Asymmetric Reductions of Prochiral Ketones with *B*-3-Pinanyl-9-borabicyclo[3.3.1]nonane (Alpine-Borane) at Elevated Pressures

M. Mark Midland,* Jim I. McLoughlin, and Josef Gabriel

Department of Chemistry, University of California, Riverside, California 92521

Received August 3, 1988

The reduction of unhindered ketones, such as acetylenic ketones, with *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane (Alpine-Borane, prepared by hydroboration of α-pinene with 9-BBN) provides a simple means of forming chiral, nonracemic alcohols of known absolute configuration in high enantiomeric purity. A dehydroboration–reduction mechanism leading to racemic alcohol is believed to be responsible for erosion of the enantiomeric efficiency with more hindered ketones. The use of elevated pressures (2000–6000 atm) accelerates the asymmetric reduction mode while suppressing the undesired dehydroboration mode. The use of high pressure permits a study of the scope and utility of Alpine-Borane in the absence of the competing side reaction. The reduction of ketones containing chiral centers was studied with use of the reagent from (+)-α-pinene. *d*-Carvone is reduced while *l*-carvone is not. Methyl-substituted cyclohexanones show no discrimination between enantiomers. For example, 2-methylcyclohexanone is reduced to a 1:1 mixture of *cis*- and *trans*-2-methylcyclohexanol, each of which is about 65% ee. In all cases, one may predict the absolute configuration of the product based on a simple model. The relative steric requirements of groups on the ketone may be catagorized as very small (C≡CH, C≡N, H, D); small (CH_3, CO_2CH_3); medium (*n*-alkyl, *trans*-RHC=CH); medium large (CF_3, *i*-Pr); large (Ar); and too large (*tert*-butyl). Effective asymmetric reductions are achieved when groups from nonadjacent catagories are attached to the carbonyl.

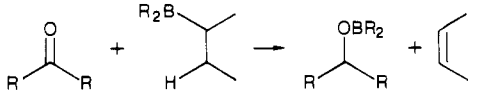
Introduction

One of the most common means of creating asymmetry in a molecular system is the enantioselective reduction of a prochiral ketone.[1] The alcohols produced by such a process may serve as chiral building blocks at the beginning of a synthesis, or they may serve as desired end products directly. In either case, the proper selection of the asymmetric inducing agent is critical, and several factors may influence which reagent one chooses.[1h]

In choosing an asymmetric reducing agent, one often seeks to mimic the action of enzymes. That is, one would like to use reagents that are catalytic, selective, yield products of high enantiomeric purity, and behave predictably with other functional groups. In addition to the selectivities often associated with enzymes, it is also desirable to employ reagents that are inexpensive, easy to handle, tolerant of "typical" organic solvents and functional groups, effective on a wide range of substrates, allow for the easy isolation of the products, and are available in both enantiomeric forms. Clearly, no one reagent can be expected to provide all the desirable traits one would like in a reducing agent. Thus, much effort has been aimed at producing reagents that provide useful compromises.

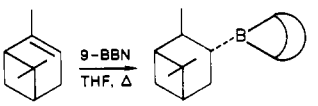
An asymmetric reducing agent need not be catalytic if it can be easily obtained and is inexpensive. The cost factor may be further reduced if the chiral ligand may be recycled. Yet the most critical factor to the synthetic chemist is often the degree of asymmetry introduced into the substrate system.

Trialkylboranes embody many desirable features as reducing agents. Organoboranes are tolerant of many functional groups and, thus may be used in the presence of a wide variety of systems. Trialkylboranes do not possess an active hydrogen on boron, and are generally the least reactive of the organoboranes toward ketones, aldehydes, and many other groups.[2] However, trialkylboranes can be made to react (e.g. with ketones) under forcing conditions of heat or by careful selection of the organoborane structure (eq 1).[3]



(1)

B-3-Pinanyl-9-borabicyclo[3.3.1]nonane (Alpine-Borane,[4] **1**), is the addition product of α-pinene and 9-BBN (eq 2).



(2)

1

Alpine-Borane has been demonstrated to be one of the most selective reducing agents known.[4-6] Aldehydes are

(1) Mosher, H. S.; Morrison, J. D. *Science (Washington, D.C.)* **1983**, *221*, 1013. For a recent and extensive review of the current state of asymmetric synthesis, see: *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: 1983–1984; Vol. 1–4. (a) Imai, T.; Tamura, T.; Yamamuro, A.; Sato, T.; Wollmann, T. A.; Kennedy, R. M.; Masamune, S. *J. Am. Chem. Soc.* **1986**, *108*, 7402. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (c) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (d) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2039. (e) Itsuno, S.; Nakano, M.; Ito, K.; Hirao, A.; Owa, M.; Kanda, N.; Nadahama, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2615. (f) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539. (g) Brown, H. C.; Cho, B. T.; Park, W. S. *J. Org. Chem.* **1988**, *53*, 1231 and references within these papers. (h) For a comparison of relative effectiveness of various reducing agents, see: Brown, H. C.; Park, W. S.; Cho, B. T.; Ramachandran, P. V. *J. Org. Chem.* **1987**, *52*, 5406.

(2) (a) Brown, H. C.; Subba Rao, B. C. *J. Am. Chem. Soc.* **1956**, *78*, 2582. For reviews of the uses of organoboranes in synthesis, see: (b) Brown, H. C. *Hydroboration*; Benjamin: New York, 1962. (c) Brown, H. C. *Boranes in Organic Chemistry*; Cornell University: Ithaca, NY, 1972. (d) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis Via Boranes*; Wiley-Interscience: New York, 1975.

(3) Mikhailov, B.; Bubnov, Y. N.; Kiselev, V. G. *J. Gen. USSR* **1966**, *36*, 65.

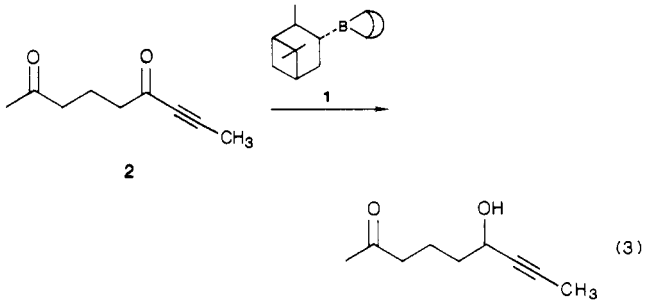
(4) Alpine-Borane is a trademark of Aldrich Chemical Co. (a) Midland, M. M.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1977**, *99*, 5211. (b) Midland, M. M.; Greer, S.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2352. (c) Midland, M. M.; McDowell, D. D.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867. (d) Midland, M. M.; Tramontano, A.; Kazubski, A.; Graham, R. S.; Tsai, D. J. S.; Cardin, D. B. *Tetrahedron* **1984**, *40*, 1371.

(5) Midland, M. M.; Petre, J. E.; Zederic, S. A.; Kazubski, A. *J. Am. Chem. Soc.* **1982**, *104*, 528.

(6) (a) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1985**, *50*, 1384. (b) Brown, H. C.; Pai, G. G. *Ibid.* **1983**, *48*, 1784. (c) Brown, H. C.; Pai, G. G. *Ibid.* **1982**, *47*, 1606. (d) Brown, H. C.; Pai, G. G.; Jadhav, P. K. *J. Am. Chem. Soc.* **1984**, *106*, 1531. (e) Midland, M. M.; Lee, P. E. *J. Org. Chem.* **1985**, *50*, 3237.

0022-3263/89/1954-0159$01.50/0

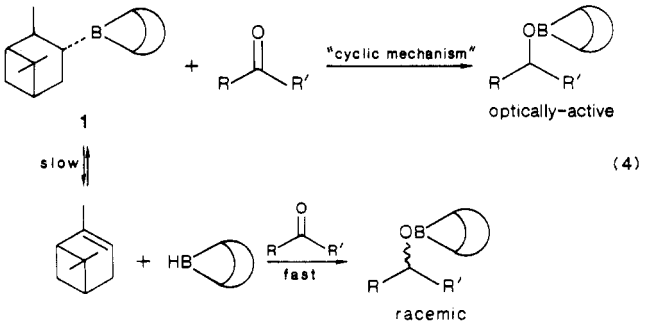
reduced rapidly, in 4–10 h, and propargyl ketones may be reduced overnight. Most other functional groups such as olefins, acetylenes, esters, acid chlorides, pyridines, alkyl halides, and ethers are all untouched by Alpine-Borane (however, after prolonged periods, more than 2 days, there may be reaction with 9-BBN liberated by dehydroboration). Alpine-Borane is highly selective in most cases, and discriminates between hindered and unhindered ketones. The propargyl ketone of 2-nonyne-4,8-dione (**2**) was selectively reduced without significant reduction of the methyl ketone (eq 3).[4d]



(3)

The exceptional chemoselectivity, high degree of asymmetric induction in the reduction of propargyl ketones, ease of formation, availability of both enantiomeric forms, and ability to recycle the pinene ligand all make Alpine-Borane an attractive reducing agent for the preparation of chiral nonracemic propargyl alcohols. It, thus, seemed prudent to delineate the scope and limitations of the reagent with regard to other ketones.

Following work that demonstrated that electron-withdrawing groups increased the rate of reduction of aldehydes,[4,5,7] Brown and co-workers found that ketones of moderate steric bulk that contained electron-withdrawing groups could be reduced in high ee.[8] α-Haloketones and α-keto esters were shown to be good substrates.[6a–d] We investigated the reduction of cyano ketones and found these lead to amino alcohols in high ee.[6e] The reduction of typical ketones proved to be less straightforward. Alkyl ketones and aryl–alkyl ketones were reduced only slowly; often several days or even weeks were required for complete reaction. The use of neat reagents improves the rate and selectivity.[8] In most cases, the longer the reactions required to reach completion, the lower the enantiomeric purity of the alcohol became. The rate differences seemed to be largely due to competition between the cyclic reduction pathway leading to optically active alcohol products and a dehydroboration pathway leading to racemic products (eq 4). Clearly both pathways were operative, and as reaction times increased, the dehydroboration–reduction manifold began to account for a significant portion of the product.



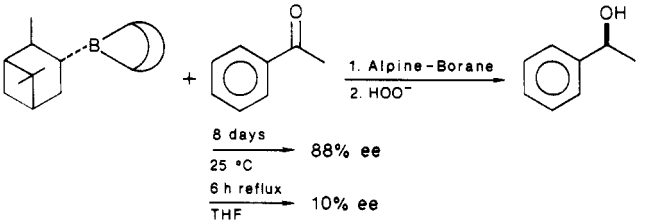
(4)

(7) Midland, M. M.; Tramontano, A.; Zderic, S. A. *J. Organomet. Chem.* **1977**, *C17*, 134; **1978**, *156*, 203.
(8) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1982**, *47*, 1606.

It was felt that it would be possible to accelerate the rate of the desired cyclic reaction process and at the same time suppress the undesired dehydroboration–reduction process by the use of high pressures.[9] This prediction was verified by the reduction of a variety of ketones with Alpine–Borane at elevated pressures. Initial experiments were performed on a small scale (2–3 mmol of ketone) at pressures of 2000 atm by using readily available equipment.[10c] The effects of temperature on the rates and selectivities of the reductions were also investigated at 2000 atm. These results indicated that further increases in pressure would allow faster rates of reduction. A study of a variety of ketones was conducted at 6000 atm.[11]

Results and Discussion

Reductions at 2000 atm. In previous studies, reductions with Alpine-Borane were conducted in a 0.5 M THF solution.[4] Early attempts at the reduction of acetophenone with 0.5 M solutions of Alpine-Borane provided the corresponding alcohol in low ee and required long reaction times.[6] Running the same reaction under neat conditions increased the rate and selectivity of the process, but the reaction still required 8 days to reach 80% completion and provided *sec*-phenethanol of 87% ee.[6a] Though the selectivity of the reduction was promising, the long reaction times were considered unacceptable.



The reduction of acetophenone at 2000 atm and 25 °C showed a dramatic increase in rate. Within 3 days, the reaction was complete as indicated by the absence of starting material (<3%, by ^{1}H NMR). The product alcohol was obtained in 92% ee; the α-pinene used to generate the Alpine-Borane was of 92% optical purity, as determined by rotation. The reduction of acetophenone was thus accomplished with complete enantioselectivity. When the high-pressure reduction of acetophenone was repeated with 98.4% ee α-pinene,[12] *sec*-phenethanol of 98.4% ee was obtained. This high enantiomeric purity indicated that at readily available pressures, as low as 2000 atm, completely selective reductions of moderately hindered ketones could be accomplished. The asymmetric, cyclic reduction pathway was favored by elevated pressures, and the dissociative dehydroboration–reduction pathway could be completely suppressed.

The reduction of a variety of ketones with Alpine-Borane at 2000 atm showed results comparable to those obtained for acetophenone. As indicated in Table I, both the rates and selectivities of the reductions were enhanced. For example, 2-octanone required more than 7 days to reach 90% reduction in the presence of 2 equiv of neat Apline-

(9) The use of high pressure in synthesis has recently been reviewed: (a) Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* **1985**, 1. (b) Matsumoto, K.; Sera A. *Synthesis* **1985**, 999.
(10) (a) Lockyer, G. D., Jr.; Owen, D.; Crew, D.; Neuman, R. C., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7303. (b) Lockyer, G. D.; Dissertation, Chemistry, University of California, Riverside, 1975. (c) Rodgers, V. E.; Angell, C. A. *J. Chem. Ed.* **1983**, *60*, 602.
(11) (a) Midland, M. M.; McLoughlin, J. I. *J. Org. Chem.* **1984**, *49*, 1316. For discussions of the design and use of high-pressure equipment of the type used in this study, see: (b) Neuman, R. C., Jr.; Behar, J. V. *J. Am. Chem. Soc.* **1969**, *91*, 6024. (c) Le Noble, W. J. *Ibid.* **1963**, *85*, 1470.
(12) Available from Aldrich Chemical Co.

Table I. Asymmetric Reduction of Prochiral Ketones with Alpine-Borane at 2000 atm

ketone	pressure, atm	reaction time, days	% ee[a]	% red.
acetophenone	1	8	87	80
	2000	2.5	92 (100)	78
2-octanone	1	7	57	
	2000	3.5	63 (68)	90
3-methyl-2-butanone	1	29	52	50
	2000	10	79 (86)	71

[a] 92% ee *d*-pinene was used. The values in parantheses are corrected for the pinene purity.

Borane under typical "bench-top" conditions, at room temperature. At 2000 atm, the reduction of 2-octanone was nearly complete in less than 4 days. The reduction of α-tetralone, which was only 50% complete in 29 days at 1 atm, was more than 70% complete in 10 days at 2000 atm. The enantiomeric purities of the product alcohols from 2-octanone and α-tetralone were correspondingly improved from 57% ee and 52% ee at 1 atm to 63% ee and 79% ee at 2000 atm, respectively.

The reduction of acetophenone at 2000 atm indicated that the undesired dehydroboration–reduction process was completely suppressed. The reduction had required 2.5 days to reach completion, but the enantiomeric efficiency of the reduction was 100%; all of the reduction had occurred via the enantioselective pathway. The reduction of 2-octanone and α-tetralone indicated that steric differences in a particular ketone might limit the absolute asymmetry attainable by Alpine-Borane. As the steric differences between the groups flanking the carbonyl became less pronounced, the selectivity of the reduction also decreased.

Having demonstrated that both the rates and selectivities of Alpine-Borane reductions were enhanced at high pressures, the influence of temperature on the rate of reduction at 2000 atm was investigated. The use of elevated temperatures alone was not a viable means of accelerating reductions with Alpine-Borane.[9b] In THF at reflux, the rate of reduction of acetophenone was greatly increased, but the product alcohol was nearly racemic; the dissociative reduction mechanism was accelerated to a much greater extent than was the cyclic asymmetric reduction pathway. The reduction of acetophenone at 66 °C and 2000 atm was complete in only 14 h (Table II). The reductions of 2-octanone and α-tetralone were 100% and 70% complete in 16 h at 55 °C and 57 °C, respectively, but the enantioselectivity of the reduction decreased. It is not clear if the decline in optical purity was due to competition of the limiting reduction pathways, cyclic versus dissociative, or to a loss of fidelity of Alpine–Borane in discrimination of the ketone, i.e. a reversal of large and small groups in the transition state, or if both factors were operative.

Reactions at 6000 atm. Faster rates of reduction were desired in order to further increase the utility of the method. Since increases in temperature caused loss of enantioselectivity, the use of still higher pressures seemed appropriate. The results for the reduction of ketones at 6000 atm and 25 °C are shown in Table III. As we had anticipated, the reductions at 6000 atm were accelerated to a greater degree than those at 2000 atm. The reduction of acetophenone, which required more than 8 days to reach completion at 1 atm and nearly 3 days to reach completion at 2000 atm, was complete in less than 1 day at 6000 atm as determined by disappearance of the starting material by NMR (^{1}H NMR, >98% reduction, none of the ketone was detected).

Table II. Asymmetric Reduction of Prochiral Ketones at Elevated Temperatures and Pressure

ketone	pressure, atm	reaction time	temp, °C	% ee[a]	% red.
acetophenone	1	8 days	25	87	80
	2000	2.5 days	25	92	78
	2000	13 h	40	88	88
	2000	14 h	66	71	100[b]
2-octanone	1	7 days	25	57	
	2000	3.5 days	25	63	90
	2000	16 h	55	46	100[b]
α-tetralone	1	29 days	25	52	50
	2000	10 days	25	79	71
	2000	16 h	57	38	70

[a] 92% ee pinene was used: in all cases the *S* alcohol was obtained % ee was determined by chiral shift study. [b] No ketone was detected.

The reductions of other ketones showed similar rate increases. Most aliphatic ketones were completely reduced at 6000 atm in less than 1 day. Ketones of moderate steric bulk and some aromatic ketones required 1–3 days for complete reduction. α-Tetralone, which required 29 days to reach 50% reduction at 1 atm, was completely reduced in only 3 days at 6000 atm.

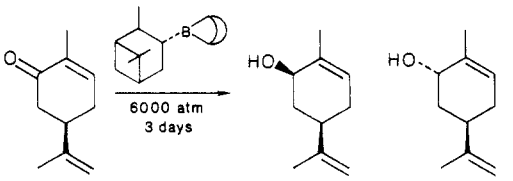
Pinacolone, 3,3-dimethyl-2-butanone, was not reduced at 6000 atm, even after reaction times of more than 9 days. At 1 atm it was found that pinacolone was slowly reduced to the racemic alcohol as determined by a chiral shift study of the alcohol. H. C. Brown et al. also found that pinacolone was reduced very slowly and reported the alcohol to be racemic within experimental error (0.2% ee).[6a] These results suggested that the reduction of pinacolone was occurring via the dissociative dehydroboration pathway only. The lack of reduction at high pressure confirmed the suppression of the dehydroboration of Alpine-Borane at pressures in excess of 2000 atm. An upper limit of steric constraint of the ketone had been exceeded. The combination of a *tert*-butyl group and a methyl group was too big to be accommodated into the Alpine-Borane transition state.

Reductions of Ketones Containing Chiral Centers. The reduction of cyclohexenone proceeded in a moderate 65% ee. The reduction of α-tetralone proceeded with a relatively high 82% ee using 92% ee α-pinene. These results suggested that synthetically useful α,β-unsaturated cyclic ketones could be reduced with high enantiomeric efficiencies. The high enantiomeric purity of the α-tetralol suggested that substitution of the unsaturated site α to the carbonyl provided a greater steric bias in the asymmetric reduction and thereby provided enhanced optical purities. In order to further explore the reduction of substituted cyclohexenone systems, the reduction of carvone was investigated. Carvone provided the desired substituted cyclohexenone system with a methyl group α to the ketone center; but carvone also contains a second alkyl group in the 4-position. The presence of the substituent at the 4-position creates a chiral center, and reduction of the ketone could produce epimeric products.

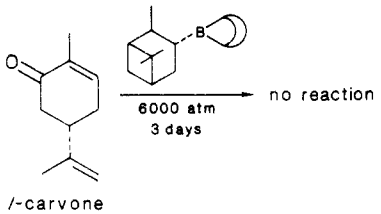
The reduction of chiral ketones had not been extensively studied. It was initially thought that the remote asymmetric center would have little effect on the reduction. Fortunately both *d*-carvone and *l*-carvone are readily available in optically pure form, and any differences in the rate or selectivity of the reductions could be measured. The reductions were carried out under the usual conditions at 6000 atm.

Surprisingly, after 24 h, the reduction of *d*-carvone was more than 50% complete (eq 5) while *l*-carvone showed no sign of reduction (eq 6). Within 3 days the reduction

of *d*-carvone was greater than 90% complete. The reduction of *l*-carvone showed no significant progress after 5 days. The reactions were stopped after 5 days. *l*-Carvone could be recovered in approximately 80% yield, and no alcohol products were observed. The reduction of *d*-carvone provided two epimeric alcohols in a 4.6:1 ratio. Comparison of the products with an authentic sample of the diequatorital alcohol produced by $NaBH_4$ reduction indicated that the diequatorial carveol predominated.[13]



(5)



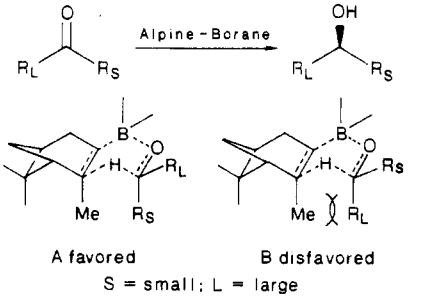
(6)

The remote asymmetric center clearly plays an important role in determining the selectivities and rates of the reduction in the carvone system. *R*-Alpine-Borane, from (+)-α-pinene, did not reduce *l*-carvone. Models indicated that for *l*-carvone to approach Alpine-Borane, either the sterically demanding vinyl methyl group or the isopropylene group would interact with the 3-methyl group of the pinene or the bicyclononane group of 9-BBN. For the reduction of pinacolone, models had suggested that interactions of the substituents on the ketone with the bicyclooctane ring system had come into play. Attempts to predict such interactions, at sites away from the direct reaction centers via the use of simple molecular models, are tentative at best. Secondary interactions between substituents flanking the carbonyl and the framework of the borane undoubtedly contribute to the high degree of selectivity often observed in Alpine-Borane reductions, but the absolute degree to which they interact is difficult to quantify.

The unusual results obtained for the reduction of *d*-carvone led us to explore other chiral ketones. The results are summarized in Table IV. After reduction, the product alcohols were separated (HPLC, silica) to determine the diastereoselectivity of the reductions. The reduction 2-methylcyclohexanone produced 1:1 mixture of the two epimeric alcohols with moderate (65% ee) asymmetric induction. The reduction of three other substituted cyclohexanones resulted in virtually no asymmetric induction or enantioselection. Apparently, the interactions of substituted cyclohexanones and Alpine-Borane are very sensitive to steric factors. The steric interactions are complicated by changes in the conformations of the cyclohexyl rings and by the position of the substituents.

The reduction of two α-methyl propargyl ketones (entries 6 and 7, Table IV) did result in some kinetic resolution.[14] In the reduction of a β-methyl propargyl ketone (entry 8, Table IV), the remoteness of the chiral center prevented any significant interaction, and the ketone was reduced with the same selectivity typically found for the reduction of propargyl ketones.

Transition-State Model. A major contributing factor to the degree of asymmetry observed in the product alcohols is the specificity of Alpine-Borane for the substrate ketone. The ketone is postulated to approach the borane such that a boatlike transition state is formed. Two possible transition states are possible. The bulkier substituent could be accommodated in either an axial or an equatorial position. The preference for reduction by transition state A or transition state B would limit the absolute degree of asymmetry that could by introduced into the alcohol. Other competing modes of reduction, i.e. dehydroboration–reduction, or the use of α-pinene of less than 100% ee, will lower the asymmetric induction observed.



By use of the results summarized in Table III regarding rates and enantiomeric efficiencies for reductions with Alpine-Borane, along with other data, it is possible to categorize the groups flanking the carbonyl of a ketone according to relative steric bulk. Groups can be categorized as ranging from very small (C≡CH, C≡N, H, D); small (CH_3, CO_2CH_3); medium (*n*-alkyl, *trans*-RHC=CH); medium large (CF_3, *i*-Pr); large (Ar); and too large (*tert*-butyl) for Alpine-Borane reduction. A ketone consisting of substituents from adjacent categories, such as 1-butyn-3-one or 2-octanone, would be reduced with only moderate asymmetric induction. A ketone bearing two groups from nonadjacent categories, such as 4-methyl-1-pentyn-3-one or acetophenone, would potentially be reduced with a high degree of asymmetry. The ability to predict quickly the approximate enantiomeric purity of the alcohol products significantly enhances the utility of the Alpine-Borane. The use of these categories also allows one to easily predict the absolute configuration of the product alcohol one would obtain upon reduction. Fitting the ketone substituents into the proposed model transition state such that the smaller group occupies the pseudoaxial position, one may predict the configuration of the asymmetric carbinol center generated.

Experimental Section

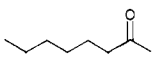
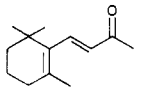
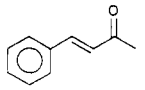
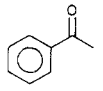
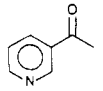
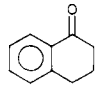
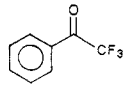
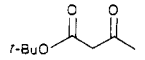
General Reaction Procedures. All operations involving air-sensitive reagents or organometallics were conducted under a nitrogen atmosphere.[15] The reaction flasks were equipped with a septum-capped side arm, magnetic stirring bar, and a stopcock adapter connected to a mercury bubbler. Commercially dried ether was used without further purification unless noted. Dry tetrahydrofuran (THF) was prepared by distillation from potassium benzophenone ketyl. All glassware for reactions was dried in an oven overnight at 135 °C, assembled hot, and cooled under a stream of nitrogen. Temperatures of 0 °C were obtained with an ice/water bath; temperatures of −78 °C were obtained with an acetone/dry ice bath; temperatures of 25–70 °C were obtained

(13) Eliel, E. L.; Gianni, M. H.; Williams, Th. H.; Stothers, J. B. *Tetrahedron Lett.* **1962**, 741.

(14) (a) Midland, M. M.; Kwon, Y. C. *Tetrahedron Lett.* **1985**, *26*, 5017. (b) Midland, M. M.; Kwon, Y. C. *Tetrahedron Lett.* **1985**, *26*, 5021.

(15) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis Via Boranes*; Wiley-Interscience: New York, 1975; Chapter 9.

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

entry	ketone	reaction time	isol yield, %	% ee[a] (6000 atm)	% ee (1 atm)	configuration[b]
1		1 day	63	58 (63)	57	*S*
2		1 day	47	83 (90)	67	*S*
3		9 days	nr	- (0)	0[c]	
4		11 h	67	45 (49)		*S*
5		18 h	69	45 (49)	38	*S*
6		23 h	90	65 (71)	58	*S*
7		1 day		38 (41)	34	*S*
8		1 day	80	92 (100)	87	*S*
9		1.5 day	67	92 (100)	90	*S*
10		3 days	43	82 (89)	52	*S*
11		3 days	46	50 (54)	18	*R*
12		1.5 days	60	57 (62)	52	*R*
13		5.5 days	65	69 (75)		*S*

[a] 92% ee pinene was used, values in parentheses are corrected for the pinene purity. [b] Absolute configuration determined by sign of rotation. [c] Pinacolone is reduced slowly at 1 atm to the racemic alcohol.

maintained with an Endocal, Model RTE-80, constant temperature circulating bath.

Sodium chloride solution and sodium bicarbonate solution refer to the saturated solutions. Sodium hydroxide solution refers to a 3.0 M solution, unless otherwise noted. Drying and concentration refers to the drying of an ethereal solution over magnesium sulfate and filtration and rotary evaporation of volatile solvents under reduced pressure (water aspirator at 40 mmHg).

Kugelrohr distillation boiling points refer to the oven temperature used; pressures are reported in millimeters of mercury. Melting points were obtained with a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Spectral Data. Rotations were measured on a Perkin-Elmer Model 241 polarimeter at the sodium D line, 589 nm. Infrared (IR) spectra were recorded on a Nicolet 5-DX fourier transform spectrophotometer with neat samples on sodium chloride plates or potassium bromide pellets.

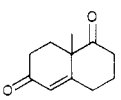
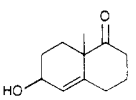
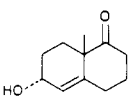
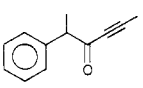
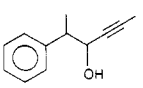
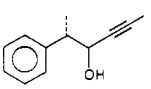
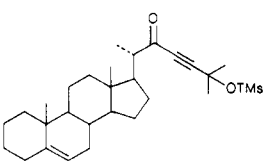
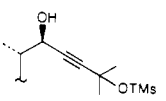
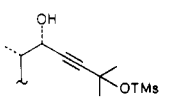
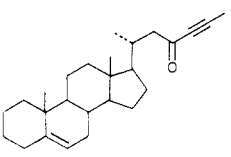
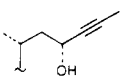
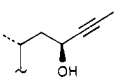
Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian EM-390 continuous-wave 90-MHz spectrometer or a JEOL FX-200 FT 200 MHz spectrometer. Samples were dissolved in deuteriochloroform, 99.8% deuterium (Aldrich Chemical Co.). Tetramethylsilane (TMS) or residual chloroform were used as internal standards at 0.0 or 7.27 ppm, respectively. Chemical shifts are reported in δ values, and coupling constants (J) are reported in hertz. Carbon NMR (^{13}C NMR) spectra were recorded on a JEOL FX-200 FT spectrometer at 50.1 MHz in deuteriochloroform and are broadband decoupled unless otherwise noted. Chemical shifts are reported in δ units downfield from TMS with deuteriochloroform as internal reference at 77.0 ppm.

Enantiomeric purities were measured with lanthanide-shifted ^{1}H NMR spectra recorded at 90 and 200 MHz and were compared to the lanthanide-shifted spectra of the racemic compounds. Areas of carbinol protons were determined by cutting and weighing three copies of the expanded spectrum. Tris((heptafluoropropylhydroxymethylene)-*d*-camphorato)europium (III), Eu(hfc)$_3$, obtained from Aldrich was used unless noted. Absolute configurations were determined by comparison of the sign of rotation to that provided in the literature.

Chromatographic Separations. High-performance liquid chromatography (HPLC) was performed on a Waters 6000A solvent delivery system equipped with a U6K 2.0-mL injector, a Waters model 401 differential refractive index detector, and a Waters Model M-450 variable-wavelength ultraviolet detector. A Whatman M9 10/50 Partisil (9.4 mm × 50 cm) column was used. A Regis Pirkle Type-1[16] column with chiral stationary phase was

(16) Pirkle, W. H.; Finn, J. M. *J. Org. Chem.* **1981**, *46*, 2935.

Table IV. Reduction of Chiral Ketones with Alpine-Borane

entry	ketone structure	alcohol reduction products[b] A	alcohol reduction products[b] B	% ee A/B	ratio A:B
1				63/68	1:1
2				0/0	1:1
3				0/0	1:1
4		decomposition			
5				0/0	1:1
6				92/92	2.4:1
7				*a*	125:1
8				*a*	24:1

[a] Only one enantiomer of the ketone was used. [b] Excess neat Alpine-Borane was used. Ketones 1–5 were reduced with 2.0 equiv, and ketones 6–8 were reduced with 1.5 equiv.

used to determine enantiomeric purities where indicated. Flash chromatography was performed according to the procedure of Still et al.[17a] Flash vacuum chromatography using E. Merck Kieselgel 60H grade was performed according to the procedure of Erikson.[17b] Thin-layer chromatography (TLC) was accomplished with precoated 60F 254 plastic plates (EM Reagents) and visualized by UV light at 254 nm, development in a iodine chamber or by phosphomolybdic acid 1% spray in ethanol, and heating. Gas chromatography was done on a Varian 3700 gas chromatograph equipped with thermoconductivity detector and a 10% SE-30 100/120 3 mm × 2 m Chromosorb column with helium carrier gas.

Oxidative Workup of Trialkylboranes, General Procedure. Following reaction with a trialkylborane, 1.1 equiv of freshly distilled propionaldehyde was added at 0 °C. The mixture was stirred to room temperature over 3 h, and the volatile materials were removed under reduced pressure (40 mm, water aspirator, 30 min; and then 0.05 mm, 30 min); a nitrogen atmosphere was then reintroduced, and the reaction flask was fitted with a condensor. Dry THF (5 mL per millimole of borane) was added. Sodium hydroxide solution (3.0 M 0.34 mL per millimole) was quickly added, followed by the *slow* addition of 30% hydrogen peroxide solution (0.34 mL per millimole). Hydrogen peroxide was added at such a rate as to maintain the temperature of the reaction below 60 °C. The reaction was stirred for 4 h. The organic materials were extracted with two portions of ether, and the ethereal layer was washed with solium chloride solution, separated, dried, and concentrated. The product was isolated by chromatography and/or distillation.

Ethanolamine Precipitative Workup of Trialkylboranes. The reaction was quenched, and volatile materials were removed as described above. Dry ether, 10 mL per millimole borane, was added, and the reaction, mixture was cooled to 0 °C. Ethanolamine (1.0 equiv) was slowly added via syringe to the rapidly stirred solution. The mixture immediately turned yellow. The solution was warmed to room temperature and stirred for 2 h. The white precipitate was removed by vacuum filtration, and the ethereal layer was dried and concentrated. The product was isolated by chromatography and/or distillation.

General Procedure for the Reduction of Ketones at 1 atm of Pressure with Alpine-Borane. The ketones used were all commercially available (Aldrich) and were distilled prior to use. Purities of the ketones were determined by GLC analysis and by comparison of ^{1}H NMR spectra to literature spectra.

Neat Alpine-Borane (15.0 mmol) was prepared in a 100-mL sidearm flask and kept under nitrogen according to the procedure of Midland and Graham.[18] The borane was cooled in an ice bath (0 °C), and a ketone (10.0 mmol) was added via syringe. The ice bath was removed, and the mixture was stirred for 20 min at room temperature. The homogeneous solution was maintained at room temperature. The progress of the reaction was monitored by NMR, with aliquots periodically transferred by syringe to an NMR tube containing deuteriochloroform. When the reaction was complete as determined by the disappearance of the starting ketone (^{1}H NMR), excess borane was quenched by the addition of propionaldehyde (10 mmol). The product alcohol was obtained after appropriate workup as described above. The alcohols gave satisfactory GLC and NMR analyses. Enantiomeric purities were determined by NMR chiral shift studies with Eu(hfc)$_3$. Absolute

(17) (a) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923. (b) Brennan, M. R.; Erickson, K. L. *J. Org. Chem.* **1982**, *47*, 3917.

(18) Midland, M. M.; Graham, R. S. *Org. Synth.* **1984**, *63*, 57.

configurations were assigned by comparison of the sign of rotation with literature values. Yields and enantiomeric purities are given in Table II or III.

General Procedure for the Reduction of Ketones with Alpine-Borane at 2000 atm. A room temperature mixture of Alpine-Borane and ketone was prepared as described in the general procedure for reductions at 1 atm above, and 2.0 mL of the mixture was taken up in a 2-mL polypropylene disposable syringe.[19] The syringe needle was replaced with a syringe cap thereby providing the high-pressure sample cell directly, without the need for further transfer. The sample cell was loaded into the high-pressure apparatus and immediately taken to 2000 atm. The reaction was monitored, quenched, and worked up as described in the general procedure for reduction at 1 atm. The yields and enantiomeric purities are reported in Table I.

Reductions at elevated temperatures and pressures were carried out by equilibrating the 2000 atm pressure vessel in a water bath at the desired temperature for 1 h. The reaction vessel was removed only long enough for the sample to be loaded and replaced in the bath. The reaction was monitored and worked up as described above.

General Procedure for the Reduction of Ketones with Alpine-Borane at 6000 atm. A room-temperature solution of Alpine-Borane (15.0 mmol) and ketone (10.0 mmol) was prepared as described in the general procedure for reactions at 1 atm. The solution was taken up into a 20-mL polypropylene disposable syringe. The volume of the solution was measured, and half was replaced into the reaction flask for reduction at 1 atm. The syringe needle was then replaced by a syringe cap. The capped syringe served as the high-pressure sample vessel without further need for transfer. The syringe was immediately loaded into the high-pressure cell, and the system was pumped to 6000 atm. Aliquots could be obtained by releasing the pressure of the system, retrieving the sample cell, and removing material for NMR analysis. If the reaction was not complete, the sample was replaced and the system returned to 6000 atm.

After the reaction was deemed to be complete, the sample cell was removed and the cap was replaced with a syringe needle. The contents were transferred to a 50-mL round-bottom flask, and the excess borane was quenched with propionaldehyde. The alcohol product was worked up as described in the general procedure for the oxidative workup of trialkylboranes. The yields and enantiomeric purities are reported in Table III along with the enantiomeric purities obtained from the concurrently run reductions at 1 atm.

$NaBH_4$ Reduction of *l*-Carvone. A solution of *l*-carvone (1.50 g, 10.0 mmol) in 10% ethanol–ether (20 mL) was cooled to 0 °C and treated with $NaBH_4$ (0.76 g, 20.0 mmol, 2.0 equiv) for 3 h. The solution was eluted through a pad of silica with ether (30 mL). The ethereal solution was concentrated and provided 1.40 g (93%) 2-methyl-5-(1-methylethenyl)-2-cyclohexen-1-ol as a single isomer, which was used without further purification: ^1H NMR ($CDCl_3$ δ 1.40 (m, 1 H), 1.70 (s, 3 H), 1.75 (d, J = 2 Hz, 3 H), 1.8–2.4 (m, 4 H, OH), 4.18 (m, 1 H), 4.73 (m, 2 H), 5.48 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.4, 21.0, 31.2, 38.3, 41.0, 70.5, 109.5, 123.0, 137.2, 144.7.

Pressure-Promoted Alpine-Borane Reduction of *l*-Carvone. Via the standard reduction at 6000 atm and oxidative workup, 2-methyl-5-(1-methylethenyl)-2-cyclohexene-1-ol, 1.1 g (73%), was isolated after chromatography (SiO_2, 15% EtOAc–hexanes) with care not to alter the diastereomeric ratio. ^1H NMR analysis indicated a 4.6:1 mixture of alcohol epimers favoring the diequatorial product by integration of the vinyl resonances at 5.48 (axial, trans) vs 5.55 (equatorial, cis), 4.73 (axial, trans) vs 4.69 (equatorial, cis), and the carbinol resonances at 4.18 (axial, trans) vs 4.03 (equatorial, cis). The absolute configurations of the authentic samples were assigned as described by Eliel.[13]

Attempted Reduction of *d*-Carvone. Following treatment with Alpine-Borane at 5000 atm for 5 days under the usual pressure promoted conditions, there was no indication of reaction of *d*-carvone. Quenching of the borane followed by ethanolamine workup in the usual manner allowed isolation of the starting material (80%) by chromatography (SiO_2, 10% EtOAc–hexanes).

Acknowledgment. We thank the National Institutes of Health (Grant No. GM-24517) for support of this work. We thank Dr. Y. C. Kwon for performing the reductions of the propargyl steroid ketones and Professor R. C. Neuman for helpful discussions and for the use of the high-pressure apparatus.

(19) Available from Aldrich Chemical Co. See: *Aldrichimica Acta* **1984**, *17*, 2.