data or some unusual deviations from expected behavior. This is particularly true for resonance effects since heretofore no method was available to evaluate $\lambda_R - \beta_B$ (eq 7) apart from predicting whether it is positive or negative. As shown in this Account and further elaborated upon in a recent review,[20] eq 14 now provides a means to estimate λ_R numerically that elevates eq 7 (which becomes eq 15) to at least a semiquantitative tool in dealing with the effect of delayed resonance development in proton transfers. We have further demonstrated that the model which forms the basis of eq 14 also allows the development of eq 21, which, through eq 17, provides a qualitative assessment of how k_0 is affected by the polarizability of an adjacent sulfur or phosphorus substituent.

Although not discussed in this Account due to space limitations, the possibility of estimating λ_R also facilitates the semiquantitative treatment of nonsynchronous solvation/desolvation effects of carbanions, another important factor that affects the magnitude of intrinsic rate constants and their variation with changing solvent.[63] Since the lag in the solvation of a developing carbanion is strongly affected by the lag in the charge delocalization, the capability of estimating λ_R helps in evaluating the solvational lag. A recent application of this type of treatment has been published elsewhere.[64]

I gratefully acknowledge the contributions of my co-workers whose names are cited in the references and the financial support by the National Science Foundation (Grant No. CHE-8921739). Special thanks also go to Joseph F. Bunnett, who for nearly 30 years has been a truly inspiring teacher and colleague to me.

(63) For a detailed discussion, see ref 20.
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Asymmetric Reduction with Chiral Organoboranes Based on α-Pinene†

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Received September 13, 1991 (Revised Manuscript Received November 6, 1991)

Current trends in organic synthesis show that asymmetric synthesis has become a primary focus of activity for many of the leading researchers in both the academic and industrial worlds.[1] The tragedy of the thalidomide babies emphasized the importance of achieving the synthesis of optically pure drugs.[2] Optical resolution as a method to prepare optically pure compounds is often uneconomical and impractical. Frequently the most desirable method for synthesizing optically pure materials is asymmetric synthesis.[3] A decade ago we initiated a program on asymmetric synthesis via chiral organoboranes derived from terpenes.[4] The program included asymmetric reduction, asymmetric synthesis via hydroboration, asymmetric allyl- and crotylboration, asymmetric enolboration, asymmetric ring opening of epoxides, and asymmetric homologation. α-Pinene and pinene-derived chiral auxiliaries proved to be exceptionally successful for all of our programs in asymmetric synthesis. We have reviewed our success in asymmetric hydroboration in an earlier Account.[5] In this Account we are discussing our progress in the field of asymmetric reduction, especially those with chiral organoboranes based on α-pinene and its simple derivatives.

Asymmetric reduction of the ubiquitous carbonyl group occupies a position of prime importance in asymmetric synthesis.[6] The optically active alcohol products, if not the desired end product, serve as starting materials for many syntheses. Selection of an appropriate chiral reducing agent for a particular type of ketone in hand often posed major difficulty a decade ago. However, brisk research in this area has largely solved these problems, leading to various reagents that can mimic enzymes in their selectivity.

Recently we compiled the data available in the literature for all the asymmetric reducing agents reported

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† Based on a lecture at the Retirement Symposium for Professor Joseph F. Bunnett. This lecture, entitled "Discovery of New Continents of Chemistry Through Research", dealt with a number of approaches based on chiral organoboranes for asymmetric synthesis. Since developments in the asymmetric hydroboration area were the subject of a recent Account, it appeared desirable to emphasize an area that has not been reviewed previously. Therefore this Account deals solely with asymmetric reduction.

(1) Crosby, J. *Tetrahedron* **1991**, *47*, 4789.
(2) Thalidomide is a tragic example of one optical isomer being a safe drug, whereas the other is a potent mutagen. Teratogenic activity is ascribed exclusively to the *S* isomer. Blaschke, G.; Kraft, H. P.; Fickentscher, K.; Koehler, F. *Arzneim.-Forsch.* **1979**, *29*, 1640.
(3) Morrison, J. D., Ed. *Asymmetric Synthesis*; Academic: New York, 1983; Vols. 1-5.
(4) Brown, H. C.; Ramachandran, P. V. *Pure Appl. Chem.* **1991**, *63*, 307.
(5) Brown, H. C.; Singaram, B. *Acc. Chem. Res.* **1988**, *21*, 287.
(6) (a) Reference 3, Vol. 2, Chapters 2-5. (b) Midland, M. M. *Chem. Rev.* **1989**, *89*, 1553.

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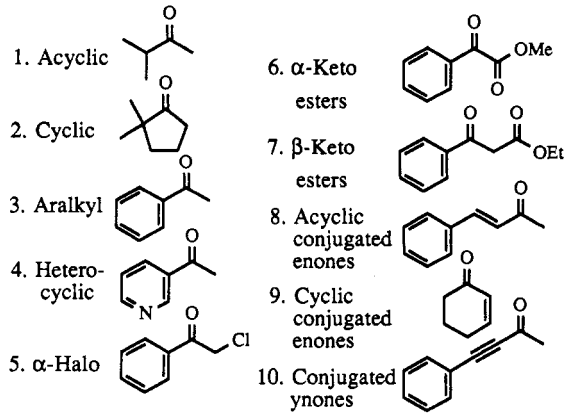

Figure 1. Representative examples of 10 classes of ketones.

and classified the effectiveness of each reagent for a particular type of ketone.[7] We found that some reagents show exceptional promise for a limited type of structure. Few reagents show promise for a wide range of ketone structure, and data are not usually provided for less favorable applications. Consequently, comparison of the relative effectiveness over the full range of carbonyl compounds of interest was difficult. We divided the ketones of interest into 10 different classes with the hope of making possible the systematic study of asymmetric reduction and the development of reagents that can effectively handle all these classes of ketones (Figure 1).

Initial research in asymmetric reduction via asymmetric Meerwein–Ponndorf–Verley (MPV) reductions and asymmetric Grignard reductions was not successful.[8] Later, modifications of lithium aluminum hydride (LAH) with chiral alcohols, amines, or amino alcohols were explored by several research groups. This was followed by the examination of modifications of sodium and lithium borohydride ($NaBH_4$ and $LiBH_4$). Though much research work went into developing chiral reducing agents for several decades, it was only around 1980 that good reagents finally became available. Much of the thrust in the research on asymmetric reduction and development of excellent chiral reducing agents has occurred in the last decade. Today, chiral reducing agents can be categorized mainly as based on aluminum or boron. With the exceptions of Mosher's Darvon alcohol–LAH complex,[9] Noyori's Binal-H,[10] and Terashima's *N*-methylephedrine–LAH complex,[11] all other aluminum-based reagents proved ineffective. Together these three reagents can reduce alkynyl and olefinic ketones in high ee. The only successful $LiBH_4$-modified reagent is Kenso Soai's *N*-benzoylcystine complex, which is effective for the reduction of β-keto esters.[12] All other borohydride-modified reagents are also ineffective. In most of these cases the real nature of the reagent is not known, which makes further improvements possible only by trial and error methods. On the other hand, organoborane reagents have proved to be very effective chiral reducing agents whose structure and behavior are well defined.

Since our compilation in 1986, Itsuno described the catalytic nature of his amino alcohol–borane mixture for the reduction of *O*-alkyl ketoximes.[13] E. J. Corey and his co-workers isolated and characterized the catalyst and made modifications to prepare very effective borane-based catalysts (CBS catalysts) for chiral reduction.[14] Though catalytic activity of a reagent is very much desirable, stoichiometric reducing agents with certain characteristics may be competitive or preferable. Such reducing agents should reduce most classes of ketones with a chiral auxiliary that is economical, with both enantiomers readily available, and easily recovered and recycled. The reagents should be easily prepared, and the reaction conditions should be simple. The enantiomeric excess of the products should be high. The nature of the reagent and its mode of action should be known with predictability of configuration for the product alcohols so that modifications of the reagent can be made. With these conditions in mind, we developed a number of chiral reducing agents. α-Pinene proved to be a chiral auxiliary satisfying most of these conditions.

α-Pinene-Based Asymmetric Reducing Agents

The hydroboration reaction led to the first practical asymmetric synthesis.[15] The possibility of synthesizing optically active organoboranes by hydroborating suitable optically active terpenes led us to examine the possibility of achieving asymmetric reduction of prochiral ketones with chiral organoboranes and borohydrides derived from such organoboranes.

Diisopinocampheylborane (Ipc_2BH) and Isopinocampheylborane ($IpcBH_2$). Although Ipc_2BH and $IpcBH_2$ are good chiral hydroborating agents, they proved unsatisfactory as chiral reducing agents for prochiral ketones (Figure 2).[16,17]

Alpine-Hydride. Another chiral reducing agent derived from α-pinene, lithium *B*-3-pinanyl-9-borabicyclo[3.3.1]nonyl hydride (Aldrich: Alpine-Hydride) also proved ineffective in transferring chirality to the product alcohols (Figure 3).[18]

***B*-Isopinocampheyl-9-borabicyclo[3.3.1]nonane (Alpine-Borane).** The reactions of trialkylboranes with carbonyl compounds under forcing conditions (150 °C) are known in the literature.[19] M. M. Midland and co-workers demonstrated the chiral version of this reaction by synthesizing the first successful chiral organoborane reducing agent, *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane (Aldrich: Alpine-Borane), utilizing it to prepare a series of deuterated alcohols in essentially optically pure form.[20] The steric environment of the pinane moiety made the reactions quite facile at

(7) Brown, H. C.; Park, W. S.; Cho, B. T.; Ramachandran, P. V. *J. Org. Chem.* **1987**, *52*, 5406.
(8) Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*; American Chemical Society: Washington, DC, 1976; Chapter 5.
(9) Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870.
(10) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709.
(11) Terashima, S.; Tanno, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1980**, 1026.
(12) Soai, K.; Oyamada, H.; Yamanoi, T. *J. Chem. Soc., Chem. Commun.* **1984**, 413.
(13) Itsuno, S.; Sakurai, Y.; Ito, K.; Hirao, A.; Nakahara, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 395.
(14) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.
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(16) Brown, H. C.; Mandal, A. K. *J. Org. Chem.* **1977**, *42*, 2996.
(17) Brown, H. C.; Mandal, A. K. *J. Org. Chem.* **1984**, *49*, 2558.
(18) Krishnamurthy, S.; Vogel, S.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 2534. Alpine-Hydride is a trademark of Aldrich Chemical Company.
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(20) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867.

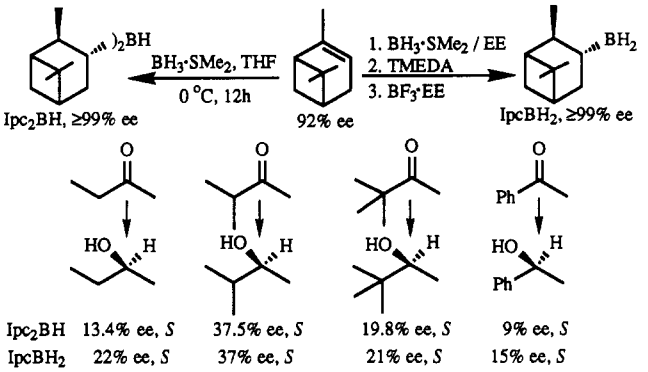


Figure 2. Asymmetric reduction of representative ketones with Ipc_2BH and $IpcBH_2$ at 0 °C.

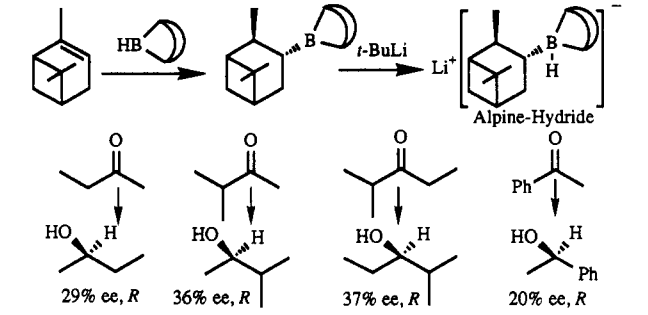


Figure 3. Preparation and reactions of Alpine-Hydride with representative ketones at −78 °C.

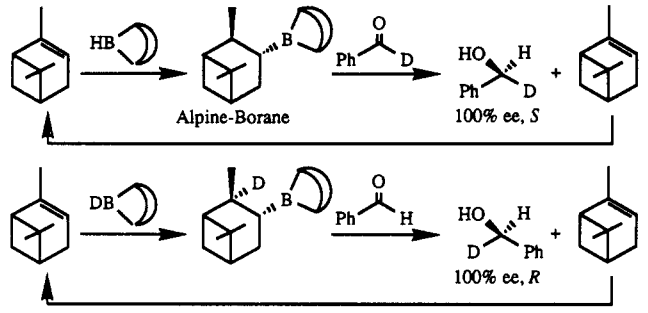
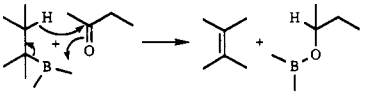


Figure 4. Preparation of deuterio alcohols of high optical purity.

room temperature. The reductions involve an MPV type of process, and the chiral auxiliary, α-pinene, is readily recovered from the reaction mixture (eq 1).[19]



(1)

The opposite enantiomer of the deuterated alcohol can be prepared either by treating the deuterated aldehydes with Alpine-Borane prepared from the opposite enantiomer of α-pinene or by treating aldehydes with deuterated Alpine-Borane, prepared from deuterated 9-BBN and the same enantiomer of α-pinene (Figure 4).

Alpine-Borane fails to reduce simple prochiral ketones, such as acetophenone and 3-methyl-2-butanone. However, reactive carbonyls, such as α,β-acetylenic ketones, α-keto esters, α-halo ketones, and acyl cyanides, can be converted to the corresponding alcohols in very high ee with Alpine-Borane (Figures 5 and 6).[21] This aspect makes Alpine-Borane a chemoselective reagent. For example, Alpine-Borane can selectively

(21) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1985**, *50*, 1384.

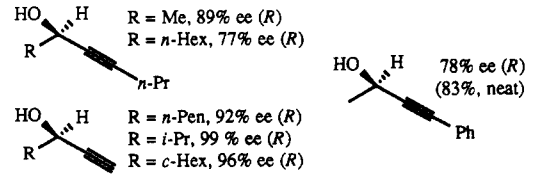


Figure 5. Preparation of α,β-propargylic alcohols of high optical purity.

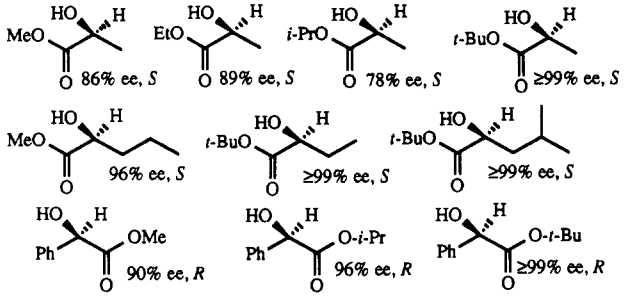


Figure 6. Preparation of α-hydroxy esters of high optical purity.

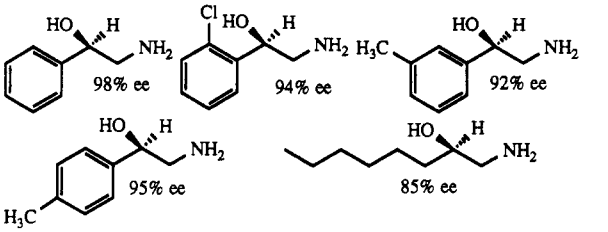


Figure 7. Preparation of 1,2-amino alcohols of high optical purity.

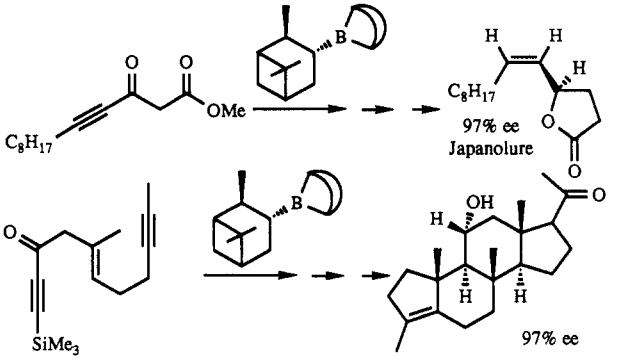


Figure 8. Applications of Alpine-Borane reductions in synthesis.

reduce an aldehyde in the presence of a ketone or an acetylenic ketone in the presence of an ordinary ketone.[22]

Acyl cyanides are rapidly reduced by Alpine-Borane to cyanohydrins, converted in situ by $NaBH_4$/cobaltous chloride to the 1,2-amino alcohols of high ee (Figure 7).[23]

Alpine-Borane is widely used in organic synthesis for the reduction of acetylenic ketones. Synthesis of Japanolure, the Japanese beetle pheromone,[24] and synthesis of a corticosteroid intermediate[25] are representative examples of the applications of Alpine-Borane in synthesis (Figure 8). Japanolure is a good example of the desirability of asymmetric synthesis since even the presence of as little as 1% of the wrong enantiomer causes a 50% decrease in the activity.

(22) Midland, M. M.; Tramontano, A.; Kazubski, A.; Graham, R.; Tsai, D. J.-S.; Cardin, D. B. *Tetrahedron* **1984**, *40*, 1371.
(23) Midland, M. M.; Lee, P. E. *J. Org. Chem.* **1985**, *50*, 3237.
(24) Midland, M. M.; Tramontano, A. *Tetrahedron Lett.* **1980**, 3549. (b) Midland, M. M.; Nguyen, N. H. *J. Org. Chem.* **1981**, *46*, 4107.
(25) Johnson, W. S.; Frei, B.; Gopalan, A. S. *J. Org. Chem.* **1981**, *46*, 1513.

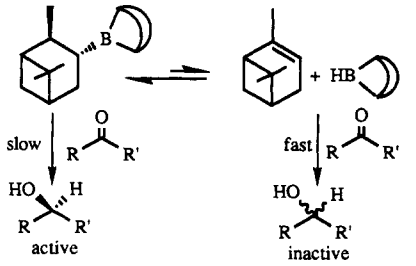


Figure 9. Dehydroboration of Alpine-Borane in slow reductions results in decreased enantioselection.

Table I
Asymmetric Reduction of Prochiral Ketones with Alpine-Borane at 6000 atm

ketone	reactn time, h	% yield isol	% ee 6000 atm	% ee 1 atm
2-octanone	24	63	63	57
3-methyl-2-butanone	24	47	90	67
3,3-dimethyl-2-butanone	9 days	no reaction		0
acetophenone	24	80	100	87
3-acetylpyridine	36	67	100	90
α-tetralone	72	43	89	52
α,α,α-trifluoroaceto-phenone	72	46	54	18

The Dehydroboration Problem. The cause for the poor selectivity in the reduction of simple ketones with Alpine-Borane is presumed to be the dehydroboration of the reagent in slow reductions followed by an achiral reduction of the carbonyl group by 9-BBN produced in the dehydroboration stage (Figure 9). This problem can be overcome by minimizing the dissociation by conducting the reductions either in high concentrations at as low a temperature as is practical[21] or at elevated pressures (Table I).[26] Even then the reagent is not really useful for the reduction of unactivated ketones.[26]

***B*-Chlorodiisopinocampheylborane (Ipc_2BCl, DIP-Chloride).** Another method utilized for increasing the rate of reduction is by changing the electronic environment of the boron atom. Our investigations had indicated that sterically hindered R_2BCl derivatives are more stable toward dissociation than R_3B. Accordingly, we synthesized *B*-chlorodiisopinocampheylborane (Aldrich: DIP-Chloride) which proved extremely efficient for the reduction of aralkyl ketones (Figure 10).[27]

DIP-Chloride shows extraordinary consistency in the reduction of aralkyl ketones with predictable stereochemistry. Testing the reagent for a series of substituted aralkyl ketones showed that representative substituents do not affect the chiral outcome (Figure 11).

DIP-Chloride is being used more and more in organic synthesis involving the reduction of aralkyl ketones. Our route for the synthesis of either enantiomer of the currently widely used antidepressant *N*-methyl-γ-[4-(trifluoromethyl)phenoxy]benzenepropanamine hydrochloride (fluoxetine hydrochloride, Eli Lilly: Prozac) in optically pure form is outlined in Figure 12.[28]

Another representative application of DIP-Chloride is found in the synthesis of (1*R*,3*S*)-1-(aminomethyl)-3,4-dihydro-5,6-dihydroxy-3-phenyl-1*H*-2-benzopyran, a potent and selective D1 agonist, and its enantiomer

(26) Midland, M. M.; McLoughlin, J. I.; Gabriel, J. *J. Org. Chem.* **1989**, *54*, 159.
(27) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539. DIP-Chloride is a trademark of Aldrich Chemical Company.
(28) Srebnik, M.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.* **1988**, *53*, 2916.

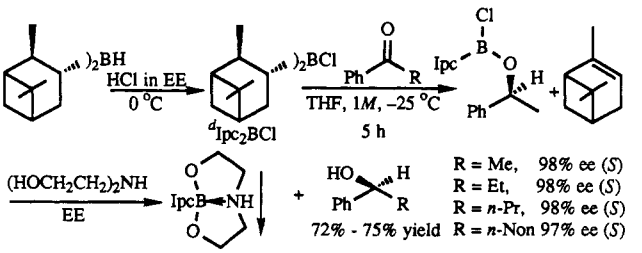


Figure 10. Preparation of DIP-Chloride and reduction of aralkyl ketones.

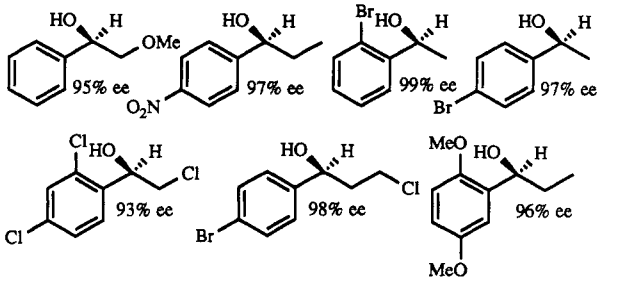


Figure 11. Substituents that are compatible with DIP-Chloride reductions.

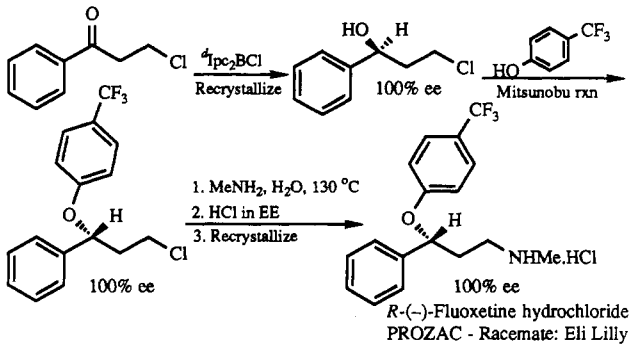


Figure 12. Application of DIP-Chloride in synthesis. Enantioselective synthesis of Prozac.

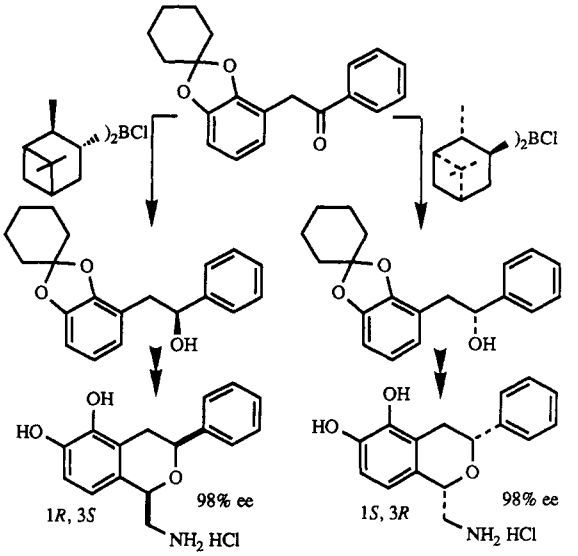


Figure 13. Application of DIP-Chloride in synthesis. Enantioselective synthesis of a selective D1 agonist.

(Figure 13). Pharmacological study of the enantiomers shows that all of the dopaminergic activity resided exclusively in the 1*R*,3*S* enantiomer.[29]

Mechanism of Reduction. The tentative mecha-

(29) DeNinno, M. P.; Schoenleber, R.; Asin, K. E.; MacKenzie, R.; Kebabian, J. W. *J. Med. Chem.* **1990**, *33*, 2948.

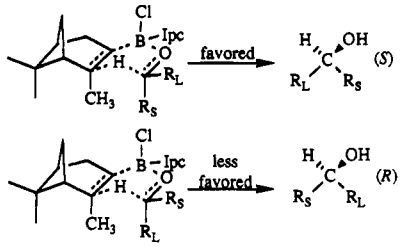


Figure 14. Proposed transition-state model for asymmetric reduction with DIP-Chloride.

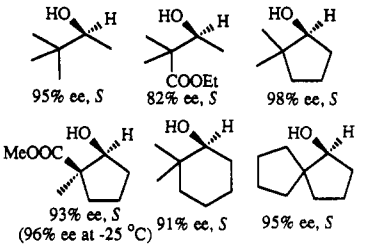


Figure 15. Asymmetric reduction of hindered ketones with DIP-Chloride.

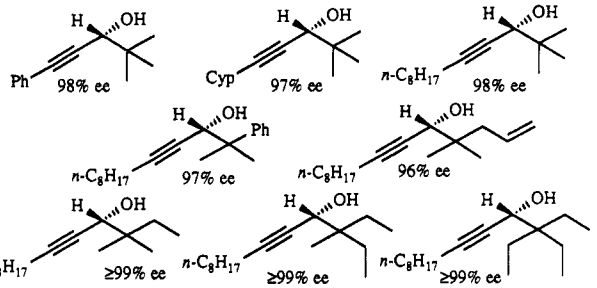


Figure 16. Asymmetric reduction of hindered acetylenic ketones with DIP-Chloride.

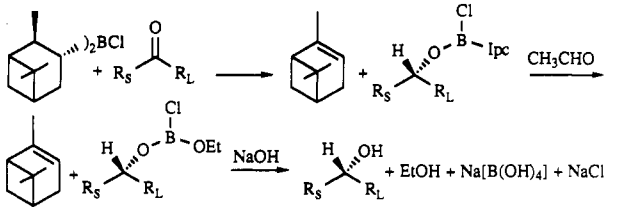


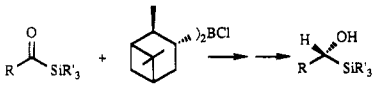
Figure 17. Modified workup procedure for asymmetric reduction with DIP-Chloride.

nism of reduction of ketones with DIP-Chloride provides a predictability of the configuration of product alcohols (Figure 14). This has been used for predicting configurations of products in synthetic schemes[30a] and for the correction of erroneous assignments.[30b]

Aliphatic ketones do not yield good enantioselection with DIP-Chloride. 2-Butanone and 3-methyl-2-butanone are reduced in 4% and 32% ee, respectively. However, the mechanism of reduction suggested that hindered ketones could be reduced in very high ee. Indeed, the reduction of 3,3-dimethyl-2-butanone with DIP-Chloride provides the corresponding alcohol in 95% ee. This aspect is further exemplified in Figure 15.[27]

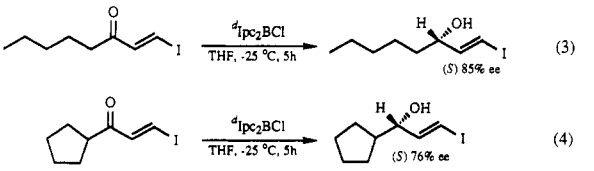
We utilized this capability of DIP-Chloride to reduce highly reactive hindered ketones, such as hindered α,β-acetylenic ketones, in very high ee (Figure 16). These type of hindered ketones are not reduced in satisfactory ee by any of the chiral reducing agents currently available.[31]

Aliphatic acylsilanes undergo facile reduction with DIP-Chloride to provide 1-silylated alcohols in high ee (96–98%) and in good isolated yields (59–67%) (eq 2).[32]



R = Me, R' = Me: 96% ee; R = Et, R' = Me: 98% ee
R = *i*-Pr R' = Me: 98% ee; R = Me, R' = *n*-Bu: 96% ee
R = Me, R' = *i*-Pr: 98% ee (2)

Reduction of olefinic ketones gave encouraging results. Prostaglandin intermediates such as iodovinyl ketones are reduced in 85% ee (eqs 3 and 4).[33]



Together, Alpine-Borane and DIP-Chloride satisfactorily handle six of the 10 classes of ketones.

Modified Workup Procedure. Though DIP-Chloride is being utilized for chiral reduction involving aromatic ketones, a recent report on a large-scale application stated difficulty in isolation of the products.[34] We have since developed a considerably improved workup procedure for the isolation of product alcohols after reduction.[31] The new procedure involves treatment of the reaction mixture following reduction with 1 molar equiv of acetaldehyde at room temperature. This achieves the complete elimination of the second unit of α-pinene from the reagent. The recovered α-pinene is collected, in vacuum and the product is obtained by a simple hydrolysis of the chloroborate ester, R*O(EtO)BCl (Figure 17).

This simplified procedure avoids formation of the solid diethanolamine complex, thus avoiding the problem of its disposal. The yields of the product alcohols are also improved considerably. Finally, the α-pinene is readily recovered from the reaction mixture essentially quantitatively, in easily recyclable form.

Comparison of CBS Reduction with DIP-Chloride

As mentioned earlier, while it is desirable to have a catalytic method for chiral reduction, efficient, economical reagents provide good alternatives to the catalytic method. A comparison of the DIP-Chloride with the CBS methodology[14,35] for the reduction is instructive.

DIP-Chloride Method. The reduction sequence involves four steps.

Step 1. Formation of the reagent by treatment with $H_2BCl{\cdot}SMe_2$ or $H_2BCl{\cdot}OEt_2$ (eq 5):

(30) (a) Potin, D.; Dumas, F.; d'Angelo, J. *J. Am. Chem. Soc.* **1990**, *112*, 3483. (b) Oberlender, R. A.; Nichols, D. E.; Ramachandran, P. V.; Srebnik, M. *J. Pharm. Pharmacol.* **1987**, *39*, 1055.

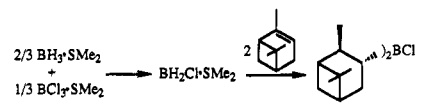
(31) Ramachandran, P. V.; Teodorović, A. V.; Rangaishenvi, M. V.; Brown, H. C., manuscript in preparation.

(32) Soderquist, J. A.; Anderson, C. L.; Miranda, E. I.; Rivera, I.; Kabalka, G. W. *Tetrahedron Lett.* **1990**, *31*, 4677.

(33) Brown, H. C.; Ramachandran, P. V., unpublished results.

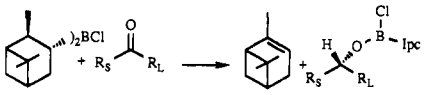
(34) Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Jones, E. T. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751.

(35) Jones, T. K.; Mohan, J. J.; Xavier, L. C.; Blacklock, T. J.; Mathre, D. J.; Sohar, P.; Jones, E. T. T.; Reamer, R. A.; Roberts, F. E.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 763.



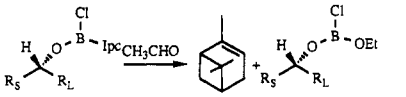
(5)

Step 2. Asymmetric reduction of the ketone (eq 6):



(6)

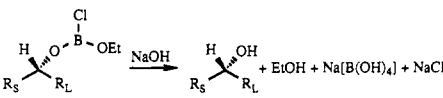
Step 3. Treatment with acetaldehyde and elimination of the second unit of α-pinene (eq 7):



(7)

α-Pinene eliminated during steps 2 and 3 is quantitatively collected by distillation under reduced pressure.

Step 4. Hydrolysis of the product mixture (eq 8):



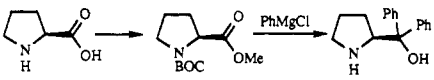
(8)

The product alcohol is readily isolated by extraction with ethyl ether and distillation.

Thus, starting with 2 equiv of α-pinene and 1 equiv of BH_2Cl, 1 equiv of the ketone is reduced. α-Pinene is recovered readily without any loss of optical activity and is recycled; 1.5 mol of ketone is reduced per mole of BH_3.

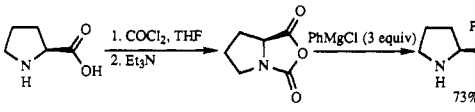
CBS Reduction. The reaction sequence involves the following four steps.

Step 1. Preparation of the chiral auxiliary α,α-diphenyl-2-pyrrolidinemethanol (eq 9):



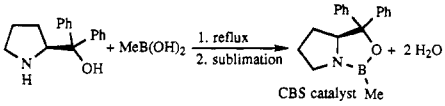
(9)

The Merck group has developed an improved procedure for the preparation of the amino alcohol.[34] This procedure involves reaction of phosgene with proline to form proline-*N*-carboxanhydride (Pro-NCA), followed by treatment with PhMgCl to obtain the required α,α-diphenyl-2-pyrrolidinemethanol in improved yields (eq 10):



(10)

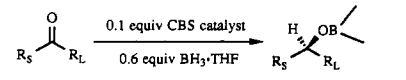
Step 2. Preparation of the *B*-methyloxazaborolidine. Reaction of the amino alcohol with methaneboronic acid provides the catalyst (eq 11):[14]



(11)

The catalyst gives erratic results if water is not completely removed.[34] This problem was overcome by making the catalyst with $(CH_3BO)_3$, followed by three successive azeotropic distillations with toluene to remove residual water.

Step 3. Asymmetric reduction of the ketone (eq 12):



(12)

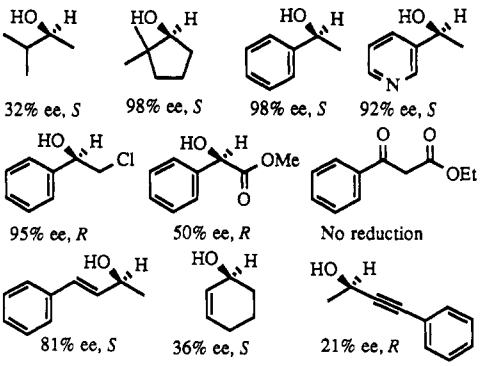


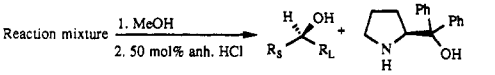
Figure 18. Asymmetric reduction of representative ketones with DIP-Chloride.

Table II
Reaction of Diisopinocampheylhaloboranes with Representative Ketones at −25 °C

	alcohol products, % ee	
reagent	acetophenone	3-methyl-2-butanone
Ipc_2BF	65	30
Ipc_2BCl	98	32
Ipc_2BBr	98	28
Ipc_2BI	no reduction	poor reduction

Less than 0.1 equiv of catalyst decreases the enantioselection.[14] Increasing the amount of BH_3·THF above 0.6 equiv often decreases the enantioselection.[14] Blacklock et al. report that in the preparation of MK-0417 approximately 1 mg of water/1 g of the substrate ketone decreases the ee from 95% to 50%.[35] Careful drying of the ketone was essential to obtain high ee.

Step 4. Hydrolysis (eq 13):



(13)

Thus both the DIP-Chloride and CBS reductions involve four steps, though step 1 in the CBS methodology is done only once in the cycle. Both enantiomers of α-pinene are readily available, and the preparation of DIP-Chloride is very easy. However, D-Proline is 50 times costlier than L-proline. Conversion of proline to the diphenylprolinol involves reaction of phosgene with Pro-NCA. Methaneboronic acid must be prepared or purchased for the preparation of the catalyst. These procedures make the catalyst much costlier on a molar basis compared to the naturally available α-pinene. *In both cases, 1.5 equiv of ketone is reduced per mole of BH_3.* It is not clear that the process cost of the catalytic procedure will be more economical than for the DIP-Chloride procedure. Consequently, the DIP-Chloride method appears competitive, even though it involves a stoichiometric reaction.

Modified Reagents. As pointed out earlier, Alpine-Borane and DIP-Chloride satisfactorily handle only six of the 10 classes of ketones that we had set out to conquer in the beginning (Figure 18).

Hence our search for a more effective reagent continued. Fortunately, our tentative mechanism for the chiral reduction gave some pointers for further modification. First, modifications in the reagent keeping α-pinene as the chiral auxiliary were examined. Reagents substituting for the chlorine atom in DIP-Chloride with other halogen atoms were easily prepared as shown in eqs 14–16. The results of chiral reduction were mixed (Table II).[33]

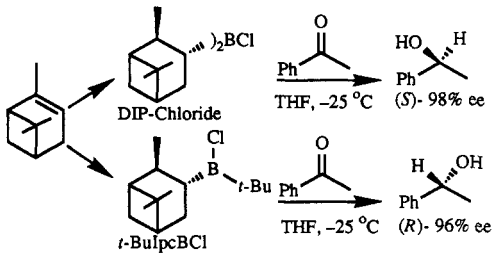


Figure 19. Preparation of both enantiomers of aralkyl alcohols starting from the same enantiomer of α-pinene.

$$Ipc_2BH \xrightarrow[-H_2]{HX} Ipc_2BX \quad (X = Cl, Br, F) \tag{14}$$

$$Ipc_2BH \xrightarrow[-1/2\ H_2]{1/2\ X_2} Ipc_2BX \quad (X = Br, I) \tag{15}$$

$$Ipc_2BCl \xrightarrow[CH_2Cl_2]{1/3SbF_3} Ipc_2BF + 1/3SbCl_3 \tag{16}$$

The mechanism of reduction suggested that one pinane unit is sufficient for inducing chirality. Accordingly, a study was next made of the effect of the second pinane unit by substituting the pinane group with halo groups or alkyl groups of increasing steric requirements. The monoisopinocampheyldihaloboranes were synthesized as shown in eqs 17–20 and were used for chiral reductions. They reacted with aralkyl ketones to form the corresponding halides. Our representative alkyl ketone, 3-methyl-2-butanone, was reduced to alcohols in ~50% ee and poor yields (Table III).[33]

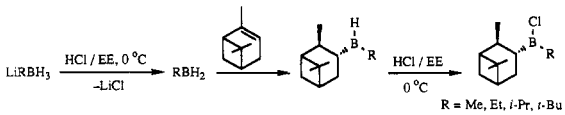
$$IpcBH_2 \xrightarrow[-2\ H_2]{2\ HX} IpcBX_2 \quad (X = Cl, F) \tag{17}$$

$$IpcBH_2 \xrightarrow[-H_2]{X_2} IpcBX_2 \quad (X = Br) \tag{18}$$

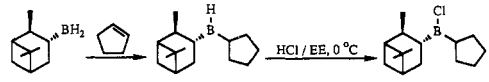
$$\alpha\text{-Pinene} \xrightarrow{X_2BH\cdot SMe_2} IpcBX_2 \quad (X = Cl, Br) \tag{19}$$

$$IpcBX_2 \xrightarrow{2/3\ SbF_3} IpcBF_2 + SbX_3 \tag{20}$$

The alkylmonoisopinocampheylchloroboranes were synthesized as shown in eqs 21–23. Increasing the steric requirements of the alkyl group showed a clear effect on the chiral outcome in reductions (Table IV).[36] The



(21)



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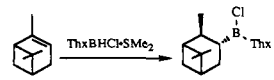


(23)

enantiomeric excess 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 dependency on the steric requirement of the alkyl group on the boron atom. This study revealed that *tert*-butylisopinocampheylchloroborane can be used as a complimentary reagent for producing optically active aralkyl alcohols of opposite configuration in very high ee. Thus we can obtain either enantiomer

(36) Brown, H. C.; Srebnik, M.; Ramachandran, P. V. *J. Org. Chem.* **1989**, *54*, 1577.

Table III
Reaction of Isopinocampheyldihaloboranes with Representative Ketones at -25 °C

	alcohol products, % ee	
reagent	acetophenone	3-methyl-2-butanone
$IpcBF_2$	no reduction	59
$IpcBCl_2$	chloride formed	43
$IpcBBr_2$	bromide formed	bromide formed

Table IV
Reduction of Representative Ketones with Alkylisopinocampheylhaloboranes (RIpcBCl)

RIpcBCl	alcohol products, % ee	
R	acetophenone	3-methyl-2-butanone
Me	15	48
Et	33	36
i-Pr	81	25
Cyp[a]	84	28
Ipc	98	32
t-Bu	96[b]	44
Thx[c]	83[b]	18

[a] Cyclopentyl. [b] Alcohol of opposite configuration was obtained. [c] Thexyl.

Table V
Asymmetric Reduction of Prochiral Ketones with DIP-Chloride, *t*-BuIpcBCl, and *t*-BuEapBCl

	alcohol products, % ee		
ketone	DIP-Chloride, -25 °C	*t*-BuIpcBCl, rt[a]	*t*-BuEapBCl, rt
acetophenone	98	91	81
3-methyl-2-butanone	32	37	84
cyclohexyl methyl ketone	26	48	90
cyclohexyl ethyl ketone	23	53	73
cyclohexyl *n*-propyl ketone	38	53	73
cyclopentyl methyl ketone	45	26	72
2-cyclohexen-1-one	36	46	50
2-octanone	6	18	33

[a] Room temperature.

Table VI
Comparison of Asymmetric Reduction of Representative α,β-Acetylenic Ketones at 25 °C with Alpine-Borane, Eapine-Borane, and *n*-Prapine-Borane

	alcohol products, % ee		
ketone	Alpine-Borane	Eapine-Borane	Prapine-Borane
3-butyn-2-one	77	82	82
1-octyn-3-one	88	96	99
3-hexyn-2-one	80	88	88
3-nonyn-2-one	82	88	91
5-methyl-3-hexyn-2-one	88	88	88
4-phenyl-3-butyn-2-one	82	89	96

Table VII
Comparison of Asymmetric Reduction of Representative Ketones with Alpine-Hydride, NB-Enantride, and Eapine-Hydride

	alcohol products, % ee				
	Alpine-Hydride	NB-Enantride		Eapine-Hydride	
ketone	-78 °C	-78 °C	-100 °C	-78 °C	-100 °C
2-octanone	33	62	75	70	77
3-methyl-2-butanone	36		68		77
acetylcyclohexane	27	65	80	70	80
acetophenone	20	63	70	56	61
2-chloroacetophenone	4	41		48	

Table VIII
Reduction of Prochiral Ketones with Eap_2BCl in EE at −25 °C

class of ketone[a]	representative ketone	reactn time	% yield, isolated	% ee Eap_2BCl	confign	% ee Ipc_2BCl
1	3-methyl-2-butanone	2 days	65	95	*R*	32
1	acetylcyclohexane	3 days	65	97	*R*	26
2	2,2-dimethylcyclopentanone	24 h	68	≥99	*R*	98
3	acetophenone	24 h	80	≥99	*R*	98
4	acetylpyridine	7 days	60	≥99	*R*	92
5	2-chloroacetophenone	7 days	65	≥99	*S*	96
6	methyl benzoyl formate	1 h	78	70	*S*	50
7	ethyl benzoyl acetate	no reduction				
8	*trans*-4-phenyl-3-buten-2-one	14 days	60	82	*R*	81
9	2-cyclohexen-1-one	7 days	60	74	*R*	36
10	4-phenyl-3-butyn-2-one	5 h	82	33	*S*	21

[a] Reference 7.

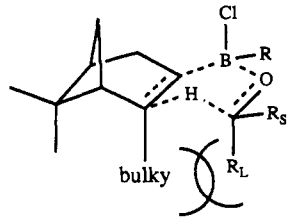


Figure 20. Transition-state model for modified reagents.

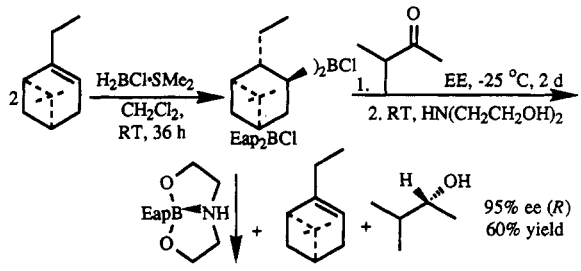
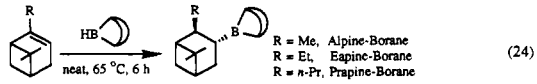


Figure 21. Preparation and reaction of Eap_2BCl.

of aralkyl alcohols by treating the ketone with the appropriate reagent, DIP-Chloride or *t*-BuIpcBCl (Figure 19).

***tert*-Butyl(iso-2-ethylapopinocampheyl)chloroborane (*t*-BuEapBCl).** We did not achieve any major improvement in the ee obtained in the reduction of those classes of ketones where DIP-Chloride failed. A closer look into the proposed reaction mechanism suggested that the ee could be improved, probably, by having a group of larger steric requirement at the 2-position of apopinene (Figure 20). Accordingly, we synthesized and tested *tert*-butyl(iso-2-ethylapopinocampheyl)chloroborane, *t*-BuEapBCl. The chiral auxiliary, 2-ethylapopinene, is readily prepared from α- or β-pinene. As expected, the results were encouraging (Table V).[37] For example, 3-methyl-2-butanol was obtained in 84% ee as against 32% realized with DIP-Chloride.

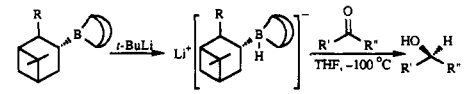
***B*-(Iso-2-ethylapopinocampheyl)-9-borabicyclo[3.3.1]nonane (Eapine-Borane).** We then tested this hypothesis by preparing the trialkylboranes similar to Alpine-Borane (eq 24) and treating them with acetylenic ketones. *B*-(Iso-2-ethylapopinocampheyl)-9-borabicyclo[3.3.1]nonane (Eapine-Borane) and *B*-(iso-2-*n*-propylapopinocampheyl)-9-borabicyclo[3.3.1]nonane



(24)

(Prapine-Borane) showed improvements over Alpine-Borane in those cases tested (Table VI).[38]

Lithium *B*-(Iso-2-ethylapopinocampheyl)-9-borabicyclo[3.3.1]nonyl Hydride (Eapine-Hydride). The same theory held true with the corresponding borohydride reagents also (eq 25).[39] Considerable improvements were realized for the reduction of simple aliphatic ketones, such as 2-octanone, over the parent reagent, Alpine-Hydride, which we synthesized a decade ago. Results of reductions with Eapine-Hydride showed that the high ee obtained in the case of Midland's NB-Enantride could be due to the steric effects of the (benzyloxy)ethyl group at the 2-position of apopinene rather than the coordination of the lithium cation to the oxygen of the ether group, which was thought to provide a steric fit in the transition state of such reductions (Table VII).



(25)

R = Me, Alpine-Hydride; R = -CH_2CH_2OBnz, NB-Enantride; R = Et, Eapine-Hydride

***B*-Chlorobis(iso-2-ethylapopinocampheyl)borane (Eap_2BCl).** The best results thus far of this hypothesis were obtained with *B*-chlorobis(iso-2-ethylapopinocampheyl)borane, Eap_2BCl. This reagent is excellent for the chiral reduction of all those ketones that are handled very effectively by DIP-Chloride. In addition, it also handles aliphatic ketones of intermediate steric requirements, such as 3-methyl-2-butanone (95% ee) and acetylcyclohexane (97% ee) (Figure 21, Table VIII).[40]

We now have a reagent in hand that reduces more classes of ketones in very high ee than any other reagent. Indeed, Alpine-Borane, DIP-Chloride, and Eap_2BCl handle eight of the 10 classes.[7] We do not foresee any major difficulty in synthesizing reagents with increased steric requirement at the 2-position of apopinene that can handle all classes of ketones. The reagent is compatible with most of the functional groups. Both enantiomers of the reagents can be synthesized with ease from the corresponding enantiomer of α-pinene. The reaction conditions are simple, and the chiral auxiliary can be recycled. Thus, most of the conditions set forth in the beginning are satisfied by

(37) Brown, H. C.; Ramachandran, P. V. *J. Org. Chem.* **1989**, *54*, 4504.

(38) Brown, H. C.; Ramachandran, P. V.; Weissman, S. A.; Swaminathan, S. *J. Org. Chem.* **1990**, *55*, 6328.

(39) Ramachandran, P. V.; Brown, H. C.; Swaminathan, S. *Tetrahedron: Asymmetry* **1990**, *1*, 433.

(40) Brown, H. C.; Ramachandran, P. V.; Teodorović, A. V.; Swaminathan, S. *Tetrahedron Lett.* **1991**, *32*, 6691.

these chiral reducing agents derived from α-pinene, encouraging further extension of this approach to asymmetric reduction.

Financial assistance from the United States Army Research Office (Grant No. DAAL 03-91-G-0024) is gratefully acknowledged. We acknowledge the exceptionally helpful criticisms of two referees.

Registry No. α-Pinene, 80-56-8; borane, 13283-31-3.

Chemistry on Stamps (Chemophilately[1])

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Received September 27, 1991 (Revised Manuscript Received November 4, 1991)

The only science is physics. All the rest is stamp collecting.

E. Rutherford, Nobel laureate in chemistry (stamp 22)

Stamps and specific postal cancellations are issued to commemorate events and to inform and educate the public. Due to their universal circulation, stamps are rapid, powerful, and effective messengers which may raise curiosity in or enhance or degrade the image of our profession in the public eye.

Collecting chemistry-related philatelic material enables the collector to combine a hobby with professional interest, to study in a nonsystematic but a delightful way the history of chemistry, to learn about unknown chemists from remote countries who received fame both professionally and nonprofessionally, and to learn about family and student–teacher relationships in an arbitrary chosen group of professional brothers. It enables one to look with amazement, anger, or a feeling of superiority on the liberties taken by stamp designers and on the errors that they make in designing chemical formulas on stamps.[2]

Stamps can be educational tools, display the periodic table and minerals or activities of famous chemists, and even explain details in the oxygenation of hemoglobin.[3] Papers in the *Journal of Chemical Education* and occasionally in other journals cover some of these aspects, chemophilatelic exhibitions are shown in ACS meetings, and a modest journal, *Philatelia Chimica et Physica*, enters its 14th year.

Consequently, once in a quarter of a century there is a place for a paper on chemophilately in *Accounts of Chemical Research*, a journal whose first editor once wrote a paper in verse form.[4] The topic is so rich and diverse and the space so limited that any choice of material must be arbitrary. This paper reflects a personal outlook on a few subtopics that the author finds informative, interesting, and sometimes amusing.

Chemical Societies. Jubilees of large, old, and prestigious chemical societies are sometimes commemorated by stamps. The 75th and the 100th jubilees of the ACS were commemorated by stamps 1 and 2 (Figure 1), which differ not only in the 4.3-fold increase in postal rate. The brown stamp of 1951 displays a chemical distillation apparatus and the smoke-producing chimneys of a chemical plant, which today will be regarded as reflecting the negative side of chemistry. The 1976 stamp is much more lighthearted and colorfully displays simple laboratory tools. In contrast, the British Royal Society of Chemistry chose a different approach on its 100th jubilee stamps issued in 1977. They colorfully commemorate British achievements in chemistry as exemplified by activities of Nobel laureates related to chemicals known to the general public. The cholesterol structure honors D. H. R. Barton's conformational analysis (stamp 3); a vitamin C model honors its first synthesis by N. Haworth (stamp 4); starch chromatography honors A. J. P. Martin and R. L. M. Synge, who pioneered its use (stamp 5); and the NaCl crystal structure honors W. H. and W. L. Bragg, who determined it (stamp 6). Likewise, a 1990 stamp from Berlin (not shown) commemorates the 100th anniversary of the German Pharmaceutical Society by showing a model of aspirin.

Contribution of Small Countries. Although smaller chemical societies have usually to be satisfied only with special postal cancellations, small countries sometimes achieve great original chemophilatelic accomplishments, as shown by the following three examples. How much time does it take a trained scientist's eye to recognize the unusual philatelohydrocarbon produced in Monaco (stamp 7)? It is not a tetrahedral CH_4, as was presumably intended, but tetrahedral tetravalent hydrogen HC_4.[5]

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(1) We suggest the term "chemophilately" for the philatelic study of chemistry, in contrast to "philatelochemistry", which deals with topics such as the color, paper, print, or glue of stamps.

(2) Heilbronner, E.; Kettler, S.; Miller, F.; Rappoport, Z. Chomical errors on chemical stamps. *Philatelia Chim. Phys.* **1990**, *12*, 33.

(3) Stryer, L. *Biochemistry*, 2nd ed.; Freeman and Co.: San Francisco, 1981; p 77.

(4) Bunnett, J. F.; Kearley, F. J., Jr. *J. Org. Chem.* **1971**, *36*, 184.

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