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ASYMMETRIC SYNTHESES VIA CHIRAL ORGANOBORANE REAGENTS

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CONTENTS

1. INTRODUCTION

"Asymmetric synthesis" is a term first used in 1894 by E. Fischer and defined in 1904 by Marckwald[1] as "a reaction which produces optically active substances from symmetrically constituted compounds with the intermediate use of optically active materials but with the exclusion of all analytical processes". A broader definition was proposed[2] by Morrison and Mosher: "An asymmetric synthesis is a reaction in which an achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products (enantiomeric or diastereomeric) are formed in unequal amounts. This is to say, an asymmetric synthesis is a process which converts a prochiral unit into a chiral unit so that unequal amounts of stereoisomeric products result". The reactant involved can be chemical reagents, solvents, catalysts, or physical factors, such as circularly polarized light.

Asymmetric organic reactions have proven to be of value in the study of reaction mechanisms, in the determination of relative configurations, and in the practical synthesis of optically active compounds. The main interest is in the pharmaceutical area. An increasing number of drugs, food additives and flavoring agents are being prepared by total synthesis. Most often the stereoselective synthesis of these compounds is achieved in the racemic series by means of an optical resolution performed at the end of the synthetic sequence. This is a wasteful procedure preparatively, since if only one optical antipode is of use or interest, half of the synthetic product is often discarded. Moreover, resolution is usually a tedious and laborious process. It is economically and esthetically appealing to exclude unwanted optical isomers at the earliest possible stage through asymmetric creation of chiral centers. In the interest of yields, it is wise to choose an early step in the synthetic sequence for asymmetric operations and to consider carefully the principles of convergent synthesis.

In an asymmetric reaction, substrate and reagent combine to form diasteromeric transition states. One of the two reactants must have a chiral center to induce asymmetry at the reaction site. Most often asymmetry is created upon conversion of trigonal carbons to tetrahedral ones at the site of the functionality, involving groups such as carbonyl, enamine, enol, imine and olefin. Such asymmetry at carbon as well as induction by, and creation of asymmetry at sulphur is currently the major area of interest to the synthetic organic chemist.

By far, the best asymmetric synthesis is done in nature by enzymes. However, a considerable effort has been put forward by chemists to achieve comparable results. There is the challenge to develop chemical systems as efficient as enzymatic ones. For a long time it was questioned whether high optical yields could be effectively attained by organic chemists without the help of enzymes. However, an increasing amount of recent results demonstrates that versatile and efficient non-enzymatic asymmetric syntheses are indeed possible. Of course, much work must be done to find general methods. The most serious obstacle continues to be the lack of a basic understanding of the factors affecting asymmetric induction.

The increase in synthetic methodology for asymmetric synthesis is exemplified by the numerous reviews that have appeared in the literature, in particular, the recent ones by Morrison and Mosher (1971),[2] Scott and Valentine (1974),[3] Meyer (1978),[4] Kagan and Fiaud (1978),[5] Valentine and Scott (1978),[6] and Apsimon and Sequin (1979).[7] These reviews, however, did not cover in depth the recent advances in asymmetric synthesis by chiral organoborane reagents. It has been observed recently that some of these chiral boranes can approach and may even match the selectivity provided in nature by enzymes. The synthesis of optically active products *via* chiral organoborane reagents satisfies most of the criteria for a good asymmetric synthesis (i) high enantiomeric and chemical yields, (ii) easy separation of the chiral products from the chiral auxiliary reagent, (iii) capability to synthesize both the enantiomers of the product and (iv) ready availability of naturally occurring terpenes needed to prepare these chiral organoborane reagents. Although these chiral auxiliary reagents could doubtless be recycled, it is an advantage at this stage that they need not be recycled because of the natural abundance and low cost of such terpenes.

Hydroboration is perhaps one of the most efficient reactions in synthetic organic chemistry.[8-10] The functionality available through hydroboration and subsequent modification of the resulting organoborane is extensive. Monoalkyl- or dialkylboranes exhibit a remarkable stereospecificity and regioselectivity for the hydroboration of olefins. This property, coupled with the capability for asymmetric creation of chiral centers with chiral hydroborating agents, makes this reaction a most valuable one for asymmetric organic synthesis. Diisopinocampheylborane, an excellent chiral hydroborating agent, was discovered[11] in the early sixties. The report[12] of the second chiral hydroborating agent came almost 15 years later. The limiting factor was the inability to stop the hydroboration at the monoalkylborane stage. The discovery of new reagents, new methods for their synthesis, and new applications made possible the synthesis of the first chiral monoalkylborane, monoisopinocampheylborane, a reagent which is proving highly valuable in asymmetric synthesis.[13,14] The highly hindered diisopinocampheylborane achieves almost quantitative asymmetric induction in unhindered *cis*-olefins,[15] whereas, the less hindered monoisopinocampheylborane is very effective for more hindered[13,14] olefins. Very recently, dilongifolylborane, a new chiral hydroborating agent of intermediate steric requirements, has been discovered.[16]

Although these chiral hydroborating agents achieve an exceptionally high degree of asymmetry in olefinic systems, their application as chiral reducing agents for prochiral carbonyl compounds has been less effective.[17] Reduction of prochiral carbonyl compounds using chiral borohydrides (superhydrides) provide alcohols in moderate enantiomeric purities.[18] Very recently, Midland and coworkers have discovered a new class of chiral reducing agents.[19] Their extensive search[20] for effective chiral *B*-alkyl-9-borabicyclo[3.3.1]-nonanes led them to the discovery that *B*-3-pinanyl-9-BBN reduces 1-deuterated aldehydes[20] and α,β-acetylenic ketones[21] to the corresponding chiral alcohols with remarkable consistency and enzyme-like selectivity.

The purpose of this review is therefore to illustrate the various reactions that the chiral organoboranes undergo to yield optically active products. Most of the asymmetry created by these reagents is by the conversion of trigonal carbons at the site of either olefin or carbonyl functionalities to asymmetric tetrahedral carbon atoms. For convenience and clarity, the material is arranged according to two types of reactions: (1) the asymmetric hydroboration of olefinic systems, and (2) the asymmetric reduction of carbonyl compounds. The processes of kinetic resolution of olefins and dienes do not qualify as asymmetric syntheses, since a new asymmetric center is not produced; however, it may be appropriate to discuss this application under the topic asymmetric hydroboration.

2. ASYMMETRIC HYDROBORATION

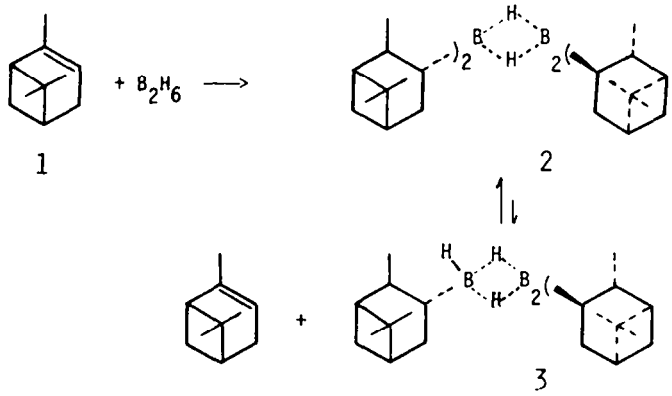
A. Diisopinocampheylborane

Diisopinocampheylborane (IPC_2BH) is perhaps one of the most versatile chiral reagents readily available for laboratory use. It has been used for the synthesis of many chiral products, such as alcohols,

halides, amines, ketones, hydrocarbons and α-amino-acids. It has also been used for reduction of prochiral ketones to chiral alcohols. The kinetic resolution of alkenes, dienes and allenes with this valuable reagent has also been extensively studied. A major advantage of IPC_2BH is the ready availability of both enantiomers of α-pinene. Consequently, chiral centers of opposite configuration can be generated using IPC_2BH derived from the appropriate antipode of α-pinene.

1. Preparation

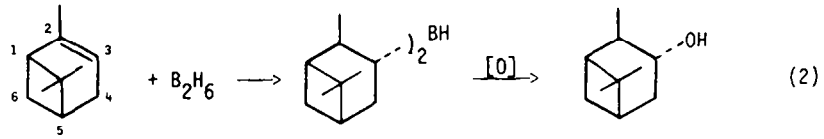
α-Pinene **1** readily undergoes hydroboration[22] at 0° to form *sym*-tetraisopinocampheyldiborane[23,24] **2**. Even in the presence of excess α-pinene, the reaction does not proceed further. In the absence of excess α-pinene, there is evidence for a significant dissociation of **2** into α-pinene and triisopinocampheyldiborane[25] **3** (eqn 1). Consequently, it is desirable to prepare and utilize the reagent in diglyme in order



(1)

to minimize the amount of dissociated product. The product evidently exists in the solid state and in ether solvents as the dimeric diborane derivative,[23,24] but it is usually named as the monomer for the sake of convenience. Hydroboration of (+)-α-pinene ($[\alpha]_D$ +47.6°, neat) affords (−)-IPC_2BH($[\alpha]_D$ −37.1°, THF). Similarly, the hydroboration of (−)-α-pinene gives (+)-IPC_2BH.

Hydroboration involves the *cis*-addition of boron and hydrogen to the double bond from the less hindered side of the molecule. Oxidation of the organoborane with alkaline hydrogen peroxide proceeds with complete retention of configuration[26] (eqn 2). Thus, hydroboration-oxidation of (+)-α-pinene provides



(2)

1, (1*R*,5*R*)-(+)- 4, (1*R*,2*S*,3*R*,5*R*)-(-)- 5, (1*R*,2*R*,3*R*,5*S*)-(-)-

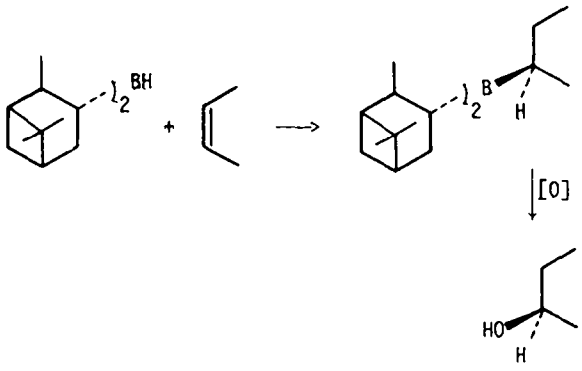
(−)-isopinocampheol **5** ($[\alpha]_D$ −32.4°) with absolute configuration (1R, 2R, 3R, 5S). Therefore, (−)-IPC_2BH **4** formed by the hydroboration of (+)-α-pinene possesses the absolute configuration (1R, 2S, 3R, 5R).

The reagent, IPC_2BH, is prepared by treating the calculated quantity of α-pinene and sodium borohydride in diglyme at 0° with the theoretical quantity of boron trifluoride etherate over a period of 15 min (eqn 3).

$$8\ \alpha\text{-pinene} + 3NaBH_4 + 4BF_3{\cdot}O(C_2H_5)_2 \longrightarrow 4IPC_2BH + 3NaBF_4 + 4(C_2H_5)_2O. \quad (3)$$

The reaction mixture is maintained at 0° for an additional 4 hr prior to use, in order to ensure completion of the hydroboration reaction.

The reagent, (−)-IPC_2BH, thus prepared from (+)-α-pinene ($[\alpha]_D$ +47.6°, 93% e.e.) has been used for the asymmetric hydroboration of *cis*-2-butene to afford (R)-(−)-2-butanol **6** in 87% enantiomeric excess (e.e.) after oxidation of the organoborane with alkaline hydrogen peroxide[11] (eqn 4). The

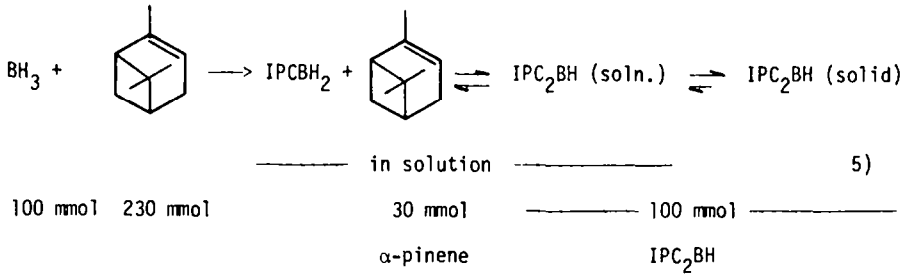


(4)

hydroboration of *cis*-2-butene with the reagent prepared from the same α-pinene in a more convenient solvent, tetrahydrofuran (THF), followed by oxidation, affords 2-butanol of slightly lower optical purity (78% e.e.) than that realized in diglyme[22] (87% e.e.). The less satisfactory result in THF is attributed to the greater solubility of IPC_2BH in THF, resulting in more dissociation of the total IPC_2BH present in this medium than in diglyme.

A more systematic study[15] of the preparation of IPC_2BH in THF has been carried out recently. The study revealed that the reaction of α-pinene with BH_3·THF proceeds rapidly to the triisopinocampheyldiborane stage and much more slowly thereafter. The preparation of IPC_2BH in more dilute solution for a shorter period of time results in the formation of a considerable amount of triisopinocampheyldiborane, or monoisopinocampheylborane ($IPCBH_2$), named as the monomer. This species is expected to react faster than IPC_2BH with the olefin. For example, according to this study, the reaction of 0.5 M BH_3 solution with two equivalents of α-pinene for 24 hr at 0°, gives 12% $IPCBH_2$ and 88% IPC_2BH. It is known that $IPCBH_2$ on asymmetric hydroboration-oxidation gives alcohols of configuration opposite to that produced by IPC_2BH (see Section II.B). Therefore, a good asymmetric hydroboration is not achieved with such a mixture of reagents.

This detailed study for the preparation of IPC_2BH led to a convenient, advantageous synthesis of IPC_2BH of high optical purity. It was established that the reaction of 15% excess α-pinene (94% e.e.) with borane in THF at 0° for 3 days led to the formation of IPC_2BH in quantitative yield (eqn 5). The



longer reaction time is accompanied by the selective incorporation of the major isomer of α-pinene into the reagent, whereas the minor isomer accumulates in the solution (eqn 5). Indeed, it is found that the α-pinene obtained by dehydroboration of solid IPC_2BH with triethylamine is 99.8% enantiomerically pure (compared to 94% e.e. for the α-pinene used). Similarly, the enantiomeric purity of isopinocampheol obtained after oxidation of the solid IPC_2BH is considerably higher than those previously reported. The enantiomeric purity of the excess (+)-α-pinene in the solution decreased considerably, from 94% e.e. of the original material to 80.2% e.e. Thus IPC_2BH prepared with excess α-pinene for 3 days at 0° has an exceptionally high optical purity. Apparently the formation of IPC_2BH of higher optical purity than the purity of the (+)-α-pinene utilized is due to the preferential precipitation of (+)(+)-IPC_2BH over (+)(−)-IPC_2BH (Scheme 1). The (+)(−)-IPC_2BH present in the solution would be expected to undergo exchange with the excess α-pinene to give chiefly (+)(+)-IPC_2BH, since the excess α-pinene consists of more than 90% of (+)-α-pinene and less than 10% (−)-α-pinene.

$$(+)(-)\text{-IPC}_2\text{BH} \rightleftharpoons (+)\text{-IPCBH}_2 + (-)\text{-}\alpha\text{-pinene}^*$$

or

$$(+)(-)\text{-IPC}_2\text{BH} \rightleftharpoons (-)\text{-IPCBH}_2 + (+)\text{-}\alpha\text{-pinene}$$

$$(+)\text{-IPCBH}_2 + \text{excess } \alpha\text{-pinene} \rightarrow (+)(+)\text{-IPC}_2\text{BH} + (+)(-)\text{-IPC}_2\text{BH}$$

$$(+) > 90\%,\ (-) < 10\% \qquad > 90\% \qquad < 10\%$$

$$(-)\text{-IPCBH}_2 + \text{excess } \alpha\text{-pinene} \rightarrow (-)(+)\text{-IPC}_2\text{BH} + (-)(-)\text{-IPC}_2\text{BH}$$

$$(+) > 90\%,\ (-) < 10\% \qquad > 90\% \qquad < 10\%$$

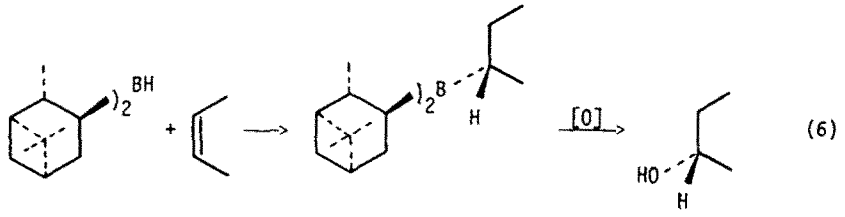
*$(+)$-$IPCBH_2$ corresponds to $(+)$-α-pinene

Scheme 1.

Thus, IPC_2BH of high enantiomeric purity (99.8% e.e.) is obtained from enantiomerically less pure α-pinene (94% e.e.). This preparation has a great advantage in view of the fact that high optical purity α-pinene is often not easily accessible. We recommend this method of preparation of IPC_2BH to the users of this reagent.

2. *Synthesis of chiral alcohols*

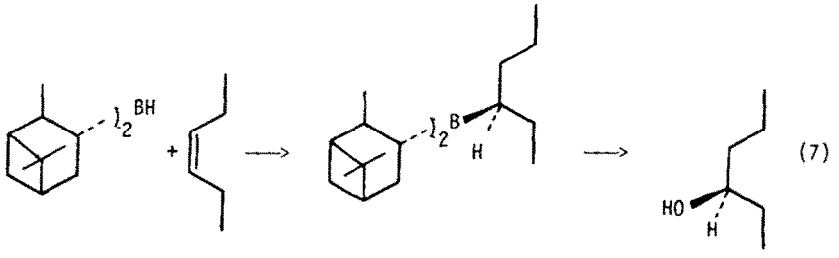
Asymmetric hydroboration of cis olefins. Hydroboration of cis olefins with IPC_2BH proceeds rapidly to the trialkylborane stage. The organoboranes do not undergo significant racemization over periods[22] of up to 48 hr at 25°. Oxidation with alkaline hydrogen peroxide gives isopinocampheol and the corresponding alcohol. Thus $(-)$-IPC_2BH **4**, obtained by the hydroboration of $(+)$-α-pinene (93% e.e.), reacts readily with *cis*-2-butene to yield, after oxidation, (R)-(−)-2-butanol **6** in 87% e.e. (eqn 4).



(6)

7 8, (S)-(+)-

Similarly, $(+)$-IPC_2BH **7** affords (S)-(+)-2-butanol **8** in 86% e.e. (eqn 6). The 2-butanol obtained by hydroboration of *cis*-2-butene with the high optical purity IPC_2BH now available, as described earlier, followed by oxidation, provided 2-butanol of 98.4% enantiomeric purity.[15] Similarly, *cis*-3-hexene on hydroboration with such enantiomerically pure $(-)$-IPC_2BH, followed by oxidation, provides (R)-(−)-3-hexanol in 95% e.e.[27] (eqn 7). High optical purity IPC_2BH has been applied thus far only to these two systems. Consequently, application to other olefins should give alcohols in higher optical purities than



(7)

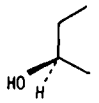
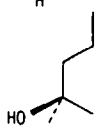
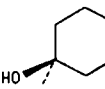
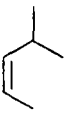
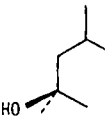
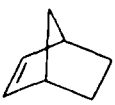
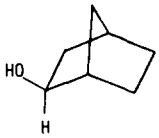
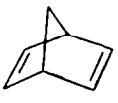
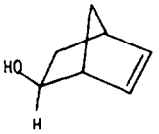
(R)-(-)-

those realized earlier. The results realized by asymmetric hydroboration of other *cis*-acyclic, cyclic and bicyclic olefins and dienes are summarized in Table 1.

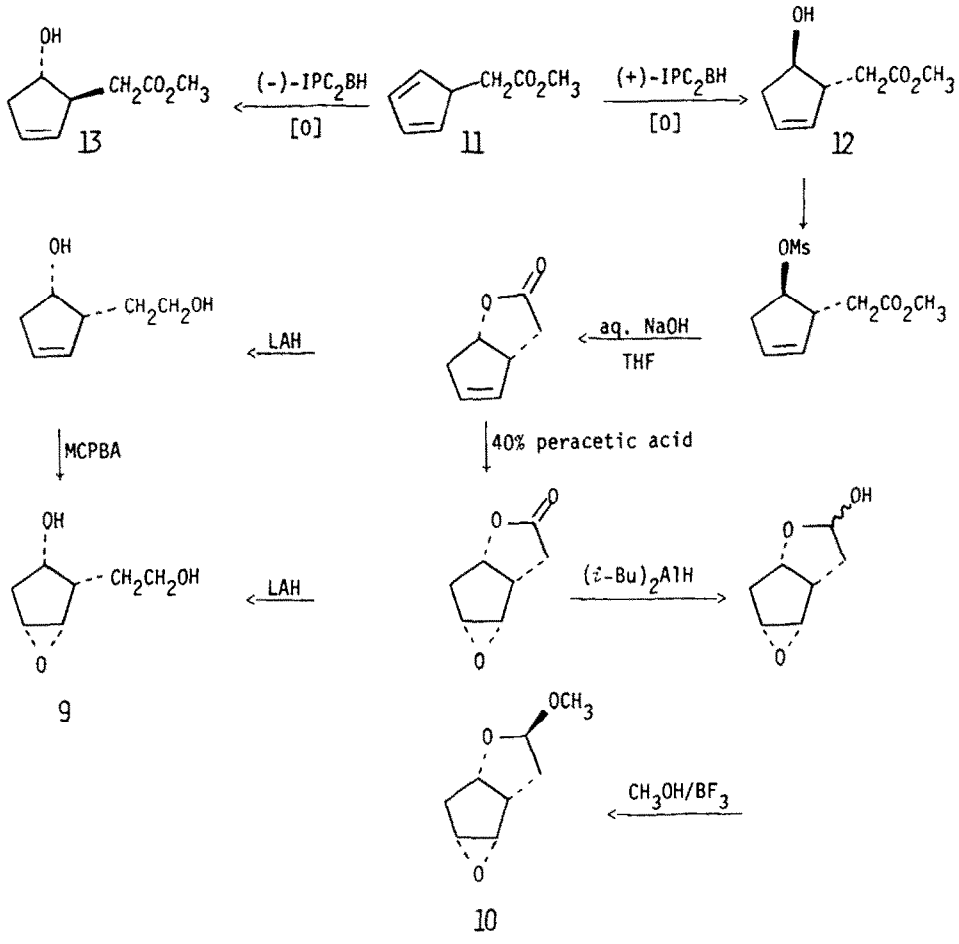
This unique, high degree asymmetric induction property of IPC_2BH toward *cis*-olefins has been utilized to achieve an asymmetric synthesis of prostaglandin intermediates[29] **9** and **10**. These intermediates required to synthesize prostaglandin $F_{2\alpha}$ possess four nuclear chiral centers. IPC_2BH was used in a key step to create two chiral centers with a high degree of asymmetry. Thus, diene **11**, on treatment with (+)-IPC_2BH, followed by oxidation, gives hydroxy ester **12**. Similar treatment of **11** with (−)-IPC_2BH affords **13**, an antipode of **12**. NMR study of the corresponding (R)-(+)-α-methoxy-α-trifluoromethylphenylacetates of hydroxy esters **12** and **13** established that the enantiomeric purity of both the antipodes is at least 92% e.e. The hydroxy ester **12** and **13** of high optical purity were then elaborated into the prostaglandin intermediates (Scheme 2). These results open additional routes for the facile preparation of optically active prostaglandins in substantial quantities.

Another useful application of IPC_2BH has been demonstrated in the asymmetric synthesis of the natural product loganin,[30] an important building block in much of the plant world. A high degree of asymmetry is induced during the hydroboration of the prochiral diene **14** with (+)(-IPC_2BH. Thus, the homoallylic alcohol of the intermediate organoborane (eqn 8). Similarly, (−)-IPC_2BH gives (1S,

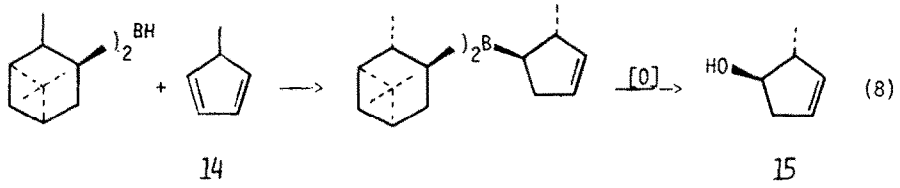
Table 1. Hydroboration of *cis*-olefins with (−)-IPC_2BH[a]

NO	Olefin	Alcohol	ROH $[\alpha]_D^{20}$	ROH e.e., %	ROH Config.
1			-11.8(-13.3)[b]	87(98.4)[b]	*R*
2		 76% (24% 3-pentanol)	- 8.6[c]	82[d]	*R*
3			- 6.5(-6.7)[b]	91(95)[b]	*R*
4		 96% (4% 2-methyl-3-pentanol)	-16.0[e]	76[f]	*R*
5			- 2.0	67-70(40)[g]	1*S*,2*S*
6			+ 5.8	48-51[h]	1*R*,2*S*

[a]To minimize confusion, all rotations and configurations are referred to reagents prepared from (+)-α-pinene, $[\alpha]_D$ + 47.6°, 93% e.e. [b]Results obtained by using high optical purity (+)-IPC_2BH; ref. 15 and 27. [c]For the mixture of 2- and 3-pentanol. [d]Calculated for pure 2-pentanol. [e]For the mixture of 4-methyl-2-pentanol and 2-methyl-2-pentanol. [f]Calculated for pure 4-methyl-2-pentanol. [g]Enantiomeric excess is found to be 40% by NMR using chiral shift reagent Eu(hfc)$_3$. [h]Ref. 28.

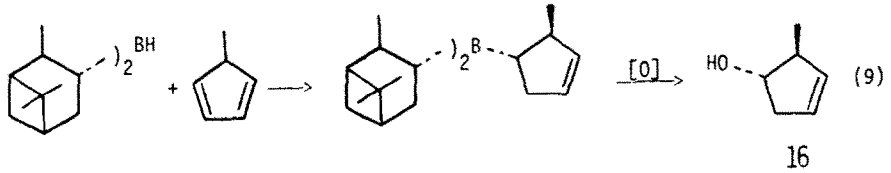


Scheme 2



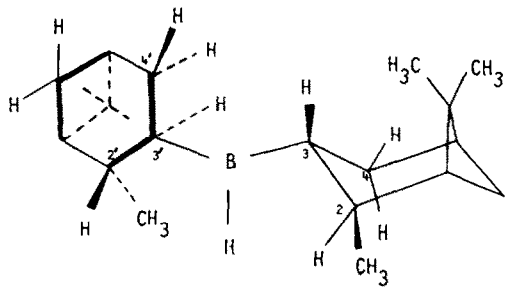
(8)

2S)-2-methyl-3-cyclopenten-1-ol, **16**, in equivalent optical purity (eqn 9). The intermediate **15** is then elaborated to the desired product. In this way a resolution step is avoided by introducing the chirality in the first step of the total synthesis.

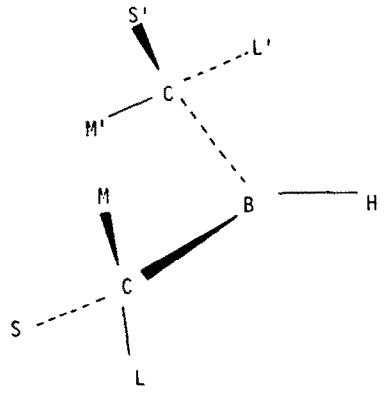


(9)

The alcohols obtained by hydroboration-oxidation of unhindered *cis* olefins using (−)-IPC_2BH have the same absolute configuration consistently. Hence there is a definite steric relationship between the absolute configuration of the product alcohol and the absolute configuration of the reagent. A model was proposed to predict the absolute configuration of the products obtained by using IPC_2BH.[31] The proposed model is based on the most stable rotameric conformation[22,31] of (−)-IPC_2BH where the borane group and the *trans*-methyl on pinane moiety have a diequatorial arrangement and anti- or nearly

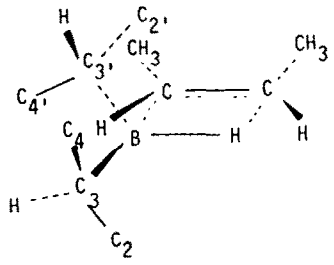


17

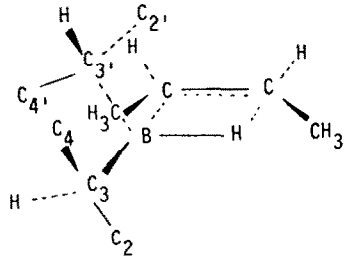


18

antiparallel orientation of the two methyl groups, as shown in **17**. The model was further simplified into **18** in the usual manner, using the symbols S (small) for the hydrogen, M (medium) for the methylene and L (large) for the methyl group. On the basis of the usual four-center transition state, it is possible to draw two different transition states for the addition of a *cis* olefin, as shown in **19** and **20**. The transition state **19** was favored over **20** because there is a greater interaction between the methyl group of *cis*-2-butene and the methylene of the pinane moiety in **20** than between the methyl and hydrogen in **19**.

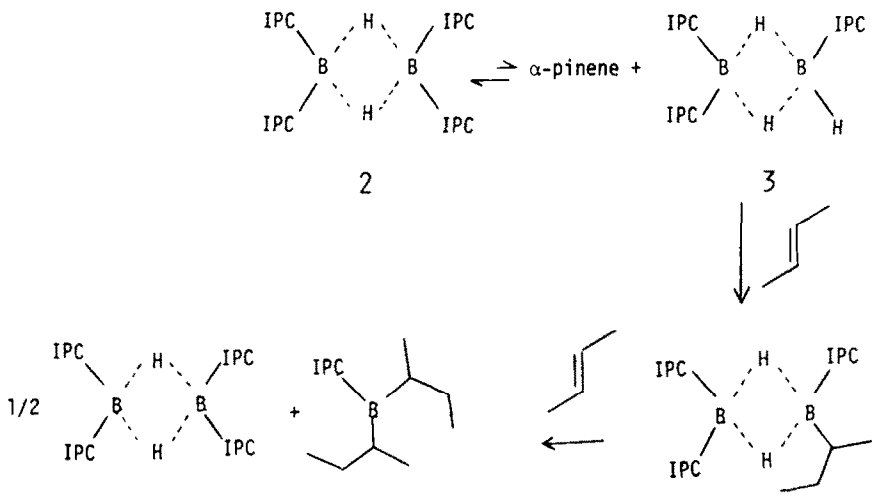


19



20

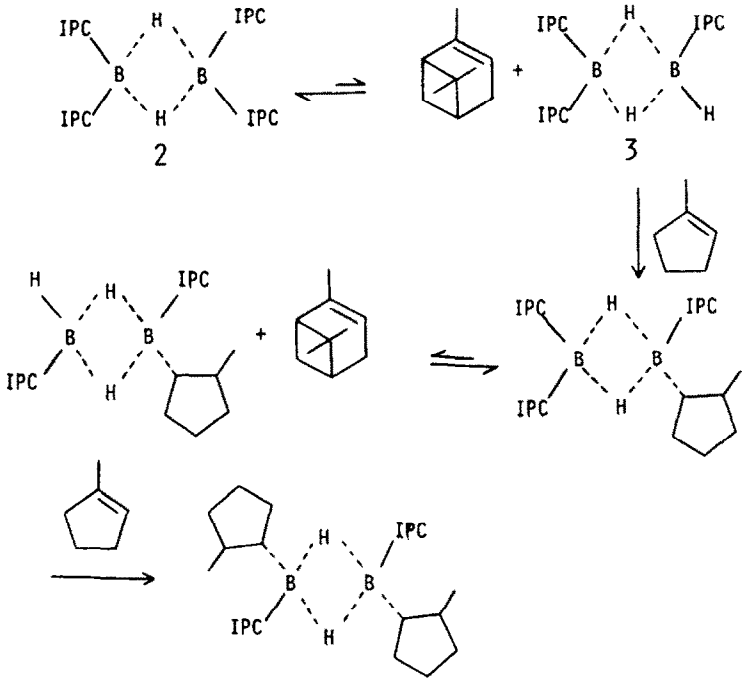
Asymmetric hydroboration of hindered olefins. The reaction of *cis*-2-butene with IPC_2BH is virtually complete in 2 h, whereas *trans*-2-butene requires 24 hr for essentially complete reaction.[32] Furthermore, the oxidation of the trialkylborane from *cis*-2-butene yields 2-butanol in 87% e.e. as compared to only 13% e.e. from the *trans* isomer. Moreover, *trans*-2-butene displaces 1 mole of α-pinene from the reagent for every 2 moles of olefin hydroborated. This suggests the possibility that each mole of IPC_2BH reacts with 2 moles of *trans*-2-butene (Scheme 3).



Scheme 3.

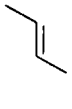
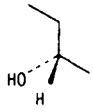
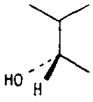
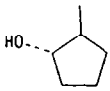
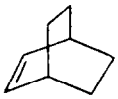
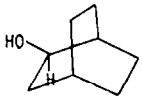
Hydroboration of the more hindered olefins, such as 2-methyl-2-butene and 1-methylcyclopentene, with IPC_2BH is extremely slow (0°, 60 hr) and proceeds with displacement of 1 mole of α-pinene for each mole of olefin hydroborated, to give oxidation products of low optical purities, 17% and 22% e.e. respectively.[32]

The lower hydroboration rate, the lower enantiomeric purities of the alcohols following oxidation, and, particularly, the displacement of α-pinene suggest that when the olefin is sufficiently hindered the hydroborating agent is not IPC_2BH or its dimer, **2**, but triisopinocampheyldiborane, **3**, formed by elimination of α-pinene from the dimer. This conclusion is supported by the observation that the reagent prepared with a 3:2 molar ratio of α-pinene and borane in THF hydroborates a trisubstituted olefin at a reasonable rate, and the alcohols obtained by oxidation have about the same enantiomeric purities as those obtained from the slow hydroboration of these alkenes with IPC_2BH. With these hindered olefins it appears that a second mole of α-pinene is displaced after **3** reacts with the first mole of olefin and then a second hydroboration occurs (Scheme 4). The results of the hydroboration of representative trans and hindered olefins are given in Table 2.



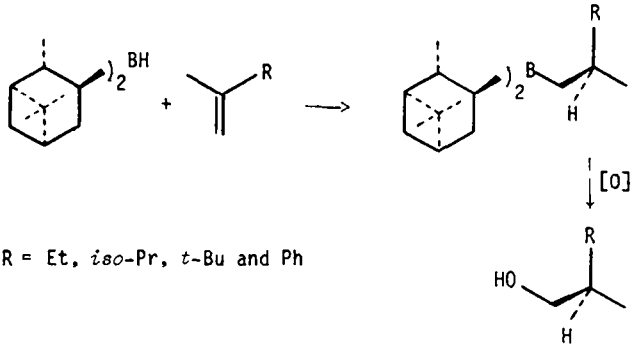
Scheme 4

Table 2. Hydroboration of hindered[a] olefins with (−)-IPC_2BH[b]

NO	Olefin	Alcohol	ROH $[\alpha]_D^{20}$	ROH e.e., %	ROH Config.
1			+1.44	13	*S*
2			+0.75	14	*S*
3			+6.1	22	1*S*,2*S*
4			-6.9[c]	17	2*R*

[a]In all of the reactions of hindered olefins with IPC_2BH, α-pinene is displaced from the reagent. [b]To minimize confusion, all rotations and configurations are referred to reagents prepared from (+)-α-pinene, $[\alpha]_D$ +47.6, 93% e.e. [c]Ref 33.

Asymmetric hydroboration of 2-methyl-1-alkenes. Hydroboration of 2-methyl-1-alkenes with IPC_2BH provides a synthetic route to optically active 2-methyl-1-alkanols[34] (eqn 10). The enantiomeric

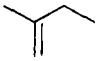
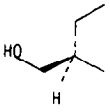
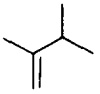
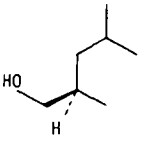
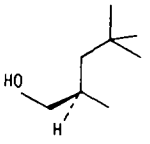
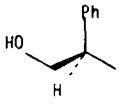


R = Et, *iso*-Pr, *t*-Bu and Ph (10)

excesses of alcohols obtained in this way are not as high as those of alcohols from the hydroboration of *cis*-olefins. The new asymmetric carbon is not that to which boron becomes attached and is therefore more remote from the chiral center in the transition state. Moreover, the reagent must discriminate between two very similar alkyl groups in order to achieve asymmetric synthesis. Considering these facts, the 21% enantiomeric purity realized in the synthesis of (R)-(−)-2-methylbutan-1-ol by hydroboration-oxidation of 2-methyl-1-butene with (+)-IPC_2BH, must be considered remarkable and reasonably satisfactory. By increasing the steric difference between the two alkyl groups, an increase in asymmetric induction is observed (Table 3, Entry 2).

A further increase in the steric difference between the two alkyl groups, *tert*-butyl and methyl, makes the alkene more sterically hindered (Table 3, Entry 3) to the extent that it reacts with IPC_2BH with considerable displacement of α-pinene (32%). This suggests that the hydroboration must be complex, involving both addition and displacement pathways. Consequently, a decrease in enantiomeric purity is not surprising.

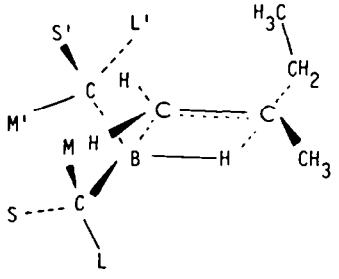
Table 3. Hydroboration of 2-methyl-1-alkenes with (+)-IPC_2BH[a]

NO	Olefin	Alcohol	ROH $[\alpha]_D^{20}$	ROH e.e., %	ROH Config.
1			+1.25	21	*R*
2			-1.88	30	*R*
3			-5.10	13	*R*
4			+0.80	5	*R*

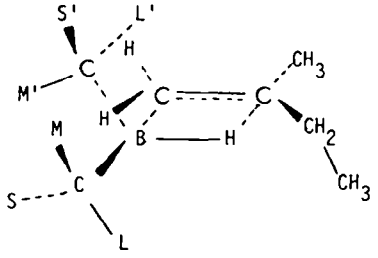
[a](+)-IPC_2BH prepared from (-)-α-pinene, $[\alpha]_D$ -47.9°, 93.5% e.e.

The reagent apparently discriminates between methyl and ethyl groups more effectively than it does between methyl and phenyl. The observation that the replacement of an alkyl group by a phenyl group leads to a decrease in enantiomeric purity is not unprecedented.[35]

The configuration of the optically active alcohols obtained *via* hydroboration with IPC_2BH exhibit a definite steric relationship to the configuration of the reagent. The configurations of the 2-methyl-1-alkanols are consistently R when (+)-IPC_2BH is used to hydroborate the olefin. To accommodate these results, it was proposed that slightly different steric interactions must be considered in arriving at stereochemical correlations using the reagent in conformation **17**. On the basis of the usual four-center transition state, it is possible to draw two different transition states (**21**, **22**) for the addition of terminal olefins, such as 2-methyl-1-butene, to the reagent.



21

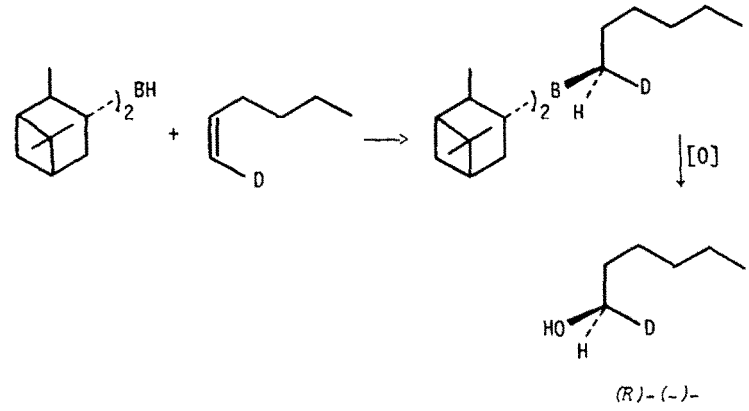


22

It is proposed that model **22** is favored over **21** by a modest factor because there are small but significantly greater interactions of the ethyl group with L'-group in **21** than with M-group in **22**. The configuration of (−)-2,3,3-trimethylbutan-1-ol, unknown at that time, was predicted to be R on the basis of these considerations.[34] Later, the predicted configuration was confirmed when independently established by correlation.[36]

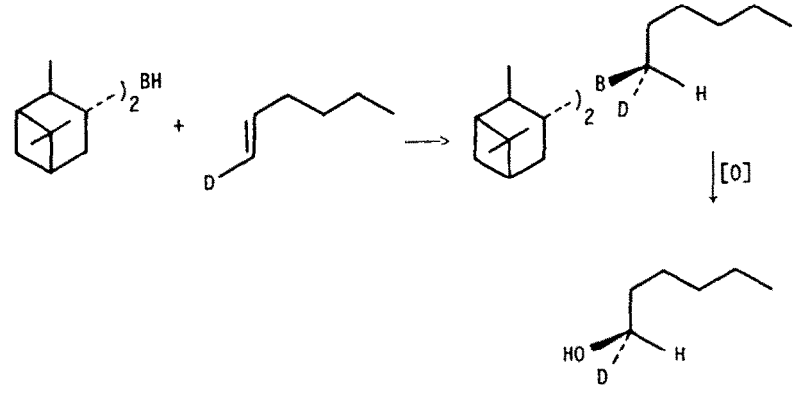
Asymmetric hydroboration of deuterated olefins and asymmetric deuterioboration of olefins. Diisopinocampheylborane and diisopinocampheyldeuterioborane derived from (+)-α-pinene have been applied for the asymmetric hydroboration of deuterated olefins and the deuterioboration of unlabeled olefins to provide ready access to chiral alcohols which are optically active attributable to

deuterium substitution.[37-40] Thus, the hydroboration of (Z)-, and (E)-1-hexene-1-d with (−)-IPC_2BH, followed by oxidation, yields (R)-(−)-, and (S)-(+)-1-hexanol-1-d in 42% and 86% e.e. respectively[37] (eqns 11 and 12).



(11)

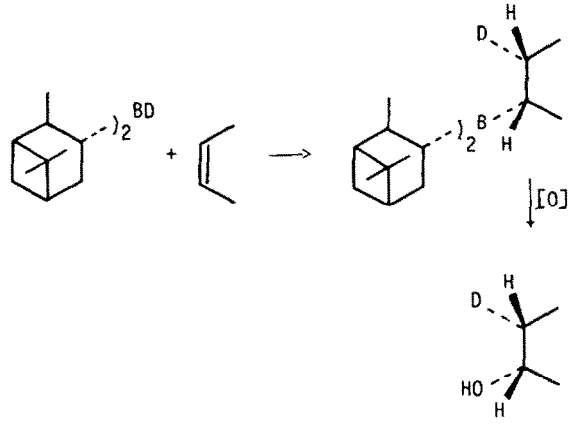
(R)-(−)-



(12)

(S)-(+)-

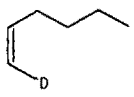
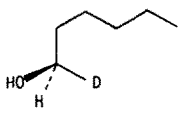
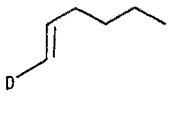
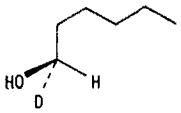
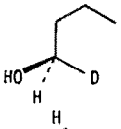
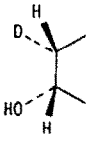
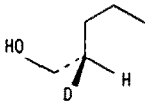
Similarly, *cis*-2-butene on deterioboration with IPC_2BD, followed by oxidation, yields (2S, 3R)-2-butanol-3-d in 64% e.e. (eqn 13). Other examples are summarized in Table 4.



(13)

(2S, 3R)

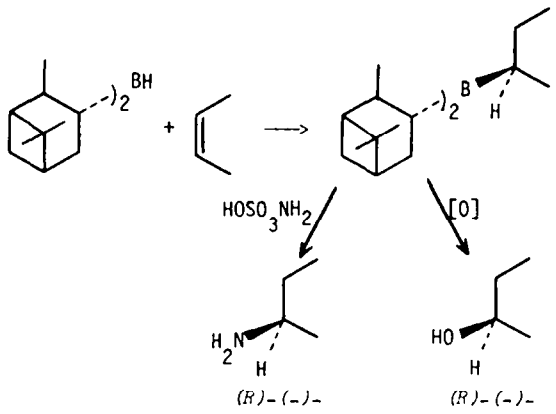
Table 4. Asymmetric synthesis of deuterated alcohols

NO	Olefin	Alcohol	α-Pinene $[\alpha]_D$ °C e.e., %	Reagent	ROH e.e., %	Config.	Ref.
1				IPC_2BH	42	*R*	37
2				IPC_2BH	86	*S*	37
3			+41.1, 80% e.e.	IPC_2BH	56	*R*	39
4			+44.9, 88% e.e.	IPC_2BD	64	2*S*, 3*R*	38
5			+38.75, 76% e.e.	IPC_2BD	48 ± 7	*R*	40

3. *Other asymmetric syntheses*

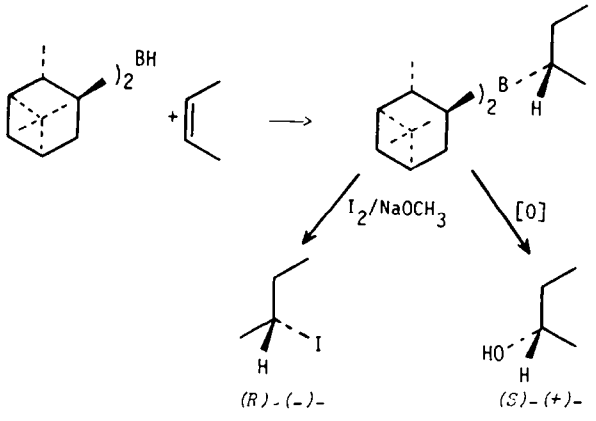
The intermediate chiral trialkylboranes obtained by the hydroboration of prochiral olefins with IPC_2BH can be transformed into a variety of functionalities other than alcohols with both complete retention or with complete inversion of configuration. Thus, protonolysis, halogenolysis, oxidation (CrO_3), amination and thiolation should provide a convenient route to optically active hydrocarbons, halides, ketones, amines and thioethers respectively. It should also be possible to transfer asymmetric alkyl groups from boron to carbon to form asymmetric derivatives with carbon-carbon bonds at the asymmetric center.[9] Though not much activity has been reported for this area, the availability of new chiral hydroborating agents recently reported for asymmetric hydroboration of prochiral olefins of different steric requirements should encourage more research in this area, providing ready access to such chiral products (see Sections 2.B and 2.C). However, several such transformations based on IPC_2BH as the chiral hydroborating agent have been reported and will be reviewed.

Asymmetric hydroboration-amination. Asymmetric hydroboration of *cis*-2-butene with (−)-IPC_2BH, followed by treatment with hydroxylamine-O-sulfonic acid, gives (R)-(−)-butylamine in 75% e.e., whereas, the peroxide oxidation of the same trialkylborane gives (R)-(−)-2-butanol in 76% e.e.[41] (eqn 14). The same absolute configuration and degree of optical purity of *sec*-butylamine and 2-butanol indicate that amination takes place with complete retention of configuration. This reaction provides a method for establishing the configurational inter-relationship between the appropriate alcohols and amines.



(14)

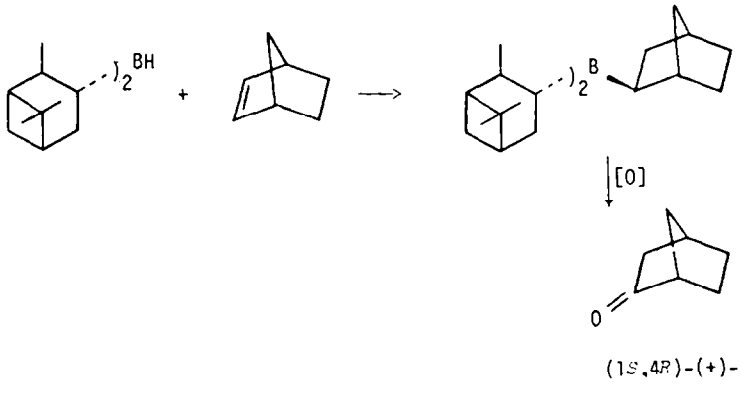
Asymmetric hydroboration-iodination. The base-induced reaction of iodine with trialkylborane derived from (+)-IPC_2BH and *cis*-2-butene produces (R)-(−)-2-iodobutane in 84% enantiomeric purity with configuration opposite to that of the (S)-(+)-2-butanol (86% e.e.) produced in the oxidation of the borane by alkaline hydrogen peroxide[42] (eqn 15). It is therefore evident that the iodination reaction, in



(15)

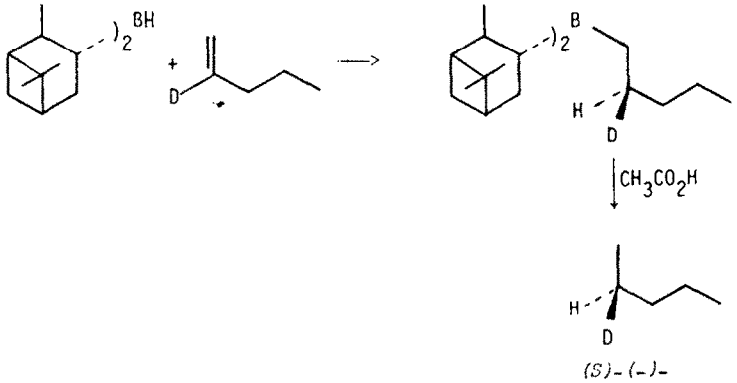
contrast to the large majority of reactions of organoboranes, involves substitution of the boron-carbon bond with clean inversion. The reaction not only provides a synthetic route to optically active iodides but also provides a new promising way to correlate the configurations of appropriate alcohols, amines, and halides.

Asymmetric hydroboration-oxidation. One or more than one chiral centers can be created by using an appropriate prochiral olefin for asymmetric hydroboration. In cases where more than one chiral center is formed, the chiral center bearing the boron substituent can be destroyed by chromic acid oxidation in order to form optically active ketones. Thus, the hydroboration of norbornene with (−)-IPC_2BH, followed by oxidation of the intermediate organoborane with chromic acid, provides optically active (1S, 4R)-(+)-norcamphor in 21% e.e.[43] (eqn 16).

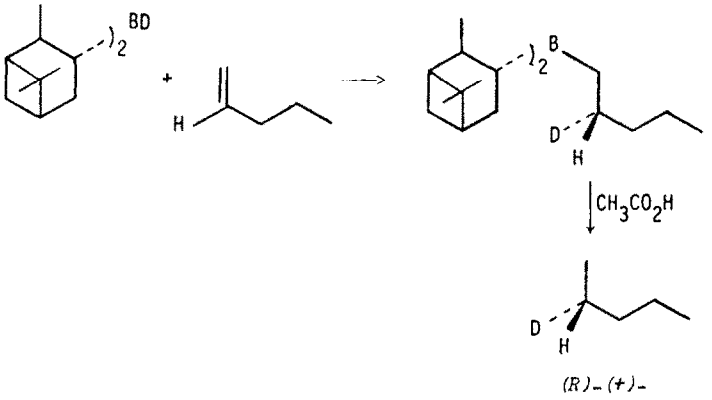


(16)

Asymmetric hydroboration-protonolysis. Organoboranes are susceptible to protonolysis by carboxylic acids.[44a] The protonolysis appears to proceed with the retention of configuration.[44b] Therefore, one can take advantage of the unique properties of hydroboration reaction to achieve stereospecific hydrogenations. This reaction has been applied for the synthesis of optically active pentane-2-d by asymmetric hydroboration of 1-pentene-2-D with (+)-IPC_2BH (eqn 17) or asymmetric deuterioboration of 1-pentene with IPC_2BD, followed by protonolysis of the resulting organoboranes[40] (eqn 18). The enantiomeric purity is 56%, correcting for optically pure α-pinene.

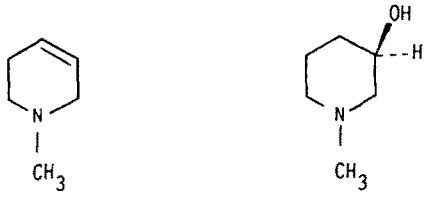


(17)



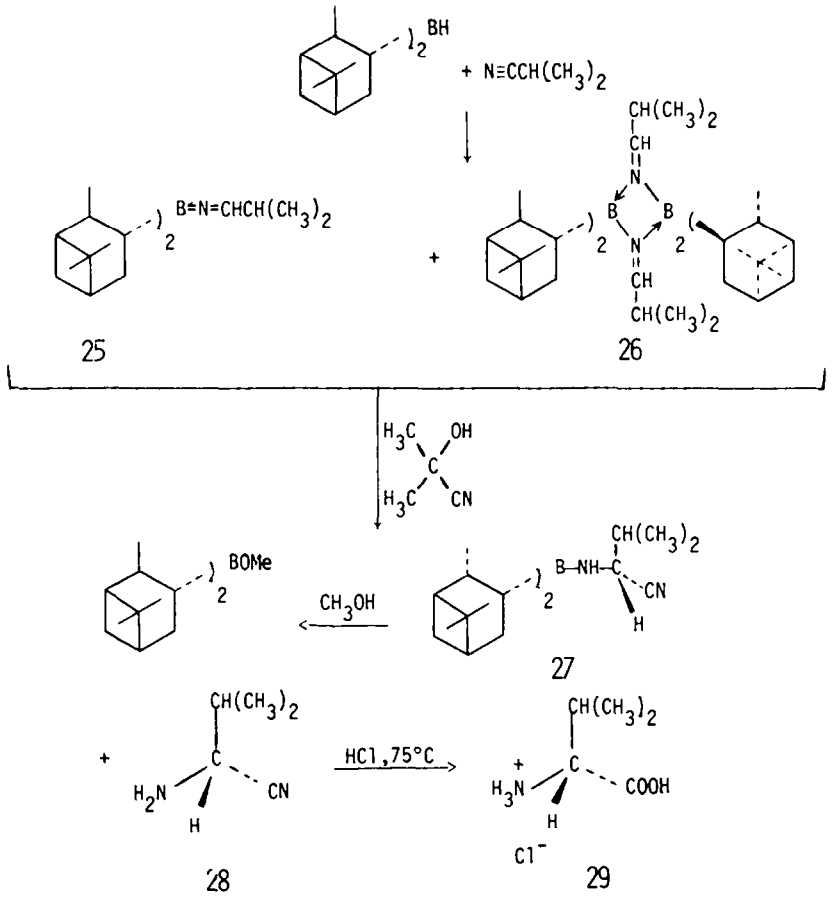
(18)

Asymmetric hydroboration of heterocyclic cis-olefins. 1-Methyl-1,2,3,6-tetrahydropyridine, **23**, on treatment with (−)-IPC_2BH, followed by oxidation gives (R)-(+)-1-methyl-3-piperidinol[45] **24**. It appears that the hydroboration involves the Lewis salt of the amine rather than the free base.



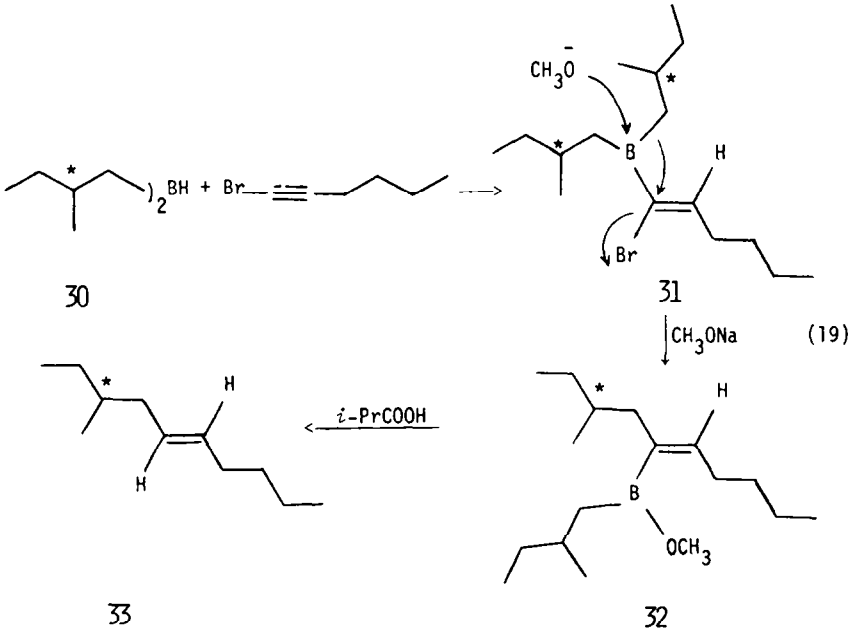
23 24

Synthesis of optically active α-amino-acids. IPC_2BH has been utilized for the synthesis of chiral α-amino-acids.[46] The reaction of (−)-IPC_2BH with 2-methylpropionitrile provides the ketiiminoborane **25** and its dimer **26**. This product, on treatment with acetone cyanohydrin, adds hydrogen cyanide, and is thereby converted into the aminoborane **27**. The chirality of the potential α-amino-acid is presumably induced when the elements of HCN are added preferentially to one of the diastereotopic faces of **25** or its dimer, **26**. The optically active cyanomine, **28**, is obtained by methanolysis of **27**. Hydrolysis of **28** with conc. HCl affords (R)-(−)-valine hydrochloride, **29**, in 45% overall yield with 12.4% enantiomeric purity (Scheme 5). Alanine was similarly prepared from acetonitrile.

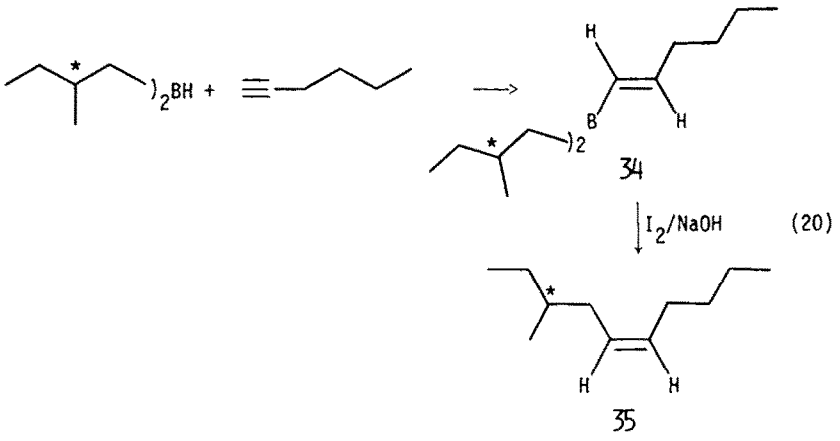


Scheme 5

Synthesis of chiral cis-*and* trans-*olefins.* The hydroboration of 1-bromo-1-hexyne with *bis*-[(R)-2-methylbutyl]borane, **30**, provided α-bromovinylborane, **31**. The base-induced migration of one of the two alkyl groups, followed by protonolysis of the vinylboronate, **32**, provided *trans*-3-methyl-5-decene, **33**, in an optical yield[47] of 85% (eqn 19). Similarly, the hydroboration of 1-hexyne with **30** provided the



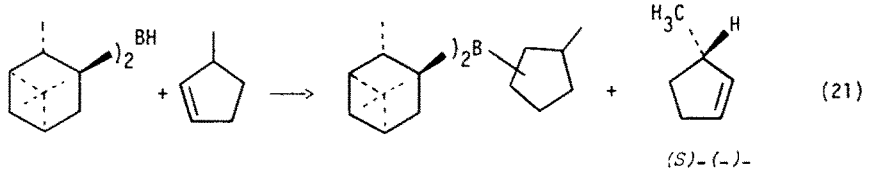
vinylborane, **34**, which on treatment with iodine and sodium hydroxide, provided *cis*-3-methyl-5-decene, **35**, (eqn 20) in optical yield[47] 100%. Although the chiral dialkylborane, **30**, was not prepared by asymmetric hydroboration, it may be possible to make chiral dialkylboranes of this type more conveniently by asymmetric hydroboration. This is a desirable objective, still to be achieved.



4. *Kinetic resolution of racemic olefins and allenes*

Kinetic resolution of racemic olefins is based on the principle that the hydroboration of an olefin racemate with a deficient amount of chiral hydroborating agent should result in an accumulation of one enantiomer in the reaction mixture as the more reactive enantiomer is converted into the organoborane. Indeed, the usefulness of diisopinocampheylborane for such resolution of olefins has been demonstrated.[48] This technique was utilized by Caserio and coworkers for the resolution of allenes.[49] Related resolution of dienes, spirodienes and trienes are also recorded.

Resolution of olefins. Diisopinocampheylborane reacts faster with one enantiomer of a prochiral olefin than its antipode. Thus, the treatment of 3-methylcyclopentene racemate with 50 mol percent (+)-IPC_2BH yielded residual olefin in 45% e.e. (eqn 21). The hydroboration of such racemic olefins with



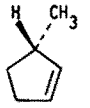
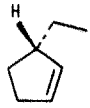
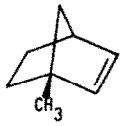
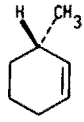
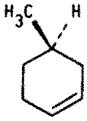
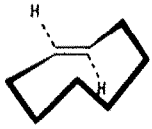
more than 50 mol percent IPC_2BH should provide the chiral olefin with higher optical purities. Indeed, treatment of (±)-3-methylcyclopentene with 80 mol percent (+)-IPC_2BH provided (S)-(−)-3-methylcyclopentene in 65% enantiomeric purity. Similarly, 3-ethyl-cyclopentene, 1-methylnorbornene, 3-methylcyclohexene, 4-methylcyclohexene and *trans*-cyclooctene have been resolved using this technique (Table 5). The low enantiomeric purity in the case of 3-methyl-[28] and 4-methylcyclohexenes[50] can be accounted in terms of its complex reaction involving both displacement and hydroboration. In contrast to the sluggish reaction of IPC_2BH with aliphatic trans olefins, IPC_2BH reacts rapidly with strained cyclic systems containing trans double bonds[51] (e.g. *trans*-cyclooctene).

The unique advantage of this method is its convenience. These are simple reactions to perform and provide products in reasonable optical purities in an area where such resolutions have been quite difficult. Since the absolute configurations of the resolved olefins bear a consistent relationship to the absolute configuration of the reagent, it is possible to predict the absolute configurations of the resolved olefins. This is especially true for *cis*-olefins, where IPC_2BH reacts cleanly by simple hydroboration, without concurrent displacement of α-pinene from the reagent.

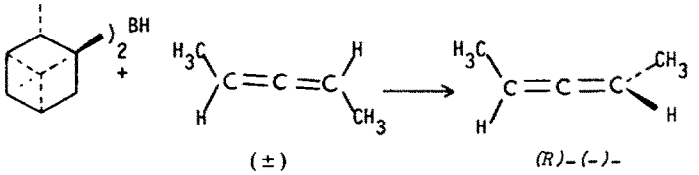
Resolution of allenes. The resolution of asymmetric allenic hydrocarbons is difficult. The known

general method for the resolution of 1,3-disubstituted allenes involves several synthetic steps.[52] To circumvent these difficulties, Caserio *et al.* developed a simple, general method for the partial resolution of 1,3-disubstituted allenes based on partial hydroboration of the racemic mixture with diisopinocampheylborane.[49,53] In one case, a level of asymmetric induction was comparable to that realized by the known method. Thus, the treatment of (±)-1,3-dimethylallene with 50 mol percent (+)-IPC_2BH provided unreacted (R)-(−)-1,3-dimethylallene (eqn 22). The results realized in the resolution of allenes are summarized in Table 6.

Table 5. Kinetic resolution of olefins

No	Olefin resolved	Reagent	Olefin $[\alpha]_D$	Olefin e.e., %	Olefin Config.	Ref.
1		(+)-IPC_2BH[a]	-50.8	65	*S*	22,48
2		(+)-IPC_2BH[a]	-45.2	37	*S*	22,48
3		(+)-IPC_2BH[a]	- 6.5		(1*R*,4*S*)	22,48
4		(-)-IPC_2BH[b]	- 4.4	3	*S*	32
5		(-)-IPC_2BH[c]	+ 1.11	1	*R*	50
6		(-)-IPC_2BH[d]	-95.5	20	*R*	51

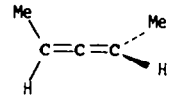
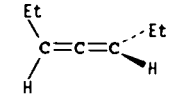
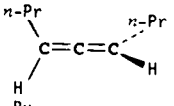
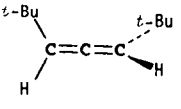
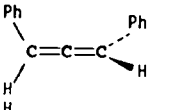
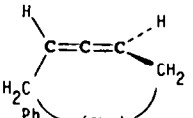
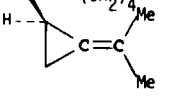
[a] α-Pinene, $[\alpha]_D$ -47.9° (neat) 93.5% e.e. [b] α-Pinene, $[\alpha]_D$ +47.6° (neat), 93% e.e. [c] α-Pinene, $[\alpha]_D$ +19.3° (neat), 37.6% e.e. [d] α-Pinene, $[\alpha]_D^{27}$ +57.1° (c 5, $CHCl_3$) has been used to prepare the reagent.



(±) (*R*)-(-)- (22)

The generality of the reaction has been tested for the kinetic resolution of racemic allenes of many different structures[54] (Table 6). It has been observed that the sterically less hindered allenes are hydroborated relatively rapidly. Consequently, it was essential to add the allene very rapidly to the IPC_2BH in order to insure that the enantiomeric composition was always maintained. However, on larger scale preparative runs, it would be advisable to reverse the addition to insure that the allene is

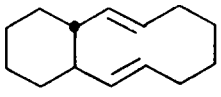
Table 6. Kinetic resolution of allenes by IPC_2BH

NO	Allene resolved	Reagent	Allene $[\alpha]_D$	Allene Config.	Ref.
1		(+)-IPC_2BH[a]	-43.8	*R*	49,53
2		(+)-IPC_2BH[b]	-57.6	*R*	54
3		(+)-IPC_2BH[c]	-51.7	*R*	54
4		(+)-IPC_2BH[b]	-18.2	*R*	54
5		(+)-IPC_2BH[a]	-180.0	*R*	49,53
6		(+)-IPC_2BH[d]	+26.5	*R*	55
7		(+)-IPC_2BH	-19.0	*R*	56

[a] α-Pinene, $[\alpha]_D^{24}$ -55.3° (c 8, $CHCl_3$). [b] α-Pinene, $[\alpha]_D^{22}$ -51.4° (c 8.3, $CHCl_3$). [c] α-Pinene, $[\alpha]_D^{22}$ -48.5° (c 8.4, $CHCl_3$). [d] α-Pinene, $[\alpha]_D^{28}$ -47.1° (neat), 92% e.e. has been used to prepare the reagent.

always present in excess to avoid loss of the selectivity. The enantiomeric purities appear to increase in the order: 1,3-dimethylallene < 1,2-cyclononadiene < 1,3-di-*tert*-butylallene < 1,3-diethyallene < 1,3-di-*n*-propylallene. The configuration of the allenes resolved with (+)-IPC_2BH is consistently R. Since both enantiomers of α-pinene are readily available, it should be possible to obtain allenes of opposite configurations.

The above technique has been extended for the resolution of dienes,[57] spirodienes[58] and trienes.[59] The optically active *trans,trans*-2,8-*trans*-bicyclo[8.4.0]tetradecadiene, **36**, required for a study of the Cope rearrangement was obtained by this method.[57] Both of the enantiomers of spiro[3.3]-hepta-1,5-diene,[58] **37**, and trimethylcyclodedecatriene (mixture of isomers)[59] have been obtained by this partial resolution of the racemates.



36

(*R*)-(+)-

37

5. Transition state models for hydroboration and resolution of olefins

Several models have been proposed[22,31,32,34,39,54,60–62] to explain and predict the outcome of the asymmetric hydroboration of olefins with IPC_2BH. These models represent empirical correlation and, for the most part, do not represent the actual transition state, although they are believed to incorporate some of the features which may characterize it. In the simplest approach, steric interactions in the four-centered transition state involving monomeric IPC_2BH in its conformation, **17**, assumed to be the most stable one, are considered. This model nicely accommodates the results observed with *cis*-olefins (**18**, **19**, **20**) and 2-methyl-1-alkenes (**21**, **22**), but predicts configurations opposite to those realized in the case of *trans*-olefins, tertiary hindered olefins and *cis*-1-buten-1-d. In spite of several other proposals, no one model explains the absolute configuration of the alcohols derived from the reaction of IPC_2BH and all types of olefins. The hydroboration of the different types of olefins with IPC_2BH appears to be mechanistically different, so it is doubtful that a single model can handle all of these reactions. Consequently, it appears that the precise mechanism of the asymmetric hydroboration should be established before a model for a particular reaction is proposed.

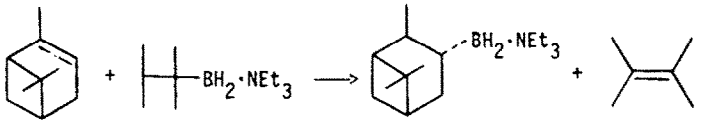
B. Monoisopinocamphenylborane ($IPCBH_2$)

The reactions of diisopinocampheylborane with relatively more hindered olefins are slow and mechanistically complicated, proceeding with partial displacement of α-pinene from the reagent. In such cases, the product alcohols are obtained in much lower enantiomeric purities, in the range of only 14–22% e.e.[32] To overcome these difficulties, monoisopinocampheylborane ($IPCBH_2$), a sterically less hindered and more reactive reagent has been developed.[12] It reacts smoothly with aliphatic[12] or phenyl substituted[13] tetiary acyclic, tertiary cyclic and *trans*-olefins. The enantiomeric purities of the product alcohols are in the range of 50–100% e.e. Several syntheses of $IPCBH_2$ have been developed, simplifying the preparation of this valuable reagent.[12,63–66] The chemistry uncovered during the development of these syntheses is interesting.

1. Preparation

Hydroboration of olefins with borane generally proceeds rapidly past monoalkylborane stage.[9,67] Consequently, with rare exception, such as thexylborane,[69] it is not possible to synthesize monoalkylborane by the direct reaction of olefins with borane in a 1:1 molar ratio. Therefore, such monoalkylboranes must be prepared by indirect methods.[68]

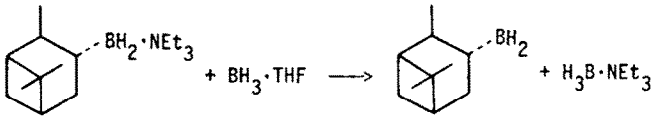
Monoisopinocampheylborane-triethylamine adduct ($IPCBH_2 \cdot NEt_3$) **38**. α-Pinene, on treatment with the thexylborane-triethylamine complex, displaces tetramethylethylene to form $IPCBH_2 \cdot NEt_3$[12,70] (eqn 23). The slow reactivity of **38** towards olefins necessitates the removal of triethylamine (Et_3N) from **38** to



(23)

38

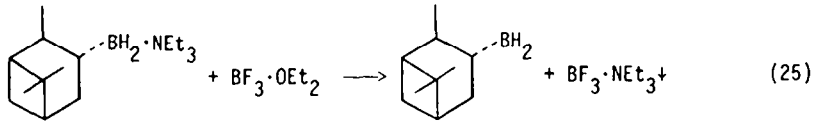
liberate free $IPCBH_2$, **39**. Removal of Et_3N with boron trifluoride etherate ($BF_3 \cdot OEt_2$) in THF is disappointingly slow. However, $BH_3 \cdot THF$ provided the solution (eqn 24). The borane-triethylamine



(24)

39

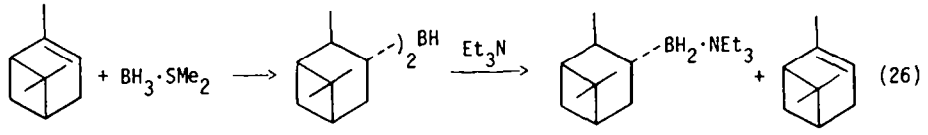
adduct, though inert toward hydroboration, interferes with the isolation of the products. Vigorous conditions are required to achieve complete hydrolysis and destruction of $BH_3 \cdot NEt_3$. Such conditions are not desirable in reactions involving asymmetric synthesis. The reaction of **38** with $BF_3 \cdot OEt_2$ is fast in pentane (eqn 25). The boron trifluoridetriethylamine adduct formed cyrstallizes out of solution at $-5°$, and hence can be separated from free **39**.[63]



(25)

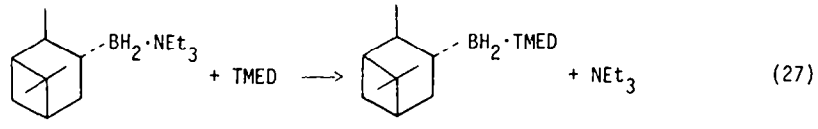
39

The treatment of diisopinocampheylborane with Et_3N displaces α-pinene, providing another simple synthesis of **38** (eqn 26). In all of these procedures, **38** is obtained as a neat viscous liquid and cannot be purified easily.



(26)

Monoisopinocampheylborane-N,N,N′,N′-*tetramethylethylenediamine adduct* (*IPCBH*$_2$·*TMED*) **40**. Treatment of **38** with TMED gives $IPCBH_2 \cdot TMED$ (eqn 27) as a white crystalline solid (m.p. 113–115°), which can readily be purified by crystallization from pentane. The compound **40** is air stable

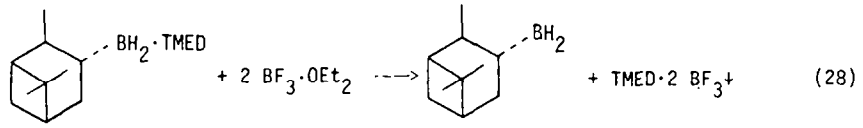


(27)

40

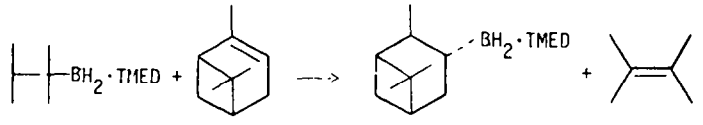
and can be stored in THF solution for several weeks at 25° without noticeable hydride loss, isomerization, or disproportionation.

TMED is readily removed from **40** by treatment with BF_3OEt_2 in THF (eqn 28). TMED·2 BF_3 readily



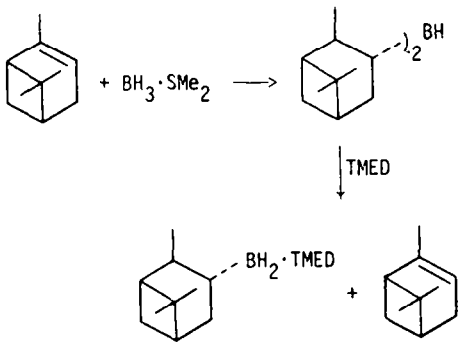
(28)

precipitates out of the THF solution. Hence, it can be removed by filtration to provide a THF solution of free $IPCBH_2$. The compound **40** can also be prepared by displacement of tetramethylethylene from $ThBH_2$·TMED by α-pinene (eqn 29).



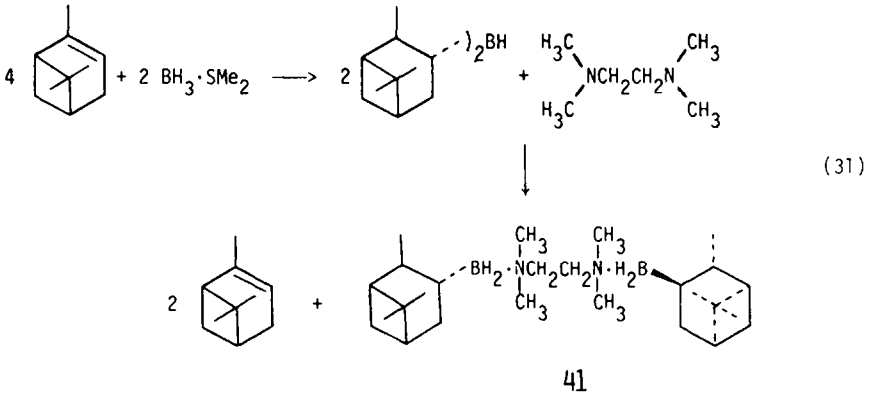
(29)

The most simple and rapid preparation of **40** is achieved by reaction of neat α-pinene with neat BH_3·SMe_2, followed by displacement of α-pinene from the resulting IPC_2BH by TMED (eqn 30), followed by removal of the dehydroborated α-pinene under high vacuum.



(30)

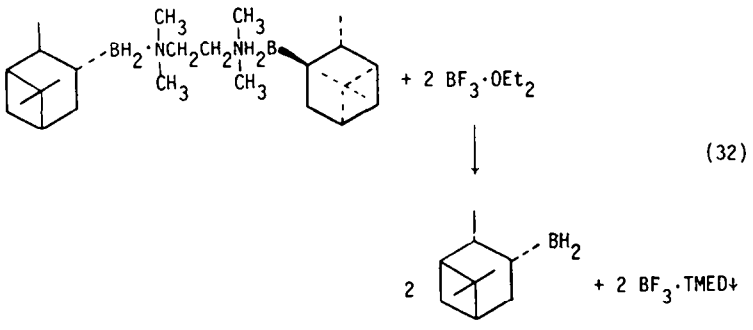
Bis-adduct of monoisopinocampheylborane with TMED (2 *IPCBH₂·TMED*) **41**. It was discovered that $IPCBH_2$ forms a *bis*-adduct[71] with TMED. This observation led to the most convenient and highly advantageous synthesis of optically pure $IPCBH_2$. The *bis*-adduct 2 $IPCBH_2$·TMED, **41**, is a crystalline solid, m.p. 140–141°. The present procedure utilizes $BH_3·SMe_2$ in ethyl ether for the rapid preparation of IPC_2BH, followed by fast displacement of α-pinene by a one-half equivalent of TMED to yield 2 $IPCBH_2$·TMED, **41**. It crystallizes out of the reaction mixture and is readily purified (eqn 31). The



(31)

41

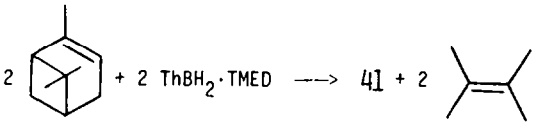
bis-adduct, **41**, separates in much higher enantiomeric purity (~100% e.e.) than the enantiomeric purity (94% e.e.) of the (+)-α-pinene used.[64] This is confirmed by the oxidation of **41**, following methanolysis, to isopinocampheol, $[\alpha]_D^{25} - 35.79°$, a value which corresponds to ~100% e.e. On the other hand, the enantiomeric purity of the isopinocampheol obtained by the oxidation of dissolved **41** present in the mother liquor is only 84%. Therefore, this procedure achieves preparation of **41** in higher enantiomeric purity than the enantiomeric purity of the initial α-pinene. This purification results from the preferential crystallization of the diastereomeric product, (+)-2 $IPCBH_2$·TMED, leaving (+)(−)- and (−)(−)-2 $IPCBH_2$·TMED as minor impurities in the mother liquid. Treatment of **41** with $BF_3·OEt_2$ in THF gives free $IPCBH_2$ as the insoluble adduct, 2 BF_3·TMED, rapidly precipitates out of the reaction mixture (eqn 32). Removal of the precipitate by decantation, filtration, or centrifugation provides a clear solution of



(32)

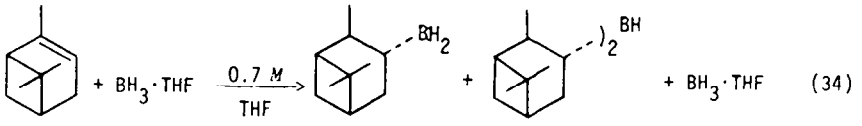
$IPCBH_2$ in THF ready for hydroboration. This is the most convenient and advantageous preparation of $IPCBH_2$ and we recommend it to those wishing to apply this reagent.

Another convenient method for the preparation of **41** is outlined in eqn (33). Thus, treatment of 2 $ThBH_2 \cdot TMED$ with α-pinene in refluxing di-ethyl ether provides crystalline **41** in high optical purity.[65]



(33)

Direct synthesis of $IPCBH_2$ by the equilibration of 1:1 *α-pinene and $BH_3 \cdot THF$.* The reaction of α-pinene with BH_3THF in a 1:1 molar ratio in 0.7M THF at 25° first forms predominantly triisopinocampheyldiborane. This product undergoes redistribution with free borane over 96 hr giving a product which consists of 91% $IPCBH_2$ and 4.5% each of IPC_2BH and $BH_3 \cdot THF$[66] (eqn 34). Alter-



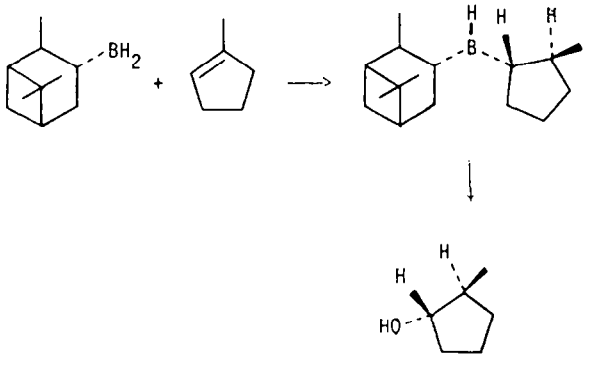
25°C, 96 h	91%	4.5%	4.5%
50°C, 4 h	86%	7%	7%

(34)

natively, the reaction mixture attains equilibrium at 50° in 3.5–4 hr, with the mixture containing 86% $IPCBH_2$ and 7% each of IPC_2BH and $BH_3 \cdot THF$. Addition of an appropriate amount of TMED leads to the selective precipitation of 2 $BH_3 \cdot TMED$. This material can be removed by filtration, if desired. However, its presence in the reaction mixture does not interfere with the application of $IPCBH_2$. Thus the reaction of α-pinene with $BH_3 \cdot THF$ in a 1:1 molar ratio gives rise to $IPCBH_2$ in ~90% yield. A claim[72] to have produced $IPCBH_2$ by direct hydroboration in THF has been disproved.[27]

2. *Synthesis of chiral alcohols*

Asymmetric hydroboration of aliphatic tertiary olefins. In contrast to IPC_2BH, monoisopinocampheylborane reacts smoothly with aliphatic olefins without any significant displacement of α-pinene. The product alcohols, obtained after the oxidation of the organoborane intermediate, exhibit enantiomeric purities in the range of 53–72% e.e. The asymmetric hydroboration of 1-methylcyclopentene with $IPCBH_2$ [derived from (+)-α-pinene], followed by oxidation, provides (1S,2S)-(+)-2-methylcyclopentanol in 66% e.e. (eqn 35). Other examples are listed in Table 7. In comparison to the enantiomeric

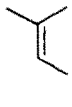
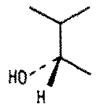
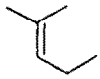
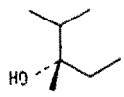
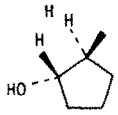
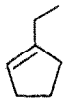
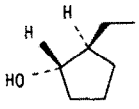
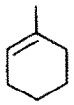
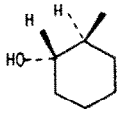


(35)

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

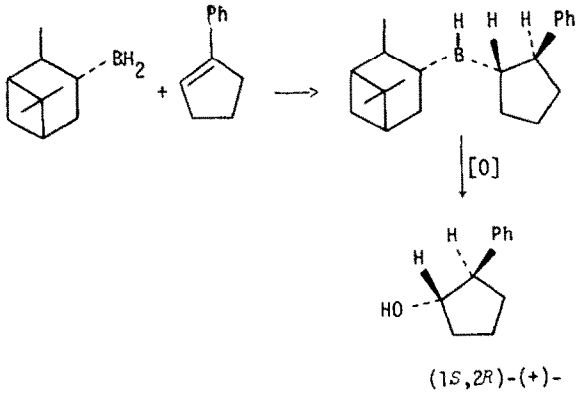
purities obtained with IPC_2BH (Table 2, Entries 2 and 3), those with $IPCBH_2$ (Table 7; Entries 1 and 4) are much higher, indicating that $IPCBH_2$ is far superior to IPC_2BH as an asymmetric hydroborating agent for the relatively hindered trisubstituted (tertiary) olefins. Moreover, monoisopinocampheylborane is an even better chiral hydroborating agent for tertiary cyclic olefins than for tertiary acylic olefins. The enantiomeric purities appear to increase with the increasing steric requirements of the olefins.

Table 7. Hydroboration of aliphatic tertiary olefins with $IPCBH_2$[a,b]

NO	Olefin	Alcohol	ROH e.e., %	ROH Config.	Ref.
1			53[a]	*S*	12
2			58[b]	*S*	73
3			55[a](66)[b]	1*S*,2*S*	12,73
4			60[b]	(1*S*,2*S*)	73
5			72[a]	1*S*,2*S*	12

[a] $IPCBH_2$ of 94% e.e. prepared from (+)-α-pinene, $[\alpha]_D$ +48.0, 94% e.e. has been used for hydroboration. [b] $IPCBH_2$ of ~ 100% e.e. prepared from (+)-α-pinene, $[\alpha]_D$ +48.1°, 94% e.e. has been used for hydroboration.

Asymmetric hydroboration of phenyl-substituted tertiary olefins with IPCBH₂. Monoisopinocampheylborane reacts smoothly with phenyl-substituted tertiary cyclic or acylic olefins to provide alcohols after oxidation of the organoborane intermediate, with exceptionally high enantiomeric purities.[13] Thus, hydroboration of 1-phenylcyclopentene with $IPCBH_2$ at −25° requires 24 hr for essential completion. Oxidation of the resulting organoborane provides *trans*-2-phenylcyclopentanol in 100% enantiomeric purity (eqn 36).



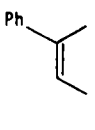
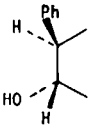
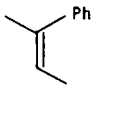
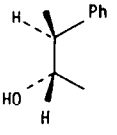
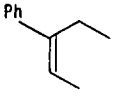
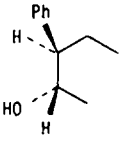
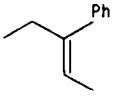
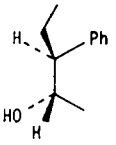
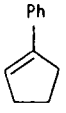
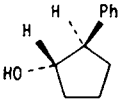
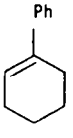
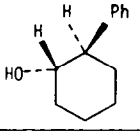
(36)

(1*S*,2*R*)-(+)-

The hydroboration of 1-phenylcyclohexene with the reagent is much slower. Even at 0°, the reaction requires about 7 days to achieve 80% completion. Subsequent oxidation furnishes *trans*-2-phenylcyclohexanol in 88% e.e.

The enantiomeric purities appear to increase with increasing steric requirements of the olefin (Table 8). However, the enantiomeric purity decreases in the case of 1-phenylcyclohexene, although it is the

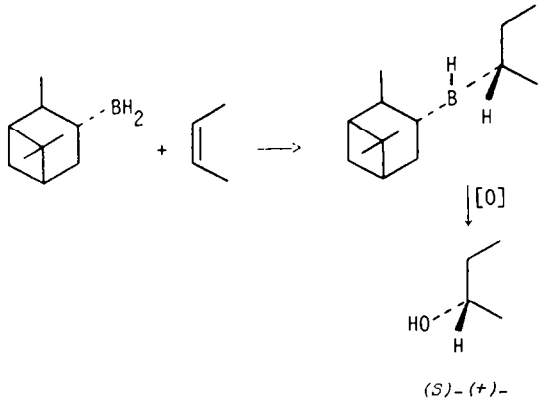
Table 8. Hydroboration of phenyl-substituted tertiary olefins with $IPCBH_2$[a]

NO	Olefin	Alcohol	ROH e.e., %	ROH Config.
1			81	2S,3R
2			82	2S,3S
3			85.5	2S,3R
4			85	2S,3S
5			100	1S,2R
6			88	1S,2R

[a] $IPCBH_2$ of ~ 100% e.e. prepared from (+)-α-pinene, $[\alpha]_D$ +48.1°, 94% e.e. has been used for hydroboration.

most hindered olefin studied. It appears that the steric requirements of 1-phenylcyclohexene may exceed the optimum steris fit required by the chiral hydroborating agent. This probably results in the lower optical induction.

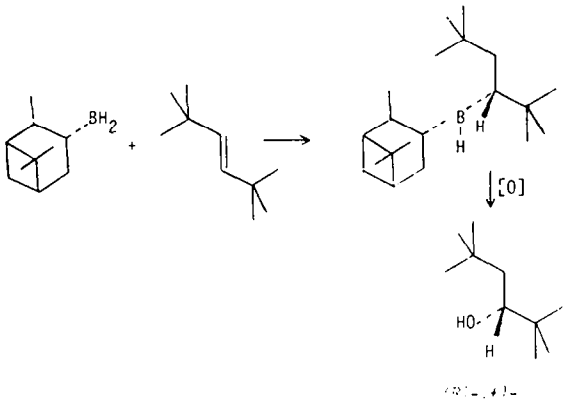
Asymmetric hydroboration of cis- and trans-olefins with IPCBH₂. Monoisopinocampheylborane hydroborates *cis*-olefins smoothly. However, the alcohols obtained after oxidation exhibit low enantiomeric purities, in the range of 20 to 24% e.e. Thus, *cis*-2-butene provides (S)-(+)-2-butanol in only 24% e.e. (eqn 37). Probably, the steric requirements of *cis*-olefins are too small for the less hindered reagent, $IPCBH_2$, to provide an optimum fit and high asymmetry in the reaction.



(S)-(+)-

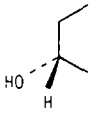
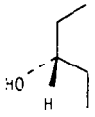
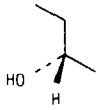
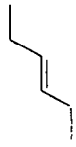
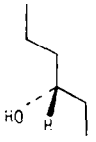
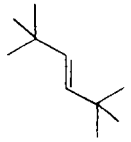
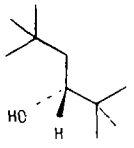
(37)

In contrast to the poor asymmetry realized with the *cis*-olefins, $IPCBH_2$ hydroborates *trans*-olefins with a satisfactory high degree of asymmetry. The product alcohols exhibit enantiomeric purities in the range of 72–93% e.e. (Table 9). Thus, the asymmetric hydroboration of *trans*-2,2,5,5-tetramethyl-3-hexene with $IPCBH_2$, followed by oxidation, provides (R)-(+)-2,2,5,5-tetramethyl-3-hexanol with an optical purity of 92% e.e. (eqn 38). The enantiomeric purities appear to increase with increasing steric requirements of the *trans*-olefins.



(38)

Table 9. Hydroboration of *cis* and *trans* olefins with $IPCBH_2$[a,b]

NO	Olefin	Alcohol	ROH e.e., %	ROH Config.	Ref.
1			24[c]	S	27
2			20[c]	S	27
3			72[b]	S	14
4			75[b]	S	14
5			92[b]	S	14

[a] $IPCBH_2$ of 95% e.e. prepared from (+)-α-pinene, $[\alpha]_D$ +48.7°, 95% e.e. has been used for hydroboration. [b] $IPCBH_2$ of ≥ 100% e.e. prepared from (+)-α-pinene, $[\alpha]_D$ +48.1°, 94% e.e. has been used for hydroboration.

The results suggest that the large steric requirements of IPC_2BH make it a favorable reagent for asymmetric hydroboration of *cis*-olefins, with relatively low steric requirements. On the other hand, the lower steric requirements of $IPCBH_2$ make it more favorable for the asymmetric hydroboration of the more sterically demanding trans and trisubstituted olefins.

Unfortunately, it is not clear at this time why the results realized with the *trans*-olefins are more favorable than those with aliphatic tertiary olefins, although the steric requirements of the latter class of olefins should be greater than those of the former.

The new asymmetric center at the alcohol position is consistently enriched in the S-enantiomer, utilizing the reagent prepared from (+)-α-pinene, with no exceptions encountered thus far. Therefore, the reagent is consistent and highly promising for both configurational assignments and stereochemical correlations.

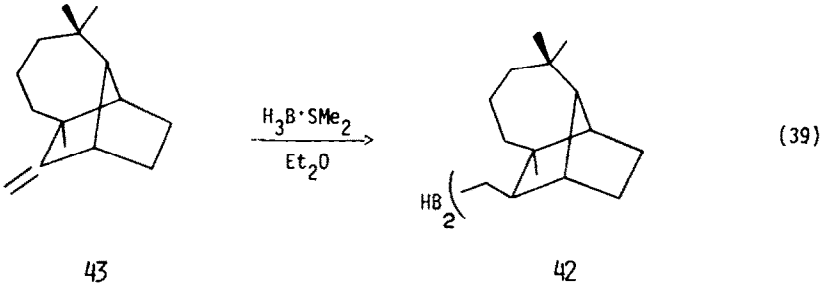
Monoisopinocampheylborane is evidently an excellent chiral hydroborating agent for *trans* and tertiary hindered olefins. The product alcohols are obtained in exceptionally high enantiomeric purities. It is effective for olefins of a broad range of steric and structural requirements. It is interesting to note that $IPCBH_2$ is a complementary reagent to IPC_2BH in two respects (1) IPC_2BH is an excellent chiral hydroborating agent for *cis*-olefins, where $IPCBH_2$ fails to give good asymmetric induction. On the other hand, $IPCBH_2$ gives excellent results with *trans* and tertiary hindered olefins where IPC_2BH fails. (2) Both of the reagents derived from the same enantiomer of α-pinene furnish alcohols of opposite configuration in the case of *cis*-olefins. It is not clear at this time why there is a reversal of configuration, even though the same enantiomer of α-pinene is used to prepare these reagents.

C. Dilongifolylborane (Lgf_2BH)

Diisopinocampheylborane gives poor results with olefins of high steric requirements, whereas, $IPCBH_2$ fails to give good results with sterically less hindered olefins. It appeared that a chiral hydroborating agent of intermediate steric requirements might achieve favorable optical induction with both hindered and unhindered olefins. Very recently, dilongifolylborane[16] (Lgf_2BH, **42**), a new chiral hydroborating agent with such intermediate steric requirements, has been discovered. Indeed, it achieves hydroboration of both unhindered *cis*-olefins and relatively hindered tertiary olefins with a high degree of asymmetric induction (Table 10).

1. *Preparation*

(+)-Longifolene, **43**, a sesquiterpene, contains a substituted bicyclo-[2.2.1]heptane moiety with a large bridge effectively shielding the double bond from the exo face of the molecule. Consequently, in contrast to the behavior of norbornene itself, the hydroboration[74] of (+)-longifolene with diborane occurs exclusively from the less hindered endo side. Thus, hydroboration of (+)-longifolene with borane-methyl sulfide ($BH_3 \cdot SMe_2$) in a 2:1 ratio in refluxing ethyl ether proceeds rapidly to the dialkylborane stage (eqn 39). Lfg_2BH, **42**, is a strongly dimeric, high melting, snow-white crystalline

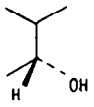
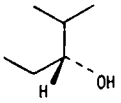
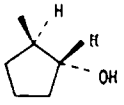
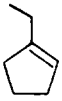
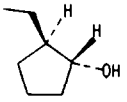
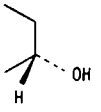
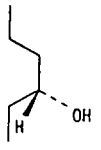


(39)

43 42

solid. It can be readily isolated free of solvent and stored at 25° for a few weeks without any appreciable hydride loss, disproportionation or isomerization. This stability is convenient from the practical point of view. It is only sparingly soluble in common organic solvents. However, the suspended material is capable of achieving hydroboration at reasonable rates.

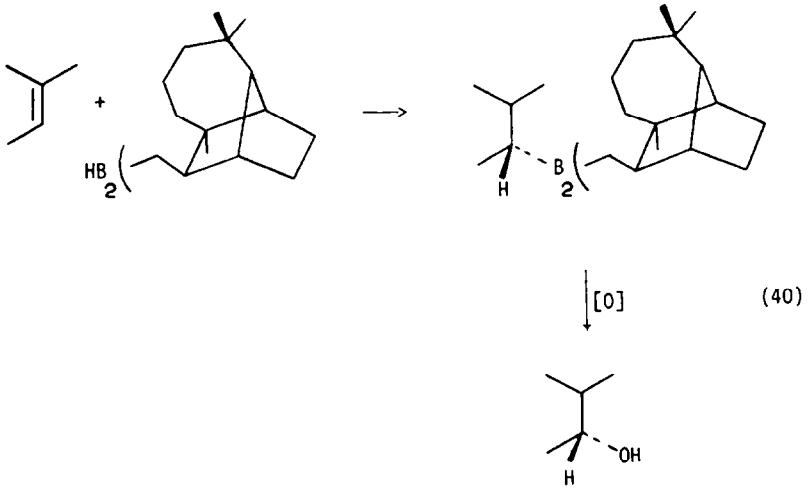
Table 10. Hydroboration of tertiary and *cis*-olefins with Lgf_2BH[a]

NO	Olefin	Alcohol	ROH e.e., %	ROH Config.
1			70	*R*
2			75	*R*
3			63	1*R*,2*R*
4			59.6	(1*R*,2*R*)
5			78	*R*
6			71	*R*

[a]Longifolene $[\alpha]_D$ +44.2° (c 4.6, $CHCl_3$) has been used to prepare the reagent.

2. *Synthesis of chiral alcohols*

Asymmetric hydroboration of aliphatic tertiary olefins. Dilongifolylborane (Lgf_2BH) hydroborates aliphatic tertiary acyclic or cyclic olefins with a high degree of optical induction. The product alcohols reveal enantiomeric purities in the range of 60–75% e.e. Thus, 2-methyl-2-butene on treatment with Lgf_2BH, followed by oxidation of the resulting organoborane, provides (R)-(−)-3-methyl-2-butanol in 70% e.e. (eqn 40).



(40)

The results are summarized in Table 10.

Asymmetric hydroboration cis-olefins. Lgf_2BH is also an effective reagent for the asymmetric hydroboration of unhindered *cis*-olefins, although the induction of asymmetry is not as high as that exhibited by IPC_2BH (Table 10). Thus, hydroboration of *cis*-2-butene, followed by oxidation, gives (R)-(−)-butanol in 78% e.e. The new asymmetric center at the alcohol position is consistently enriched in the R enantiomer, utilizing the reagent prepared from (+)-longifolene. Unfortunately, (−)-longifolene. although known to occur in few species, is not as readily available as (+)-longifolene. It is therefore not possible to prepare the chiral products of opposite configuration. Nevertheless, Lgf_2BH is an excellent chiral hydroborating agent and appears to be the best available for the asymmetric hydroboration of aliphatic trisubstituted acylic olefins. It is certainly a significant addition to the list of known chiral hydroborating agents.

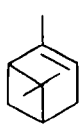
D. Conclusion

The present results suggest the possibility of developing a family of asymmetric hydroborating agents of varying steric requirements. It would then be possible to select the hydroborating agent that would provide a favorable fit with a given olefinic structure. At the present time, it is apparent that excellent results are realized in the case of the unhindered *cis*-olefins by using a reagent with large steric requirements, IPC_2BH. The hydroboration of olefins with large steric requirements is favorable with a reagent of low steric requirements, $IPCBH_2$. Lgf_2BH, a reagent of intermediate steric requirements, works well with both *cis* and trisubstituted olefins. Indeed, it appears to be a reagent of choice for the latter olefins. These asymmetric hydroborating agents handle three of the four major classes of olefins. IPC_2BH gives moderate results in the case of the fourth class, the 2-methyl-1-alkenes. Consequently, there remains a need for a reagent which will provide access to 2-methyl-1-alkanols of high enantiomeric purity. A large number of new and novel reactions of achiral organoborenes have been reported. Application of some of these reactions to chiral organoboranes, now available *via* asymmetric hydroboration, remain to be explored.

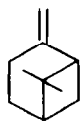
3. ASYMMETRIC REDUCTION

A. Chiral trialkylboranes

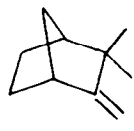
Trialkylboranes are noted for their tolerance of a wide variety of functional groups.[9] However, it is known that under vigorous conditions trialkylboranes will react with benzaldehyde.[75,76] Very recently Midland and coworkers demonstrated that certain B-alkyl-9-borabicyclo[3.3.1]nonanes, in contrast to many other trialkylboranes, can reduce benzaldehyde to benzyl alcohol under exceptionally mild conditions.[77] In this reduction, the B-alkyl group is converted into the corresponding olefin. In their extensive study, it was established that the rate of reduction is dramatically enhanced by alkyl substituents in the β-position of the B-alkyl group of 9-BBN. Thus, the presence of a tertiary β-hydrogen favors a fast reaction. The ability to form a *syn*-planar B–C–C–H configuration is also important. No participation by the cyclooctyl ring of the 9-BBN moiety has been observed, presumably because the rigid cyclooctyl ring of 9-BBN cannot achieve the proper geometry required for a cyclic transition state. Thus, *B*-siamyl-9-BBN is a mild chemoselective reducing agent for aldehydes. This observation has been brilliantly extended to the asymmetric reduction of benzaldehyde-1-*d* to optically active benzyl-α-*d*-alcohol using various chiral *B*-alkyl-9-BBN reagents.[19,20] Optically active terpenes, such as (+)-α-pinene, **1**, (−)-β-pinene, **44**, (−)-camphene, **45**, and (+)-3-carene, **46**, have been used to prepare the asymmetric *B*-alkyl-9-BBN reagents. Among these reagents, *B*-3α-pinanyl-9-BBN is the most effective chiral reducing agent (Table 11). These reagents have the reducing "hydride" transferred



1



44



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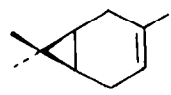


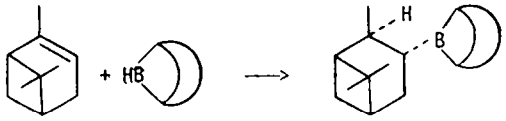
46

from a chiral center of the alkyl group to a new chiral center of the carbonyl group of the aldehydes. The transfer is remarkably effective in inducing optical activity into the reduced product.

B. 3α-Pinanyl-9-borabicyclo[3.3.1]nonane 47

1. *Preparation*

Preparation of *B*-3-pinanyl-9-BBN, **47**, from the commercially available 9-BBN and α-pinene is simple. The treatment of α-pinene with a refluxing solution of 9-BBN in THF readily furnishes **47** (eqn 41). The substrate to be reduced is added to the reagent in the same reaction flask. The chiral auxiliary

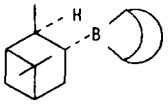
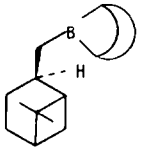
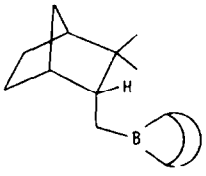
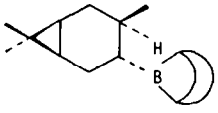


(41)

47

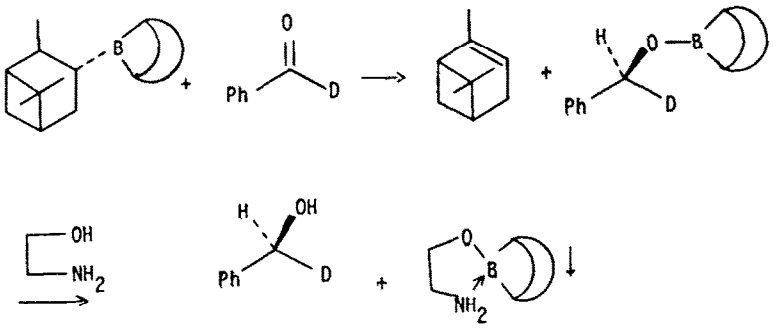
reagent and the 9-BBN moiety are removed very easily. This kind of convenience is very rare in asymmetric organic synthesis. The α-pinene formed after the reduction can be recycled without any significant loss of enantiomeric purity.

Table 11. Reduction of benzaldehyde-1-*d* with Chiral *B*-Alkyl-9-BBN reagents

NO	Reagent	e.e., %	Config.
1		90	*S*
2		47	*S*
3		75	*R*
4		61	*S*

2. *Synthesis of chiral 1-deuterated primary alcohols*

Optically active primary 1-deuterio alcohols constitutes a very important class of compounds which have been extensively used for mechanistic studies of chemical and biochemical reactions. These compounds are usually prepared by the fermenting yeast reduction of the corresponding deuteriated aldehydes. Although high optical purity is obtained, the process is tedious and not amenable to large-scale preparation. It has been discovered that **47** is a highly enantioselective, stereoselective, and chemoselective reducing agent for deuteriated aldehydes, to provide optically active 1-deuterio primary alcohols.[19,20] Thus, **47**, readily prepared by the hydroboration of (+)-α-pinene with 9-BBN, rapidly reduces benzaldehyde-1-*d* to (*S*)-(+)-benzyl-α-*d*-alcohol of 90% enantiomeric excess (eqn **42**). Since the starting α-pinene was only 92% enantiomerically pure, the results represent an essentially complete asymmetric induction. Such an exceptionally high degree of asymmetric induction in the reduction of deuteriated aldehydes was thus far unknown in nonenzymatic systems.



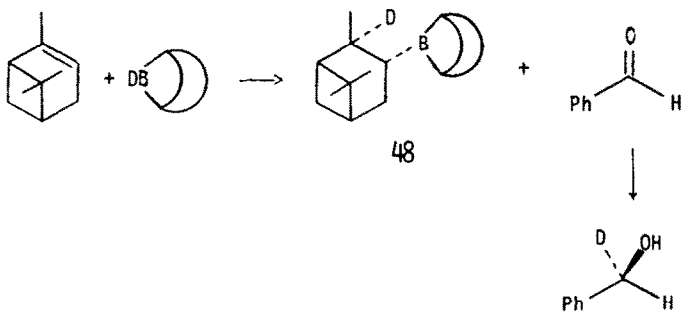
(42)

It has been observed that the β-hydrogen is actually utilized for the reduction. Therefore, the hydrogen added *via* the hydroboration process is the reducing hydrogen. Indeed, the organoborane, **48**, obtained by deuterioboration of α-pinene with 9-BBN-9-*d* quantitatively transfers deuterium to benzaldehyde (eqn 43). The availability of the deuterated reagent, **48**, allows the asymmetric reduction of a variety of aldehydes without the necessity of the prior preparation of the 1-deuterated aldehydes. The results of the reduction of aldehydes with **48** are summarized in Table 12. The reaction gives high

Table 12. Reduction of aldehydes with **48**

NO	Aldehydes	Alcohols	a e.e., %	b e.e., %	c e.e., %
1	$CH_3CH_2CH_2CHO$	$CH_3CH_2CH_2CHDOH$	83	101	101
2	$CH_3(CH_2)_4CHO$	$CH_3(CH_2)_4CHDOH$	64	83	89
3	$(CH_3)_3CCHO$	$(CH_3)_3CCHDOH$	70	91	98
4	$C_6H_5CH{=}CHCHO$	$C_6H_5CH{=}CHCHDOH$	60	78	84
5	$(CH_3)_2C{=}CHCH_2CH_2{-}$ $CCH_3{=}CHCHO$	$(CH_3)_2C{=}CHCH_2CH_2{-}$ $CCH_3{=}CHCHDOH$	58	75	81
6	C_6H_5CHO	C_6H_5CHDOH	70	91	98
7	p-ClC_6H_4CHO	p-ClC_6H_4CHDOH	87	94	101
8	p-$O_2NC_6H_4CHO$	p-$O_2NC_6H_4CHDOH$	86	93	100
9	p-$CH_3C_6H_4CHO$	p-$CH_3C_6H_4CHDOH$	76	83	89
10	p-$CH_3OC_6H_4CHO$	p-$CH_3OC_6H_4CHDOH$	70	76	82
11	p-$(CH_3)_2NC_6H_4CHO$	p-$(CH_3)_2NC_6H_4CHDOH$	61	66	71

[a]Determined by chiral LSR Eu(hfc)$_3$. [b]Corrected for % deuterium. [c]Corrected for % e.e. of α-pinene.

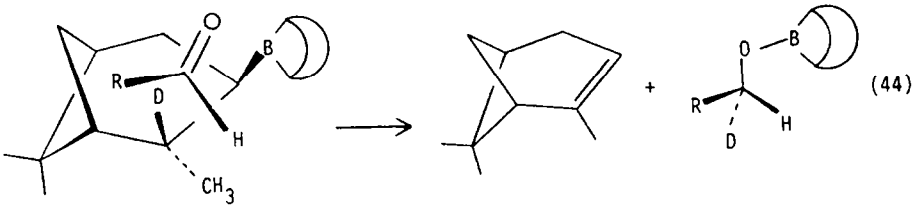


48

(43)

enantiomeric purity in all cases studied. Steric effects appear to have little influence on the reduction. However, electron-withdrawing groups in benzaldehyde tend to increase the enantiomeric purities of the product (Table 12, entries 8–11). Surprisingly, such an increase in selectivity is accompanied by an increase in the rate of reduction. Normally, one would expect that the faster the reaction, the less selective it should be. The loss of selectivity may be attributed to a competitive dehydroboration-reduction mechanism which leads to inactive product.[78,79] The absolute configurations of the major products are consistently *R* when **48** is used for the reduction. The products of *S* configurations can be readily obtained by using deuterated *B*-3-pinanyl-9-BBN prepared from (−)-α-pinene and 9-BBN-9-*d*.

The stereochemical approach observed in the reduction with **48** seems to contradict the simple theory of asymmetric reduction. The large *R* group approaches over the pinanyl ring and the hydrogen over the methyl group (eqn 44). The bridgehead hydrogen is held away from the *R* group, whereas, the pinanyl

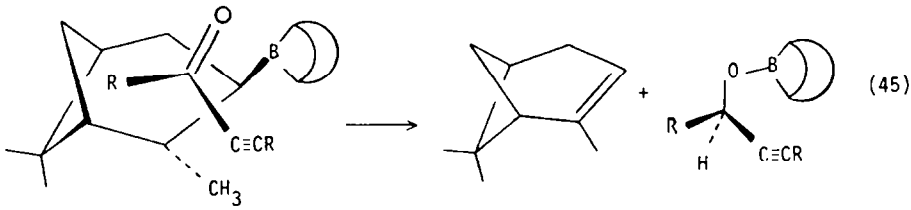


(44)

methyl group is freely rotating and its hydrogens would interfere if the *R* group were to approach from this side. The consistent stereochemical outcome of this reaction can be useful in assigning the absolute configuration to chiral primary 1-deuterio alcohols. The reagent can also be used to prepare tritium-labeled alcohols.

3. *Synthesis of chiral propargylic alcohols*

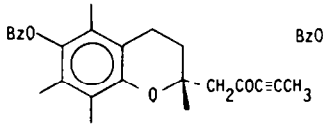
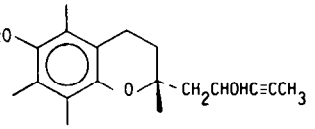
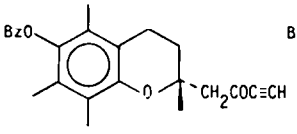
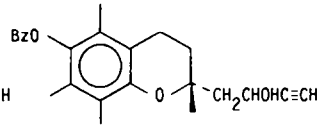
The reduction of prochiral ketones to high enantiomeric purity alcohols is an important reaction in asymmetric synthesis. There are several reagents to achieve this goal in simple aryl substrates, but these reagents are less successful in aliphatic ketones of interest to most synthetic chemists. Very recently, Midland and coworkers demonstrated that *B*-3-pinanyl-9-BBN reduces a variety of α,β-acetylenic ketones to the corresponding propargylic alcohols in exceptionally high enantiomeric purities, in the range of 73–100% e.e.[21] Reduction of certain acetylenic keto esters and terminal enynones proceeds with virtually quantitive asymmetric induction. This is a rare event in prochiral non-aromatic systems and compares favorably with the $LiAlH_4$-Darvon alcohol complex.[80] The propargylic alcohols thus obtained have the same absolute configuration consistently. In principle, alcohols of opposite configuration can be obtained by using the appropriate antipode of α-pinene to prepare the reagent. The results are summarized in Table 13. The acetylene moiety seems to have the same steric influence as hydrogen in the aldehyde reductions (eqn 45).



(45)

Reduction of α,β-acetylenic ketones is slower than that of aldehydes. However, the reduction can be driven to completion by using 2 equiv of the reagent. Terminal acetylenic ketones and acetylenic keto esters are reduced faster than internal acetylenic ketones. Higher reaction temperatures, as a means of accelerating the reaction, result in significant lowering of the enantiomeric purities. The loss of selectivity may be attributed to a competitive dehydroboration-reduction mechanism.[78,79]

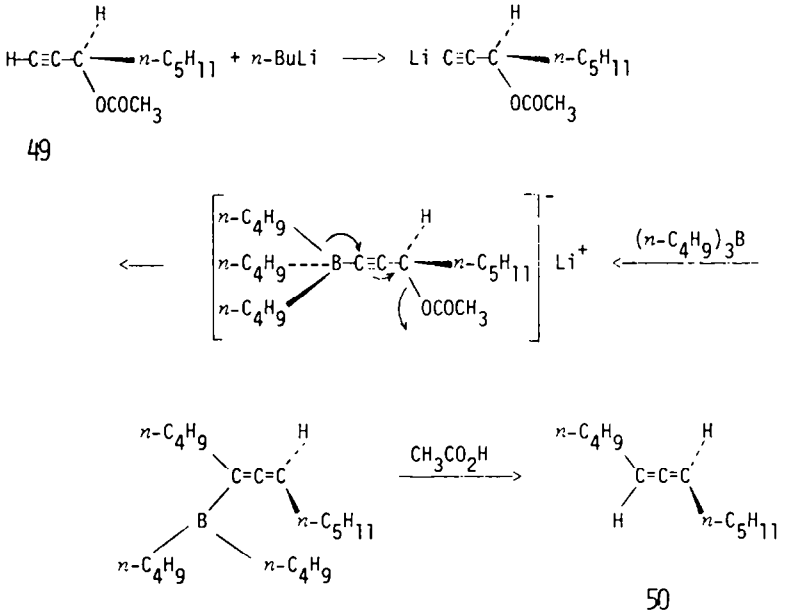
Table 13. Reduction of α,β-acetylenic ketones with **47**

NO	Ketone	Alcohol	e.e., %
1	$C_6H_5COC{\equiv}C(CH_2)_3CH_3$	$C_6H_5CHOHC{\equiv}C(CH_2)_3CH_3$	89
2	$CH_3COC{\equiv}CC_6H_5$	$CH_3CHOHC{\equiv}CC_6H_5$	78
3	$CH_3(CH_2)_2COC{\equiv}C(CH_2)_5CH_3$	$CH_3(CH_2)_2CHOHC{\equiv}C(CH_2)_5CH_3$	77
4	$CH_3(CH_2)_4COC{\equiv}CH$	$CH_3(CH_2)_4CHOHC{\equiv}CH$	92
5	$(CH_3)_2CHCOC{\equiv}CH$	$(CH_3)_2CHCHOHC{\equiv}CH$	99
6			88:15[a]
7			91:9[a]
8	$CH_3COC{\equiv}CCO_2CH_2CH_3$	$CH_3CHOHC{\equiv}CCO_2CH_2CH_3$	77
9	$CH_3(CH_2)_4COC{\equiv}CCO_2CH_2CH_3$	$CH_3(CH_2)_4CHOHC{\equiv}CCO_2CH_2CH_3$	92
10	$C_6H_5COC{\equiv}CCO_2CH_2CH_3$	$C_6H_5CHOHC{\equiv}CCO_2CH_2CH_3$	100
11	$(CH_3)_3CCOC{\equiv}CCH_3$	$(CH_3)_3CCHOHC{\equiv}CCH_3$	—[b]
12	$CH_3COC{\equiv}CC(CH_3)_3$	$CH_3CHOHC{\equiv}CC(CH_3)_3$	73

[a]Diastereomeric ratio. [b]Does not react.

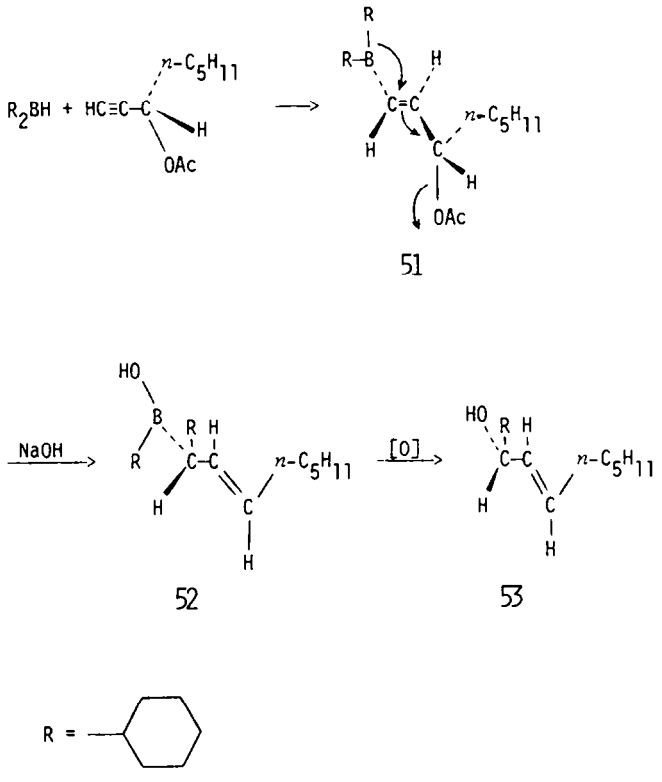
Chiral propargylic alcohols are very useful synthetic intermediates. For example, the alcohol from the enantiomer of **6** (Table 13), has been used in the synthesis of α-tocopherol.[81]

Propargyl acetate has been used in the synthesis of optically active allenes.[82] Thus, (*R*)-(+)-1-octyn-3-ol acetate, **49**, is transformed into chiral 5,6-dodecadiene, **50** (Scheme 6).



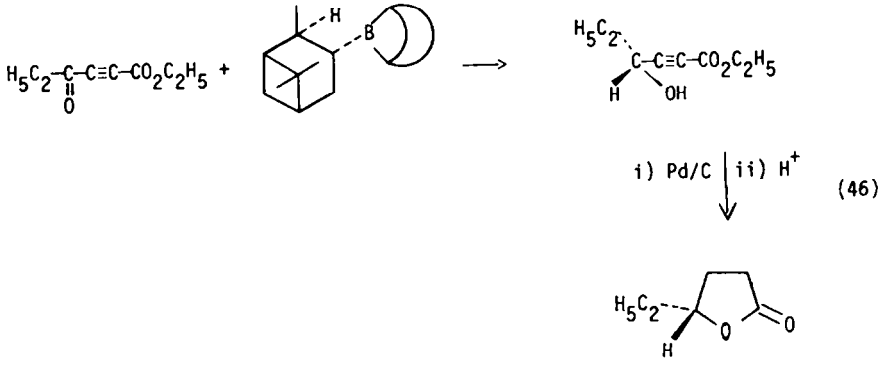
Scheme 6

Another useful application of propargyl acetate is demonstrated in the synthesis of optically active trans allylic alcohols[83] (Scheme 7). The hydroboration of (*S*)-3-hydroxy-1-octynyl acetate with dicyclohexylborane, followed by rearrangement of the vinylborane, **51**, provides the trans allylic alcohol, **53**, following oxidation of the allyl borinic acid, **52**. The double bond, formed after the migration, is exclusively trans and the enantiomeric composition is 87:13, with *R* as the major isomer. An increase in the enanteoselectivity has been observed with increasing degree of substitution at the α-carbon of the migrating group. The overall transformation achieves an alkylation and a 1,3-alcohol transposition with a high degree of stereoselectivity at the new alcohol center and about the double bond.



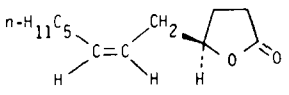
Scheme 7

Optically active 4-substituted γ-lactones are often found in nature as pheromonal constituents. 4-Hydroxy-2-alkynoates are useful precursors for the synthesis of such naturally occurring γ-lactones. A general asymmetric synthesis of 4-substituted-γ-lactones has been recently demonstrated.[84] Optically active 4-hydroxy-2-alkynoates are readily obtained by the reduction of 4-oxo-2-alkynoates with *B*-3-pinanyl-9-BBN. Hydrogenation of 4-hydroxy-2-alkynoate, followed by acid-catalyzed lactonization, directly provides optically active 4-alkyl-γ-lactones (eqn 46).

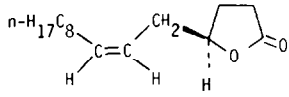


(46)

In an alternative route, the acetylene linkage is partially hydrogenated to provide the chiral butenolide upon acidification. The required lactones are then obtained by conjugate reduction using "copper hydride." This alternative route can accommodate an unsaturated side-chain. The black-tailed deer pheromone, **54**, and the Japanese beetle pheromone, **55**, have been synthesized using this strategy.



54

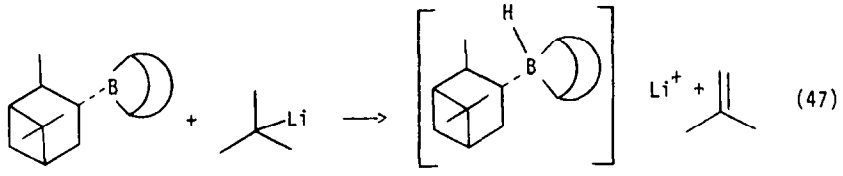


55

Regrettably, the reduction of saturated aliphatic ketones, such as 2-butanone, by **47**, is not satisfactory for producing the chiral 2-butanol. It appears that the reaction with **47** is slower, so that the reaction proceeds predominantly through a concurrent dissociation of the reagent into α-pinene and 9-BBN. Reduction of the ketone by the latter reagent produces the racemic alcohol.[82b]

B. Chiral borohydride reagents

Recently a class of very powerful reducing agents, the trialkylborohydrides, have been developed. By increasing the size of the alkyl groups, very high stereoselectivities have been achieved. It was therefore anticipated that the incorporation of optically active alkyl groups into the borane would provide an attractive route to the asymmetric reduction of carbonyl compounds. Thus, lithium *B*-3-pinanyl-9-boratabicyclo[3.3.1]nonyl hydride, **56**, a highly hindered trialkylborohydride containing an asymmetric alkyl group, was obtained[18] by treatment of **47** with *t*-butyllithium at $-78°$ (eqn 47). It reduces[18] rapidly

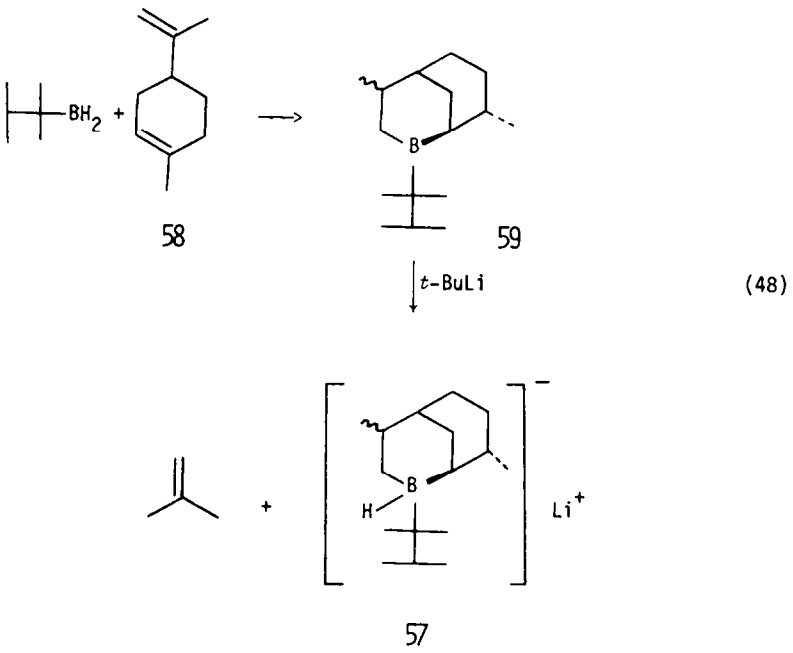


(47)

47 56

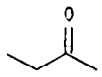
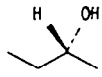
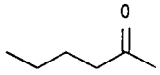
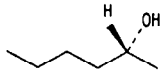
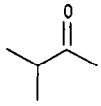
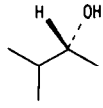
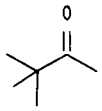
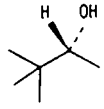
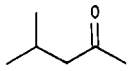
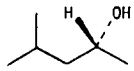
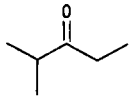
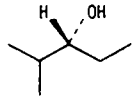
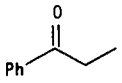
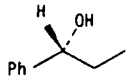
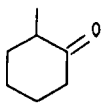
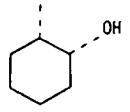
and quantitatively a variety of ketones to the corresponding optically active alcohols at $-78°$ (Table 14). The reagent prepared from (+)-α-pinene consistently gives *R* as the major enantiomer. The enantionselectivity observed with the borohydride, **56**, is very less as compared to the corresponding trialkylborane, **47**. The hydride transfer in **56** takes place one atom away from the chiral center, whereas, the hydride is directly transferred from a chiral center in **47** by a cyclic mechanism. This factor may be responsible for the lower selectivity achieved in reductions with **56**.

A chiral trialkylborohydride, **57**, has been developed to control the remote chiral center at C-15 in the prostaglandin synthesis.[85] The cyclic hydroboration of limonene, **58**, with thexylborane, followed by the treatment of the trialkylborane, **59**, thus formed with *t*-butyllithium, provides thexyllimonylborohydride, **57** (eqn 48). The stereoselective reduction of a C-15 ketone derivative, **60**, relies on the use of the 4-phenylphenyl carbamate moiety as a protecting group on the C-11 OH. The van der Waals attraction between this rigid substituent and the enone sidechain favors a conformation in which these two groups protect the α-face of the ketone. Thus the bulky borohydride, **57**, preferentially attacks from the β-face to provide a ratio of 92:8 for the 15*S* to the 15*R* isomers in the reduced product, **61**.



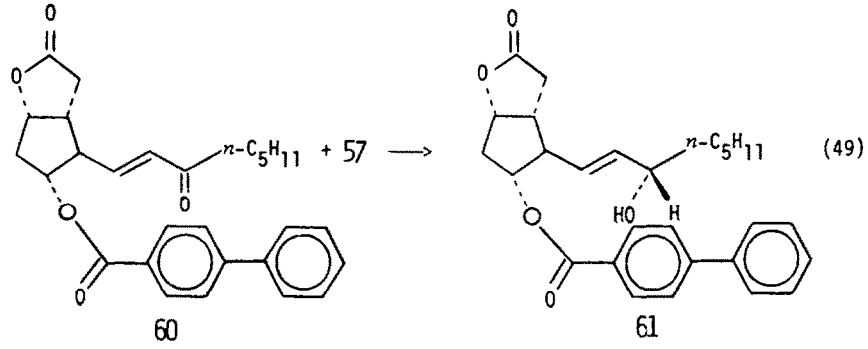
(48)

Table 14. Asymmetric reduction of ketones with 56[a]

NO	Ketones	Alcohol	e.e., %	Config.
1			29	*R*
2			30	*R*
3			36	*R*
4			3	*R*
5			16	*R*
6			17	*R*
7			37	*R*
8			13	*R*
9			14	1*R*,2*S*

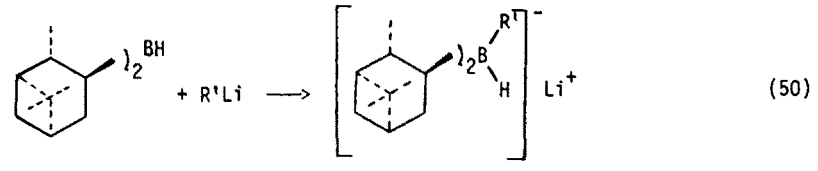
[a]The reagent is prepared from (+)-α-pinene, $[\alpha]_D$ +49.3°, 96% e.e.

It was reported that IPC_2BH on treatment with organolithium reagents (MeLi, *n*-BuLi, PhLi) resulted



60 61

in the formation of chiral trialkylborohydrides,[86,87] **62** ,(eqn 50). However, the recent study has established



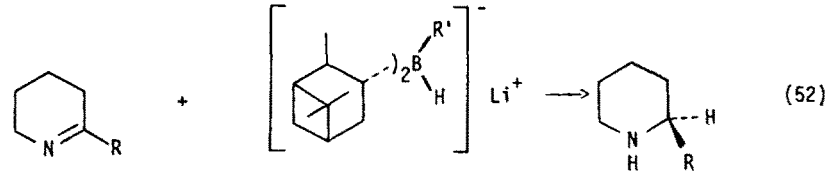
62 R' = Me, *n*-Bu, Ph

that the treatment of dialkylboranes with primary alkyl and aryl organolithium reagents (MeLi, *n*-BuLi, PhLi) does not produce the expected lithium trialkylborohydrides ($LiR_2R'BH$), but a 1:1 mixture of lithium tetraalkylborate ($LiR_2R'_2B$) and lithium dialkylborohydride[88] (LiR_2BH_2) (eqn 51). Reductions of a series of representative

$$2R_2BH + 2R'Li \longrightarrow [R_2R'_2B]^-Li^+ + [R_2BH_2]^-Li^+ \qquad (51)$$

ketones, such as 2-butanone, 3-methyl-2-butanone, 3,3-dimethyl-2-butanone and 2-methyl-3-pentanone with **62** (R' = Me, *n*-Bu) produced by the proposed reaction yielded the corresponding alcohols in 5, 4, 8, and 46% e.e. respectively.[87]

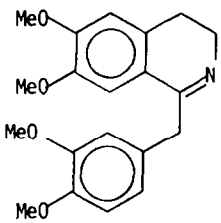
Asymmetric reduction of cyclic imines,[89a] e.g. 2-alkyltetrahydropyridine (**63**, R = *n*-Pr, Et, Me), with the trialkylborohydride (**65**, R' = Me, *n*-Bu, Ph) prepared from (+)-α-pinene gave a predominance of (*R*)-(−)-2-alkylpiperidines (**64**, R = *n*-Pr, Et, Me) in 4–25% e.e. (eqn 52). The borohydride, **62**, has been



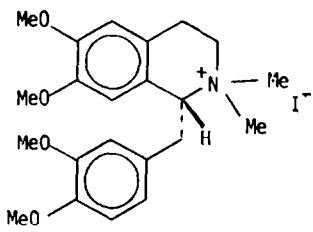
63 65 64

(R)-(-)-

used for the synthesis of the optically active alkaloid laudanosine, **66**, from 3,4-dihydropapaverine,[89b] **67**.



67



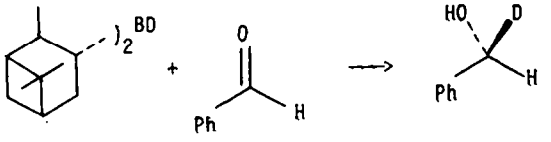
66

C. Diisopinocampheylborane

Diisopinocampheylborane has been utilized for the asymmetric reduction of a series of alkyl methyl ketones.[90-92] The asymmetric induction observed in the reduction of ketones is not as high as that observed with hydroboration of *cis*-olefins. In the case of reduction using IPC_2BH, the hydride transfer takes place one atom away from the chiral center. This situation is comparable to the hydroboration of the 2-methyl-1-alkenes. This factor may be responsible for the low optical purities observed in the reductions of ketones using IPC_2BH.

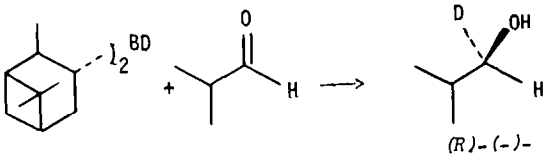
Reports from two separate laboratories differ considerably with regard to both the extent of asymmetric induction and the configuration of the predominant isomer formed.[90,91] To resolve this conflicting result, IPC_2BH of high enantiomeric purity has been utilized for the asymmetric reduction of representative alkyl methyl ketones.[92] The enantiomeric purities of the product alcohols are in the range of 9–37% e.e. The results are summarized in Table 15. In contrast to earlier studies in which the reagent evidently contained small amounts of sodium borohydride and other minor constituents, the results are consistent and reproducible. It is also observed that small quantities of sodium borohydride in the reagent can diminish considerably the enantiomeric purities of the product alcohols.[92]

Diisopinocamphyldeuterioborane has been utilized for the asymmetric reduction of banzaldehyde[93] and isobutyraldehyde[94] to the corresponding deuterio alcohols in 30% and 27% e.e. respectively (eqns 53 and 54).



(S)-(+)-

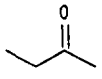
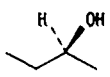
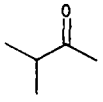
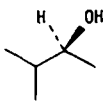
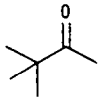
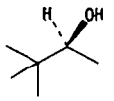
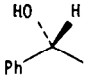
(53)



(R)-(-)-

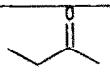
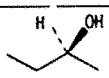
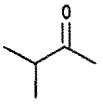
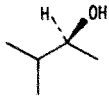
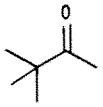
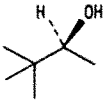
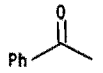
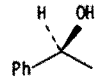
(54)

Table 15. Asymmetric reduction of ketones with (−)-IPC_2BH[a]

NO	Ketones	Alcohols	e.e., %	Config.
1			13.4	*S*
2			37	*S*
3			20	*S*
4			9	*R*

[a](−)-IPC_2BH of ∿ 100% e.e. is prepared from (+)-α-pinene, $[\alpha]_D$ +48.0, 94% e.e.

Table 16. Asymmetric reduction of representative ketones with $IPCBH_2$[a]

NO	Ketones	Alcohols	e.e., %	Config.
1			22	*S*
2			46	*S*
3			21	*S*
4			15	*S*

[a] $IPCBH_2$ of ~ 100% e.e. is prepared from (+)-α-pinene, $[\alpha]_D$ +48.1°, 94% e.e.

D. Monoisopinocampheylborane

Monoisopinocampheylborane has been used for the reduction of representative ketones. The enantiomeric purities are in the range of 15 to 46% e.e.[95] The results are modestly better than those obtained with IPC_2BH (Table 16).

E. Conclusion

In conclusion, *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane is an excellent enantioselective and chemoselective chiral reagent for reduction of deuterated aldehydes and α,β-acetylenic ketones. The deuterated reagent is particularly useful for the synthesis of chiral primary alcohols since it does not involve the prior preparation of deuterated aldehydes. Unfortunately, the reagent fails with non-acetylenic aliphatic ketones. Lithium *B*-3-pinanyl-9-boratabicyclo[3.3.1]nonyl hydride, diisopinocampheylborane, and monoisopinocampheylborane give only moderate asymmetric induction in the reduction of prochiral aliphatic ketones. An effective chiral organoborane reagent for the asymmetric reduction of such aliphatic and acylic ketones remains to be developed.

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