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Journal of Organometallic Chemistry 500 (1995) 1–19

Journal of Organometallic Chemistry

Invited review

Versatile α-pinene-based borane reagents for asymmetric syntheses

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Received 10 February 1995

Abstract

The discovery of hydroboration in 1956 made organoboranes readily available. Systematic study of the chemistry of organoboranes made clear their versatility for organic synthesis. An unexpected development was the discovery that the substitution reactions of organoboranes proceed predominantly with retention of configuration, in contrast to substitution in carbon derivatives. Consequently, the ready synthesis of R*B< by hydroboration of alkenes with mono- and diisopinocampheylboranes, $IpcBH_2$ and Ipc_2BH, provided a new general route to asymmetric synthesis. *B*-Ipc-9-BBN (Alpine-Borane®) and Ipc_2BCl (DIP-Chloride™) made asymmetric reduction easy. $Ipc_2BAllyl$ and $Ipc_2BCrotyl$ made asymmetric allyl- and crotylboration readily available for asymmetric synthesis. The ring-opening reaction of *meso*-epoxides with Ipc_2BI provided a convenient route for optically pure halohydrins. Ipc_2BOTf has been utilized by Paterson for asymmetric enolboration reactions. Matteson developed asymmetric homologation reactions using pinanediol boronates. All of these developments justify the title: Versatile α-pinene-based borane reagents for asymmetric synthesis. Examination of the scope of this synthesis of pure enantiomers reveals that the achievement of the synthesis of 34 R*B< systems in ≥ 99% ee makes possible the simple synthesis of over 100,000 essentially optically pure enantiomers.

Keywords: Asymmetric syntheses; Boron; Borane reagents; α-Pinene

1. Introduction

A quarter of a century ago, Morrison and Mosher [1] compiled the literature on non-enzymatic asymmetric organic reactions in a single volume. A decade later, Morrison [2] edited a five-volume series on asymmetric synthesis. Several new books and reviews have since been published on this subject [3]. The current socio-economic and political climate provided an impetus to this program and organic chemists focused their attention on developing superior reagents and methodologies for application in asymmetric synthesis [4]. Reagent-controlled asymmetric synthesis, catalytic or stoichiometric, attracted very widespread chemical interest, more so than substrate-based synthesis. The effectiveness of this approach is frequently dictated by the nature of the organometallic reagent used and the choice of a proper chiral auxiliary.

The boron atom occupies a unique position in asymmetric synthesis attributable to the characteristics of this element [5]. Organoboranes prepared from readily available chiral auxiliaries offer viable, cost-effective alternatives to many catalytic procedures for executing a synthetic step [6]. The first highly successful non-enzymatic asymmetric synthesis involved the hydroboration of *cis*-2-butene with diisopinocampheylborane, Ipc_2BH, prepared from α-pinene and borane [7]. This seminal experiment, originally carried out to study the sensitivity of the pinene structure toward rearrangement during hydroboration, marked the beginning of a new era in organic chemistry. Thirty years later, α-pinene and boron have become an inseparable couple, a powerful combination, the full potential of which has not been explored completely. Some of the reagents currently used for asymmetric synthesis are shown in Chart 1. In this review, we have attempted to highlight the impressive accomplishments of these pinane-based reagents in organic synthesis.

2. Diisopinocampheylborane, Ipc_2BH, for asymmetric hydroboration

In the original reaction, Ipc_2BH was prepared by treating a known quantity of α-pinene and sodium borohydride in diglyme at 0°C with a stoichiometric

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SSDI 0022-328X(95)00509-9

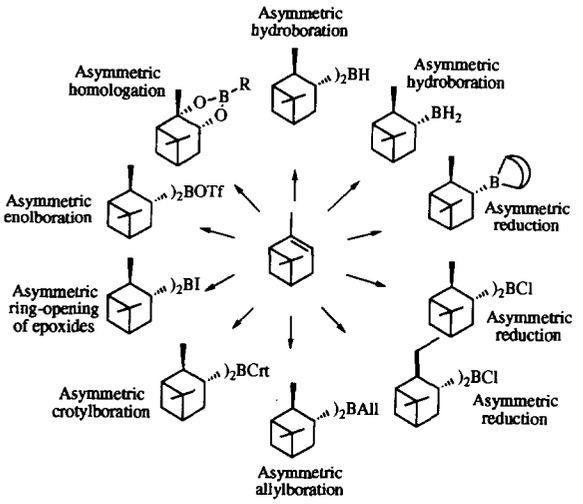
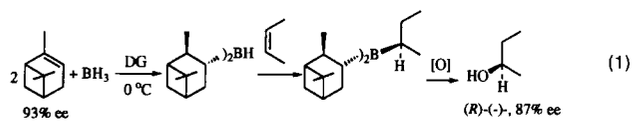


Chart 1. α-Pinene, the super chiral auxiliary.

amount of trifluoroborane etherate ($BF_3 \cdot EE$) and maintaining the reaction mixture at 0°C for 4 h [7]. Since the commercially available α-pinene is of 92% ee, the maximum induction that can be obtained after the reaction is also 92%. The optical induction obtained in the primal experiment, 87% ee, was impressive, considering the poor ee that was the norm for reactions of this kind in 1960 (Eq. 1). Later we achieved the preparation of optically pure crystalline Ipc_2BH from α-pinene of 92% ee by treating the terpene with borane–methyl sulfide complex in THF at 0°C [8].

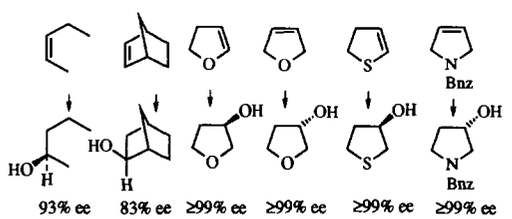


(1)

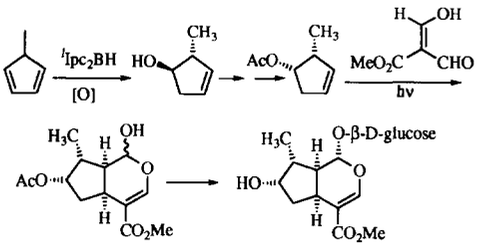
Asymmetric hydroboration of prochiral alkenes with this crystalline material at −25°C followed by oxidation provided optically active alcohols. In the case of *cis*-alkenes, the product *sec*-alcohols were obtained in excellent ee for most types of *cis*-alkenes, including heterocyclic alkenes (Scheme 1) [9,10].

3. Applications of Ipc_2BH

The exceptional ability of Ipc_2BH to hydroborate *cis*-alkenes has been applied to the preparation of key



Scheme 1. Asymmetric hydroboration of *cis*-alkenes.



Scheme 2. Application of Ipc_2BH: synthesis of loganin.

intermediates in several multistep syntheses. The representative example shown in Scheme 2 describes the elegant synthesis of loganin by Uskoković and coworkers [11].

This reagent has been utilized for the synthesis of prostaglandins [12], the carotenoids: (3*R*, 3′*R*)-, (3*S*, 3′*S*)- and (3*R*, 3′*S*; *meso*)-zeaxanthins [13], (3*S*, 5*R*, 3′*S*, 5′*R*)-capsorubin and also a carotenoid found in the red paprika *Capsicum annuum* [14]. Greene et al. [15] exploited the asymmetric hydroboration for the stereocontrolled synthesis of a linearly fused triquinane, (+)-hirsutic acid.

Most of the applications of Ipc_2BH, however, are achieved in an indirect way, that is, as a starting material for the preparation of many of the reagents that are discussed subsequently.

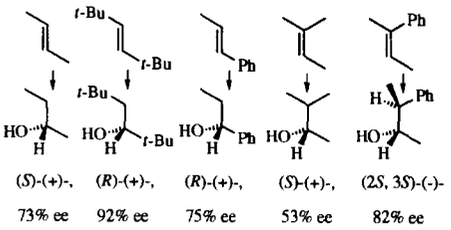
4. Monoisopinocampheylborane, $IpcBH_2$, for asymmetric hydroboration

While *cis*-alkenes could be hydroborated in up to 100% ee, 2-methyl-1-alkenes, *trans*-alkenes and trisubstituted alkenes could be hydroborated in only ~20% ee (Table 1). Evidently, the effectiveness of the asymmetric hydroboration reaction depends upon a fit between the steric requirements of the alkyl groups of the alkene and the hydroborating agent.

Apparently, the steric requirements of 2-methyl-1-alkenes are too low to provide a good steric fit with the reagent. On the other hand, the steric requirements of *trans*- and trisubstituted alkenes appear larger than the reagent can handle. This led to a search for a more appropriate asymmetric hydroborating agent. Monoisopinocampheylborane, $IpcBH_2$, appeared to provide a possible solution. Unfortunately, hydroboration of α-pinene cannot be stopped at the monoalkylborane stage

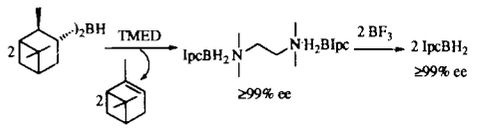
Table 1
Asymmetric hydroboration of alkenes with Ipc_2BH

Class	Alkene	ee (%)
I	2-Methyl-1-alkenes	~ 20
II	*cis*-Alkenes	≥ 99
III	*trans*-Alkenes	~ 20
IV	Trisubstituted alkenes	~ 20



Scheme 3. Asymmetric hydroboration of *trans*- and trisubstituted alkenes.

[16]. However, $IpcBH_2$ could be synthesized via an indirect route. As in the case of Ipc_2BH, various methods for preparing pure $IpcBH_2$ were developed [17]. The most successful of these involves the treatment of Ipc_2BH with a 0.5 equiv. of *N*, *N*, *N'N'*-tetramethylethylenediamine (TMEDA) to provide the crystalline $(IpcBH_2)_2 \cdot TMEDA$ complex (Aldrich: Alpine-Boramine™). The $IpcBH_2$ can then be conveniently liberated with $BF_3 \cdot EE$, which removes TMEDA by precipitating it as a solid complex (Eq. 2) [18].



(2)

$IpcBH_2$ proved to be a useful reagent for the asymmetric hydroboration of *trans*-alkenes [19] and trisubstituted alkenes [20]. Increasing the steric bulk of the alkenes improves the optical induction realized in hydroborations with $IpcBH_2$. For example, a more favorable match between the alkene and the hydroborating agent was apparently achieved in the hydroboration of phenyl trisubstituted alkenes (Scheme 3) [21].

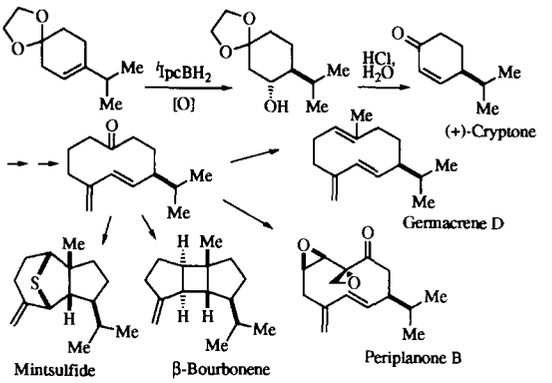
Superior results have now been obtained by the recrystallization of the dialkylboranes formed in the hydroboration (see below). Thus, Ipc_2BH and $IpcBH_2$ are complementary to each other and together handle three of the four classes of alkenes with good to excellent asymmetric induction (Table 2).

Although we planned to explore more hindered asymmetric hydroborating agents for the hydroboration of the class I alkenes, we discovered that we could

Table 2
Asymmetric hydroboration of alkenes with Ipc_2BH and $IpcBH_2$

Class	Alkene	ee (%)	
		Ipc_2BH	$IpcBH_2$
I	2-Methyl-1-alkenes	~ 20	~ 1
II	*cis*-Alkenes	≥ 99	~ 25
III	*trans*-Alkenes	~ 20	70–90 [a]
IV	Trisubstituted alkenes	~ 20	60–99 [a]

[a] On crystallization of the initial product the ee is increased to ≥ 99%.



Scheme 4. Application of $IpcBH_2$ in organic synthesis.

obtain the desired asymmetric boron intermediates by applying the homologation procedures developed by Matteson and co-workers. These are discussed subsequently.

5. Applications of $IpcBH_2$

Numerous applications of $IpcBH_2$ have been made in several syntheses and in our general asymmetric synthesis program. For example, Schreiber and coworkers applied this reagent to the synthesis of cryptone [22], a precursor for germacrene-D [23], mintsulfide [23], β-bourbonene [23] and periplanone-B [24] (Scheme 4).

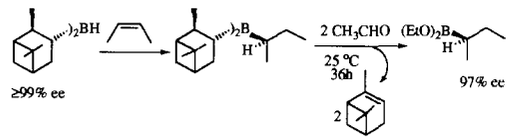
6. Pinane-based general asymmetric synthesis

The reactions of $IpcBH_2$ or Ipc_2BH with suitable alkenes provide dialkyl or trialkylboranes in high ee. It was now desirable to convert these chiral organoboranes $R^*B<$ into pure enantiomers and recover the chiral auxiliary, α-pinene. We accomplished these in our program directed towards the development of a general asymmetric synthesis via chiral organoboranes.

7. Synthesis of optically pure boronic esters

Since the alkyl group on boron is most efficiently utilized in transformations with boronic esters, these esters have emerged as important organoborane intermediates in asymmetric synthesis. Of particular importance is the facile formation of carbon–carbon bonds. The products of hydroboration of alkenes with $IpcBH_2$ are often solids, derivatives of diborane itself, $IpcRBH_2BRIpc$, which on recrystallization provide products of essentially 100% optical purity [25]. These products on treatment with acetaldehyde release α-pinene to give the boronic ester without loss of optical

activity. Therefore, it is now possible to obtain the hydroboration products, Ipc_2BR^* and $IpcR^*BH$, and the derived boronic esters $R^*B(OR')_2$ in essentially 100% ee (Eq. 3) [26].



(3)

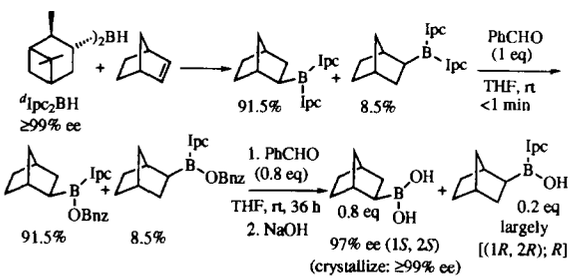
An alternative approach for obtaining optically pure boronic esters via asymmetric hydroboration consists of an optical upgrading of the initial boronates by treating them with a chelating agent to furnish a crystalline material. This is then recrystallized to yield the boronic ester derivatives in essentially optically pure form [27]. This method of optical upgrading can also be applied to borinic esters.

Yet another method of enriching the initial hydroborated product was discovered recently. The controlled treatment of the initial product of lower ee with less than 1 equiv. of benzaldehyde results in a kinetic resolution liberating α-pinene selectively from one isomer, thus providing the boronate ester in essentially 100% ee. For example, the product of hydroboration of norbornene with Ipc_2BH, *exo*-norbornyldiisopinocampheylborane, obtained in 83% ee, upon treatment with 1.8 equiv. of benzaldehyde, liberates 1.8 equiv. of α-pinene, providing the boronate in 97% ee. The boronate is readily separated from the reaction mixture by extraction with base. A simple crystallization of the boronic acid then gives the product in $\geq$ 99% ee (Scheme 5) [28].

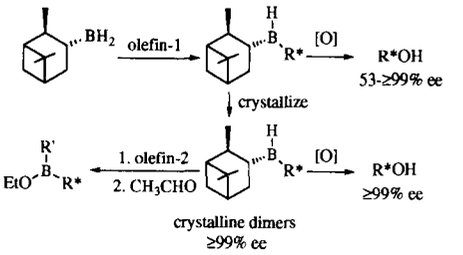
Preparation of optically active boronate esters using the Matteson homologation procedure is discussed subsequently.

8. Synthesis of borinate esters

Although most of the general asymmetric syntheses utilize boronate esters, there are certain reactions that proceed via the borinate esters. In such cases, the

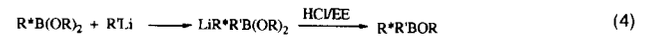


Scheme 5. Upgrading of boronic esters.



Scheme 6. Synthesis of optically pure borinate esters.

boronates are converted into the borinates by reaction with an alkylmetal followed by treatment with ethereal HCl or acid chlorides (Eq. 4) [29].



(4)

Alternately, the borinates can be synthesized by successive hydroboration of two appropriate alkenes with $IpcBH_2$, followed by treatment with aldehyde to eliminate α-pinene (Scheme 6) [30]. Crystallization of the initially formed $IpcR^*BH$ upgrades the optical purity of the final product.

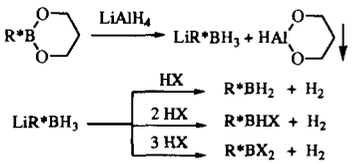
9. Applications of boronate and borinate esters

There is an ever-increasing number of reactions that are carried out using chiral boronate esters, which can be readily converted into the lithium monoalkylborohydride without loss of optical activity by treatment with lithium aluminum hydride [30]. These optically active monoalkylborohydrides in turn can be readily transformed into R^*BH_2, R^*BHCl, R^*BCl_2 and similar derivatives (Scheme 7) [30]. These can then be used as such for hydroboration followed by transformations of the organoboranes as shown in Chart 2 (the broken arrows in the chart indicate reactions not yet demonstrated experimentally).

A complete survey of all of these reactions in Chart 2 would be unduly space consuming, so we limit the discussion to a few representative examples.

10. α-Chiral aldehydes and acids and β-chiral alcohols

The treatment of chiral 2-alkyl-1,3,2-dioxaborinanes with methoxy(phenylthio)methyllithium (MPML) fol-



Scheme 7. Preparation of alkylboranes from alkylboronates.

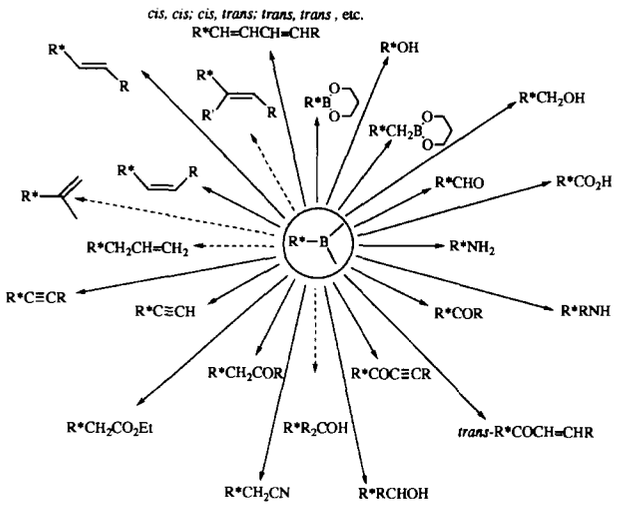
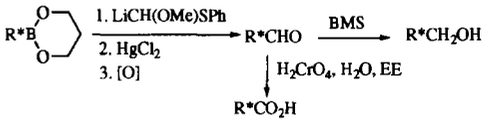


Chart 2. A general synthesis of pure enantiomers via asymmetric hydroboration.



Scheme 8. Preparation of α-chiral aldehydes and acids.

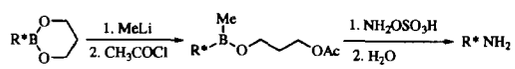
lowed by $HgCl_2$ furnishes the homologated α-methoxyalkyl derivatives which, upon oxidation with hydrogen peroxide in a pH 8 buffer, are smoothly converted into the corresponding chiral aldehydes (Scheme 8) [31]. Oxidation of these aldehydes by chromic acid provides the α-chiral acids (Scheme 8) [31,32]. Treatment of these aldehydes with BMS, followed by oxidation, provides the corresponding β-chiral alcohols.

These aldehydes can also be prepared from chiral boronates prepared via the Matteson homologation procedure (see below) [32].

11. α-Chiral amines

11.1. Primary amines

Conversion of the optically active boronic esters into amines is achieved by converting the boronate into a borinate ester by treatment with methyl lithium and acetyl chloride, followed by reaction with hydroxylamine-*O*-sulfonic acid (Eq. 5) [33].



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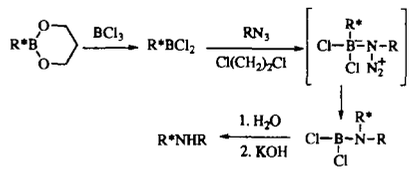
11.2. Secondary amines

Reaction of organic azides with alkyldichloroboranes is an established procedure for the synthesis of secondary amines [34]. The chiral dichloroboranes prepared from chiral boronates by treatment with LAH followed by 3 equiv. of HCl in EE [31], or directly by treatment of the boronates with BCl_3 [35], provide an excellent route to chiral secondary amines (Eq. 6) [36].



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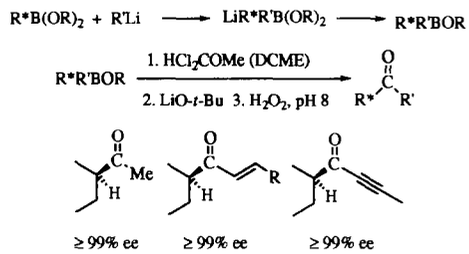


Scheme 9. Synthesis of α-chiral ketones.

12. α-Chiral ketones

12.1. Alkanones

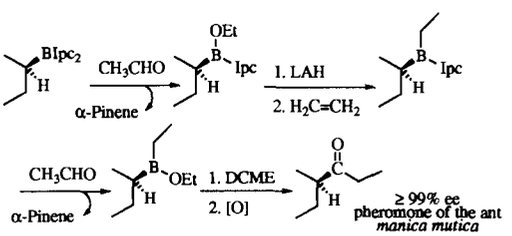
The conversion of the chiral borinate esters into an α-chiral ketone is achieved via the DCME (α,α-dichloromethyl methyl ether) reaction (Scheme 9) [37]. The versatility of this approach is exemplified by the synthesis of the optically active alarm pheromone of the ant *Manica mutica* (Scheme 10) [38]. This procedure can be adopted for the synthesis of α-chiral α'-*trans*-alkenyl or α'-alkynyl ketones also (Scheme 9) [39,40].

α-Chiral alkenones can also be prepared from borinates prepared via the hydroboration of terminal acetylenes with IpcR* BH. Treatment of the thus formed trialkylborane with acetaldehyde provides the borinates, which are converted by the DCME reaction into alkenones (Scheme 11) [41].

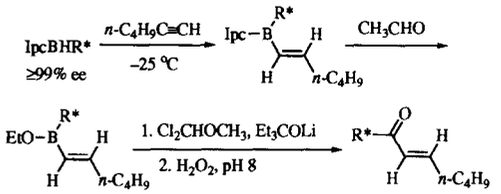
13. α-Chiral alkenes

13.1. (Z)-Alkenes

IpcBR* H is treated in steps with (1) a terminal alkyne, (2) acetaldehyde, and (3) iodine in the presence



Scheme 10. Synthesis of *Manica mutica*, pheromone.



Scheme 11. Synthesis of α-chiral alkenones.

of sodium methoxide, to provide (*Z*)-alkenes in high yields and ee (Scheme 12) [42].

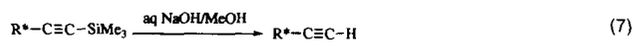
13.2. (E)-Alkenes

α-Chiral (*E*)-alkenyl boronates can be prepared by treating IpcR* BH with 1-bromoalkyne followed by, in steps, (1) acetaldehyde, (2) aqueous sodium hydroxide and (3) trimethylene glycol. This boronate on protonolysis with acetic acid yields optically pure (*E*)-alkenes (Scheme 13) [42].

14. α-Chiral alkynes

The chiral boranes synthesized from chiral boronates can be converted into chiral internal alkynes as shown in the Scheme 14 [43].

Chiral terminal alkynes were prepared by a two-step process. First, lithium (trimethylsilyl)acetylide was treated as above to form an α-chiral trimethylsilylacetylene. This was then desilylated by treatment with aqueous sodium hydroxide (Eq. 7) [44].



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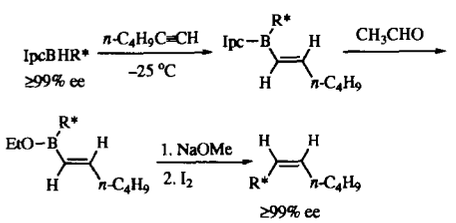
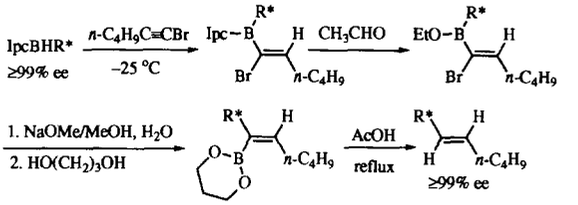
15. β-Chiral esters, nitriles and ketones

Hydroboration of 1,5-cyclooctadiene with chiral boranes followed by thermal isomerization provide B-R*-9-BBN, which can be readily converted into β-chiral esters, nitriles and ketones (Scheme 15) [45].



Scheme 12. Synthesis of chiral (*Z*)-alkenes.

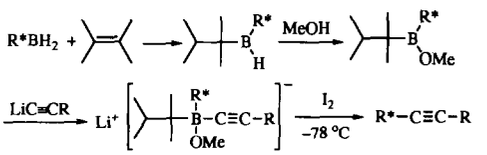


Scheme 13. Synthesis of chiral (*E*)-alkenes.

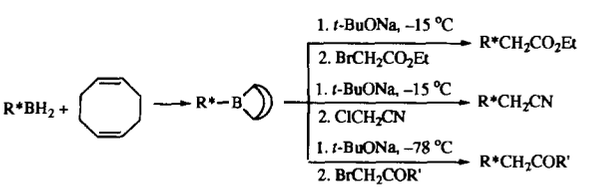
16. Lithium-*B*-3-pinanyl-9-borabicyclo[3.3.1]nonyl hydride, Alpine-Hydride®, for asymmetric reduction

Asymmetric reduction of the ubiquitous carbonyl group occupies a prime position in asymmetric synthesis [46]. Although some reagents showed exceptional promise for the reduction of certain classes of ketones, they failed miserably for other classes of ketones, and results were rarely reported for those less favorable applications. Consequently, comparisons became difficult. We divided the ketones of interest into 10 different classes, selecting a representative member of each class, with the hope of making possible the systematic study of asymmetric reduction and the development of reagents that could effectively handle each of these classes of ketones [47].

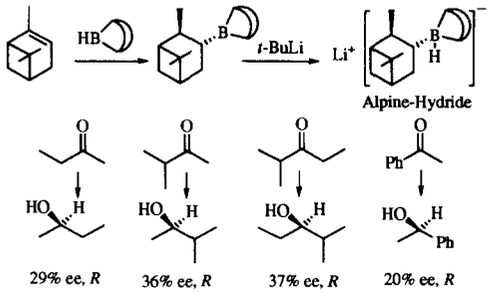
Although Ipc_2BH and $IpcBH_2$ are excellent chiral hydroborating agents, as described earlier, they proved unsatisfactory as chiral reducing agents for prochiral ketones [48]. This is to be expected because a ketone would be similar to class I alkenes in steric requirements and, as discussed earlier, both of these reagents fail to achieve the asymmetric hydroboration of this class of alkenes in satisfactory ee. This led us to another reducing agent derived from α-pinene, lithium-*B*-3-pinanyl-9-borabicyclo[3.3.1]nonyl hydride (Aldrich: Alpine-Hydride®), which also proved ineffective in



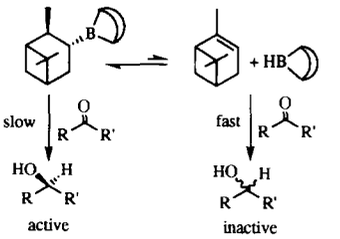
Scheme 14. Synthesis of α-chiral alkynes.



Scheme 15. Synthesis of β-chiral ketones, nitriles and esters.



Scheme 16. Preparation and reactions of Alpine-Hydride.



Scheme 18. Dehydroboration causes a decrease in ee.

transferring chirality to the product alcohols (Scheme 16) [49].

17. *B*-Isopinocampheyl-9-borabicyclo[3.3.1]nonane, Alpine-Borane®, for asymmetric reduction

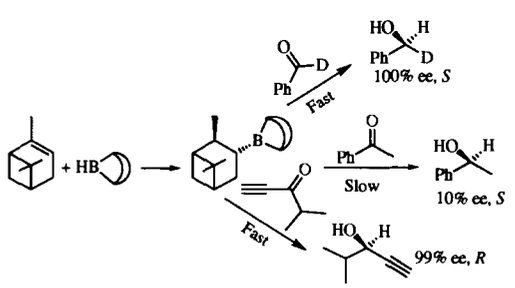
On the basis of Mikhailov et al.'s report on the reactions of trialkylboranes with carbonyl compounds under forcing conditions (150°C) [50], Midland and co-workers established the precursor of Alpine-Hydride, *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane (Aldrich: Alpine-Borane®), as the first successful chiral organoborane reducing agent. They used it to prepare a number of deuterated alcohols by reduction of the deuteroaldehydes, RCDO, in essentially optically pure form (Scheme 17) [51]. The steric environment of the pinane moiety makes the reactions facile at room temperature. The reductions involve a Meerwein–Pondorf–Verley (MPV) [52] type of process, with a six-membered transition state, and the chiral auxiliary, α-pinene, is readily recovered from the reaction mixture. The kinetics of the reaction are bimolecular and the hydride transfer is believed to be the rate-limiting step [53].

Alpine-Borane reduces reactive carbonyls, such as α,β-acetylenic ketones [54], α-keto esters and α-halo ketones, converting them into the corresponding alcohols in very high ee [55]. Acyl cyanides are rapidly reduced by Alpine-Borane to cyanohydrins, which are converted in situ by $NaBH_4$-cobalt (II) chloride into the 1,2-amino alcohols of high ee [56]. However, Alpine-Borane fails to reduce simple prochiral ketones, such as acetophenone and 3-methyl-2-butanone. This aspect makes Alpine-Borane a chemoselective reagent. For example, Alpine-Borane can selectively reduce an aldehyde in the presence of a ketone, or reduce an acetylenic ketone in the presence of an ordinary ketone [57].

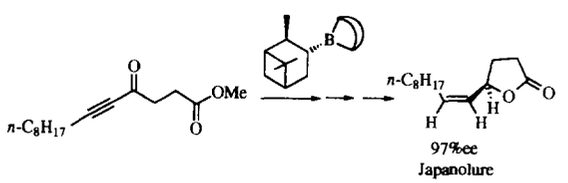
The poor selectivity in the reduction of simple ketones with Alpine-Borane is presumed to be due to a concurrent dehydroboration of the reagent in slow reductions followed by an achiral reduction of the carbonyl group by the 9-BBN produced in this stage (Scheme 18) [58]. This problem can be overcome by minimizing the dissociation by conducting the reductions either in high concentrations at room temperature [55] or at greatly elevated pressures [59]. These procedures are still impractical for the reduction of unactivated ketones.

18. Applications of Alpine-Borane

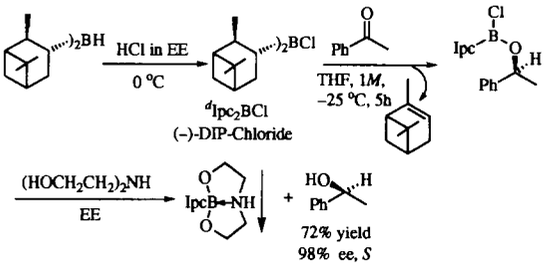
Alpine-Borane is the only organoborane reagent that handles unhindered acetylenic ketones effectively. Another very efficient reagent capable of achieving this reduction is Noyori's Binal-H, prepared by modifying lithium aluminum hydride with Binaphthol [60]. Alpine-Borane is preferred owing to its low cost and the simple reaction conditions (neat, room temperature). Since the acetylenic moiety provides a reactive center for further modifications after asymmetric reduction of the ketone, Alpine-Borane has found many applications in organic syntheses. The synthesis of japanolure, the Japanese beetle pheromone [61], is a representative example of the application of Alpine-Borane in synthesis (Scheme 19). Further examples of the applications of Alpine-Borane include the syntheses of a corticosteroid intermediate [62a], (−)-pestalotin [62b], pseudomonic



Scheme 17. Preparation and reactions of Alpine-Borane.



Scheme 19. Application of Alpine-Borane: synthesis of japanolure.



Scheme 20. Preparation and reaction of Ipc_2BCl.

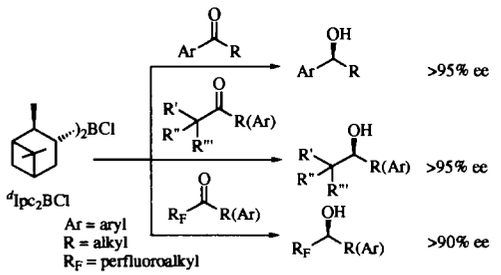
acid [62c], Prelog–Djerassi lactone [62d], mevinic acid subunits [62e], prosynthon C-14 for LTB_4 [62f] and the hydroxypentenoic acid isolated from the aquatic plant *Lemma trisulca* [62g].

19. *B*-Chlorodiisopinocampheylborane (Ipc_2BCl, DIP-Chloride™) for asymmetric reduction

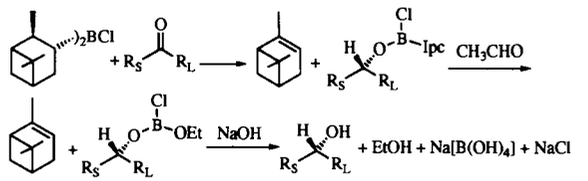
We postulated that the rate of reduction of Alpine-Borane might be enhanced by changing the electronic environment of the boron atom. Accordingly, we synthesized *B*-chlorodiisopinocampheylborane (Aldrich: DIP-Chloride™) by treating Ipc_2BH with hydrogen chloride in diethyl ether or via the direct hydroboration of α-pinene with monochloroborane (Scheme 20) [63]. The former is the preferred procedure since commercial α-pinene is optically enriched during the preparation of Ipc_2BH [64].

This reagent proved extremely efficient for the reduction of aralkyl ketones, α-hindered ketones and α-perfluoroalkyl ketones with predictable stereochemistry (Scheme 21) [63,65]. Testing the reagent for a series of substituted aralkyl ketones showed that representative substituents do not affect the chiral outcome [66].

The original work-up procedure for Ipc_2BCl reductions involved a non-oxidative removal of the boron by-product as the diethanolamine complex. We have since developed a considerably simplified work-up procedure for the isolation of product alcohols which involves treatment of the reaction mixture following reduction with 1 mol equiv. of acetaldehyde at room temperature [67]. This allows complete recycling of



Scheme 21. Ipc_2BCl efficiently reduces aralkyl, α-tertiary, and α-perfluoroalkyl ketones.



Scheme 22. Modified work-up procedure for Ipc_2BCl reductions.

α-pinene and avoids the disposal of the voluminous precipitate that may cause environmental problems (Scheme 22).

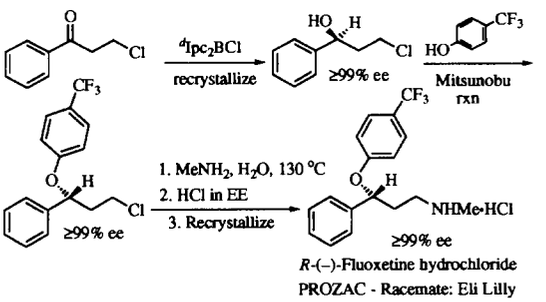
20. Applications of Ipc_2BCl

Ipc_2BCl is frequently used in organic synthesis involving the reduction of aralkyl or α-hindered ketones [68]. The application of this reagent in the first enantioselective synthesis of the currently widely used antidepressant, *N*-methyl-γ-[(4-trifluoromethyl)phenoxy]benzenepropanamine hydrochloride (fluoxetine hydrochloride; Eli Lilly: Prozac®), is outlined in Scheme 23 [69]. We also synthesized the analogs of this serotonin and norepinephrine uptake inhibitor, tomoxetine and nisoxetine [69]. Using our procedure, Kung and co-workers [70] prepared iodinated derivatives of tomoxetine and evaluated them in radioligand binding assays in order to develop selective radioactive ligands for the study of presynaptic monoamine uptake sites.

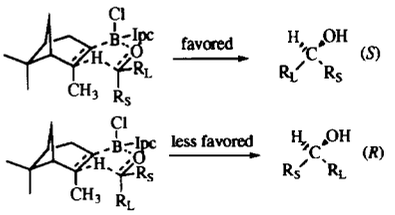
More recent applications of Ipc_2BCl include the synthesis of LTD_4 antagonist L-699,392 [64], frenolicin B [71a], terfenadine [71b], azaperol [71c], new chiral ligands [71d], PAF-antagonists L-659,989 [71e] and MK-287 [71f], an analog of a potential antipsychotic, BMS 181100 [71g], and the bronchodilator eprozinol [71g].

21. Isopinocampheylboron halides, Ipc(R)BX and $IpcBX_2$, for asymmetric reduction

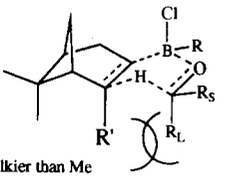
Ipc_2BCl works satisfactorily with five of the ten classes of ketones that we had set to reduce. Alpine-



Scheme 23. Application of Ipc_2BCl: synthesis of Prozac.



Scheme 24. Mechanism of Ipc_2BCl reductions.



Scheme 26. Model for improved asymmetric reducing agents.

Borane handles a sixth class, α,β-acetylenic ketones. Hence our search for a more effective reagent continued. Our tentative mechanism for the chiral reduction gave some pointers for further modification (Scheme 24).

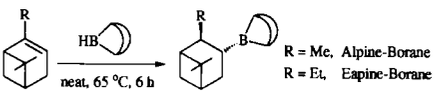
First, modifications in the reagent, keeping α-pinene as the chiral auxiliary, were examined. Reagents substituting for the chlorine atom in Ipc_2BCl with other halogen atoms were easily prepared and tested, but the results were mixed [63b]. A study was next made of the effect of replacing the second pinane group by halo groups or alkyl groups of increasing steric requirements. The monoisopinocampheyldihaloboranes reacted with acetophenone to form the corresponding halides. Our representative alkyl ketone, 3-methyl-2-butanone, was reduced to alcohols in ~ 50% ee and poor yields [63b].

However, increasing the steric requirements of the alkyl group showed a clear effect on the chiral outcome in reductions [72]. The ee of the product from the reduction of the representative aralkyl ketone, acetophenone, increased with increasing steric requirement of the alkyl group until the configuration of the product alcohol was reversed in the case of the tert-butyl group as the substituent. Alkyl ketones did not show much dependence on the steric requirement of the alkyl group on the boron atom. Thus either enantiomer of aralkyl alcohols can be obtained by treating the ketone with the appropriate reagent, Ipc_2BCl or ^{t}BuIpcBCl (Scheme 25), prepared from the same enantiomer of α-pinene.

22. *B*-Iso-2-ethylapopinocampheyl-9-borabicyclo [3.3.1]nonane, Eapine-Borane, for asymmetric reduction

The above modifications did not achieve any major improvement in ee for the products in the reduction of those classes of ketones where Ipc_2BCl fails. A closer look into the proposed mechanism suggested that the ee could probably be improved by increasing the steric requirement of the alkyl group at the 2-position of apopinene as in 2-ethylapopinene (Scheme 26, R' = Et) [73]. This chiral auxiliary falls within the scope of this review since it can be easily synthesized from α-pinene [74].

B-(Iso-2-ethylapopinocampheyl)-9-borabicyclo-[3.3.1]nonane (Eapine-Borane) was prepared using a procedure identical with the preparation of Alpine-Borane (Eq. 8) and treatment with acetylenic ketones showed modest improvements over Alpine-Borane in those cases tested (Table 3) [74a].



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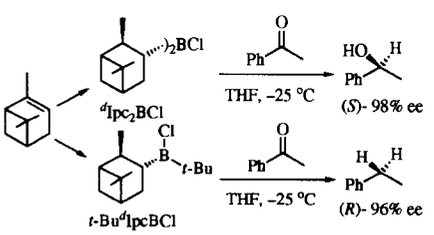


Scheme 25. Enantiomers of products from the same enantiomer of α-pinene.

23. Lithium (*B*-iso-2-ethylapopinocampheyl-9-borabicyclo[3.3.1]nonyl) hydride, Eapine-Hydride for asymmetric reduction

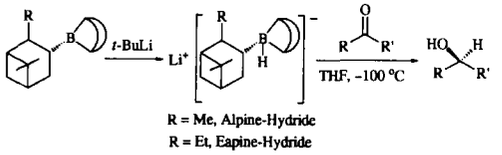
The corresponding borohydride reagent, lithium (*B*-iso-2-ethylapopinocampheyl-9-borabicyclo[3.3.1]nonyl) hydride, Eapine-Hydride, showed considerable improvements for the reduction of simple aliphatic ketones, such as 2-octanone, over the parent reagent, Alpine-Hydride (Eq. 9)(Table 4) [74b].

Table 3
Comparison of asymmetric reduction of representative α,β-acetylenic ketones at 25°C with Alpine-Borane and Eapine-Borane

ketone	Alcohol products, ee (%)	
	Alpine-Borane	Eapine-Borane
3-Butyn-2-one	77	82
1-Octyn-3-one	88	96
3-Hexyn-2-one	80	88
3-Nonyn-2-one	82	88
5-Methyl-3-hexyn-2-one	88	88
4-Phenyl-3-butyn-2-one	82	89

Table 4
Comparison of asymmetric reduction of representative ketones with Alpine-Hydride and Eapine-Hydride

Ketone	Alcohol products, ee (%)		
	Alpine-Hydride, −78°C	Eapine-Hydride	
		−78°C	−100°C
2-Octanone	33	70	77
3-Methyl-2-butanone	36		77
Acetylcyclohexane	27	70	80
Acetophenone	20	56	61
2-Chloroacetophenone	4		48



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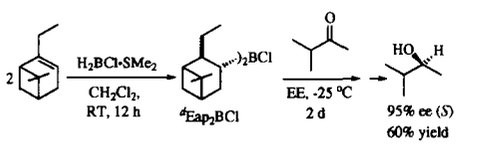
24. *B*-Chlorodiiso-2-ethylapopinocampheylborane, Eap_2BCl, for asymmetric reduction

The best results thus far in support of our hypothesis was obtained with *B*-chlorodiiso-2-ethylapopinocampheylborane, Eap_2BCl. This reagent is excellent for the chiral reduction of all those ketones that are handled very effectively by Ipc_2BCl. In addition, it also handles aliphatic ketones of intermediate steric requirements, such as 3-methyl-2-butanone (95% ee) and acetylcyclohexane (97% ee) (Eq. 10) (Table 5) [75].



(10)

We now have a reagent available that reduces more classes of ketones in very high ee than any other. Indeed, together Alpine-Borane, Ipc_2BCl and Eap_2BCl handle eight of the ten classes [47]. We do not forsee any major difficulty in synthesizing reagents with increased steric requirement at the 2-position of apopinene that can handle all classes of ketones.

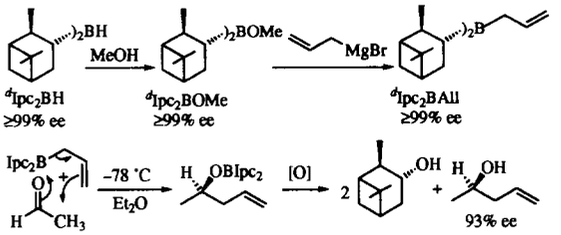
25. *B*-Allyldiisopinocampheylborane, Ipc_2BAll, for allylboration

Allylic organometallic reactions producing homoallylic alcohols have attained considerable importance in the art of asymmetric synthesis of highly sophisticated conformationally non-rigid systems [76]. The product contains an alkene moiety which can be further transformed into other functional groups, as exemplified in the synthesis of macrolide and ionophore antibiotics with a plethora of stereodefined *vic*-diols or β-methyl alcohols [77]. Here, not only the enantioselectivity but also the diastereoselectivity of the reaction are highly important. Accordingly, numerous searches have been made for the most efficient reagent that can achieve both these selectivities in a single step [78]. Chiral organoboranes have revealed their uniqueness and advantages for achieving these desired transformations.

Two decades ago, Mikhailov [79] pointed out that allylboron derivatives, in marked contrast to the saturated trialkylboranes, undergo a fast addition to carbonyl groups with allylic rearrangement. The super chiral auxiliary, α-pinene, was tested in allylboration and this provided another major application of Ipc_2B– in organic synthesis. The synthesis of Ipc_2BAll is simple and the reaction with aldehydes at −78°C, followed by either alkaline hydrogen peroxide or ethanolamine work-up, provides the homoallylic alcohols in very

Table 5
Reduction of prochiral ketones with Eap_2BCl in diethyl ether at −25°C

Class of ketone [47]	Representative ketone	ee (%), Ipc_2BCl	Configuration	ee (%), Eap_2BCl
1	3-Methyl-2-butanone	32	(*S*)	95
1	Acetylcyclohexane	26	(*S*)	97
2	2,2-Dimethylcyclopentanone	98	(*S*)	≥ 99
3	Acetophenone	98	(*S*)	≥ 99
4	Acetylpyridine	92	(*S*)	≥ 99
5	2-Chloroacetophenone	96	(*R*)	≥ 99
6	Methyl benzoyl formate	50	(*R*)	70
7	Ethyl benzoyl acetate		No reduction	
8	*trans*-4-Phenyl-3-buten-2-one	81	(*S*)	82
9	2-Cyclohexen-1-one	36	(*S*)	74
10	4-Phenyl-3-butyn-2-one	21	(*R*)	33



Scheme 27. Preparation of Ipc_2BAll and allylboration of acetaldehyde.

good yields in very high enantiomeric excesses (Scheme 27) [80].

26. *B*-Methallyldiisopinocampheylborane for methallylboration

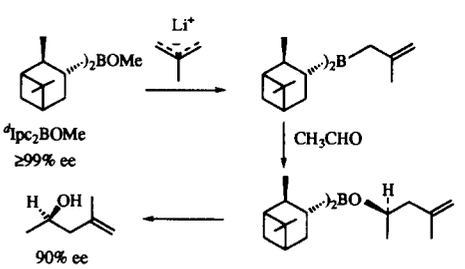
This reagent, readily prepared from Ipc_2BOMe by treatment with methallyllithium, produces in very high ee methallyl alcohols that are valuable intermediates for the elaboration into more complex acyclic compounds (Scheme 28) [81]. For example, the epoxidation and iodocyclizations proceed with excellent diastereoselectivity.

27. 3,3-Dimethylallyldiisopinocampheylborane

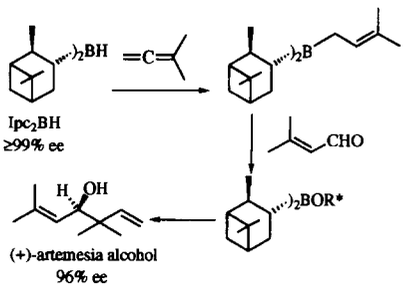
Artemesia alcohol, an "irregular" acyclic monoterpene isolated from *Artemesia annua L.* and *Artemesia herba-albai* with the unconventional non-head-to-tail union of isoprene units, attracted our attention. We envisaged the synthesis of this terpene via an allylboration reaction using the 3,3-dimethylallyl derivative. The synthesis of this reagent involves a simple hydroboration of 1,1-dimethylallene, and allylboration normally provides products in 89–96% ee with predictable configuration (Scheme 29) [82].

28. (*Z*)-3-Methoxyallyldiisopinocampheylborane for the synthesis of vicinal *syn*-diols

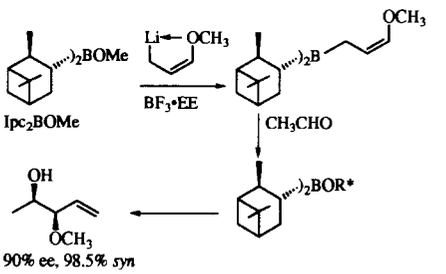
The success of the above allylborations led us to (*Z*)-γ-methoxyallyldiisopinocampheylborane, since we



Scheme 28. Methallylboration of acetaldehyde.



Scheme 29. Synthesis of artemesia alcohol.



Scheme 30. Synthesis of optically active vicinal *syn*-diols.

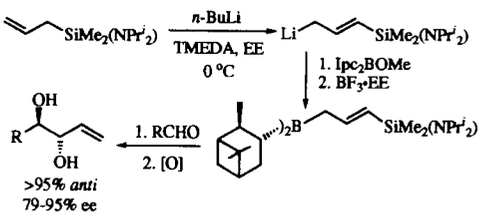
observed the need for this type of reagent in the syntheses of certain carbohydrates and antibiotics. Access to this reagent was made possible by the reaction of the lithium salt of allyl methyl ether with *B*-methoxydiisopinocampheylborane, followed by treatment with $BF_3 \cdot EE$. The reaction of this reagent with aldehyde exhibits a high selectivity for the *threo*-alcohols in high ee (Scheme 30) [83].

29. *B*-[3-((Diisopropylamino)dimethylsilyl)allyl]diisopinocampheylborane for the synthesis of vicinal *anti*-diols

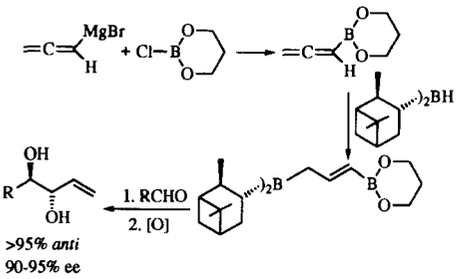
Adopting our allylboration and Tamao et al.'s allyl(diisopropylamino)dimethylsilane reagent [84], Barrett and Malecha [85] synthesized the diisopinocampheylallylsilane as a surrogate for the preparation of vicinal *anti*-diols with excellent absolute and relative stereocontrol (Scheme 31).

30. (*E*)-3-(2,6-Dioxaborolyl)allyldiisopinocampheylborane for the synthesis of vicinal *anti*-diols

Recently we achieved the synthesis of an equivalent reagent via the hydroboration of allenylboranes. This



Scheme 31. Synthesis of optically active vicinal *anti*-diols.



Scheme 32. Synthesis of optically active vicinal *anti*-diols.

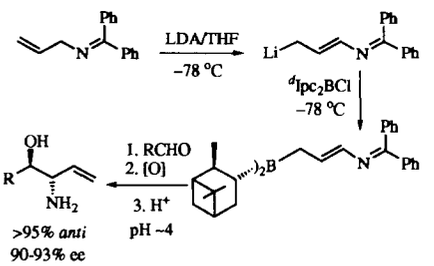
reagent attains the synthesis of vicinal *anti*-diols in excellent isomeric and enantiomeric purities (Scheme 32) [86].

31. (*E*)-3-Diphenyliminodiisopinocampheylborane for the synthesis of *anti*-β-amino alcohols

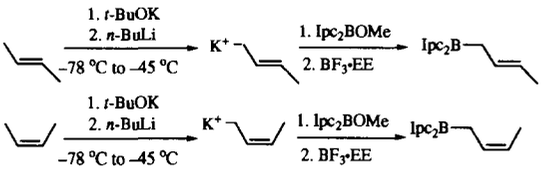
Barrett and co-workers [87] extended our allylboration methodology for the convenient synthesis of *anti*-β-amino alcohols (Scheme 33). Their "imino" reagent is an improvement over their earlier "amino" reagent, [(*E*)-3-diphenylamino)allyl]diisopinocampheylborane, since the deprotection of the *anti*-diphenylamino alcohol to release the free amino alcohol is cumbersome [87b].

32. *B*-(*E*)- and (*Z*)-crotyldiisopinocampheylborane for crotylboration

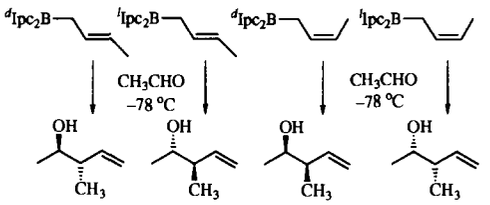
Based on our successes with various allylborating agents, we believed that crotylborations would also be highly successful with our reliable chiral auxiliary α-pinene. However, the fast equilibrium of pure (*E*) and (*Z*)-crotylboron derivatives via a borotropic rearrangement involving the 1-methallyl compound as an intermediate offered potential problems for the synthesis of pure isomers of the crotyl derivatives. Fortunately, the timely publication of a procedure by Fujita and Schlosser [88] for preparation of t-butylpotassium aided in the synthesis of isomerically pure crotylpotassium. Practical procedures were developed for the synthesis of pure Ipc_2BCrt^E and Ipc_2BCrt^Z (Scheme 34) [89].



Scheme 33. Synthesis of optically active vicinal *anti*-amino alcohols.



Scheme 34. Preparation of diisopinocampheylcrotylboranes.



Scheme 35. Crotylboration of acetaldehyde.

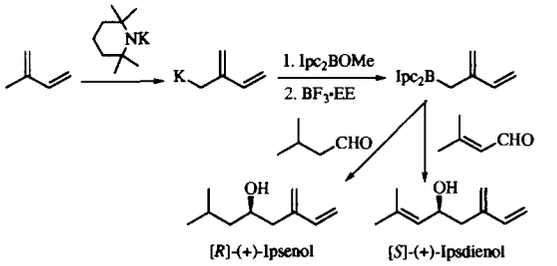
The reaction of these derivatives with aldehydes achieved asymmetric crotylboration with remarkable optical and geometric efficiencies. Consequently, it is now possible to synthesize each of the four possible isomers of β-methylhomoallylic alcohols (Scheme 35) [89].

33. *B*-2′-Isoprenyldiisopinocampheylborane for isoprenylation

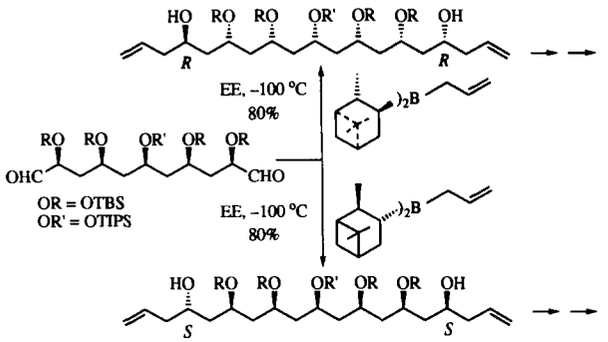
Our success with crotylpotassium persuaded us to prepare the *B*-2′-isoprenyldiisopinocampheylborane from isoprenylpotassium and *B*-methoxydiisopinocampheylborane. Condensation of this reagent with aldehydes provided isoprenylated chiral alcohols (Scheme 36) [90]. This methodology was applied for an efficient one-pot synthesis of both enantiomers of the bark beetle *Ips paraconfusus* Lanier, ipsenol and ipsdienol. This simple synthesis is in sharp contrast to multistep syntheses (13 and 17 steps) by Mori [91].

34. Applications of allyl- and crotylboration

Abundant examples of applications of Ipc_2BAll and its derivatives can be found in the literature [92]. A representative example is the enantioconvergent di-



Scheme 36. Synthesis of ipsenol and ipsdienol.

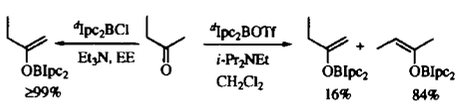


Scheme 37. Application of Ipc_2BAll: enantioconvergent synthesis of polyols.

astereoselective and enantiospecific synthesis of polyols (Scheme 37) [93].

35. Diisopinocampheylboron iodide, Ipc_2BI, for asymmetric cleavage of *meso*-epoxides

The cleavage of C–O bonds with boron reagents, especially haloboranes, is known [94]. Use of mono- and dialkylhaloboranes achieves a more selective bond rupture [95]. We carried out a systematic study of the asymmetric version of this reaction for the ring cleavage of *meso*-epoxides using mono- and diisopinocampheylhaloboranes and successfully accomplished the preparation of 1,2-halohydrins in good to excellent ee [96]. We found that diisopinocampheyliodoborane is the reagent best suited to bringing about the cleavage in high ee. The reaction occurs in an antiperiplanar manner, with an S_N2-type reaction pathway (Eq. 11). This reaction sequence provides highly valuable optically active difunctionalized compounds for asymmetric synthesis.



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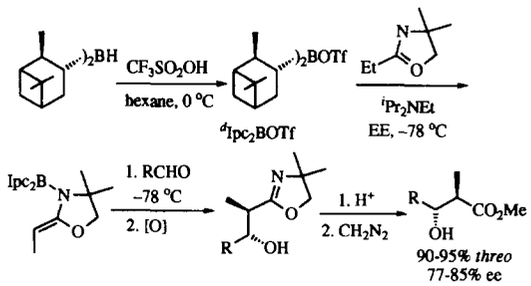
36. Diisopinocampheylboron triflate, Ipc_2BOTf, for aldol reactions

Stereoselective aldol reactions have been known for some time [97]. Of all the elements studied for application in enolization reactions, boron offers special advantages and has been used extensively [98]. Asymmetric enolboration has received considerable attention the past decade, and several researchers developed various chiral auxiliaries to induce diastereoselectivities and enantioselectivities in the reaction [99].

Meyers et al. [100] reported the preparation of Ipc_2BOTf from Ipc_2BH and trifluoromethanesulfonic acid for enantioselective aldol reactions using boron azaenolates (Scheme 38).

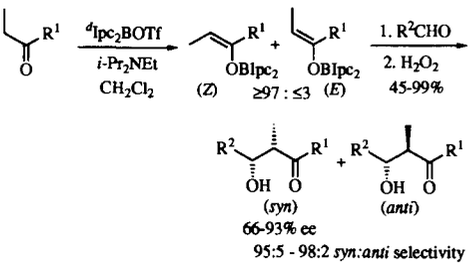


Scheme 38. Preparation of Ipc_2BOTf and aldol reaction of azaenolates.

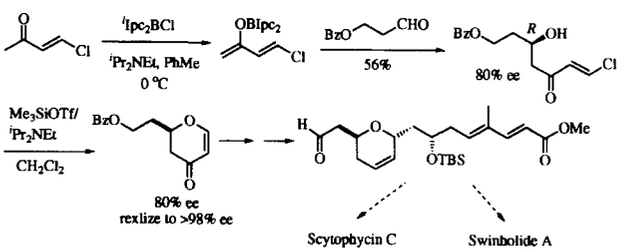
Paterson et al. [101] adopted this reagent for the preparation of asymmetric (*Z*)-enolborinates from simple ketones to carry out aldol reactions. This reagent provided aldol products in good to excellent diastereo- and enantioselectivity (Scheme 39).

37. Ipc_2BCl for aldol reactions

In keeping with our enolboration results with dicyclohexylchloroborane that provide (*E*)-enolates and *anti*-aldols [98b], Paterson and co-workers [102] demonstrated that Ipc_2BCl provides predominantly (*E*)-enolborinates and *anti*-aldol products, although the ee of the product for the cases tested was low. However, in the case of methyl ketones, Ipc_2BCl is superior to Ipc_2BOTf, exhibiting unparalleled regioselectivity. Even in the case of 2-butanone, Ipc_2BCl shows > 100 : 1 of selectivity toward the methyl group whereas Ipc_2BOTf gave poor selectivity and the selectivity is reversed to

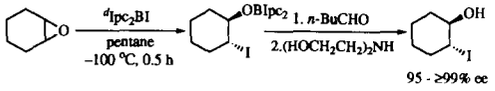


Scheme 39. Enolboration with Ipc_2BOTf.



Scheme 40. Application of Ipc_2BCl for the synthesis of swinholide A.

the ethyl group (5.4 : 1) under thermodynamic conditions [102c,103]. For methyl ketones with bulkier groups at the α'-position of the carbonyl, Ipc_2BOTf shows a regioselectivity of 90 : 1 towards the methyl group (Eq. 12) [103].



(12)

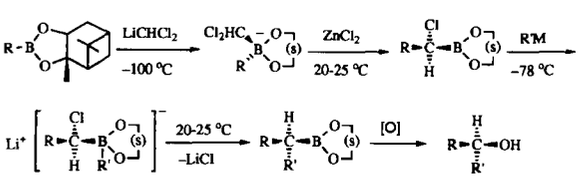
38. Application of diisopinocampheylboron enolates in synthesis

Paterson [102b,c] has demonstrated the applicability of Ipc_2BOTf and Ipc_2BCl in several stereoselective syntheses. An example of the application of $^dIpc_2BCl$ in the synthesis of C_1–C_{15}/C_{16} subunits of swinholide A and scytophycin C is shown in Scheme 40 [104].

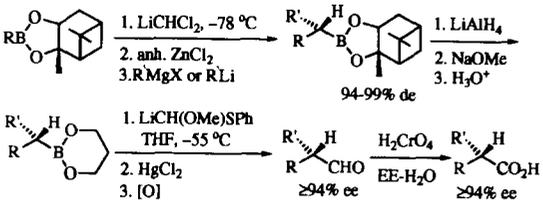
39. Pinanediolboronates for asymmetric homologation

Matteson et al. [105] developed an ingenious and elegant procedure for the preparation of α-chiral boronate esters via an asymmetric homologation. Thus the reaction of cyclic boronate esters derived from pinanediol with pre-formed dichloromethyllithium, $LiCHCl_2$, at −100°C, followed by transfer of the organic group from boron to carbon induced by anhydrous $ZnCl_2$, provides the asymmetric boronate ester with ≥ 99% enantioselectivity (Scheme 41).

While the Matteson procedure provides a method for the synthesis of many optically pure compounds that cannot be achieved via direct hydroboration, it has certain drawbacks. The rigorous requirement for the use of inconvenient temperatures, such as −100°C, for the pre-formation of $LiCHCl_2$, and the difficulty in recycling the chiral auxiliary, pinanediol, limited the scaling-up of this procedure. We overcame these limitations by utilizing $LiCHCl_2$ prepared in situ and carrying out the reaction at −78°C [106]. Procedures were also developed for recycling the pinanediol chiral auxiliary without loss of optical activity [107]. We applied the



Scheme 41. Matteson homologation reaction using pinanediol boronates.



Scheme 42. Synthesis of α-chiral aldehydes and acids via Matteson homologation.

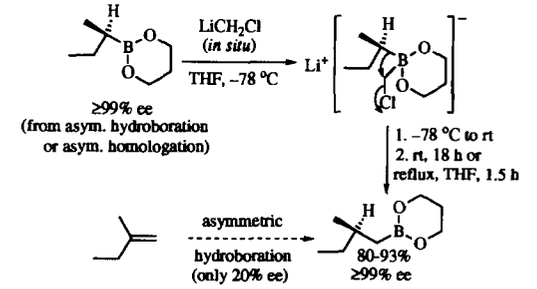
chiral boronates derived by the modified procedure to the synthesis of aldehydes, acids, amines, ketones, etc., using our established procedures described earlier (see above) (Scheme 42) [32].

Again, it is very satisfying to notice that this procedure is also an asymmetric synthesis via chiral organoboranes based on α-pinene. The chiral auxiliary, pinanediol, is derived from α-pinene by a catalytic oxidation using OsO_4 [108]. Matteson and co-workers have applied the chiral boronates derived via homologation chemistry to the synthesis of insect pheromones [109a,b], sugars [109c], amino acids [109d,e], etc.

40. Alternatives for asymmetric hydroboration of 2-substituted-1-alkenes

Matteson's homologation helped to circumvent a major deficiency in our asymmetric hydroboration procedure. Using a one-carbon homologation of α-chiral boronates, we are now in a position to synthesize the boronates that cannot be obtained in high ee via the direct hydroboration of 2-substituted 1-alkenes. We applied this homologation procedure to our α-chiral boronates prepared from asymmetric hydroboration and succeeded in the synthesis of β-chiral boronate esters (Scheme 43) [106a,110].

The above β-chiral boronates can now be utilized for further reactions of organoboranes to give β-chiral molecules. Another homologation of the above β-chiral boronates provides γ-chiral boronates, and a third homologation, δ-chiral boronates. Now we can use these



Scheme 43. Alternative for asymmetric hydroboration of methallyl compounds.

β-, γ- and δ-chiral boronates for the general asymmetric synthesis.

41. Broad scope of organoborane chemistry

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

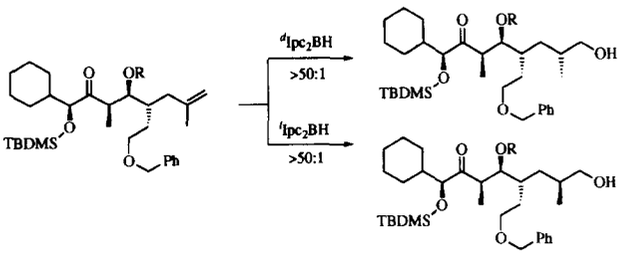
We have shown 24 major reactions in Chart 2 (other, less important, reactions are also known). Each of the above boronates can undergo the 24 major reactions in the chart. This makes a total of 13 056 optically pure compounds. Many of the functional groups contained in some of these 13 056 compounds can be transformed to new functional groups. Thus we are now capable of synthesizing more than 100 000 pure enantiomers using simple organoborane chemistry. On the basis of our successes in a relatively short period of time, we believe that even greater success awaits those willing to undertake new applications of this chemistry. Needless to say, this chemistry is still very young.

42. Double asymmetric synthesis

One of fascinating areas of research in asymmetric synthesis is the study of double diastereoselection, the match and mismatch between the chirality in the reagent and the substrate [77d]. It is interesting to note that pinane-based asymmetric reagents invariably override the influence of the proximal chiral center and control the diastereselectivity of the reaction. This has been observed in asymmetric hydroboration, reduction, allyl and crotylboration and enolborations, as discussed below.

42.1. Asymmetric hydroboration

Although there are several reports of alkene hydroboration directed by pre-existing chiral centers [111], no study of double asymmetric hydroboration of chiral alkenes with a chiral hydroborating agent has been made [112]. Masamune et al. [113] reported such a

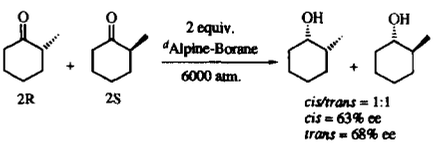


Scheme 44. Double asymmetric hydroboration with Ipc_2BH.

reaction en route to the synthesis of both epimers of a precursor of tylonolide, the aglycone of tylosin which is a member of the 16-membered polyoxomacrolide antibiotics (Scheme 44). Contrary to what has been reported, we believe that the configuration of the newly formed chiral center seems to be influenced by the interaction of the existing chiral center and the enantiomer of the hydroborating agent. With both antipodes of the reagent, the same selectivity (50 : 1) was achieved.

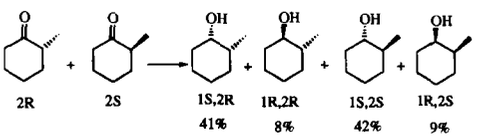
42.2. Asymmetric reduction

Although Midland and Kwon [114] and Noyori et al. [60] have reported the asymmetric reduction of steroidal acetylenic ketones with their reagents, no systematic detailed study of the reagent-controlled double asymmetric reduction has been made so far. However, Midland et al. [59] reported that the reduction of 2-methylcyclohexanone with (*R*)-Alpine-Borane provides a 1 : 1 mixture of *cis* and *trans* isomers of the corresponding alcohol in 63% and 68% ee, respectively (Eq. 13).



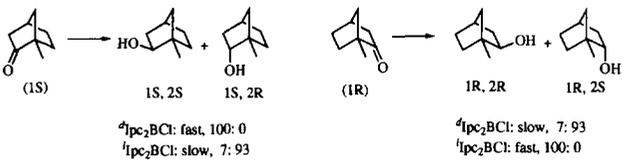
(13)

A closer look reveals a diastereoselectivity of 85 : 15 favoring either the *cis*- or *trans*-alcohol, depending on the pairing of the chirality of the ketone and reagent. In other words, if the optically pure ketones were reduced with (*R*)-Alpine-Borane, the (*S*)-ketone would provide the *trans*-alcohol as the major isomer and the (*R*)-ketone would provide the *cis*-alcohol (Eq. 14).

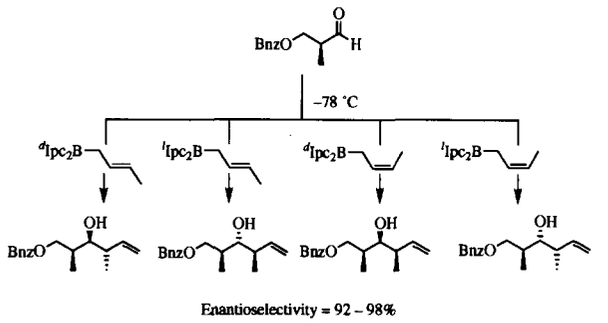


(14)

We recently studied the asymmetric reduction of optically pure ketones with Ipc_2BCl [115]. We found



Scheme 45. Double asymmetric reduction with Ipc_2BCl.



Scheme 46. Double asymmetric crotylboration with diisopinocampheylcrotylboranes.

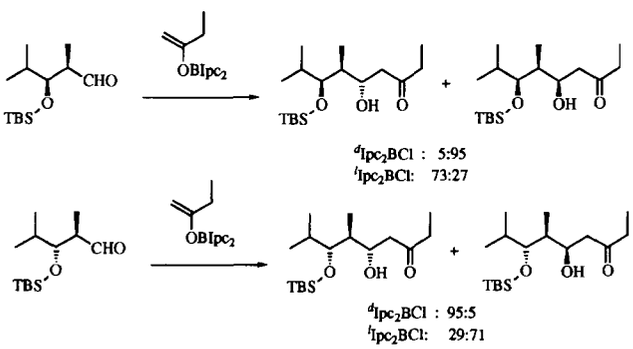
that Ipc_2BCl also demonstrates a control of diastereoselectivty in the asymmetric reduction of α-chiral ketones. For example, starting with a particular isomer of the ketone, we obtain the diastereomers of the product alcohol by using the opposite antipodes of the reagent (Scheme 45).

42.3. Asymmetric allyl- and crotylboration

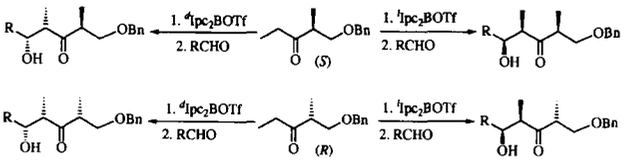
The ability of pinane-based allyl- and crotylboranes to override the chirality of the substrate aldehyde was demonstrated by us, and has been exploited amply by others in key steps in organic synthesis (Scheme 46) [116].

42.4. Asymmetric enolboration

Paterson [102c] has studied the influence of pinane based reagents, Ipc_2BOTf and Ipc_2BCl, in aldol reac-



Scheme 47. Double asymmetric aldol reaction using diisopinocampheylboron enolates and chiral aldehydes.



Scheme 48. Double asymmetric aldol reaction of chiral ketone enolates.

tions between chiral ketones and aldehydes and has shown that Ipc_2BOTf exhibits better control of diastereoselectivity than Ipc_2BCl. Representative examples involving a chiral aldehyde [117] and a chiral ketone [118] are shown in Schemes 47 and 48, respectively.

43. Conclusions

α-Pinene satisfies the requirements of an excellent chiral auxiliary, such as: (1) both isomers are readily available in very high ee and optical upgrading of the commercial material is easily attained during hydroboration; (2) the preparation of the reagents and the reaction conditions are very simple and convenient; (3) the work-up is easy; (4) the chiral auxiliary is readily recovered in all of the reactions in an easily recyclable form without loss of any optical activity; (5) a tentative mechanism is known for all of the reactions, which helps in modification wherever necessary; (6) the configuration of the products can be predicted based on the mechansim, exceptions being rare; (7) the scaling up of the reactions is easy; and, most important, (8) the enantiomeric excesses achieved in most reactions are very high.

Enantiomeric excesses of $> 95\%$ are obtained for (1) the asymmetric hydroboration of three of the four classes of alkenes (the product from the fourth (class I alkene) can be obtained indirectly via asymmetric homologation); (2) in the general asymmetric synthesis via boronates and borinates obtained from hydroboration and homologation; (3) in asymmetric homologation; (4) in asymmetric allyl- and crotylboration; (5) in asymmetric reductions; (6) in asymmetric enolboration–aldol reactions; and (7) in the cleavage of epoxides (Chart 1). The reagents based on α-pinene invariably dictate the diastereomeric outcome of a double asymmetric synthesis.

α-Pinene is truly a super chiral auxiliary.

Acknowledgements

Financial assistance from the Office of Naval Research and the United States Army Research Office is gratefully acknowledged.

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