of the alcohol **11b** was isolated. Recrystallization from hexane gave pure **11b** (45%), mp 159–159.5 °C. The proton NMR spectrum was identical with that of **11a**,[7] except for the changes associated with incorporation of deuterium. MS analysis: 171 (P – 18, 100); 170 (P – 19, 16.6), indicating 94 atom % D/mol.

Methyl Ether 12b. To an ice-cooled mixture of 30.5 mg of **11b** in 5.0 mL of HMPA was added sufficient *n*-butyllithium/hexane to reach an orange end point. Excess methyl iodide was then added and the cooling bath was removed. After 0.5 h water was added and the mixture was extracted with Skelly-solv, followed by drying and evaporation. The residue was subjected to preparative TLC (20% EtOAc in Skelly-solv) to yield 26.4 mg (81%) of **12b**. The ^{1}H NMR spectrum was identical with that of **12a**, except for the cis benzylic proton appearing as a broadened

singlet (deuterium coupling; this proton is a dd in **12a**) and the absence of absorption at δ 2.4 (where the trans proton of **12a** appears): ^{2}H NMR (CCl$_4$) δ 2.165 (s) (no other absorptions detectable, indicating that all of the deuterium incorporated is found in the trans position); MS, 171 (P – CH$_3$OH, 100), 170 (11.87), indicating 93 atom % D/mol.

Selective Reductions. 37. Asymmetric Reduction of Prochiral Ketones with *B*-(3-Pinanyl)-9-borabicyclo[3.3.1]nonane

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The chiral trialkylborane *B*-(3-pinanyl)-9-borabicyclo[3.3.1]nonane, either with the neat reagents or concentrated solutions, $\gtrsim$2 M, reduces a wide range of prochiral carbonyl compounds with good to excellent asymmetric induction. Reduction of simple dialkyl ketones, 2-butanone, 2-octanone, 3-methyl-2-butanone, and 3,3-dimethyl-2-butanone, yields the corresponding alcohols with 43%, 48%, 62%, and 0.7% asymmetric induction. Acetophenone is reduced to 1-phenylethanol in 85% ee. The α,β-unsaturated ketones 3-buten-2-one, 1-acetyl-1-cyclohexene, 3-methyl-2-cyclohexenone, and *trans*-4-phenyl-3-buten-2-one are reduced to the corresponding allylic alcohols with 57%, 64%, 11%, and 97% asymmetric induction, respectively. The α,β-conjugated acetylenic ketones 3-butyn-2-one, 4-methyl-1-pentyn-3-one, and 4-phenyl-3-butyn-2-one underwent a rapid reduction to afford the corresponding propargylic alcohols with 79%, 99%, and 91% enantiomeric purities. The α-haloalkyl aromatic ketones α-chloroacetophenone, α-bromoacetophenone, α-iodoacetophenone, α,p-dibromoacetophenone, α-bromo-*p*-cyanoacetophenone, α-bromo-2'-acetonaphthone, and α,α,α-trifluoroacetophenone afforded the corresponding halohydrins with 96%, 93%, 93%, 96%, 96%, 90%, and 35% enantiomeric purities, respectively. The corresponding aliphatic analogue 1-bromo-3-methyl-2-butanone gave the halohydrin in 66% ee. The other isomer of this ketone, 3-bromo-3-methyl-2-butanone, failed to undergo reduction. Both the aliphatic and aromatic α-keto esters underwent rapid reduction to give the corresponding α-hydroxy esters with excellent enantiomeric excesses. Thus, methyl, ethyl, isopropyl, and *tert*-butyl pyruvates afforded the corresponding lactates with 86%, 83%, 78%, and 92% ee at 25 °C, respectively. Lowering the reaction temperature to 0 °C gave the *tert*-butyl lactate in 100% ee. Other aliphatic α-keto esters such as methyl and ethyl 2-oxopentanoates, methyl 3-methyl-2-oxobutanoate, and ethyl 4-methyl-2-oxopentanoate were reduced to the corresponding α-hydroxy esters with 96%, 96%, 11%, and 82% ee. The methyl, isopropyl, and *tert*-butyl benzoylformates were reduced to the corresponding mandelic esters with 90%, 96% and 100% ee, respectively. The reduction of the β-keto esters, however, proceeded slowly and ethyl acetoacetate gave the corresponding alcohol with 55% ee.

Over the past several decades, the asymmetric reduction or carbonyl compounds has been actively investigated by organic chemists.[2] Most of the early experiments in this direction, however, gave disappointingly low optical yield. The real breakthrough came with the advent of the lithium aluminum hydride/Darvon alcohol complex by Mosher and Yamaguchi in 1973,[3] who reduced acetophenone in 100% chemical yield and 75% ee. More recently, reagents prepared by the partial decomposition of lithium aluminum hydride with chiral amine and phenols (*N*-ethylephedrine + 3,5-dimethylphenol; Vigneron),[4] chiral diamines (xylylidinomethylpyrrolidine; Mukaiyama),[5] chiral

binaphthols and simple alcohols (2,2'-dihydroxy-1,1'-binaphthyl + methanol; Noyori),[6] and chiral amine and simple amine (*N*-methylephedrine + *N*-ethylaniline; Terashima)[7] have been applied to the asymmetric reduction of carbonyl compounds with considerable success.

Boranes and borohydrides represent another family of reagents that has proved useful for asymmetric reductions. Even though monoisopinocampheylborane[8] and diisopinocampheylborane[9] are extremely selective chiral hydroborating agents, the chiral reduction of simple ketones with these reagents proceeded with only low asymmetric induction.[10] Similarly, the highly stereoselective chiral

(1) Postdoctoral research assistant, 1979–1983, on Grant GM 10937-20 from the National Institutes of Health.

(2) For a summary of earlier work, see: Morrison, J. D.; Mosher, H. S. "Asymmetric Organic Reactions"; Prentice Hall: Englewood Cliffs, NJ, 1971. Valentine, D., Jr.; Scott, J. W. *Synthesis* **1978**, 329–356. ApSimon, J. W.; Seguin, R. P. *Tetrahedron* **1979**, *35*, 2797–2842. Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1978**, *10*, 175.

(3) Mosher, H. S.; Yamaguchi, S. *J. Org. Chem.* **1973**, *38*, 1870.

(4) (a) Vigneron, J. P.; Jacquet, I. *Tetrahedron* **1976**, *32*, 939. (b) Vigneron, J. P.; Gloy, V. *Tetrahedron Lett.* **1979**, 2683; **1980**, 1735.

(5) Asami, M.; Mukaiyama, T. *Heterocycles* **1979**, *12*, 499.

(6) Noyori, R.; Tomio, I.; Tanimoto, Y. *J. Am. Chem. Soc.* **1979**, *101*, 3129. Noyori, R.; Yamada, M.; Nishizawa, M. *Tetrahedron Lett.* **1981**, *22*, 247.

(7) Terashimo, S.; Tanno, N.; Koga, K. *Chem. Lett.* **1980**, 981; *J. Chem. Soc., Chem. Commun.* **1980**, 1026.

(8) Brown, H. C.; Jadhav, P. K.; Mandal, A. K. *J. Org. Chem.* **1982**, *47*, 5074.

(9) Brown, H. C.; Desai, M. C.; Jadhav, P. K. *J. Org. Chem.* **1982**, *47*, 5065.

Scheme I[a]

[a] $\overset{\displaystyle\frown}{\bigcirc}$ BH = 9-borabicyclo[3.3.1]nonane (9-BBN).
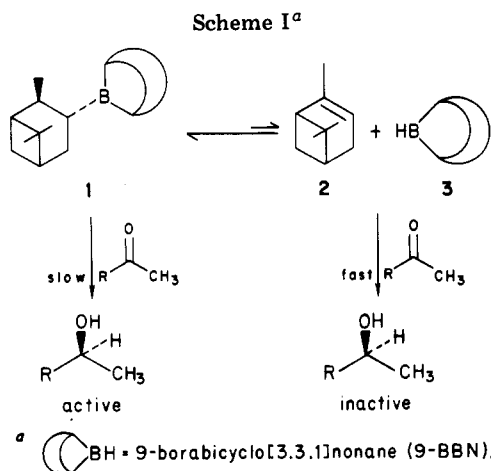
Superhydride (Aldrich), lithium *B*-(3-pinanyl)-9-borabicyclo[3.3.1]nonane hydride,[11] achieved only moderate success in the chiral reduction of ketones.[12] Recently, Midland and Kazubski have modified this reagent and applied it to the asymmetric reduction of simple ketones with great success.[13] The borohydride, prepared by the hydroboration of nopol (6,6-dimethylbicyclo[3.3.1]hept-2-ene-2-ethanol) benzyl ether with 9-borabicyclo[3.3.1]-nonane, followed by treatment with *tert*-butyllithium, developed by these workers could reduce 2-octanone with 79% ee, the highest achieved by any chemical reducing agent thus far.

It was known for a long time that trialkylboranes reduced aldehydes at moderately high temperatures (100–150 °C).[14] On the basis of a systematic investigation of this reaction,[15a] Midland and co-workers developed *B*-(3-pinanyl)-9-borabicyclo[3.3.1]nonane (1, Alpine-Borane, Aldrich[15b]) as a highly useful chiral reducing agent. The reagent embodies attractive features such as ready availability in both *d* and *l* forms, tolerance of many other readily reducible functionalities, and simple experimental procedure. It reduces reactive carbonyl compounds such as 1-deuterioaldehydes[16] and conjugated acetylenic ketones[17] in excellent optical and chemical yields.

The reagent, however, reacted with simple ketones under the relatively dilute conditions utilized in the original procedure only relatively slowly. Under these circumstances, the usual reduction by a cyclic mechanism is replaced by an alternative mechanism involving a prior dissociation of the reagent into α-pinene (2) and 9-BBN (3, Scheme I).

Reduction of the ketone by the achiral 9-BBN so formed gives an inactive product and leads to lowering the overall asymmetric induction of the reaction. Increasing the temperature as a means of enhancing the rate of the reaction is self-defeating, since it leads to increased dissociation of the reagents.[17]

It occurred to us that it should be possible to overcome these problems by carrying out the reaction in more concentrated solutions. This should both increase the reaction rate and suppress the undesirable dissociation. This approach proved very fruitful and we succeeded in reducing many simple, as well as functionalized ketones, with good to excellent asymmetric induction. Where the solubility of the ketone permitted, the reduction was carried out with the neat reagent; otherwise, highly concentrated (∼2 M to ∼5 M) solutions in THF were utilized.[18]

Midland and his co-workers have recently overcome the problem by carrying out the reduction under extremely high hydrostatic pressure (≳5000 atm). They have been able to achieve the reduction of acetophenone with 100% ee.[19]

The formation of α-pinene as the side product during the reduction makes it very convenient to monitor the reaction by either GC analysis or ^{1}H NMR. A quantitative study of the reaction could be carried out by analyzing the reaction mixture on a 6 ft × $^1/_4$ in. DC-710 column and a suitable hydrocarbon as the internal standard (*n*-nonane). It was necessary to keep the injection port temperature low (100 °C) to prevent the decomposition of the boranes from causing spurious results. Since the olefinic proton of the α-pinene has a chemical shift in an uncluttered region of the spectrum, it was quite straightforward to follow the reaction by ^{1}H NMR. This is the preferred procedure for qualitative work, especially while using the neat reagent.

In general, the reductions were carried out at 25 °C by using either a 100% excess or 40% excess (for reactive substrates) of the neat reagent prepared by the hydroboration of commercially available 92% ee (+)-α-pinene with 9-BBN (eq 1). On completion of the reduction, the

(1)
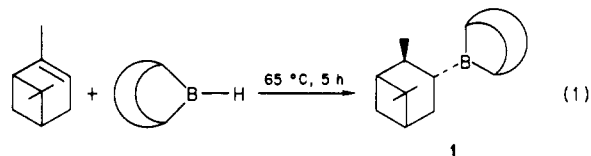
excess reagent was destroyed with acetaldehyde and the liberated α-pinene was pumped off under vacuum (40 °C (0.01 mm), 1–2 h). The free alcohol was liberated from its borinate ester (4) by exchange with ethanolamine[20] (eq 2 and 3). The 9-BBN–ethanolamine ethanolamine adduct

(2)

(3)
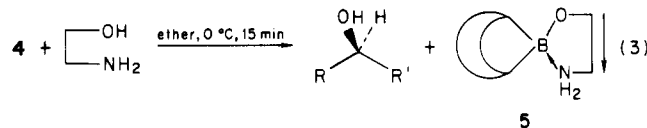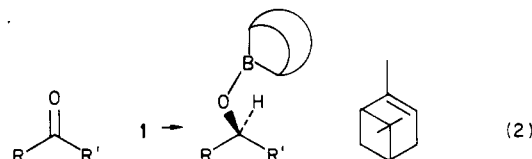
5 precipitates from the solution and can be conveniently removed by filtration. This nonoxidative workup procedure prevents the formation of isopinocampheol which could complicate the isolation of the product. The prod-

(10) Brown, H. C.; Mandal, A. K. *J. Org. Chem.* **1977**, *42*, 2996. Brown, H. C.; Jadhav, P. K.; Mandal, A. K. *Tetrahedron* **1981**, *37*, 3547.

(11) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567.

(12) Krishnamurthy, S.; Vogel, F.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 2534.

(13) Midland, M. M.; Kazubski, A. *J. Org. Chem.* **1982**, *47*, 2495. The reagent is available from Aldrich under the trademark NB-Enantride.

(14) Mikhailov, B. M.; Bubnov, Yu. N.; Kiselev, V. G. *J. Gen. Chem. USSR* **1966**, *36*, 65.

(15) (a) Midland, M. M.; Tramontano, A.; Zderic, S. A. *J. Organomet. Chem.* **1978**, *156*, 203. (b) *B*-(3-Pinanyl)-9-borabicyclo[3.3.1]nonane is commercially available from Aldrich Chemical Company under the trademark, Alpine-Borane, as a 0.5 M solution in THF.

(16) Midland, M. M.; Greer, S.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2352.

(17) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867.

(18) (a) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1982**, *47*, 1606. (b) Brown, H. C.; Pai, G. G. *Ibid.* **1983**, *48*, 1784. (c) Brown, H. C.; Pai, G. G.; Jadhav, P. K. *J. Am. Chem. Soc.* **1984**, *106*, 1531.

(19) Midland, M. M.; McLoughlin, J. I. *J. Org. Chem.* **1984**, *49*, 1316.

(20) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 1197.

Table I. Reduction of Prochiral Simple Ketones with Neat Alpine-Borane (from 92% ee (+)-α-Pinene)

| ketone	reagent, molar equiv	reactn conditns		yield, %	optically active alcohol			
		temp, °C	time, days		$[\alpha]_D$, deg	% ee		abs confign
						obsd	corr	
2-butanone	2	25	10	90[a]	−5.4 (neat)	40[d]	43	S
3-methyl-2-butanone	2	25	14	78[b]	+3.06 (neat)	57[e]	62	S
3,3-dimethyl-2-butanone	2	25	40	40[b,c]	+0.05 (neat)	0.6[f]	0.7	S
2-octanone	2	25	7	65[b]	+4.12 (neat)	44[g]	48	S
acetophenone	1	25	14	68[b]	−34.3 (neat)	80[h]	87	S
acetophenone	2	25	7	68[b]	−33.4 (neat)	78[h]	85	S
acetophenone	2	45	3–4	85[b]	−27 (neat)	63[h]	68	S

[a] GC yield. [b] Isolated yield. [c] Reaction was only 70% complete. [d] Based on $[\alpha]_D$ 13.5° (neat).[27] [e] Based on $[\alpha]_D$ 5.34° (neat).[28] [f] Based on $[\alpha]_D$ 8.1° (neat).[29] [g] Based on $[\alpha]_D$ 9.57° (neat).[30] [h] Based on $[\alpha]_D$ 42.85° (neat).[31]

ucts were purified by distillation and/or chromatography.

Our results with each individual class of carbonyl compounds are discussed below.

Simple Ketones. The reduction of acetophenone was found to proceed very slowly in 0.5 M THF solution by Midland and co-workers.[21] They found that it is necessary to reflux the reaction mixture to complete the reaction in a reasonable length of time (48 h). However, the reduction of acetophenone under these conditions proceeded with only 10% optical induction.

In our experiments under more concentrated conditions, we utilized a 100% excess of the neat reagent.[18a] The reduction was slow and most ketones required 7–14 days for complete reaction (eq 4–6). The extent of optical
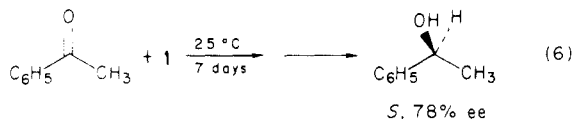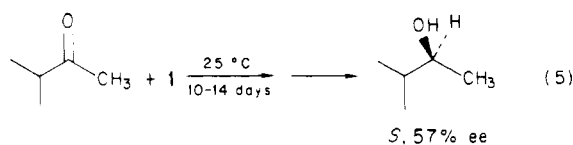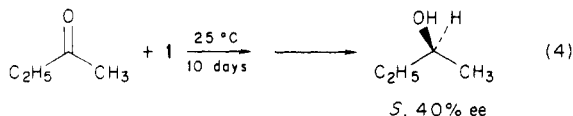
induction increases with the steric inequality of the two groups attached to the carbonyl functionality. Thus, there is an increase in optical induction as we keep one alkyl group constant and increase the size of the other group from ethyl to isopropyl to phenyl. Introduction of the *tert*-butyl group, however, breaks this trend and produces a sharp drop in asymmetric induction. The reaction proceeds extremely slowly in this case (60% reaction in 40 days at 25 °C). Presumably, the major portion of the reduction goes via the dissociation mechanism (eq 7). In
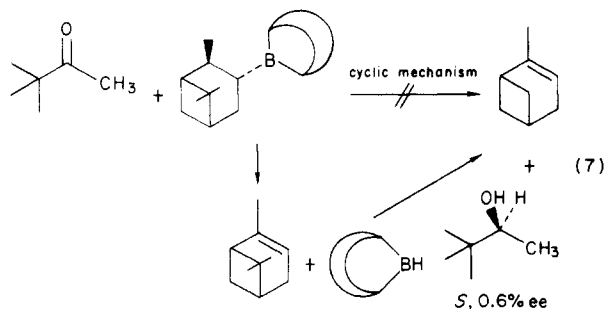

every case the reduction products had the S configuration. This is in accordance with the model proposed by Midland for these reductions[16] (eq 8).
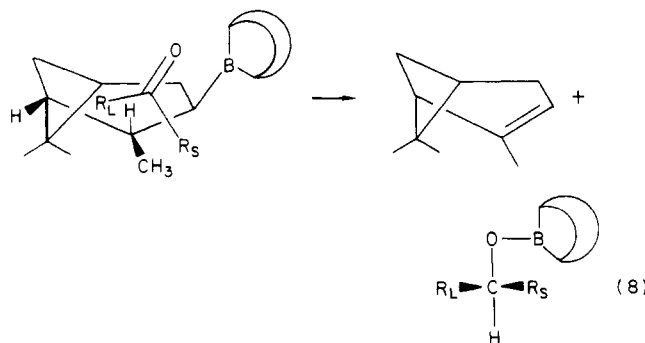
We also examined a couple of minor variations of the general procedure. Thus, the reduction of acetophenone with just 1 equiv of Alpine-Borane, a large excess of the ketone (7-fold excess), and at a slightly higher reaction temperature (45 °C instead of 25 °C) was examined. The use of a stoichiometric amount of the reagent resulted in slower reaction rate (14 days) but had no effect on the asymmetric induction. Using a large excess of the ketone had no effect on either the reaction rate or the optical induction. On the other hand, the reaction at 45 °C proceeded at a faster rate (3–4 days) but at the cost of the asymmetric induction, which dropped from 78% ee to 63% ee. The results are summarized in Table I.

α,β-Unsaturated Ketones. The α,β-unsaturated ketones also underwent reduction at a slow rate under the standard reaction conditions. Nevertheless, excellent asymmetric induction was realized in the reduction of *trans*-4-phenyl-3-buten-2-one (6, eq 9). The results were not so encouraging with other compounds (Table II). In this case also, the products had the S configuration.
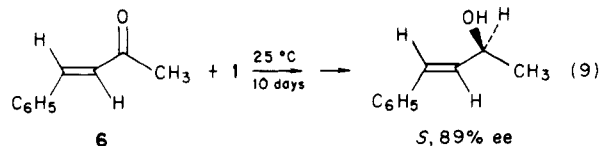
It is known that trialkylboranes undergo a facile 1,4-addition to conjugated ketones by a free radical mechanism.[22] We did not observe any 1,4-addition products in this case. Since trace amounts of oxygen act as the chain initiator, due care is needed to maintain an inert atmosphere.

α,β-Acetylenic Ketones. Midland and co-workers have carried out a detailed study of the reduction of alkynyl

(21) Midland, M. M. in "Aspects of Mechanism and Organometallic Chemistry"; Brewster, J. H., Ed.; Plenum Press: New York, 1978; p 215.

(22) Negishi, E.; Brown, H. C. J. Am. Chem. Soc. 1973, 95, 6757 and references cited therein.

Table II. Reduction of Prochiral α,β-Unsaturated Ketones with Neat Alpine-Borane (from 92% ee (+)-α-Pinene)

| | | reactn conditns | | | optically active alcohol | | | | |
		reagent, molar equiv	temp, °C	time, days	yield, %	$[\alpha]_D$, deg	% ee obsd	% ee corr	abs confign
entry	ketone						obsd	corr	
1	3-buten-2-one	1.4	25	5^a	30^b	+17.8	52^d $(60)^e$	57 (65)	S
2	1-acetyl-1-cyclohexene	1.4	25	12	90^c	-7.47 (c 4.15, CHCl$_3$)	59^f	64	S
3	3-methyl-2-cyclohexenone	1.4	25	12	70^c	-13.1 (c 4.05, CHCl$_3$)	9.6^g $(18)^e$	10.4 (19.6)	S
4	*trans*-4-phenyl-3-buten-2-one	1.4	25	10	80^b	-22.3 (c 5.2, CHCl$_3$)	89^h	97	S

^{a}90% reaction was complete. ^{b}Isolated yield. ^{c}GC yield. ^{d}Based on $[\alpha]_D$ +33.8° (neat).[32] ^{e}Determined by NMR analysis in the presence of Eu(hfc)$_3$. ^{f}Based on calculated $[\alpha]_D$ (max) 12.6° (c 4.15, CHCl$_3$).[33] ^{g}Based on calculated $[\alpha]_D$ (max) 137.08° (c 408, CHCl$_3$).[34] ^{h}Based on calculated $[\alpha]_D$ (max) 25° (c 5.16, CHCl$_3$).[35]

Table III. Reduction of Prochiral α,β-Acetylenic Ketones with Alpine-Borane (from 92% (+)-α-Pinene)

| | | reactn conditns | | | optically active alcohol | | | | |
		reagent, molar equiv	temp, °C	time, h	yield, %	$[\alpha]_D$, deg	% ee obsd	% ee corr	abs confign
entry	ketone						obsd	corr	
1	3-butyn-2-one	1.4	25	4	80^a	+37.7 (c 2.3, dioxane)	73^c	79	
2	4-methyl-1-pentyn-3-one	1.4	25	4	87^b	+14.6 (c 2, dioxane)	91^d	99	
3	4-phenyl-3-butyn-2-one	1.4	25	8–12	95^a	+69.9 (neat)	98^e	106.5	

^{a}Isolated yield. ^{b}GC yield. ^{c}Based on calculated $[\alpha]_D$ (max) 52° (c 2, dioxane).[4b] ^{d}Based on calculated $[\alpha]_D$ (max) 16° (c 2, dioxane.)[4b] ^{e}Based on calculated $[\alpha]_D$ (max) 71.9° (neat).[17]

ketones.[17] They observed that the alkynyl ketones underwent reduction in a reasonable time when 2 equiv of the reagent was used (8 h for terminal acetylenic ketones and 1–4 days for the internal ones). The chemical and optical yields were excellent and approached 100% ee in many instances.

As expected, under our experimental conditions, most acetylenic ketones underwent reduction very rapidly and we found it necessary to use only a modest excess (30–40%) of the reagent. For example, Midland and co-workers have reported that the reduction of 4-phenyl-3-butyn-2-one (7) takes 48 h for complete reduction at 25 °C, using a 100% excess of Alpine-Borane. We observed complete reduction of the ketones in just 8–12 h using a 40% excess of the neat reagent (eq 10). Our product also
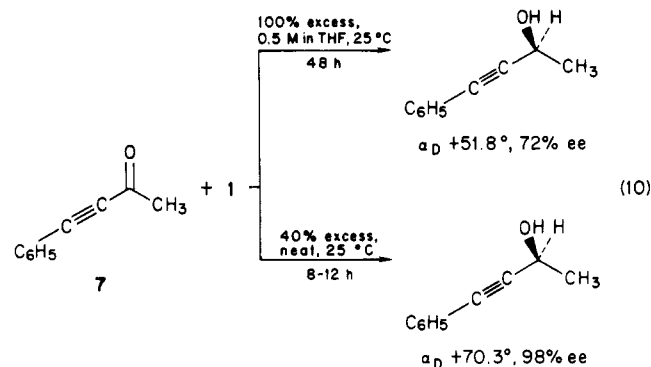
had a substantially higher optical rotation. On the basis of Midland's value, our product should have had an optical purity of 98% ee. Since we prepared the Alpine-Borane from 92% ee α-pinene, this value could not be correct. This discrepancy may be due to the fact that the earlier workers used the NMR shift reagents to determine enantiomeric purity and the rotation reported by them may be a little too low.

In dealing with low molecular weight, reactive acetylenic ketones such as 3-butyn-2-one, it was more advantageous to employ a slight excess of the ketone rather than the reagent. Even though this tends to slow down the reaction, the asymmetric induction is not affected. The advantage lies in the avoidance of destroying the excess reagent which introduces a side product such as ethanol if acetaldehyde is used to destroy the reagent. Since the two alcohols have

their boiling points fairly close, the isolation of product needs careful distillation.

The reduction products in this case had the same absolute configurations. Thus, the acetylenic moiety seems to have the same steric influence as hydrogen in aldehyde reductions, i.e., it behaves as if it were smaller than an alkyl group.[17] Our results are summarized in Table III.

α-Halo Ketones. It is known that the electron-withdrawing substituents on the carbonyl compound increase the rate of reduction.[16,23] Although not necessarily true in all cases, usually an increased reduction rate also increases the optical induction since it favors the cyclic mechanism over the dissociation mechanism (Scheme I). We reasoned that an electron-withdrawing substituent such as halogen substituted α to the carbonyl group should also provide a similar rate enhancement and improve asymmetric induction. Moreover, the reduction products in this case would be halohydrins, readily convertible to the valuable optically active epoxides or to the parent optically active alcohols.

Our expectation was realized in the reduction of α-bromoacetophenone (8).[18b] The reduction, using 100% excess Alpine-Borane, went to completion in 4 days (eq 11). The bromohydrin 9 was isolated in 95% yield and
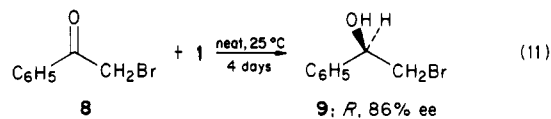
86% ee by the ethanolamine workup procedure. The enantiomeric purity and the configuration of the bromohydrin were established from the known literature values and also by conversion to (R)-styrene oxide (3 M NaOH–ether–pentane–water, 15 min at 25 °C), as well as to (S)-1-phenylethanol (lithium triethylborohydride, 24 h at 25 °C).

In order to determine which halogen had the most suitable characteristics as the activating group, we studied the reduction of α-chloro- and α-iodoacetophenones. Due to the poor solubility of the former in neat reagent, the reduction took 6 days for completion. Nevertheless, the chlorohydrin was obtained in 91% yield and 88.5% ee. α-Iodoacetophenone, on the other hand, was more soluble

(23) Midland, M. M.; Zderic, S. A. *J. Am. Chem. Soc.* **1982**, *104*, 525.

Table IV. Reduction of Prochiral α-Halo Ketones with Neat Alpine-Borane (from 92% ee (+)-α-Pinene) at 25 °C Using 100% Excess Reagent

entry	ketone	time, days	yield,[c] %	% optical inductn		abs confign
				obsd	corr	
1	α-chloroacetophenone	6–8	91	88.5[d]	96.2	R
2	α-bromoacetophenone	4	95	86[e]	93	R
3	α-iodoacetophenone	2	60	86[e]	93	R
4	α,p-dibromoacetophenone[a]	3	95	88[f]	96	R[i]
5	α-bromo-p-cyanoacetophenone[a]	2–3	60	88[f]	96	R[i]
6	α-bromo-2′-acetonaphthone[a]	3–4	90	83[g]	90	R
7	α,α,α-trifluoroacetophenone	45[b]	57	32[d,h]	35	R
8	1-bromo-3-methyl-2-butanone	14	60	61[f]	66	R[g]
9	3-bromo-3-methyl-2-butanone	nr[j]				

[a] Reaction carried out in ~5 M THF solution. [b] Reaction went to 90% completion. [c] Isolated yield of >96% pure material. [d] By comparison of specific rotation with literature value.[34] [e] By conversion to styrene oxide.[35] [f] By the ^{19}F NMR analysis of MTPA esters. [g] By conversion to the parent alcohol.[36] [h] Reference.[3] [i] Absolute configuration not known, but probably R. [j] nr = no reaction.

in the reagent, and the reaction required only 2 days for completion. The reduction, unfortunately, was accompanied by deiodination, and the yield of the iodohydrin was only 60% (86% ee). In each case, treatment of the halohydrin with alkali gave (R)-styrene oxide. Since R halohydrins give R epoxides, this establishes the configuration of the starting halohydrins as R. One might notice that the model proposed by Midland[16] correctly predicts this configuration (the bulky phenyl group comes over the α-pinene ring), and the R configuration of the products is a consequence of the Cahn–Prelog–Ingold convention rather than a change in the mode of attack.

Reduction of some other α-halo ketones such as α,p-dibromoacetophenone and α-bromo-p-cyanoacetophenone failed to proceed in neat reagent because they were almost completely insoluble (entries 4 and 5 in Table IV). In such cases, the reactions were carried out in highly concentrated (~5 M) partially heterogeneous solutions in THF. Judging from the results, this modified procedure was not detrimental, and the corresponding bromohydrins were obtained in excellent enantiomeric purity (88% ee in this case). In these cases the presence of two electron-withdrawing substituents further increased the rate of reduction. For example, under comparable conditions (2 M THF solution), α,p-dibromoacetophenone underwent complete reduction in 3 days whereas the para-unsubstituted derivative took about 2 days longer for complete reaction.

The reduction of aliphatic α-halo ketones did not give such encouraging results. Thus, the reduction of 1-bromo-3-methyl-2-butanone (10, eq 12) gave the corresponding bromohydrin 11 in 61% ee. The other isomer
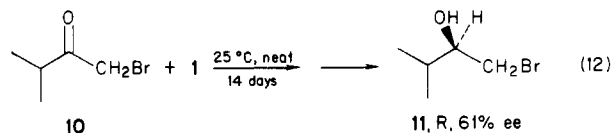
sponding bromohydrin 11 in 61% ee. The other isomer of this ketone, 3-bromo-3-methyl-2-butanone, failed to undergo reduction. Similarly, the α,α,α-trifluoroacetophenone was very sluggish to react, requiring almost 45 days to achieve ~90% reaction. The product exhibited a disappointing 32% optical induction. The slow reaction in this case may be either due to the steric bulk of the trifluoromethyl group or its extremely powerful electron-withdrawing capacity. The former might make it difficult for the ketone to approach the reagent while the latter might prevent the complexation between the reagent and the ketone by depleting the electron density at the oxygen atom of the carbonyl group.

The chiral bromohydrins obtained by this reduction are convenient intermediates for further elaboration via the corresponding chiral epoxides, as exemplified by the syn-

Scheme II
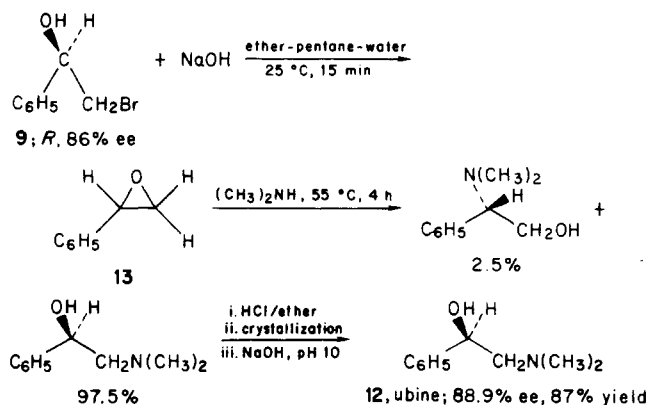
thesis of the alkaloid ubine (12, Scheme II). Thus, the bromohydrin 9 was converted to the styrene oxide (13) by treatment with an equivalent amount of aqueous 3 M sodium hydroxide in a two-phase system (water–ether–pentane). Reaction between the styrene oxide and dimethylamine resulted in the opening of the epoxide ring by a preferential attack on the terminal carbon atom (98%). From the mixture of amino alcohols so formed, the desired isomer was isolated by the fractional crystallization of their hydrochlorides. The overall yield of the alkaloid from the bromohydrin 9 was 87% (88.9% ee) and it had the configuration corresponding to the natural product.[24]
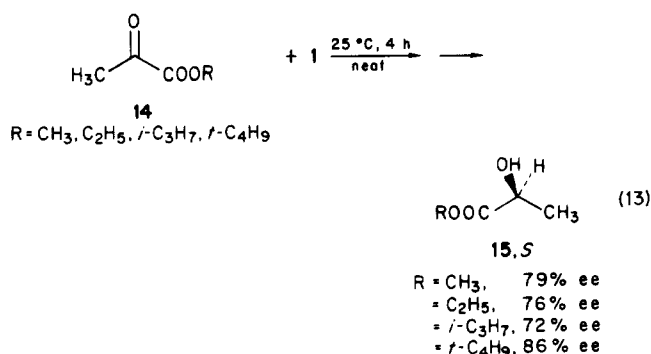
One might notice that the nonoxidative ethanolamine workup procedure was particularly suitable for the isolation of the halohydrins. The extreme lability of these compounds toward base does not permit the utilization of alkaline hydrogen peroxide or trimethylamine N-oxide oxidation procedures which are commonly used in organoborane chemistry.

α-Keto Esters. As mentioned already, the presence of an electron-withdrawing substituent on the carbonyl compounds increases the rate of reduction. We exploited this fact in the reduction of α-halo ketones, as described above. Another class of such compounds is α-keto esters. In this case the direct attachment of the ester group to carbonyl function should have an even more pronounced effect on the rate of reduction. Besides, the reduction products in this case, viz., α-hydroxy esters are an extremely useful class of compounds which can be converted to a host of other derivatives.

As we had expected, the reduction of ethyl pyruvate (14, R = C₂H₅) with neat Alpine-Borane (40% excess) proceeded rapidly at 25 °C and gave ethyl lactate (15, R =

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(24) This is adapted from a procedure reported in the literature: Ranieri, R. L.; McLaughlin, J. L. *Lloydia* 1977, 40, 173.

C₂H₅) in 76% ee (eq 13).[18a,c] It seems logical that the

14
R = CH₃, C₂H₅, *i*-C₃H₇, *t*-C₄H₉

(13)

15, S

R = CH₃, 79% ee
= C₂H₅, 76% ee
= *i*-C₃H₇, 72% ee
= *t*-C₄H₉, 86% ee

degree of asymmetric induction depends on the steric inequality of the two groups attached to the carbonyl functionality—in this case, the alkyl chain and the ester moiety. We examined the effect of varying the steric bulk of both of these groups in a systematic manner.

Since the rate of reduction at 25 °C was rapid, only a 40% excess of the neat reagent was employed for the reaction. The reduction of ethyl pyruvate gave (S)-ethyl lactate. This implies that, according to the model proposed by Midland and co-workers for these reductions,[16] the ester group is bulkier than the methyl group. Thus, increasing the steric bulk of the ester moiety should lead to an increase in asymmetric induction. However, in reality, no such trend was observed in the reduction of methyl, ethyl, and isopropyl pyruvates. The asymmetric induction for all of these derivatives was more or less the same. The reduction of the *tert*-butyl ester, however, afforded *tert*-butyl lactate with noticeably higher asymmetric induction (eq 13; **15**, R = *t*-C₄H₉).

Varying the steric bulk of the alkyl chain also had a predictable effect. Attaching a normal alkyl group in place of methyl, as in methyl 2-oxopentanoate (**16**), resulted in an increase in the asymmetric induction to 88% ee (eq 14).

(14)

**16**   S, 88% ee
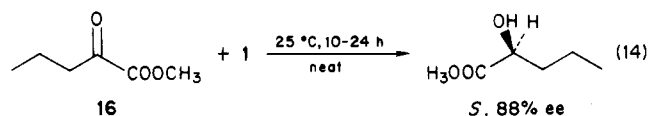
But substitution by an isopropyl group led to a drastic decrease in reaction rate, as well as in asymmetric induction (10%, eq 15). It is also interesting to note that in

(15)

R, 10% ee
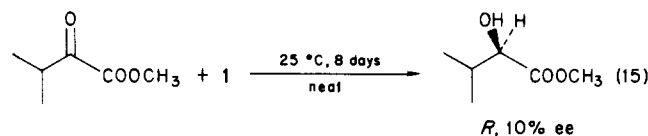
this case the α-hydroxy ester had the opposite R configuration. This implies that the isopropyl group is larger than the methyl carboxyl group. Replacement of the methyl group by isobutyl, in effect, separating the isopropyl group from the reaction center by a methylene group, resulted in both an increase in rate and an increase in the asymmetric induction back nearly to that of the parent compound (eq 16).

(16)

S, 75% ee
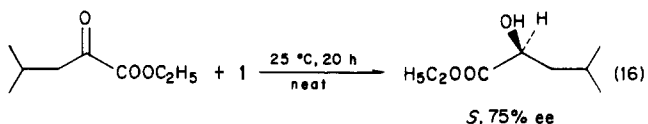
The reduction of the corresponding aromatic analogue, methyl benzoylformate (**17**, R = CH₃), gave (R)-(−)-methyl mandelate (**18**, R = CH₃) in 83% ee (eq 17). This is in accordance with Midland's model (the phenyl group is

17
R = CH₃, *i*-C₃H₇, *t*-C₄H₉

(17)

18, R

R = CH₃,   83% ee
= *i*-C₃H₇, 88% ee
= *t*-C₄H₉, 92% ee
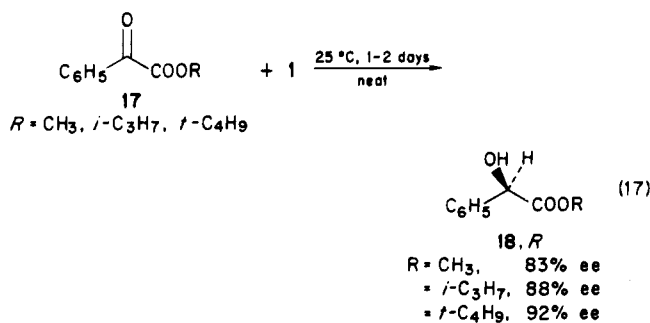
bulkier than the methyl carboxyl group). Consequently, we expected that, unlike the aliphatic series, a further increase in the steric bulk of the ester group in this case should diminish the steric inequality of the two groups attached to the carbonyl functionality, causing a detrimental effect on the asymmetric induction. Contrary to this expectation, however, the reduction of the isopropyl and *tert*-butyl esters gave the corresponding mandelates in 88% ee and 92% ee, respectively (eq 17). In every case, the product possessed the R configuration, as shown by their conversion to (R)-styrene glycol by reduction of the ester group with lithium borohydride.

We tested this unexpected effect of the *tert*-butyl esters on several representative derivatives such as *tert*-butyl 2-oxobutyrate, *tert*-butyl 2-oxopentanoate, and *tert*-butyl 4-methyl-2-oxopentanoate.[18c] The results are summarized in Table V. The effect appears to be general in the cases studied.

The large effect realized with the *tert*-butyl esters in both systems suggests that there may be an electronic component (increased +I effect of the *tert*-butyl group) to the asymmetric induction realized.

Another important factor influencing the degree of asymmetric induction is the temperature. Midland has cautioned that increasing the reaction temperature to enhance the rate of reduction should be avoided since it also increases the dissociation of the reagent.[17] Such dissociation lowers the asymmetric induction. Lowering the reaction temperature, on the other hand, has a beneficial effect. Thus, the reduction of ethyl pyruvate and *tert*-butyl pyruvate at 0 °C brought about a moderate increase in asymmetric induction (see Table V). In extending this study of the effect of temperature to the phenyl derivative, we encountered an unexpected phenomenon. Mixing methyl benzoylformate and 1 at 0 °C led to the formation of a complex, as evidenced by the development of a reddish orange color, but no significant reduction (<5%) over a period of 24 h. On warming up this mixture to room temperature, the reaction proceeded normally and went to completion in 24 h.

So far, we have seen that the substitution of either an α-halogen or an ester group had a beneficial effect on the reaction rate as well as optical induction. It was interesting to see what would happen if we had a substrate with both of these substituents. We chose ethyl α-bromopyruvate (**19**) as a representative compound. The reduction of this compound with a slightly less than stoichiometric amount of Alpine-Borane was very fast and was complete in less than half an hour. The product, however, had a disappointingly low enantiomeric purity of only 7.6% ee (eq 18).

(18)

19   7.6% ee
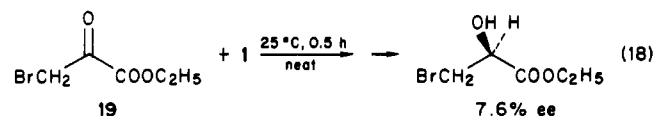
In general, when a compound undergoes rapid reduction, one expects good asymmetric induction, because in such

Table V. Reduction of α-Keto Esters with Alpine-Borane (from 92% ee (+)-α-Pinene)

| | reactn conditns | | | | optically active α-hydroxy ester | | | |
	reagent, molar equiv	temp, °C	time	yield,[a] %	optical rotation, deg	% ee obsd	corr	abs confign
methyl pyruvate	1.4	25	4 h	64	α^{23}_D −7.16 (neat, l = 1)	79[b]	86	S
ethyl pyruvate	1.4	25	4 h	81	$[\alpha]^{23}_D$ −8.83 (neat, l = 1)	76[c]	83	S
ethyl pyruvate	1.4	0	24 h	81	$[\alpha]^{23}_D$ −9.43 (neat, l = 1)	82[c]	89	S
isopropyl pyruvate	1.4	25	4 h	72	$[\alpha]^{23}_D$ −8.664 (neat, l = 1)	72[d]	78	S
tert-butyl pyruvate	1.4	25	4 h	98	$[\alpha]^{23}_D$ −8.08 (neat, l = 1)	85[e]	92	S
tert-butyl pyruvate	1.4	0	24 h	98	$[\alpha]^{23}_D$ −8.76 (neat, l = 1)	92[e]	100	S
tert-butyl 2-oxobutyrate	1.4	0	24 h	71	$[\alpha]^{23}_D$ −3.4 (c 2.0, CCl$_4$)	92	100	S
methyl 2-oxopentanoate	1.4	25	10–20 h	80	$[\alpha]^{23}_D$ +9.84 (c 1.26, CHCl$_3$)	88[d,f]	96	S
ethyl 2-oxopentanoate	1.4	25	4 h	77	$[\alpha]^{23}_D$ −4.44 (neat, l = 1)	88[g]	96	S
tert-butyl 2-oxopentanoate	1.4	0	24 h	79	$[\alpha]^{23}_D$ −3.46 (neat, l = 1)	92[l]	100	S
methyl 3-methyl-2-oxobutanoate	1.4	25	8 days	70	$[\alpha]^{23}_D$ −1.7 (c 1, CCl$_4$)	10[h]	11	R
ethyl 4-methyl-2-oxopentanoate	1.4	25	20 h	50	$[\alpha]^{25}_D$ −5.30 (neat, l = 1)	75[i]	82	S
tert-butyl 4-methyl-2-oxopentanoate	1.4	0	24 h	72	$[\alpha]^{23}_D$ −7.88 (c 7.88, CCl$_4$)	92[l]	100	S
methyl benzoylformate	1.4	25	24 h	95	$[\alpha]^{23}_D$ −144.9 (c 0.7, CHCl$_3$)	83[j]	90	R
isopropyl benzoylformate	1.4	25	2 days	91	$[\alpha]^{27}_D$ −98.9 (c 1, CHCl$_3$)	88[d,k]	96	R[k]
tert-butyl benzoylformate	1.4	25	2 days	89	$[\alpha]^{27}_D$ −119.1 (c 1.05, CCl$_4$)	92[d,k]	100	R[k]

[a] Isolated yield of ∼98% pure material. [b] Based on α^{25}_D −4.54° (neat, l = 0.5).[37] [c] Based on $[\alpha]_D$ −11.5° (neat, l = 1).[38] [d] By F[19] NMR of MTPA esters. [e] Based on $[\alpha]^{20}_D$ +9.48° (neat, l = 1).[39] [f] Literature value of $[\alpha]^{23}_D$ +16.6° (c 1.2, CHCl$_3$) appears to be in error.[40] [g] Based on $[\alpha]^{20}_D$ −5.05° (neat, l = 1).[41] [h] Based on $[\alpha]^{25}_D$ +17.5° (c 1, CCl$_4$).[42] [i] Based on $[\alpha]^{25}_D$ −7.06° (neat, l = 1).[43] [j] Based on $[\alpha]^{25}_D$ −174.2° (c 0.58, CHCl$_3$).[44] [k] By conversion to styrene glycol.[45] [l] By ^{1}H NMR in the presence of chiral shift reagent Eu(hfc)$_3$.

cases the reduction proceeds exclusively by the cyclic mechanism (Scheme I). In our experience, the bromo keto ester **19** is the only exception to this rule. It appears that the bromomethyl and ethyl carboxyl groups are comparable in size and the reagent has no preferred mode of approach.

We also explored some other α-keto esters such as 9-BBN ester and trimethylsilyl ester of pyruvic acid. Both of these compounds failed to undergo reduction. Similarly, the sodium salt of pyruvic acid failed to react with the neat reagent or its solution in diglyme. It appeared that the solubility could be a problem in this case, so we prepared lithium pyruvate and attempted its reduction in the presence of lithium cation specific crown ether–12-crown-4. In this case also, no reduction occurred. Similarly, pyruvic acid itself failed to react with Alpine-Borane.

Miscellaneous.[61] We also investigated the influence of some other electron-withdrawing substituents such as hydroxy (α-hydroxyacetone), acetoxy (α-acetoxyacetophenone), and formyl (phenyl glyoxal monohydrate) groups. All of these compounds proved completely inert to Alpine-Borane. Unlike the α-keto esters, the β-keto esters reacted slowly. Thus, the reduction of ethyl acetoacetate with a 100% excess of neat Alpine-Borane proceeded to completion in 3–5 days, and the corresponding hydroxy compound was obtained with 50.6% asymmetric induction (eq 19).

$$S, 50.6\% \text{ ee} \tag{19}$$
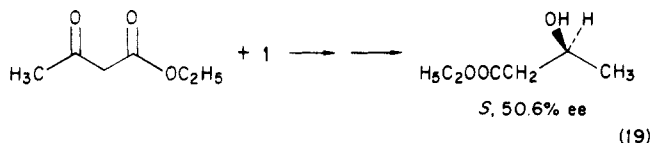
High Purity Alpine-Borane. As already mentioned, we prepared the Alpine-Borane used in these reductions from commercially available (+)-α-pinene. The relatively low enantiomeric purity (92% ee) of commercial α-pinene puts a limit on the asymmetric induction attainable in many carbonyl compound reductions. The research done on asymmetric hydroboration in our laboratory has made both (+)- and (−)-α-pinenes of optical purities approaching 100% ee readily available.[25] We carried out the reduction of α-bromoacetophenone with the Alpine-Borane derived

(25) Brown, H. C.; Yoon, N. M. *Isr. J. Chem.* **1977**, *15*, 12.

from both (+)- and (−)-α-pinenes of nearly 100% enantiomeric purity. The results showed that one can indeed extrapolate the results obtained with the 92% ee α-pinene to calculate the asymmetric induction that can be realized with reagent of 100% ee.

Conclusions

In conclusion, Alpine-Borane is an extremely versatile chiral reducing agent, capable of reducing a broad spectrum of prochiral carbonyl compounds with enantiomeric purities approaching 100% ee. With methods available to upgrade the enantiomeric purity of commercially available α-pinene, the reagent can be readily prepared in high purity in both the d and l forms. In general, the presence of the electron-withdrawing substituents has a beneficial effect on the rate of reduction and the asymmetric induction. Similarly, while lowering the reaction temperature enhances the asymmetric induction, increasing the temperature diminishes it. It is easy to predict the configuration of the products based on the model proposed. Finally, the discovery of the marked effect of high hydrostatic pressure on the enantiomeric purities achieved[19] should greatly extend the utility of the Midland reduction.

Experimental Section

General Methods. All glassware was dried at 140 °C overnight, assembled hot and cooled to room temperature in a stream of nitrogen. All reactions involving air-sensitive materials were carried out under a static pressure of nitrogen. The liquids were transferred with syringes or double-ended needles. ^{1}H NMR spectra were scanned on a Varian T-60 or a Perkin-Elmer R-32 or a Nicolet NT-470 spectrometer. ^{11}B and ^{13}C NMR spectra were obtained on a Varian FT-80Z spectrometer. [19]F spectral analysis of the MTPA estes was performed by using a Varian XL-200 spectrometer. IR measurements were conducted on a Perkin-Elmer 700 spectrophotometer or a Perkin-Elmer 1420 ratio recording spectrophotometer. GC analysis was done by using a Hewlett-Packard 5750 research chromatograph on a 6 ft × $^1/_4$ in. column or a Hewlett-Packard 5730A gas chromatograph using a 10-meter capillary column coated with SE-30. Peak areas were calculated by using a HP 3380S digital integrator. Optical rotations were measured on a Rudolph Polarimeter Autopol III.

Materials. 9-BBN and (+)-α-pinene were purchased from the Aldrich Chemical Company. Commercially available carbonyl compounds were used without further purification. 4-Methyl-1-pentyn-3-one was prepared from the corresponding, commer-

cially available alcohol by oxidation with Jones' reagent.[40] α-Iodoacetophenone was prepared from α-bromoacetophenone by exchange with sodium iodide.[47] α-Bromo-*p*-cyanoacetophenone was prepared from *p*-cyanoacetophenone by using the general method.[48] 1-Bromo-3-methyl-2-butanone was prepared by the "organic synthesis" procedure.[48] 3-Bromo-3-methyl-2-butanone was prepared by the bromination of 3-methyl-2-butanone with phenyltrimethylammonium perbromide in THF. Isopropyl pyruvate, methyl and ethyl 2-oxopentonates, and isopropyl benzoylformate were prepared from the corresponding acids[50,51] or their sodium salts[52] and respective alkyl iodides by adapting general procedures of esterification. *tert*-Butyl pyruvate and *tert*-butyl benzoylformate were prepared from the corresponding acid chlorides[53] according to the general procedure.[54] Anhydrous solvents were prepared as described elsewhere.[55]

Preparation of *B*-(3-Pinanyl)-9-borabicyclo[3.3.1]nonane (Alpine-Borane, 1). An oven-dried, 250-mL, round-bottomed flask equipped with a septum-capped side arm, magnetic stirring bar, and a stopcock adaptor was cooled to room temperature in a stream of nitrogen. The flask was charged with 125 g of solid 9-BBN (1 mol) and 175 mL (1.1 mol) of (+)-α-pinene ($[\alpha]^{22}_D$ +47.3° (neat), 92% ee, distilled from LiAlH$_4$) was added to the flask. The flask was heated in an oil bath to 65 °C for 5 h to complete the hydroboration. ^{11}B NMR (neat): +80 ppm. The reagent was transferred to a storage vial fitted with a Teflon stopcock. The reaction mixture has a density of 0.93 g/mL at 25 °C and is 95% in Alpine-Borane by weight.

Reduction of Carbonyl Compounds. General Procedure. An oven-dried, 50-mL, round-bottomed flask equipped with a septum-capped side arm, magnetic stirring bar, and a stopcock adaptor was cooled to room temperature in a stream of nitrogen. The flask was charged with 10 mmol of the carbonyl compound and 6 mL of Alpine-Borane (20 mmol) was injected into it. The

reaction was followed by either GC (see procedure for acetophenone) or ^{1}H NMR (see procedure for α-bromoacetophenone). On completion of the reaction, the flask was cooled to 0 °C, and 1 mL of acetaldehyde (preferably freshly distilled) was added to destroy the excess reagent. Liberated α-pinene was pumped off at 70 °C (0.01 mm) (1–2 h), and the residue was dissolved in 20 mL of anhydrous ether. The solution was cooled to 0 °C and 1.32 mL (22 mmol) of ethanolamine was added to remove the 9-BBN moiety. After 15 min, the flask was opened to atmosphere, and the 9-BBN–ethanolamine adduct was separated by filtration through a sintered glass funnel. The precipitate was washed twice with small amounts of cold ether. The combined filtrate and washings were washed twice with small amounts of brine and dried over sodium sulfate, and the ether was evaporated by using a rotary evaporator. The crude product so obtained was purified by distillation, bulb-to-bulb vacuum transfer, using a Kügelrohr oven or chromatography.

2-Butanone. 2-Butanone (7.2 g, 100 mmol) was reacted with 200 mmol (60 mL) of Alpine-Borane at 25 °C. Benzaldehyde was used to destroy excess reagent. The product was distilled, bp 101–103 °C. It was found to be contaminated with traces of α-pinene and was further purified by preparative GC (25 °C, SE-30): single peak by GC (6 ft × $^1/_4$ in., 10% Carbowax, 30° isothermal); $[\alpha]^{25}_D$ +5.4° (neat); 40% ee, *S*.

3-Methyl-2-butanone. The ketone (4.3 g, 50 mmol) was reacted with 100 mmol (30 mL) of neat 1 at 25 °C. The reaction was followed by ^{1}H NMR using benzene as the internal standard. After 2 weeks, the excess reagent was destroyed with acetaldehyde. Excess acetaldehyde and α-pinene were pumped off at 40 °C (0.01 mm). The residue was dissolved in ether and oxidized by the dropwise addition of 20 mL of 3 M NaOH and 10 mL of H$_2$O$_2$ at 0 °C. On completion of oxidation, the aqueous layer was extracted with ether, and the ether layer was washed with water and dried over K$_2$CO$_3$. The ether was carefully distilled by using a fractionating column and then the product was distilled: bp 110–112 °C (750 mm); yield, 3.4 g, 78%; single peak on GC (10% SE-30, 50–250 °C/10°/min); $[\alpha]^{25}_D$ +3.06° (neat); 57% ee, *S*.

3,3-Dimethyl-2-butanone. The ketone (10 g, 100 mmol) was reacted with 60 mL of 1 (200 mmol). The reaction was followed by ^{1}H NMR using benzene as internal standard. In 40 days only 70% reaction was complete. It was worked up at this stage by the standard method. The product was isolated by bulb-to-bulb distillation, found to be contaminated with some α-pinene, and was further purified by preparative GC (SE-30, 75 °C, isothermal): single peak on GC (10% carbowax 20M, 30–120 °C/10°/min); $[\alpha]^{25}_D$ +0.05° (neat); 0.6% ee, *S*.

2-Octanone. The ketone (1.28 g, 10 mmol) was treated with 6 mL of 1 (20 mmol) and worked up by the standard method. The product was isolated by bulb-to-bulb distillation (110 °C (20 mm)) [yield 0.88 g (69%)]; >98% pure by GC (Carbowax 20M, 50–200 °C/10°/min)] and further purified by preparative GC (10% Carbowax 20M, 110 °C, isothermal): $[\alpha]^{25}_D$ +4.12° (neat); 44% ee, *S*.

Acetophenone, at 25 °C. Acetophenone (1.2 g, 10 mmol) was treated with 6 mL of 1 (20 mmol). The reaction mixture was maintained at 25 °C by using a constant-temperature bath. *n*-Nonane (0.64 g, 5 mmol) was added as the GC internal standard. At regular intervals, aliquots were analyzed by GC using a 6 ft × $^1/_4$ in DC-710/Chromosorb W column. The injection port temperature was kept at 100 °C. Under analysis conditions, 50–150 °C/10°/min, 35 mL/min helium flow, the retention times of *n*-nonane, α-pinene, and acetophenone were 7.7 min, 9.8 min, and 15.3 min, respectively. On completion of the reaction, the product was isolated by the standard method. Evaporation of solvents gave 1.28 g of a liquid. It was found to be contaminated with some boronic impurity as seen by the flame test. It was distilled by using a Kügelrohr oven at 50 °C (0.01 mm): yield 0.84 g (68%). Distillation was deliberately interrupted to prevent the codistillation of boronic impurities toward the end: $[\alpha]^{25}_D$ -34.7° (*c* 5.19, methanol), -32.57° (neat); 76% ee. It was further purified by preparative GC (Carbowax 20M, 120 °C, isothermal): $[\alpha]^{25}_D$ -35.6° (*c* 5.19, methanol), -33.4 (neat); 78% ee, *S*.

At 45 °C. The above reaction was repeated at 45 ± 0.5°. The temperature was maintained by using a thermowatch; ~95% reaction was over in 48 h. It was worked up as usual after another 24 h. The product was purified as above: yield 1.04 g (85%); $[\alpha]^{25}_D$

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−28.6° (*c* 5, methanol), −26.96° (neat); 62.9% ee, *S*.

3-Buten-2-one. The ketone (2.8 g, 3 mL, 40 mmol) was treated with 16 mL of 1 (56 mmol) at 25 °C. The reaction was followed by ^{1}H NMR using benzene as the internal standard. It was worked up by the standard method. The product was isolated by bulb-to-bulb distillation (after removal of the ether using a fractionating column (loss of product ocurred at this stage.) [yield 750 mg (90% pure)] and was further purified by preparative GC (20% SE-30, 35 °C, isothermal): $[\alpha]^{25}_D$ +17.8° (neat); 52% ee, *S*; ^{1}H NMR analysis using 24 mg of the alcohol and 0.45 mL of Eu(hfc)₃ reagent (0.33 g/mL in CCl₄) showed the two enantiomers in 80:20 ratio.

1-Acetyl-1-cyclohexene. The ketone (1.24 g, 10 mmol) was treated with 4.2 mL (14 mmol) of 1. The product was isolated by bulb-to-bulb distillation (1.1 g, 80%) and was further purified by preparative GC (20% SE-30, 120 °C, isothermal): $[\alpha]^{25}_D$ −7.47° (*c* 4.15, CHCl₃); 59% ee, *S*.

3-Methyl-2-cyclohexenone. The ketone (2.2 g, 2.26 mL, 20 mmol) was treated with 8.4 mL of 1 and worked up after 14 days by the standard method. The product was isolated by bulk-to-bulb distillation [yield 2.8 g (55% pure by GC)] and was further purified by preparative GC (20% SE-30, 90 °C, isothermal): $[\alpha]^{25}_D$ −13.1° (CHCl₃, *c* 5); 9.6% ee, *S*; ^{1}H NMR analysis using Eu(hfc)₃ showed the ratio of enantiomers to be 59:41, i.e., 18% ee.

***trans*-4-Phenyl-3-buten-2-one (6).** The ketone (0.73 g, 5 mmol) was treated with 2.1 mL of 1. The ketone was insoluble in the reagent, but a homogeneous solution resulted as the reaction progressed. The product was isolated by the alkaline hydrogen peroxide oxidation and followed by bulb-to-bulb distillation: yield 0.73 g (~85% pure by GC (10% Carbowax 20M, 100–200 °C/10°/min)). It was further purified by medium pressure liquid chromatography (MPLC) using E. Merck Lobar column (Lichroprep Si 60, 60–125 μm). Cyclohexane–ethyl acetate (80/20) was used as eluent. A small amount of dehydration occurred during chromatography. The diene so formed was pumped off at 0.01 mm and pure compound was obtained: $[\alpha]^{25}_D$ −22.3° (*c* 5.2, CHCl₃); 89% ee, *S*.

3-Butyn-2-one. The ketone (1.7 g, 25 mmol) was treated with 10.5 mL of 1 (35 mmol). The reagent was added dropwise to control the exothermic reaction and the temperature was maintained at 25 °C by using a water bath. The reaction mixture acquired a deep yellow-orange color and oily globules separated out (presumably the complex). It became homogeneous within 15 min and the reduction was complete within 4 h, as evidenced by the disappearance of the CH₃ signal in the ^{1}H NMR. It was worked up as usual, and the product was isolated by distillation [yield 1.4 g (80%)] and further purified by preparative GC (10% Carbowax 20M, 65 °C, isothermal): $[\alpha]^{25}_D$ +37.7° (*c* 2.3, dioxane); 73% ee.

The reaction was repeated with 2.04 g of the ketone (30 mmol) and 7.5 mL of 1 (25 mmol). The reaction was slower in this case and took between 12 and 18 h for completion. The optical rotation was the same.

4-Methyl-1-pentyn-3-one. The ketone (0.96 g, 10 mmol) was treated dropwise with 4.2 mL of 1 (14 mmol). The reaction was rapid and was almost complete in 2 h. However, it was continued for 2 h more before working up. After pumping off α-pinene, hexadecane was added (GC standard), and the reaction worked up by oxidation with alkaline hydrogen peroxide. GC analysis of the organic layer gave the yield of the product as 87%. The product was isolated by bulb-to-bulb distillation (pot temperature 90 °C (110 mm)) and further purified by preparative GC (10% Carbowax 20M, 70 °C, isothermal): $[\alpha]^{25}_D$ +14.57 ± 0.04° (*c* 2, dioxane); 91% ee.

4-Phenyl-3-butyn-2-one (7). The ketone (3.6 g, 25 mmol) was treated with 10.5 mL of 1 (35 mmol). The reaction was followed by GC. It was complete in 8–12 h. It was worked up by the standard method. The product was isolated by bulb-to-bulb distillation (pot temperature 100 °C (0.01 mm)): yield 3.33 g (98% pure by GC (10% Carbowax 20M, 100–180 °C/10°/min)). Further purification was by chromatography on silica gel, 60–80 mesh, using pentane–ether (95/5) as eluent. Chromatography caused a small amount of dehydration. The enyne so formed was pumped off at 0.01 mm and the product was distilled to get 100% pure material: α^{25}_D +70.3° (neat): $[\alpha]^{25}_D$ +30.64° (*c* 5.15, ethanol).

α-Chloroacetophenone. The ketone (3.1 g, 20 mmol) was treated with 12 mL of 1 (40 mmol). The ketone was partially soluble in the reagent. However, as the reaction progressed, a homogeneous solution resulted (in about 3 days). The reaction was followed by monitoring the disappearance of -C(O)CH₂Cl protons (s, δ 4.5) and the appearance of α-pinene (δ 5–5.3) as well as BOCHCH₂Cl protons (d, δ 3.5). After 6 days, the excess reagent was destroyed by the addition of freshly distilled acetaldehyde and worked up by the standard ethanolamine method. The weight of crude product was 2.83 g (contaminated with traces of boronic impurities). Further purification was by MPLC using cyclohexane/ethyl acetate (90/10) as eluent: yield 2.75 g; ^{1}H NMR (CCl₄) δ 2.8 (br, 1 H, exchangeable with D₂O), 3.4–3.7 (complex, 2 H), 4.8 (br, 1 H); $[\alpha]^{25}_D$ −42.3° (*c* 2.8, cyclohexane); 88.5% ee, *R*.

α-Bromoacetophenone (8). The ketone (1.99 g, 10 mmol) was treated with 6 mL (20 mmol) of 1. The ketone was partially miscible with the reagent. A homogeneous solution resulted in 2 days with the progress of reaction. The reduction was followed by monitoring the disappearance of -C(O)CH₂Br protons (δ 4.2) and the appearance of α-pinene (δ 5–5.3) as well as BOCHCH₂Br protons (d, δ 3.5). After 4 days, acetaldehyde was added to destroy the excess reagent and worked up by the standard ethanol amine procedure. The product was isolated by bulb-to-bulb distillation (pot temperature 100 °C (0.01 mm)): yield 1.9 g (94.5%); GC analysis showed it to be >96% pure; ^{1}H NMR (CCl₄) δ 3.1–3.6 (complex, 3 H; one proton exchanges with D₂O), 4.6–4.9 (dd, 1 H), 7.1 (br, 5 H). Further purification was by MPLC using cyclohexane–ethyl acetate (90/10) as eluent and then distillation: $[\alpha]^{25}_D$ −33.54° (*c* 5, CHCl₃); 86% ee, *R*.[56]

A well-stirred solution of 1 g of the bromohydrin in 10 mL of 50:50 pentane/ether was treated with 2 mL of 3 M NaOH. After 15 min (GC showed complete conversion to styrene oxide), the organic layer was separated and dried over Na₂SO₄, and the solvents were removed by using a rotary evaporator. Distillation gave 0.595 g of styrene oxide: ~100% pure by GC (10% Carbowax 20M, 80–200 °C/10°/min). On attempted further purification (to remove trace impurities) by preparative GC on either 10% Carbowax 20M on Chromosorb W-AW-DMCS (60–80 mesh) or 20% SE-30 on the same solid support at 100 °C column temperature, the styrene oxide underwent rearrangement to C₆H₅CH₂CHO (70–80% conversion, ~15 min elution time). The styrene oxide was purified by MPLC using cyclohexane–ethyl acetate (95/5) as eluent: $[\alpha]^{25}_D$ +40.2° (*c* 1.05, benzene); 86% ee, *R*.[35]

The bromohydrin (2 g, 10 mmol) was dissolved in 10 mL of anhydrous THF and treated dropwise with 22 mL of a 1 M solution of lithium triethylborohydride in THF.[11] The mixture was stirred at room temperature overnight and then oxidized with alkaline hydrogen peroxide. The alcohol was isolated by ethereal extraction and purified by MPLC using cyclohexane–ethyl acetate (90/10) as eluent. $[\alpha]^{25}_D$ −36.3° (neat); 85% ee, *S*.[31]

α-Iodoacetophenone. The ketone 3.69 g, 15 mmol) was reacted with 9 mL of 1 (30 mmol). The ketone was more soluble than the previous two ketones, and a homogeneous solution resulted in a few hours. After 2 days, acetaldehyde was added, the reaction was worked up by the standard procedure, and the product was isolated by bulb-to-bulb distillation. The product was contaminated by 20–25% of acetophenone and 1-phenylethanol. The iodohydrin decomposed on preparative GC column. Since the iodohydrin did not appear to be very stable, its optical purity was determined by conversion to styrene oxide: $[\alpha]^{23}_D$ +41° (*c* 1.05, benzene); 86% ee, *R*.

α,p-Dibromoacetophenone. The ketone (5.56 g, 20 mmol) was treated with 12 mL of 1 (40 mmol). Most of the ketone remained undissolved in the reagent, and even after 8 days, no clear solution resulted. Five milliliters of THF were added at this stage to partially dissolve the ketone. The reaction then proceeded readily and went to completion in 2 days. Excess reagent was destroyed by the addition of acetaldehyde and worked up as usual. Distillation gave 5.3 g of the bromohydrin: ^{1}H NMR (CDCl₃) δ 2.87 (s, 1 H, exchange with D₂O), 3.3–3.5 (complex, 2 H), 4.67–4.97 (dd, 1 H), 7.33 (q, *J* = 9 Hz, 4 H).

The bromohydrin (56 mg, 0.2 mmol) was converted to its MTPA ester by the literature method.[57] ^{19}F NMR of the esters

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on a Varian XL-200 NMR spectrometer showed two peaks in the ratio 94:6. The peaks were not well resolved in CDCl$_3$. A small amount of trifluoroacetic acid was added to resolve the signals. A blank experiment conducted with *d,l*-bromohydrin (prepared by the reduction of *a,p*-dibromoacetophenone with BH$_3$·SMe$_2$) gave the same two signals in a 50:50 ratio.

α-Bromo-*p*-cyanoacetophenone. The ketone (1.13 g, 5 mmol) was treated with 3 mL of 1 (10 mmol) and 1 mL of THF. After 2 days the solution was worked up as usual and the compound was isolated by bulb-to-bulb distillation (pot temperature 100 °C (0.01 mm)): yield 0.68 g (60%); ^{1}H NMR (CDCl$_3$) δ 3.2 (br, 1 H, exchanges with D$_2$O), 3.4–3.7 (complex, 2 H), 4.8–5.2 (dd, 1 H), 7.6 (q, 4 H); IR (thin film) 3475 cm^{-1}, 2250 (C≡N). It was further purified by MPLC using cyclohexane–ethyl acetate (50/50), converted to MTPA ester, and analyzed by ^{19}F NMR: 88% ee.

α-Bromo-2′-acetonaphthone. The ketone (3.74 g, 15 mmol) and 9 mL of the reagent were reacted in 3 mL of THF, and the solution was worked up as usual: yield 4 g (contained small amounts of boronic impurities). A small amount of the compound was purified by crystallization from hexane/ether: mp 88–90 °C; ^{1}H NMR (CDCl$_3$) δ 2.7 (s, 1 H, exchanges with D$_2$O), 3.5–3.8 (complex, 2 H), 4.95–5.20 (dd, 1 H), 7.3–8.0 (complex, 7 H); [α]^{23}$_D$ −25.6° (*c* 4, ethanol).

To determine optical purity, the bromohydrin was debrominated with LiAlH$_4$. The alcohol so obtained was purified by MPLC and crystallization: [α]^{23}$_D$ −34.85° (*c* 5, ethanol). Three different crops gave values differing by <2%.

α,α,α-Trifluoroacetophenone. The ketone (3.48 g, 2.8 mL, 20 mmol) were treated with 12 mL of 1 (40 mmol) and worked up after 45 days when ^{1}H NMR showed ~90% completion of reaction. Bulb-to-bulb distillation gave 2 g of the product (57%). Further purification was by preparative GC (Carbowax 20M, 160 °C, isothermal: [α]^{23}$_D$ −4.8° (*c* 15.3, benzene); 32% ee, *R*.

1-Bromo-3-methyl-2-butanone (10). The ketone (5.062 g, 30 mmol, 96% isomerically pure) was reacted with 20 mL of 1 (60 mmol) and worked up after 14 days by the standard method. Distillation gave 3.0 g of the bromohydrin. Some decomposition of the material occurred during distillation. The compound was further purified by preparative GC (10% SE-30, 80 °C, isothermal): ^{1}H NMR (CDCl$_3$) δ 0.92 (d, *g* = 3 Hz, 3 H), 1.03 (d, *J* = 3 Hz, 3 H), 1.7–2.0 (complex, 1 H), 2.17 (s, 1 H, exchanges with D$_2$O), 3.4–3.8 (complex, 3 H); [α]^{23}$_D$ −2.15° (*c* 2, cyclohexane).

The optical purity was determined by ^{19}F NMR analysis of the MTPA esters: 61% ee.

Configuration was determined by conversion to (*S*)-(+)-3-methyl-2-butanol by reduction with LiAlH$_4$. Hence, the configuration of the bromohydrin is *R*.

Methyl Pyruvate (14, R = CH$_3$). The keto ester (1.84 g) was treated dropwise with 7.5 mL (25 mmol) of 1. A deep yellow colored layer separated immediately (presumably the complex). After 2 h at 25 °C, the reaction mixture became homogeneous, but the reaction took 2 h more for completion, [yield 1.2 g (64%)]. Further purification was by preparative GC (10% SE-30, 70 °C, isothermal): [α]^{25}$_D$ −7.160° (neat); 78.9% ee, *S*.

Ethyl Pyruvate (14, R = C$_2$H$_5$), at 25 °C. The keto ester (2.9 g, 25 mmol) was treated dropwise with 10 mL of 1 (33 mmol) at 25 °C. After 4 h, acetaldehyde (freshly distilled) was added to destroy excess reagent and the solution was worked up by the ethanolamine procedure. The ether extract was not washed with water. Distillation, after careful removal of ether, gave ethyl lactate: yield 2.39 g (81%). Further purification was by preparative GC (10% Carbowax 20M, 80 °C, isothermal): [α]^{23}$_D$ −8.83° (neat); 76% ee, *S*.

At 0 °C. The reaction was repeated at 0 °C. The ethyl lactate obtained in this case had [α]^{23}$_D$ −9.43° (neat), 82% ee, *S*.

Using Excess Keto Ester. The keto ester (2.9 g), was treated at 25 °C with 6 mL (20 mmol) of 1. The reduction was slower in this case and took 18–24 h for completion. On completion of reduction, excess keto ester and α-pinene were pumped off and the product was worked up by the ethanolamine procedure: [α]^{23}$_D$ −8.83° (neat); 76% ee, *S*.

Isopropyl Pyruvate (14, R = *i*-C$_3$H$_7$). The keto ester (1.3 g, 10 mmol) was treated with 4.2 mL of 1 (14 mmol). No complex separated from the mixture. The reduction was complete in 4 h and the solution was worked up by the standard method (no water wash). The product was isolated by bulb-to-bulb distillation:

yield 0.820 g (62%). Further purification was by GC (10% Carbowax 20M, 75 °C, isothermal): [α]^{23}$_D$ −8.664° (neat). Optical purity was determined by the ^{19}F NMR analysis of MTPA esters, 72% ee.

tert-Butyl Pyruvate (14, R = *t*-C$_4$H$_9$), at 25 °C. *tert*-Butyl pyruvate (1.44 g) was treated with 4.2 mL of 1 (14 mmol). The reaction was complete in 4–5 h and the solution was worked up as usual (the ether extract was not washed with water). The ether was removed by careful distillation. The product was isolated by bulb-to-bulb distillation (pot temperature 100 °C (20 mm)): yield of *tert*-butyl lactate, 1.43 g (98%). GC analysis on 10% Carbowax 20M, 80–200 °C/10°/min showed it to be ~98% pure. Further purification was by preparative GC (10% Carbowax 20M, 85 °C, isothermal). The compound was obtained as a low melting solid: ^{1}H NMR (CDCl$_3$) δ 1.37 (d, *J* = 7 Hz, 3 H), 1.48 (s, 9 H), 2.3 (br, 1 H, exchanges with D$_2$O), 4.12 (q, *J* = 7 H, 1 H); [α]^{23}$_D$ −8.08° (neat); 85.3% ee, *S*. (Density was calculated to be 0.9110 at 23 °C based on the following values: 16.1 °C, 0.9170; 20 °C, 0.9139; 25 °C, 0.9090; 45 °C, 0.8899);^{34} [α]^{23}$_D$ −4.92° (*c* 5.04, CCl$_4$).

At 0 °C: yield 1.43 g (98%); [α]^{23}$_D$ −8.774° ± 0.003° (neat); 92.5% ee; [α]^{23}$_D$ −5.377 ± 0.003° (*c* 5.04, CCl$_4$).

Reduction of *tert*-butyl 2-oxobutyrate, *tert*-butyl 2-oxopentanoate, and *tert*-butyl 4-methyl-2-oxopentanonate was carried out following the general procedure described under *tert*-butyl pyruvate.

Methyl Benzoylformate (17, R = CH$_3$). The keto ester (1.64 g, 10 mmol) was treated with 4.2 mL of 1 (14 mmol) and worked up after 24 h by the standard method. The yield of the crude product was 1.6 g, contaminated with traces of boronic impurities. It was distilled by using a short-path distillation assembly: yield 1.25 g; bp 58 °C (0.01 mm). (The distillation was deliberately interrupted to prevent the contamination of the product by boronic impurities which would have prevented the purification of the product by preparative GC.) GC analysis on 10% SE-30, 100-250 °C/10°/min showed it to be ~99% pure. Further purification was by preparative GC (10% SE-30, 140 °C, isothermal): [α]^{23}$_D$ −144.9° (*c* 0.7, CHCl$_3$); 83% ee, *R*.

The reaction was repeated and this time the product was purified by MPLC using cyclohexane–ethyl acetate (80/20) as eluent: yield 82%; [α]^{23}$_D$ −143.6° (*c* 0.7, CHCl$_3$); 82.7% ee. This experiment was conducted to verify that no racemization had occurred in the previous experiment during distillation or preparative GC. (It is reported in the literature that at high temperature mandelic esters undergo racemization.)

Isopropyl Benzoylformate (17, R = *i*-C$_3$H$_7$). The keto ester (3.84 g, 20 mmol) was treated with 9 mL (30 mmol) of 1. The reaction was about 90% complete in 24 h. It was worked up after 48 h by the standard method. The yield of crude isopropyl mandelate was 4.0 g. It was purified by MPLC using cyclohexane–ethyl acetate (80/20): yield 3.45 g (89%); [α]^{23}$_D$ −98.9° (*c* 1, CHCl$_3$).

Isopropyl mandelate (0.97 g, 5 mmol) was reduced with excess LiBH$_4$^{58} in ether to styrene glycol. The diol was recrystallized from ethyl acetate and sublimed: mp 65–67 °C [lit. mp 69–70 °C]; [α]^{27}$_D$ −38.6° (*c* 1.22, 95% ethanol); 96% ee, *R*. The mother liquor was evaporated and sublimed: [α]^{27}$_D$ −32.9° (*c* 1, 95% ethanol); 81.7% ee, *R*.

Isopropyl mandelate (0.97 g) was reduced with LiBH$_4$. The diol was purified by MPLC using ethyl acetate as eluent: single peak on GC (10% SE-30, 70–210 °C/10°/min); mp 60–64 °C; [α]^{27}$_D$ −34.55° (*c* 1.16, 95% ethanol); 86% ee.

Isopropyl mandelate was converted to its MTPA ester and analyzed by ^{19}F NMR, 88% ee.

tert-Butyl Benzoylformate (17, R = *t*-C$_4$H$_9$). The keto ester (2.06 g, 10 mmol) was treated with 4.2 mL of 1 (14 mmol) and worked up after 48 h by the standard method. The product was purified by MPLC using cyclohexane–ethyl acetate (80/20) as eluent and sublimed: yield of *tert*-butyl mandelate, 85%; mp 73–75 °C [lit. mp 65 °C; lit. mp 66–67 °C for racemic compound]; ^{1}H NMR (CDCl$_3$) δ 1.4 (s, 9 H), 3.5 (br, 1 H, exchanges with D$_2$O), 5.0 (br, 1 H), 7.3 (br, 5 H); [α]^{27}$_D$ −119.1° (*c* 1.05, CCl$_4$); *R*.

The hydroxy ester was converted to styrene glycol and purified by sublimation in 89% yield by LiBH$_4$ reduction:^{58} [α]^{27}$_D$ −37.1°

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(c 1.2, 95% ethanol); 92.3% ee, R.

The hydroxy ester was converted to its MTPA ester and analyzed by ^{19}F NMR; 92% ee.

Ethyl α-Bromopyruvate (19). The keto ester (8.99 g, 46 mmol) was reduced with 12 mL of 1 (40 mmol). The reaction was very vigorous and had to be controlled by dropwise addition of the reagent at 0 °C. After 0.5 h, α-pinene was pumped off, and the product was isolated by the addition of ethanolamine. The product was readily purified by passing it through a short column of alumina using ether as eluent: yield 9.94 g. Further purification was by distillation (pot temperature 80 °C (0.01 mm)) and preparative GC (20% SE-30, 125 °C, isothermal): $[\alpha]^{23}_D$ -6.13° (c 2.4, CCl$_4$); ^{1}H NMR (CDCl$_3$) δ 1.33 (t, J = 7 Hz, 3 H), 3.3 (b, 1 H, exchanges with D$_2$O), 3.71 (d, J = 4 Hz, 2 H), 4.33 (q, J = 7 Hz, 2 H), 4.5 (t, J = 4 Hz, 1 H).

The bromohydrin was converted to its MTPA ester and analyzed by ^{19}F NMR which gave 7.6% ee.

The above reduction was repeated at -78 °C in ~1 M solution of the keto ester in THR. After 18 h at -78 °C, the reaction mixture was warmed up slowly to 25 °C and worked up by the standard method. The product was purified by preparative GC: $[\alpha]^{25}_D$ -5.44° (c 2.5, CCl$_4$).

Ethyl Acetoacetate. The keto ester (1.3 g, 10 mmol) was treated with 6 mL of 1 (20 mmol). Initially, an insoluble layer separated (presumably the complex). The reaction mixture became homogeneous in 24 h and the reaction was complete in 48 h. The solution was worked up by the standard method. The product was isolated by bulb-to-bulb distillation: yield 0.650 g (45%); GC showed it to be ~96% pure. Further purification was by preparative GC (10% Carbowax 20M, 110 °C, isothermal): $[\alpha]^{25}_D$ +21.1° (c 1, CHCl$_3$); 50.6% ee, S.[59]

Synthesis of Ubine (12). The bromohydrin (1.0 g) was converted to styrene oxide as described earlier. The styrene oxide (0.6 g) was mixed in a stainless steel bomb with 6 g of dimethylamine and heated to 55 °C. The reaction was complete in 4 h. Dimethylamine was evaporated and the product was

isolated by bulb-to-bulb distillation (pot temperature 65 °C (0.01 mm)): yield of amino alcohol, 0.78 g (95%); ^{1}H NMR (CDCl$_3$) δ 2-2.4 (complex with a superimposed singlet at 2.3, 8 H), 4.0 (br, 1 H, exchanges with D$_2$O), 4.57-4.81 (dd, 1 H), 7.3 (bs, 5 H); ^{13}C NMR (CDCl$_3$) off-resonance δ 44.75 (q, NCH$_3$), 67.45 (t, -CH$_2$N-), 69.34 (d, CHOH), 124.62 (d), 126.49 (d), 128.19 (d), 142.62 (s); capillary GC (10-m SE-30, 80–260 °C/8°/min/6 min PID) showed it to be a mixture of two isomers, 97.5:2.5.

The compound was dissolved in ether and treated with an equivalent amount of ethereal hydrochloric acid. The mixture was cooled to 0 °C and filtered. The amine·HCl so obtained was dissolved in a minimum quantity of ethanol and ether was added until a turbidity appeared. It was cooled to -18 °C and filtered and dried: mp 114-116 °C [lit. mp 147-148.5 °C for racemic compound,[23] 113.5° for R];[59] $[\alpha]^{23}_D$ -70.2° (c 0.935, ethanol); 88.9% ee, R; based on $[\alpha]^{23.5}_D$ -78.9° (c 0.935, ethanol)].[60] The salt was suspended in ether and decomposed by the addition of aqueous potassium carbonate (or sodium hydroxide) until pH 10. The aqueous layer was extracted with ether twice and ether evaporated to obtain the amino alcohol: 100% pure by capillary GC; overall yield 87%.

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(61) Originally, we also examined the reduction of acyl cyanides. However, we learned from Professor M. M. Midland that he and his co-workers has also noted the facile reduction of keto esters and acyl cyanides. To minimize the overlap, it was decided that we should explore the keto esters and Midland and his co-workers would explore the acyl cyanides.

Electroreductive Dehalogenation of Fluorobenzenes

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The electroreduction of 1,3-difluorobenzene and fluorobenzene on mercury cathodes in diglyme was investigated. In preparative experiments using tetrabutylammonium tetrafluoroborate as the electrolyte, fluorobenzene formed benzene and 1,3-difluorobenzene formed a mixture of fluorobenzene and benzene. When dimethylpyrrolidinium (DMP$^+$) tetrafluoroborate was used, benzene was obtained from fluorobenzene but the electrode potential was less negative. In the reduction of 1,3-difluorobenzene, a similar effect of DMP$^+$ on the potential was observed. In addition, conditions were found for selective defluorination to fluorobenzene. Results from preparative experiments—products and reaction potentials—and cyclic voltammetry indicate that reductive defluorination in the presence of DMP$^+$ is catalytic and mercury from the electrode seems to be involved. A possible mechanism is discussed.

We are interested in preparatively useful electrochemical reactions which occur at very negative potentials. Such reactions are not easily performed by any method and we believe the electrochemical approach can give high yields and selectivity. Defluorination is one reaction of this type.

Studies of electrochemical and other reductions of simple fluoroaromatic compounds are rare. One polarographic study[1] of polyfluorobenzenes in DMF did find evidence

for fluorine loss from pentafluorobenzene, but no study of less highly fluorinated aromatics was reported. Electrochemical hydrogenation[2] of fluorobenzene on a platinum black electrode gave equal amounts of benzene and cyclohexane. Alkali-metal-promoted S$_{RN}$1 reactions have shown that fluorine can be substituted by a nucleophile.[3] This process presumably involves C–F bond cleavage of

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(2) Langer, S. H.; Yurchak, S. *J. Electrochem. Soc.* **1969,** *116,* 1228.
(3) Bunnett, J. F. *Acc. Chem. Res.* **1978,** *11,* 413.