

## The boron approach to asymmetric synthesis

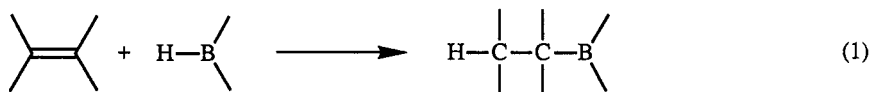
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**Abstract:** The unique chemistry of organoboranes has made possible a three-pronged approach to asymmetric synthesis: 1) asymmetric hydroboration, 2) asymmetric reduction, and 3) asymmetric allyl- and crotylboration. Consequently, boron chemistry makes possible not only a uniquely general synthesis of pure enantiomers (with purities approaching 100% ee) as well as more complex stereoisomers by processes that are simple and broadly applicable. Boron derived reagents have proven to be exceptionally versatile for the asymmetric reduction of the carbonyl group in a variety of derivatives to give products of optical purities approaching 100% ee. Finally, the synthesis of chiral organoboranes containing allyl, crotyl and related groups attached to boron is providing a highly valuable synthesis *via* allylboration of stereoisomers in purities approaching 100% ee. It is evident that boron chemistry is providing major new routes for asymmetric synthesis in organic chemistry.

### HYDROBORATION

The remarkably facile addition of diborane in ether solvents to alkenes and alkynes was discovered in 1956 (ref. 1) (1).



For the next decade my students and associates studied the hydroboration of alkenes, alkynes and their substitution until we felt that our understanding of hydroboration was satisfactory (ref. 2). These studies revealed promising characteristics (Fig. 1).

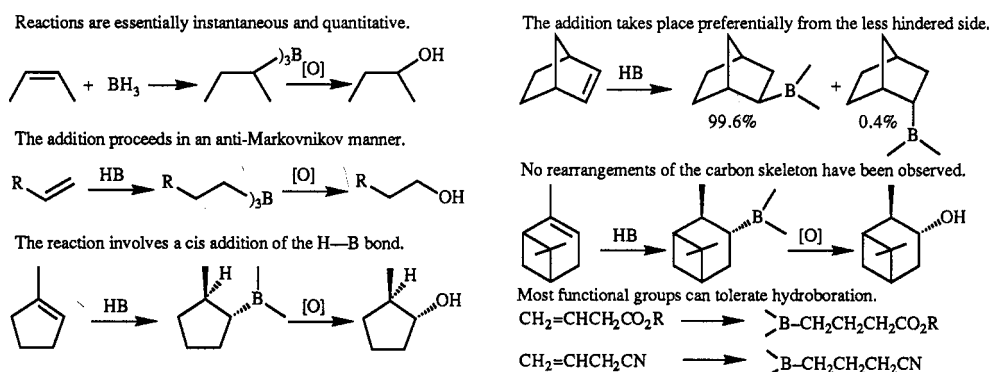


Fig. 1. Major characteristics of hydroboration.

Many borane derivatives were developed as new hydroborating agents with valuable specialized properties (ref. 3). At the time many individuals expressed scepticism as to the value of devoting so much research effort to this reaction. They took the position that hydroboration, while a clean, simple reaction, produces only organoboranes, compounds of no known use. Organoboranes had been prepared and described by E. C. Frankland in 1862 (ref. 4), but they had not been subjected to systematic research at that time. Indeed, at the time of the discovery of hydroboration only three things were really known about the chemistry of organoboranes: 1) they are oxidized by air; 2) are stable to water; 3) they form addition compounds with amines, and we had studied the factors influencing the dissociation of such addition compounds in exploring the role of steric effects (ref. 5).

### The versatile organoboranes

We bided our time. After our exploration of the hydroboration reaction had proceeded to the point where we felt we understood the reaction and could apply it with confidence to new situations (ref. 6), we began a systematic exploration of the chemistry of organoboranes, with emphasis on reactions of synthetic utility (ref. 7).

Some indication of the versatility of organoboranes for synthesis is indicated by the chart in Fig. 2.

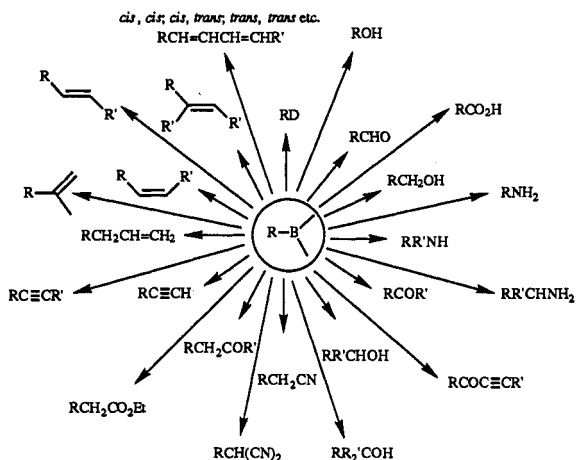


Fig. 2. Chart showing representative transformations of organoboranes.

Simple operating procedures have been developed for utilizing hydroboration/organoborane transformations for organic synthesis (ref. 8).

### Substitution with retention

An unexpected feature of the great majority of the substitution reactions of organoboranes is the fact that they proceed with complete retention of configuration of the organic group that is transferred from boron to some other element or group. This feature is illustrated for hydroboration/amination (Figs. 3 and 4).

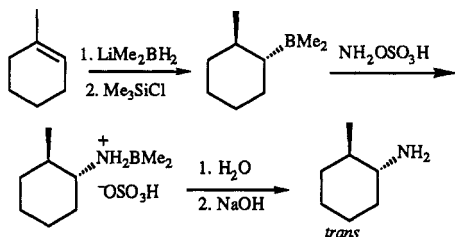


Fig. 3. Amination of organoboranes to primary amines proceeds with retention.

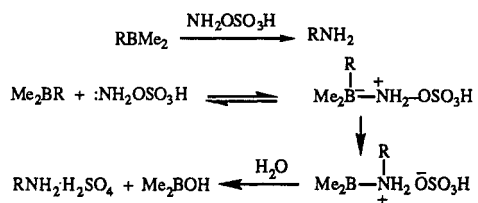


Fig. 4. Proposed mechanism of amination of organoboranes which accounts for the observed retention.

For a more detailed review of retention in the reactions of organoboranes see a lecture at IMEBORON VI (ref. 9).

### ASYMMETRIC HYDROBORATION

It was apparent that if we could achieve the synthesis of organoboranes containing optically active groups attached to boron,  $R^*B<$ , we might have a general asymmetric synthesis. Fortunately, we already had indications that this was possible.

Originally George Zweifel had undertaken to study the hydroboration of  $\alpha$ -pinene in order to establish whether an olefin as sensitive as this structure toward rearrangement could survive hydroboration. In fact, no rearrangement was observed. However, the hydroboration proceeded to  $R_2BH$  (diisopinocampheylborane,  $Ipc_2BH$ ) and then ceased. Apparently, the steric requirements of this group are so large that only two such bulky groups can attach themselves to boron. The formation of  $Ipc_2BH$  provided an optically active hydroborating agent. However, the failure of this reagent to react with a third molecule of  $\alpha$ -pinene, made it clear that the reagent could be used only for the hydroboration of less hindered alkenes, such as 2-butene. The experiment was tried (ref. 10). The results were astounding. 2-Butene was transformed by hydroboration with  $Ipc_2BH$  (from  $\alpha$ -pinene of 93% ee), followed by oxidation, to  $R(-)$ -2-butanol of 87% ee (Fig. 5).

This was the first asymmetric synthesis of high ee. Of course, asymmetric synthesis has now progressed to the point where such high optical yields are commonplace. When asymmetric hydroboration became of major importance for the development of our proposed general asymmetric synthesis, we returned to a detailed study of asymmetric hydroboration. We learned how to make  $Ipc_2BH$  of 100% ee (Fig. 6, ref. 11).

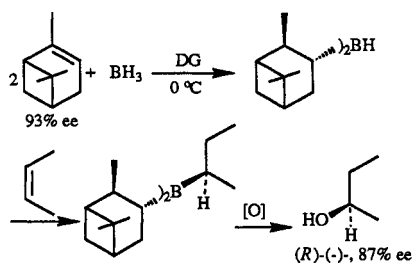
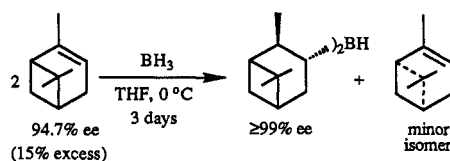


Fig. 5. Original asymmetric hydroboration.

Fig. 6. Preparation of optically pure  $\text{Ipc}_2\text{BH}$  ( $\geq 99\%$  ee).

Representative applications of pure  $\text{Ipc}_2\text{BH}$  for the hydroboration of *cis*-alkenes at  $-25\text{ }^\circ\text{C}$  are indicated in Figs. 7 and 8 (ref. 12-14).

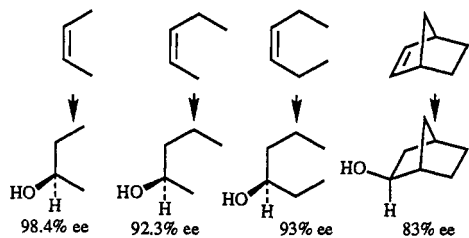
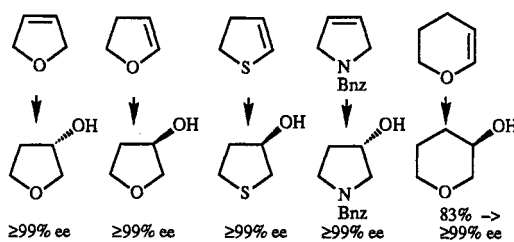
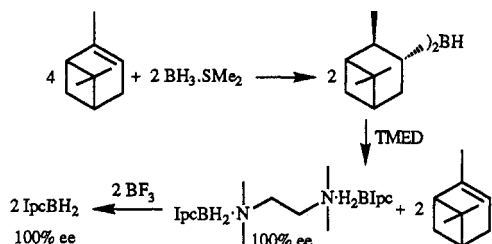
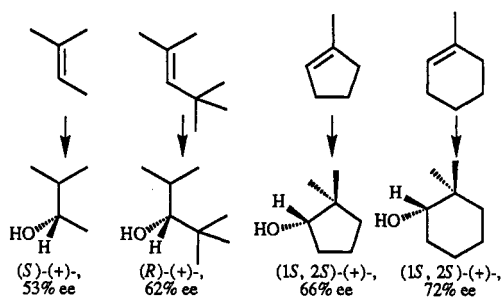
Fig. 7. Asymmetric hydroboration-oxidation of *cis*-alkenes with optically pure  $\text{Ipc}_2\text{BH}$  ( $\geq 99\%$  ee).

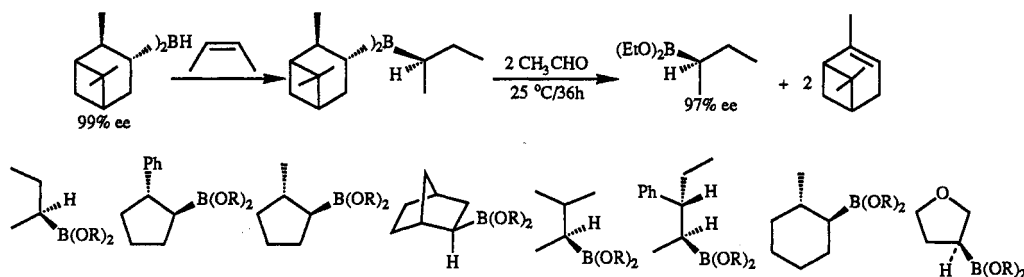
Fig. 8. Asymmetric hydroboration-oxidation of heterocyclics.

To handle more hindered olefins, we required a reagent of lower steric requirements than  $\text{Ipc}_2\text{BH}$ . Accordingly, we prepared and tested optically pure  $\text{IpcBH}_2$  (Fig. 9, ref. 15).

Although the hydroboration results were often less satisfactory, a simple recrystallization of the borane intermediate usually brought the optical purity up to 100% ee (Fig. 10).

Fig. 9. Preparation of  $\text{IpcBH}_2$  of high optical purity.Fig. 10.  $\text{IpcBH}_2$  applicable to trisubstituted alkenes.

Treatment of the hydroboration product with acetaldehyde removes the *Ipc* group as  $\alpha$ -pinene and provides the pure boronic ester (Fig. 11, ref. 16 and 17).

Fig. 11. Direct chiral synthesis of boronic acids and esters of  $\geq 99\%$  ee.

Matteson has developed an independent synthesis of optically active boronic esters involving not hydroboration, but asymmetric homologation (Fig. 12, ref. 18).

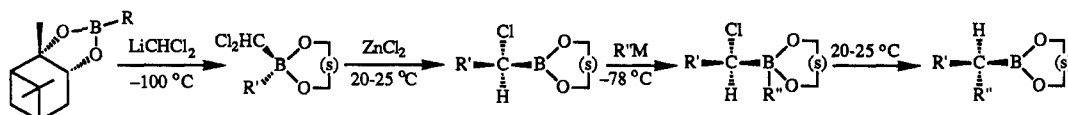


Fig. 12. Matteson's approach to asymmetric synthesis of optically active boronic esters

### A general asymmetric synthesis via chiral organoboranes

With optically active groups attached to boron, now readily achieved, either through asymmetric hydroboration or the Matteson asymmetric homologation,  $R^*B(OR')_2$ , we began a systematic program of transforming these intermediates into the desired enantiomers (Fig. 13).

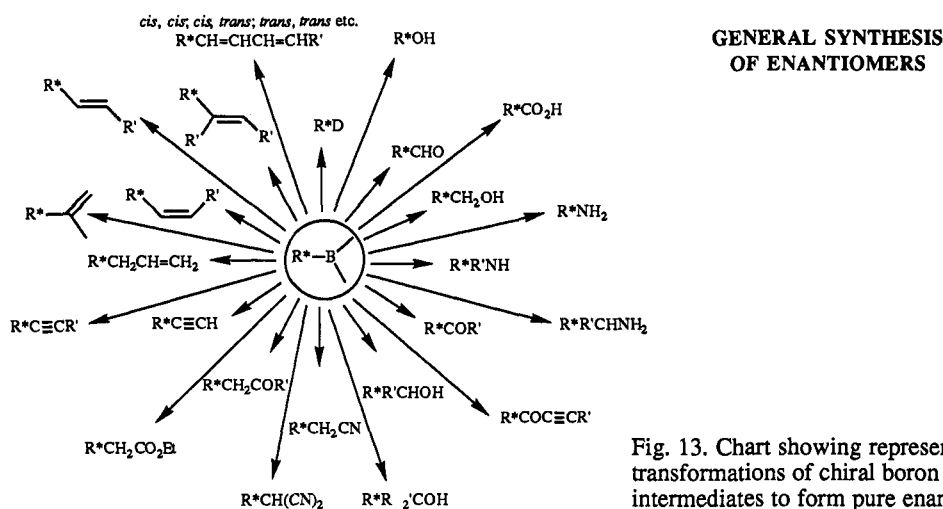


Fig. 13. Chart showing representative transformations of chiral boron intermediates to form pure enantiomers.

Space does not permit a detailed review of the individual reactions. However, representative reactions are discussed at an earlier lecture at IMEBORON VI (ref. 9). That source should be consulted. It has been necessary to overcome a number of difficulties, but we have now achieved successful application of the procedure to approximately two thirds of the reactions shown.

### ASYMMETRIC REDUCTION

The excellent results that we had achieved in asymmetric hydroboration with  $Ipc_2BH$  and  $IpcBH_2$  and that Matteson had achieved in asymmetric homologation with the diol from  $\alpha$ -pinene, encouraged us to consider this chiral auxiliary for other reactions of interest, namely asymmetric reduction and asymmetric allylboration (Fig. 14).

Our first effort in this direction was the synthesis of the lithium hydride adduct of  $B$ - $Ipc$ -9-BBN, (Aldrich: Alpine-Borane<sup>®</sup>) (ref. 20). However, this derivative (Alpine-Hydride<sup>®</sup>) proved disappointing (Fig. 15).

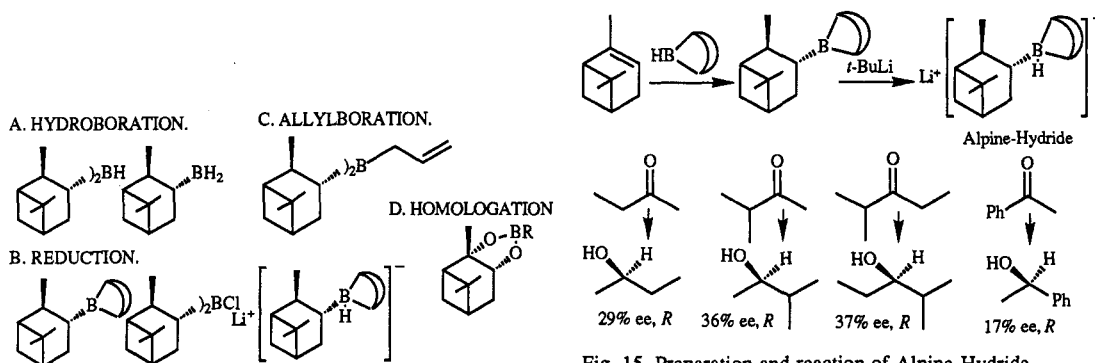


Fig. 14. Boron based chiral auxiliaries derived from  $\alpha$ -pinene.

Fig. 15. Preparation and reaction of Alpine-Hydride with representative ketones.

A major improvement was achieved by M. M. Midland and coworkers (Fig. 16, ref. 21) utilizing the benzyl ether of nopol. This reagent, NB-Enantride<sup>™</sup> showed significant improvement over Alpine-Hydride. Especially noteworthy is the high ee achieved in asymmetric reduction of straight chain ketones, such as 2-butanone and 2-octanone.

M. M. Midland discovered that Alpine-Borane is an excellent reducing agent for certain carbonyl compounds. The reduction of aldehydes was very fast and made it possible to produce the enantiomeric monodeuterated primary alcohols,  $RC^*HDOH$ , in 100% ee (Fig. 17, ref. 22).

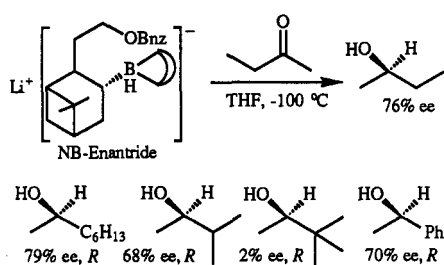


Fig. 16. Asymmetric reduction of representative ketones with NB-Enantride in THF at  $-100^{\circ}\text{C}$ .

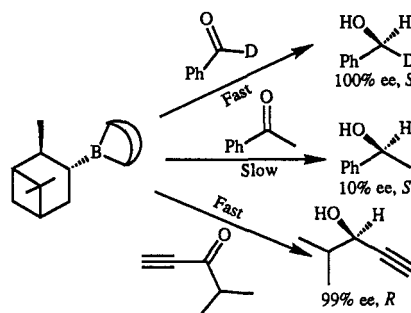


Fig. 17. Asymmetric reductions with Alpine-Borane in THF (0.5 M) at RT.

The asymmetric reduction of most ketones with this reagent under these conditions are very slow and the optical yields disappointing (Fig. 17). On the other hand, the reductions of acetylenic ketones are fast and the products usually obtained in high ee. This is nicely explained in terms of a competing dissociation of the reagent into its components. Reduction by a cyclic mechanism achieves high optical yields. In slow reductions, dissociation competes, allowing reduction by the 9-BBN component, and inactive product results (Fig. 18).

Two solutions have been proposed. Reduction of ketones by Alpine-Borane under hydrostatic pressures of 6000 atmospheres gives greatly enhanced optical yields (ref. 23). Alternatively, reduction of ketones by neat Alpine-Borane, or by concentrated solutions ( $\sim 2\text{ M}$ ) also gives greatly improved optical yields for many ketones (ref. 24).

### Diisopinocampheylchloroborane, $\text{Ipc}_2\text{BCl}$

Our investigations had indicated that sterically hindered  $\text{R}_2\text{BCl}$  derivatives are more stable toward dissociation than  $\text{R}_3\text{B}$ . Accordingly, we examined  $\text{Ipc}_2\text{BCl}$  as a reducing agent. It proved to have many advantages for many classes of ketones (Fig. 19, ref. 25).

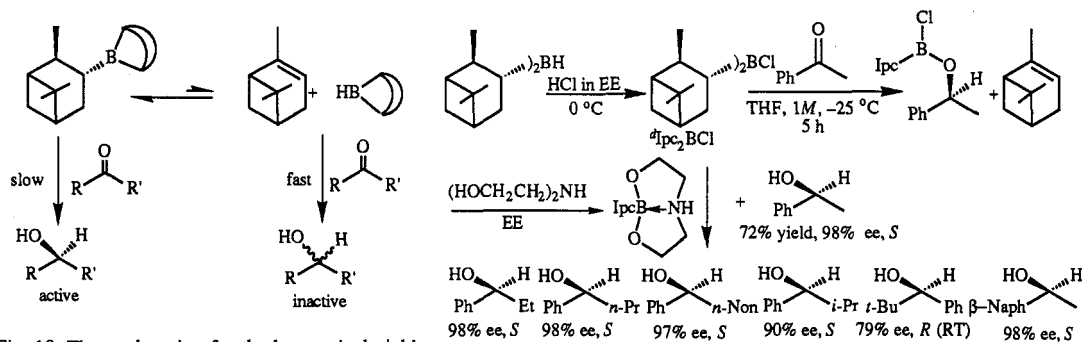


Fig. 18. The explanation for the low optical yields realized in the reduction of most ketones with Alpine-Borane under the standard conditions.

Fig. 19. Preparation and reaction of diisopinocampheylchloroborane with aralkyl ketones.

### Systematization of asymmetric reductions

Some twenty different reagents have been proposed in recent years for the asymmetric reduction of carbonyl compounds. Some of them have shown exceptional promise for a limited type of structure. However, few reagents are promising for a wide range of structure and data are generally not reported for the less favorable applications. Consequently, it becomes very difficult to compare the relative effectiveness of these reagents over the full range of carbonyl compounds of interest for asymmetric reduction.

Accordingly, we decided to select the six most promising reagents and to compare their optical efficiencies against a standard compound for each of the ten classes of ketones, getting additional data where the literature was incomplete (Fig. 20, ref. 26).

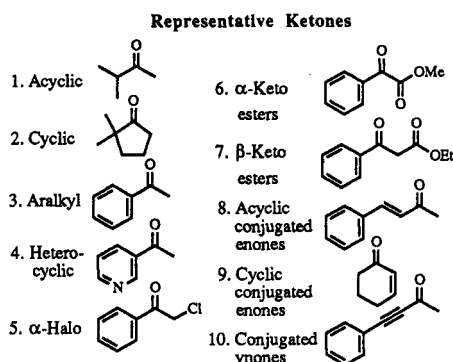


Fig. 20. Representative examples of 10 classes of ketones and six selected reagents.

**Selected Reagents**

1. Alpine-Borane
2.  $\text{Ipc}_2\text{BCl}$
3. Itsuno's Reagent
4. NB-Enantride
5. K-Gluconide
6. Binal-H

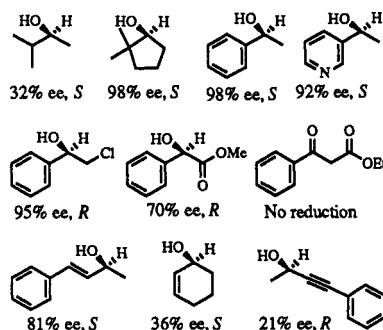


Fig. 21. Reduction of representative ketones with  $\text{Ipc}_2\text{BCl}$  in THF at  $-25^\circ\text{C}$ .

Data for the six selected reagents are summarized in Table 1. Analysis of the data indicates the preferred reagent for each class of ketone (Fig. 22).

Table 1. Asymmetric reduction of representative ketones (selected procedures)

Ketone	Reagent					
	Alpine-Borane	$\text{Ipc}_2\text{BCl}$	Itsuno's Reagent	NB-Enantride	K-Gluconide	Binal-H
1	62	32	60	68	36	78*
2	20	98**	96*	1	84*	11
3	87	98**	94*	70	78	95*
4	93*	92*	73	8	70	
5	96*	95*	96*	41	7	95*
6	90*	70	25	33	92**	24
7*						
8	56	81**	6	13	60	70*
9	30	36	35			
10**	83*	21	7	10	61	89**

\*Soai's  $\text{LiBH}_4$ -Dibenzoylcystine-*t*-BuOH mixture is excellent for  $\beta$ -keto ester reductions. \*\*NB-Enantrane gives 86%. Therefore \*\*.

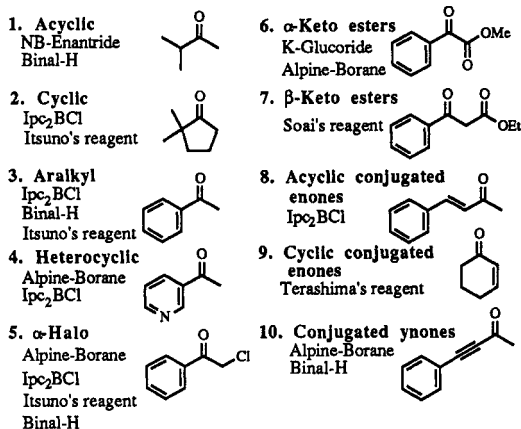


Fig. 22. Optimum reagents for asymmetric reduction of representative ketones.

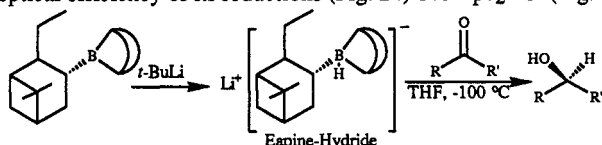
**Steric effects**

It had been puzzling why NB-Enantride had been so much more effective as a reducing agent than Alpine-Hydride (Fig. 16). One possible explanation was that the greater steric requirements of the benzyloxyethyl group at position 2 of the apopinene structure is responsible for improving the optical yield. Accordingly we undertook to synthesize the corresponding 2-ethyl derivative (Eapine-Hydride) for comparison with the parent 2-methyl derivative (Alpine-Hydride) and the 2-benzyloxyethyl derivative (NB-Enantride). The results are shown in Fig. 23 (ref. 27).

Clearly the effectiveness of the Eapine-Hydride compares favorably with that of NB-Enantride. It now remains to further test the hypothesis by synthesizing derivatives containing even bulkier alkyl groups at the 2-position of apopinene: R = *n*-propyl, isopropyl, and isobutyl.

**Biseapinechloroborane Eap<sub>2</sub>BCl**

It then appeared desirable to test the effect of replacing the methyl group of  $\alpha$ -pinene in  $\text{Ipc}_2\text{BCl}$  by an ethyl group on the steric efficiency of the reduction process. The compound, Eap<sub>2</sub>BCl, was readily synthesized by hydroborating 2-ethylapopinene with chloroborane (ref. 28). This reagent revealed consistent improvements in the optical efficiency of its reductions (Fig. 24) over  $\text{Ipc}_2\text{BCl}$  (Fig. 21).



Ketone	% ee			
	Alpine-Hydride $-78^\circ\text{C}$	NB-Enantride $-78^\circ\text{C}$ – $-100^\circ\text{C}$		Eapine-Hydride $-78^\circ\text{C}$ – $-100^\circ\text{C}$
2-Octanone	33	62	75	70
3-Methyl-2-butanone	36	68	68	77
acetylcyclohexane	27	65	80	70
acetophenone	20	63	70	56
2-Chloroacetophenone	4	41	48	61

Fig. 23. Preparation and reactions of Eapine-Hydride in THF at  $-100^\circ\text{C}$ .

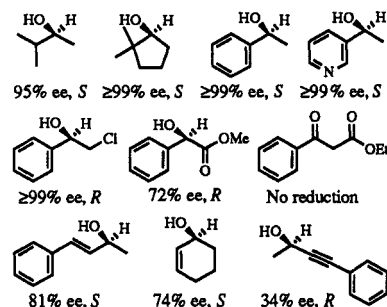


Fig. 24. Reduction of representative ketones with Eap<sub>2</sub>BCl in EE at  $-25^\circ\text{C}$ .

An examination of the data for the more promising reagents reveals the remarkable effectiveness of  $\text{Eap}_2\text{BCl}$  (Table 2).

Finally, a critical examination of the data for the reduction of the ten representative ketones indicates the most favorable reagent or reagents for each class of ketone (Fig. 25).

Table 2. Asymmetric reduction of representative ketones  
Effectiveness of  $\text{Eap}_2\text{BCl}$

Ketone	Reagent						
	Alpine-Borane	$\text{Ipc}_2\text{BCl}$	Itsuno's Reagent	NB-Enan-tride	K-Gluco-ride	Binal-H	$\text{Eap}_2\text{BCl}$
1	62	32	60	68	36	78*	95**
2	20	98**	96*	1	84*	11	$\geq 99^{**}$
3	87	98**	94*	70	78	95*	$\geq 99^{**}$
4	93*	92*	73	8	70		$\geq 99^{**}$
5	96*	95*	96*	41	7	95*	$\geq 99^{**}$
6	90*	70	25	33	92**	24	72
7*							
8	56	81**	6	13	60	70*	81**
9	30	36	35				74
10**	83*	21	7	10	61	89**	34

\*Soai's  $\text{LiBH}_4$ -Dibenzoylcystine-*t*-BuOH mixture is excellent for  $\beta$ -keto ester reductions. \*\*NB-Enantrane gives 86%. Therefore \*\*.

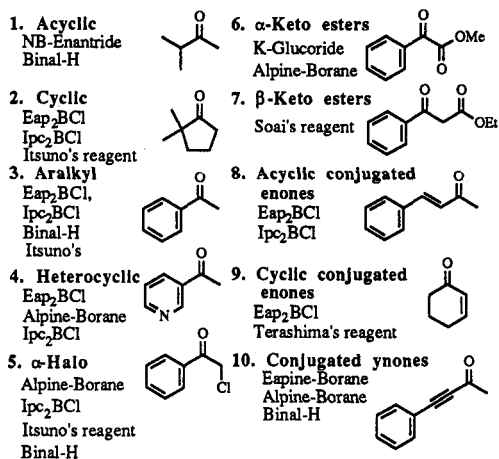


Fig. 25. Optimum reagents for asymmetric reduction of representative ketones.

It is noteworthy that with two exceptions, Binal-H and Terashima's reagent, all of the most favorable reagents are boron derivatives.

## ALLYL- AND CROTYLBORATION

Simple organoboranes, such as triethylborane do not add to the carbonyl group. However, as was first pointed out by Mikhailov, allylboron derivatives undergo a fast addition, which proceeds with allylic rearrangement (Fig. 26, ref. 29).

R. W. Hoffmann used a chiral auxiliary derived from camphor to achieve a simple asymmetric synthesis (Fig. 27, ref. 30).

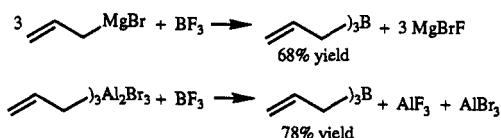


Fig. 26. Preparation of triallylborane.

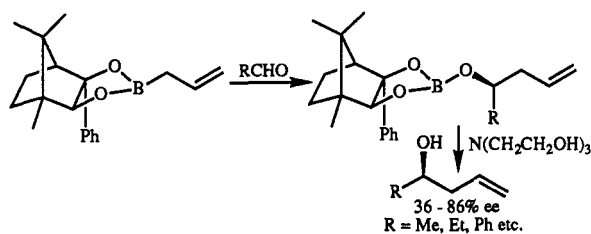


Fig. 27. Asymmetric allylboration using a camphor derivative.

The optical yields were good (40-76% ee), but not excellent ( $\geq 90\%$  ee). Accordingly, we decided to test our chiral auxiliary,  $\text{Ipc}_2\text{BAl}$  (Figs. 28 and 29, ref. 31).

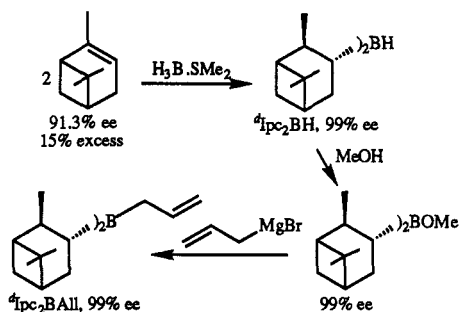


Fig. 28. Preparation of *B*-allyldiisopinocampheylborane.

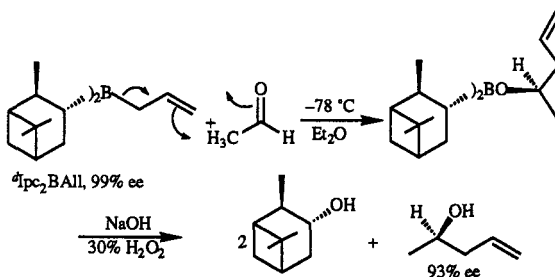


Fig. 29. Asymmetric allylboration with  $\text{Ipc}_2\text{BAl}$ .

The excellent results achieved was highly promising. We then undertook a systematic study. Many different derivatives were explored (Figs. 30 and 31, ref. 32 and 33).

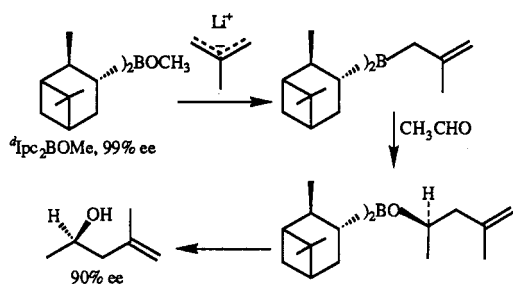


Fig. 30. Preparation and reaction of *B*-methylallyldiisopinocampheylborane.

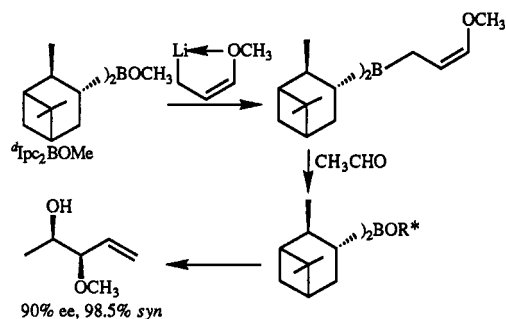


Fig. 31. Preparation and reaction of [*Z*]-3-methoxyallyldiisopinocampheylborane.

In some cases the desired  $\text{Ipc}_2\text{BALL}$  could be synthesized by hydroboration of a representative allene or diene (Figs. 32 and 33, ref. 34 and 35).

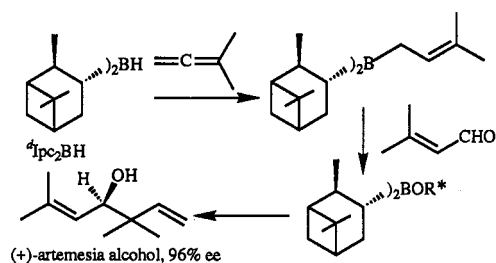


Fig. 32. Reaction of 3,3-dimethylallyldiisopinocampheylborane.

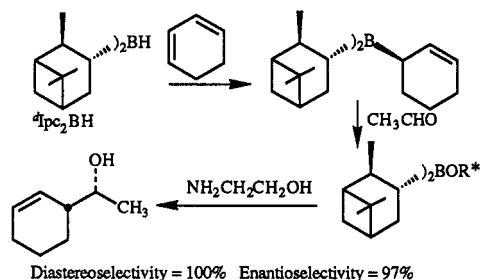


Fig. 33. Reaction of 2-cyclohexen-1-yl diisopinocampheylborane.

### Asymmetric crotylboration

We learned how to metallate [*Z*]- and [*E*]-2-butene by the Schlosser procedure (ref. 36) to produce pure [*Z*]- and [*E*]-crotylpotassium (ref. 37). These could be converted into the  $\text{Ipc}_2\text{B}$  derivatives which achieved asymmetric crotylboration with remarkable optical efficiencies. Consequently, it is now possible to synthesize at will each of the four possible isomers of the  $\beta$ -methylhomoallylic alcohols (Fig. 34, ref. 37).

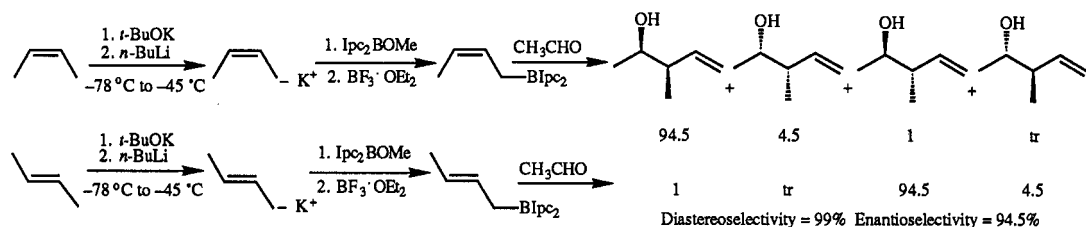


Fig. 34. Synthesis of [*Z*]- and [*E*]-crotyldiisopinocampheylboranes and asymmetric crotylboration.

Although we have illustrated asymmetric allyl- and crotylboration primarily for their reaction with acetaldehyde, a wide variety of aldehydes are applicable. Indeed, even in the case of aldehydes containing chiral Me- or BnO-groups in the  $\alpha$ -position, little effect on the optical purities of the products are observed (ref. 38).

### Rates of allylboration

Many different chiral auxiliaries have been proposed for such allylboration (Fig. 35).

It became desirable to obtain quantitative data on the relative rates of reaction of the allylboration reaction for the various structural types which have been utilized. The glycol derivatives, related to the Hoffmann chiral auxiliary, proved to be very slow. Consequently such derivatives cannot be used at low temperatures to enhance the steric efficiency of the reactions (Fig. 36, ref. 39).



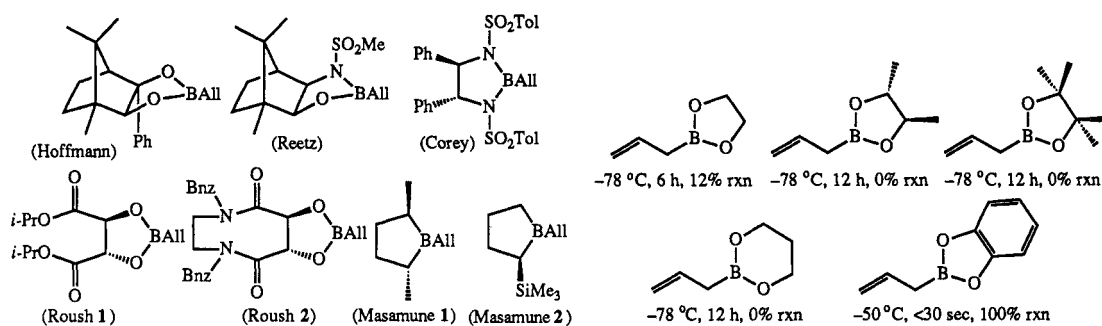


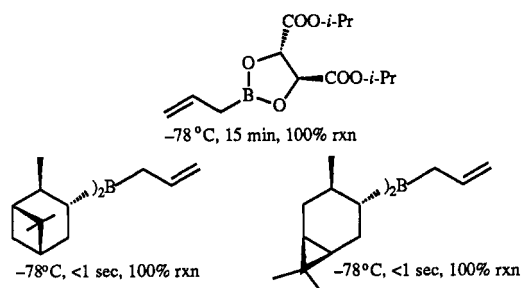
Fig. 35. Allylborating agents by different research groups.

Fig. 36. Rates of allylboronation using cyclic allylboronate derivatives in  $\text{CH}_2\text{Cl}_2$ .

Tartrates are much better, reacting in 15 min. at  $-78^\circ\text{C}$ . The surprise was our  $\text{Ter}_2\text{BALL}$  reagents. If the products were free of the magnesium salt produced in their usual preparation (Fig. 28), the reactions were essentially instantaneous at  $-78^\circ\text{C}$ , and essentially instantaneous at  $-100^\circ\text{C}$  (Fig. 37). We could now run such allylboronations at  $-100^\circ\text{C}$ , if desired, to enhance the stereoselectivities.

### Stereoselectivities of the allylborating agents

Our studies had indicated that  $\text{Ipc}_2\text{BALL}$  is highly effective for stereoselective allylboronation. Since both optical isomers are readily available, the reaction could be used to produce both enantiomers. (+)-3-Carene is readily isomerized by base to (+)-2-carene. Both compounds give reagents, 4- $\text{Icr}_2\text{BALL}$  and 2- $\text{Icr}_2\text{BALL}$ , which achieve even higher optical yields. Fortunately, different enantiomers are obtained from each reagent, making possible the synthesis of both enantiomers (ref. 40). The enantioselectivities at  $-78^\circ\text{C}$  are summarized in Table 3. The results at  $-100^\circ\text{C}$  (magnesium free reagent) are exceptional (Table 3).

Fig. 37. Rates of allylboronation using *B*-allylditerpenylboranes.Table 3. Allylboronation of aldehydes using  $\text{Ter}_2\text{BALL}$  at  $-100^\circ\text{C}$ 

aldehyde	%ee					
	$\text{Ipc}_2\text{BALL}$		4- $\text{Icr}_2\text{BALL}$		2- $\text{Icr}_2\text{BALL}$	
	$-78^\circ\text{C}$	$-100^\circ\text{C}$	$-78^\circ\text{C}$	$-100^\circ\text{C}$	$-78^\circ\text{C}$	$-100^\circ\text{C}$
acetaldehyde	92	$\geq 99$	94	$\geq 99$	98	$\geq 99$
<i>n</i> -butyraldehyde	86	96	88	98	94	$\geq 99$
<i>i</i> -butyraldehyde	88	96	95	98	94	$\geq 99$
pivalaldehyde	83	$\geq 99$	88	$\geq 99$	99	$\geq 99$
acrolein	92	96	93	98	95	$\geq 99$
benzaldehyde	94	96	87	98	95	$\geq 99$

In Table 4 are compared all the results for the different allylboronation reagents at the lowest temperature available.

Table 4. Comparison of the ee achieved by various allylborating agents

aldehyde	%ee achieved by various reagents								
	Hoffmann	Reetz	Roush (1)	Roush (2)	Masamune (1)	Masamune (2)	Corey	4- $\text{Icr}_2\text{BALL}$	2- $\text{Icr}_2\text{BALL}$
acetaldehyde	86	96						$\geq 99$	$\geq 99$
<i>n</i> -butyraldehyde	72	96	79	94	93	96	95	98	$\geq 99$
<i>i</i> -butyraldehyde	70	94			85	96		98	$\geq 99$
cyclohexanecarboxaldehyde			87	97	88	96	97		
pivalaldehyde	45	88	82	96	86	97		$\geq 99$	$\geq 99$
acrolein						97	98	98	$\geq 99$
benzaldehyde		88	71	85			95	98	$\geq 99$

## CONCLUSION

The 87% optical purity of the 2-butanol produced by the hydroboration-oxidation of *cis*-2-butene by  $\text{Ipc}_2\text{BH}$  (from 92% ee  $\alpha$ -pinene) was the first asymmetric synthesis to achieve product of such high ee (Fig.5, ref. 10). The allylboration of aldehydes by  $\text{Icr}_2\text{BALL}$  at  $-100^\circ\text{C}$ , giving products of  $\geq 99\%$  ee, appears to be the most stereoselective reaction available to chemists, achieving stereoselectivities previously achieved only by enzymes. Finally, the stereoselectivities achieved in the reduction of aralkyl ketones, such as acetophenone and hindered aliphatic and alicyclic ketones (classes 1, 2, 3, 4, and 5) now are approaching 100% ee in reductions by  $\text{Eap}_2\text{BCl}$ . Consequently, the rapidly expanding field of asymmetric synthesis appears to be an exceptionally promising area for the application of boron chemistry.

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