jadhav, P. K. *J. Org. Chem.* **1986**, *51*, 162.
(23) Brown, H. C.; Jadhav, P. K.; Desai, M. C. *J. Am. Chem. Soc.* **1982**, *104*, 4303.

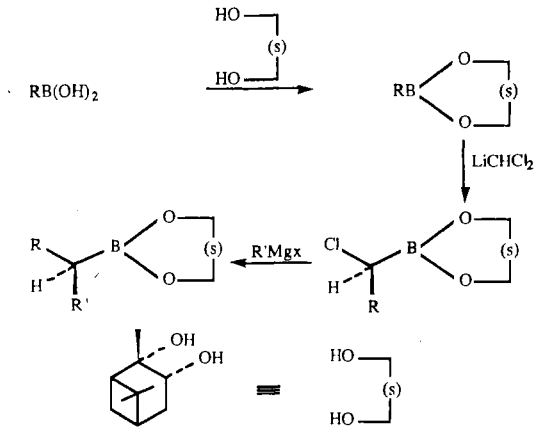


Figure 15. Matteson procedure for the synthesis of optically active boronate esters.

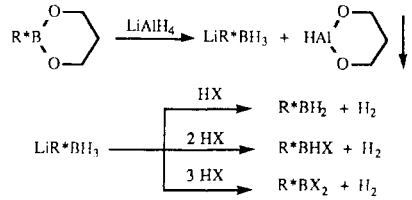


Figure 16. Conversion of optically active boronic acids into optically active borohydrides and derived boranes.

provides product of essentially 100% ee (Figure 13).[24]

We could now readily synthesize many chiral boronic esters of essentially 100% enantiomeric purity (Figure 14).[24]

Recently, Matteson and his co-workers have achieved a complementary synthesis of optically active boronic esters by a homologation procedure (Figure 15).[25] This provides an alternative procedure for synthesizing organoborane derivatives containing a chiral organic group. Unfortunately, at the present time, no practical procedure appears to be available for removing the pinanediol chiral auxiliary from the boronic ester for recycle. A solution to this problem would make available an excellent, independent source of optically active boronic acid derivatives for the general synthesis of enantiomerically pure organic compounds using organoborane chemistry.

Third, treatment of these optically active boronic esters, prepared either by asymmetric hydroboration or by Matteson's procedure, with lithium aluminum hydride converts these relatively unreactive boronic esters into very reactive, optically active lithium monoalkylborohydrides, LiR^*BH_3. By an appropriate choice of the ester group, the aluminum byproduct, $HAl(OR)_2$, readily precipitates from the reaction mixture. Simple treatment of the monoalkylborohydride with acid gives the optically active monoalkylborane and other substituted borane derivatives (Figure 16).[26]

Conversion of boronic esters into optically active monoalkylboranes circumvented a major difficulty. In the past, the chemistry of organoboranes were largely explored by using the simple trialkylboranes R_3B or certain trialkylborane derivatives, such as *B*-alkyl-9-

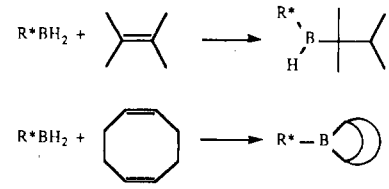


Figure 17. Synthesis of optically active thexyl and 9-BBN derivatives.

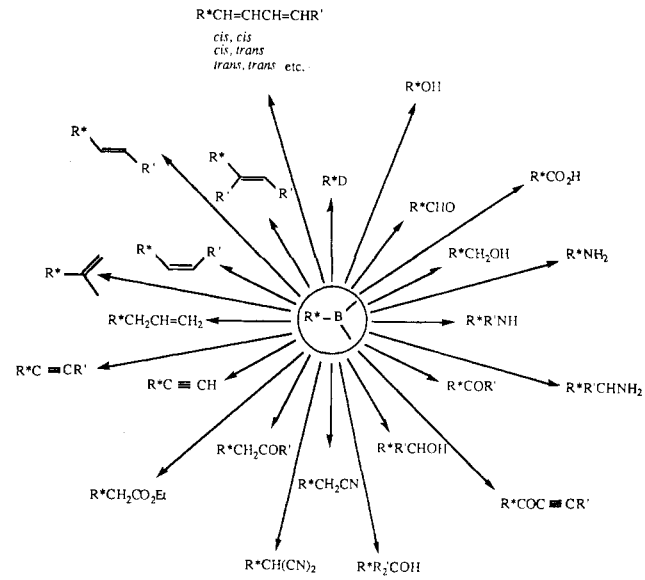


Figure 18. Borane chemistry makes possible a general synthesis of optically pure enantiomers.

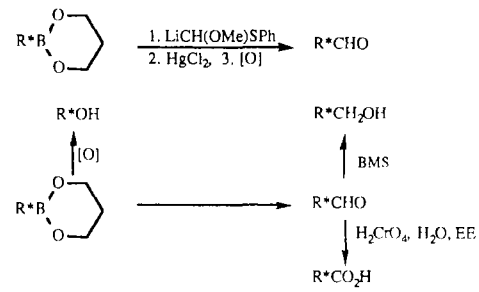


Figure 19. Conversion of optically active boronic esters into optically active aldehydes, acids, and methylol derivatives of essentially 100% ee. BMS = borane–methyl sulfide.

borabicyclo[3.3.1]nonane (B-R-9-BBN) or thexyldialkylborane ($ThxR_2B$). Boronic esters were never used as starting materials, other than in the oxidation reaction. The question then arose as to whether it would be possible to utilize the enantiomerically pure boronic acids or esters for such syntheses. Now that we can convert the boronic esters into enantiomerically pure monoalkylboranes, we can make all of the boron reagents we had previously found valuable in organic synthesis in very high enantiomeric purity (Figure 17).[27,28]

Now the remarkable synthetic versatility of organoboranes takes over. For the first time, we have a wide variety of procedures available for the synthesis of both (+) and (−) isomers, enantiomerically pure boronic esters, and other boron intermediates. It appears as if we have been building up organoborane chemistry primarily for this moment. Now we can use all of the

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(27) Brown, H. C.; Bakshi, R. K.; Singaram, B. *J. Am. Chem. Soc.* **1988**, *110*, 1529.
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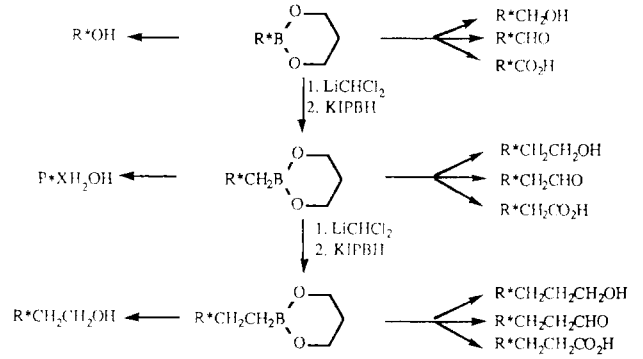


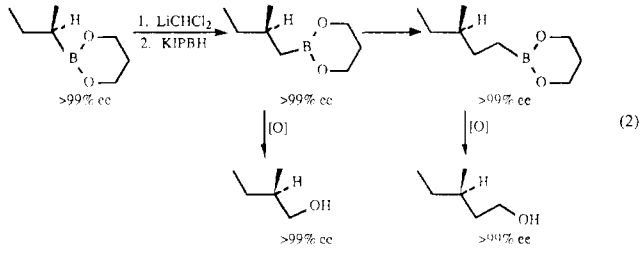
Figure 20. Synthesis of optically active derivatives via successive homologations. KIPBH = potassium triisopropoxyborohydride.

knowledge previously gained in developing organoborane chemistry and envisage a general synthesis of any pure enantiomer desired (Figure 18).

Fortunately, there are now a number of reactions that can be applied to the relatively unreactive boronic esters. Thus they are readily converted into α-chiral aldehydes, R*CHO, and these can be reduced to β-chiral alcohols, R*CH_2OH, or oxidized to α-chiral acids, R*CO_2H (Figure 19).[29]

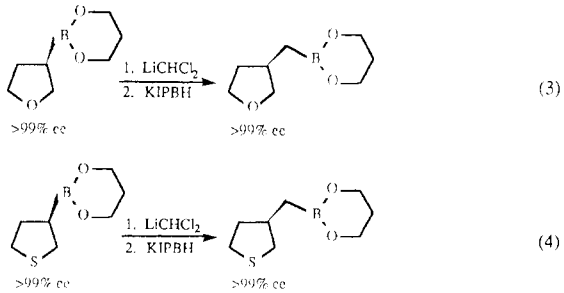
Chloromethylation by the Matteson procedure[25] followed by reduction provides the enantiomerically pure β-chiral boronic esters, which are difficult to prepare by the asymmetric hydroboration of 2-substituted 1-alkenes. A second operation provides the γ-chiral boronic esters (Figure 20).[30]

For example, (*R*)-*sec*-butylboronic ester was homologated readily and upon oxidation furnished (*R*)-2-methyl-1-butanol. A second homologation followed by oxidation gave (*R*)-3-methyl-1-pentanol. These alcohols are important chiral building blocks and are rather difficult to prepare from natural sources (eq 2).[31]



(2)

We also successfully homologated enantiomerically pure heterocyclic boronic esters using the one-carbon homologation procedure (eq 3 and 4).[32]



(3)

(4)

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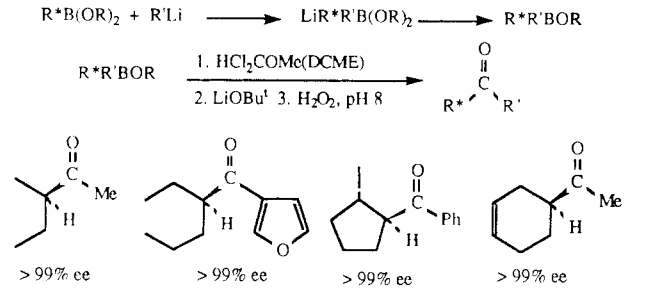


Figure 21. Synthesis of optically active ketones of essentially 100% ee.

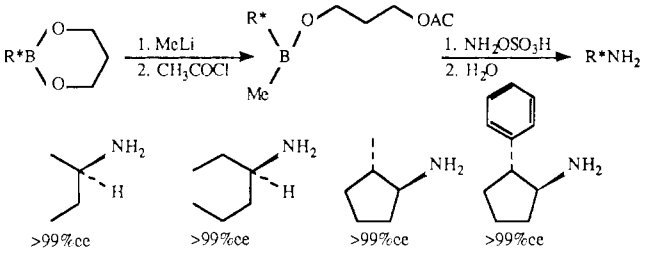


Figure 22. Procedure for the synthesis of primary amines in high enantiomeric purity.

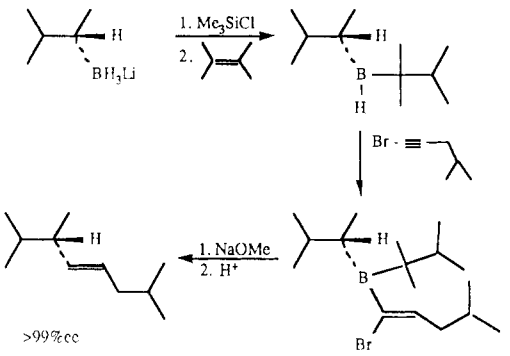
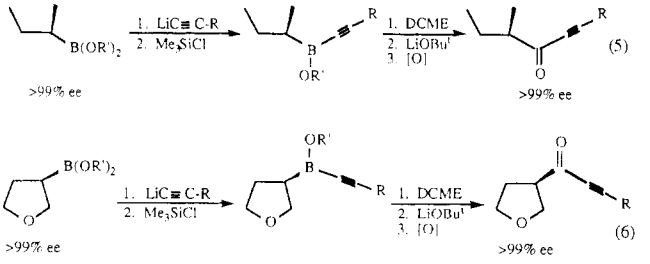


Figure 23. Synthesis of optically active *trans*-alkenes.

Enantiomerically pure boronic esters can be converted into optically active ketones of very high enantiomeric purity through the intermediate formation of the corresponding borinic esters (Figure 21).[33]

This reaction was readily extended to the synthesis of enantiomerically pure α-chiral acetylinic ketones (eq 5 and 6).[34]



(5)

(6)

Primary amines of very high optical purity can also be obtained from the boronic esters through the intermediate formation of alkylmethylborinic esters (Figure 22).[35]

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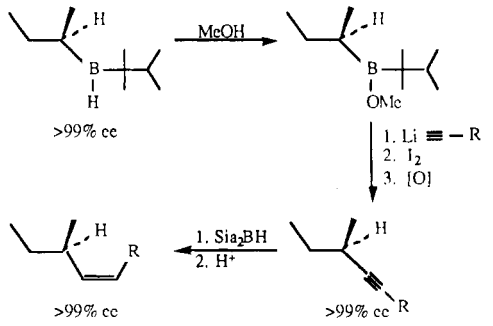

Figure 24. Preparation of optically active alkynes and *cis*-olefins.

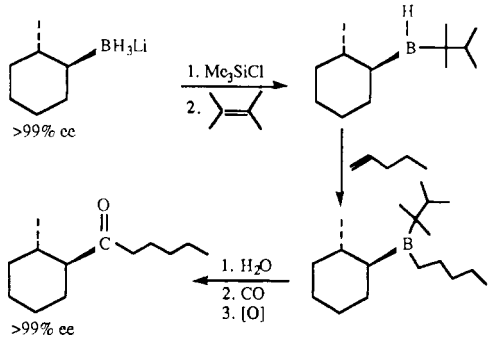

Figure 25. Conversion of optically active ThxR*BH into ketones of essentially 100% ee.

As mentioned earlier, we can now synthesize enantiomerically pure thexylmonoalkylboranes, ThxR*BH, which are versatile synthetic intermediates. We have utilized these derivatives for various carbon–carbon bond-forming reactions leading to enantiomerically pure *trans*-alkenes, *cis*-alkenes, alkynes, and ketones.[27] For example, the reaction of (*S*)-(3-methyl-2-butyl)thexylborane with 1-bromo-4-methyl-1-pentyne, followed by treatment with sodium methoxide and protonolysis provides (*S*)-*trans*-2,3,7-trimethyl-4-octene (Figure 23).[27]

Reaction of methyl (*R*)-2-butylthexylborinate with an alkynyllithium followed by iodination and oxidation furnishes the corresponding enantiomerically pure alkyne. The optically active *cis*-olefin is obtained from the alkyne by hydroboration followed by protonolysis (Figure 24).[27]

Optically active thexylmonoalkylboranes can also be converted into optically active ketones. Thus, (1*S*,2*S*)-(*trans*-2-methylcyclohexyl)thexylborane is readily converted with 1-pentene into the corresponding trialkylborane. Carbonylation of this trialkylborane, followed by oxidation, furnished optically active (1*S*,2*S*)-*trans*-2-methylcyclohexyl *n*-pentyl ketone (Figure 25).[27]

Finally, we have utilized the enantiomerically pure *B*-alkyl-9-borobicyclononane derivatives for the synthesis of homologated esters, nitriles, and ketones of very high optical purity (Figures 26–28).[28]

In this article we have described major developments, largely in our own research program, that led from the first chiral organoborane, Ipc_2BH, to the present time when we have numerous reagents, methods, and applications based on chiral organoboranes for asymmetric synthesis in organic chemistry. Recent developments in our laboratory have greatly expanded the availability of chiral organoboranes and their derivatives in a very high enantiomeric purity. Simple procedures either are available or envisioned to transfer the chiral organic group from boron to the desired organic moiety. Because both (+)- and (−)- α-pinene are readily available, the process makes it possible to synthesize either enantiomer at will. Finally, the procedure can be controlled to permit the simple recovery and recycling of the chiral auxiliary.

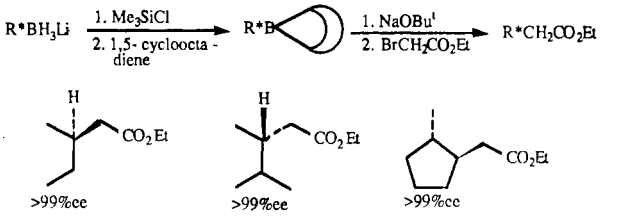

Figure 26. Preparation of optically active homologated esters.

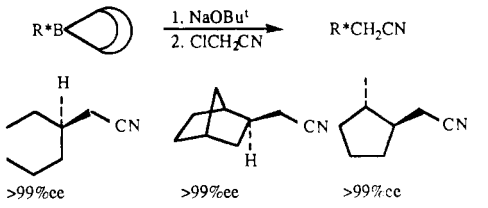

Figure 27. Conversion of optically active B-R*-9BBN into homologated nitriles of essentially 100% ee.

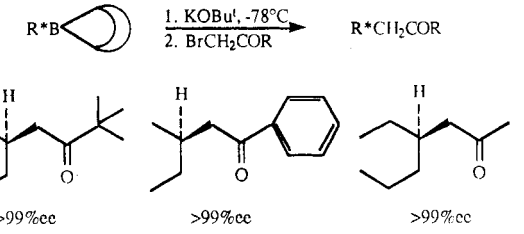

Figure 28. Synthesis of optically active homologated ketones.

While we are now only about one-third of the way around the chart (Figure 18), our experience does not reveal any major difficulties in continuing to complete the development of this general asymmetric synthesis. In recent years numerous organic chemists have developed ingenious approaches to achieve asymmetric syntheses in a variety of systems.[36] In most cases the methods are relatively limited, applicable only to the synthesis of limited groups of compounds or special structural types. In contrast, the borane route appears to provided the first truly general approach to the synthesis of almost any pure enantiomer desired.

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