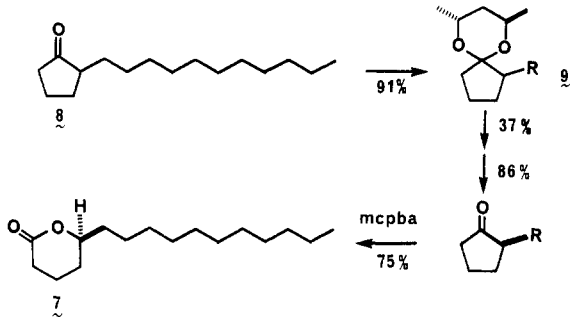
Scheme III



duced ether **5** (49%) was obtained in 90% diastereomeric purity by GC analysis.[11,12] Furthermore, pure **5** was readily prepared by terminating the reaction at 30% completion (−20 °C, 3 h). Oxidation followed by basic treatment[4] of **5** gave (+)-(1*S*,2*R*)-2-methylcyclohexanol (**6**),[13] $[\alpha]^{24}_D$ +20.3° (*c* 3.21, ethanol),[14] in 74% yield with >99% de and 98% ee.[15]

The generality of the reaction is apparent from the results summarized in Table I.

The efficiency of our new method is highlighted by a rapid and convenient synthesis of (−)-(*S*)-5-hexadecanolide (**7**), pheromone of *Vespa orientalis*.[16] The sequence of the reactions utilized is outlined in Scheme III. Acetalization of the readily available ketone **8**[17] with (−)-(2*R*,4*R*)-2,4-pentanediol gave diastereomers **9**. Treatment of **9** with 1.5 equiv of DIBAH at 0 °C for 30 min gave, after chromatographic purification, optically pure acetal (2*R*,4*R*,7*S*)-**9** in 37% yield with 97% de. Mild hydrolysis in 0.1 N HCl–acetone furnished pure (*S*)-**8** in 86% yield: $[\alpha]^{24}_D$ +81.0° (*c* 1.04, ether). Baeyer–Villiger oxidation of (*S*)-**8** with *m*-chloroperbenzoic acid in chloroform at 25 °C for 24 h yielded the lactone **7**[18] in 75% yield: $[\alpha]^{24}_D$ −38.3° (*c* 1.17, THF).[16e]

As implied above, the process is remarkably general and should in many cases provide a practical, if not unique, route to optically pure ketones. Another noteworthy aspect of this approach to chiral material is that the enol ether itself may provide a point of departure for further transformations.

Registry No. **1**, 5422-00-4; **2**, 99299-19-1; **3** (isomer 1), 99299-20-4; **3** (isomer 2), 99341-26-1; **4**, 99299-21-5; **5** (isomer 1), 99299-22-6; **5** (isomer 2), 99341-27-2; **5** (isomer 3), 99341-28-3; **6**, 15963-35-6; **7**, 59812-97-4; **8**, 99299-27-1; (*S*)-**8**, 99341-36-3; **9** (isomer 1), 99299-28-2; **9** (isomer 2), 99341-35-2; $(CH_2)_5CHO(CH_2)_2OH$, 1817-88-5; (±)-2-methylcyclohexanone, 24965-84-2; (−)-(2*R*,4*R*)-2,4-pentanediol, 42075-32-1; 2-allylcyclohexanone acetal (isomer 1), 99299-23-7; 2-allylcyclohexanone acetal (isomer 2), 99341-29-4; 2-allylcyclohexanone enol ether, 99299-24-8; 2-cyclohexylcyclohexanone acetal (isomer 1), 99299-25-9; 2-cyclohexylcyclohexanone acetal (isomer 2), 99341-30-7; 3-methylcyclohexanone acetal (isomer 1), 96249-24-0; 3-methylcyclohexanone acetal (isomer 2), 99341-31-8; 3,3,5-trimethylcyclohexanone acetal (isomer 1), 99341-32-9; 3,3,5-trimethylcyclohexanone acetal (isomer 2), 99341-33-0; 2-methylcycloheptanone acetal (isomer 1), 99299-26-0; 2-methylcycloheptanone acetal (isomer 2), 99341-34-1; 2-propylcyclohexanone acetal (isomer 1), 99299-29-3; bicyclo[3.3.0]octan-2-one acetal (isomer 1), 99299-30-6; bicyclo[3.3.0]octan-2-one acetal (isomer 2), 99341-37-4; cyclohexanone ethylene acetal, 177-10-6; (*R*)-2-methylcyclohexanone, 22554-29-6; (*S*)-2-methylcyclohexanone, 22554-27-4; cyclohexanone, 108-94-1; 2-allylcyclohexanone, 94-66-6; 2-cyclohexylcyclohexanone, 90-42-6; 3-methylcyclohexanone, 591-24-2; 3,3,5-trimethylcyclohexanone, 873-94-9; 2-methylcycloheptanone, 932-56-9; *cis*-bicyclo[3.3.0]octan-2-one, 32405-37-1.

Supplementary Material Available: Experimental Section (7 pages). Ordering information is given on any current masthead page.

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(11) 1*R*,2*R*:1*R*,2*S*:1*S*,2*R*:1*S*,2*S* = 0.7:3.0:89.6:6.7 by GC analysis.
(12) The recovered acetal was further reduced with excess DIBAH (5 equiv) at 25 °C for 6 h to give the cleavage product in 83% yield with low diastereoselectivity: 1*R*,2*R*:1*R*,2*S*:1*S*,2*R*:1*S*,2*S* = 0:64:0:36.
(13) The cis:trans ratio was >99:1 by GC analysis.
(14) Lit. $[\alpha]^{25}_D$ +15.7° (*c* 3.4, EtOH): Jones, J. R.; Takemura, T. *Can. J. Chem.* **1982**, *60*, 2950.
(15) Optical purity was determined by GC analysis of the (+)-MTPA ester.
(16) (a) Ikan, R.; Gottlieb, R.; Bergmann, E. D; Ishay, J. *J. Insect Physiol.* **1969**, *15*, 1709. For the synthesis of **7**: (b) Coke, J. L.; Richon, A. B. *J. Org. Chem.* **1976**, *41*, 3516. (c) Pirkle, W. H.; Adams, P. E. *Ibid.* **1979**, *44*, 2169. Solladié, G.; Moghadam, F. M. *Ibid.* **1982**, *47*, 91. (e) Servi, S. *Tetrahedron Lett.* **1983**, *24*, 2023. (f) Fujisawa, T.; Itoh, T. Nakai, M.; Sato, T. *Ibid.* **1985**, *26*, 771.
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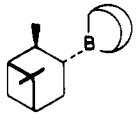
(18) Identical in all respects with the reported data.[16]

Diisopinocampheylchloroborane, a Remarkably Efficient Chiral Reducing Agent for Aromatic Prochiral Ketones

Summary: Diisopinocampheylchloroborane, readily prepared in high chemical and optical purities (99% ee) from (+)-α-pinene (92% ee) via hydroboration, followed by treatment with dry hydrogen chloride in ether, reduces ketones at convenient rates at −25 °C. The chiral induction is excellent for the reduction of aromatic prochiral ketones.

Sir: Optically active secondary alcohols are important starting materials for chiral syntheses.[1] Their synthesis by the reduction of prochiral ketones with chiral reducing agents has been actively pursued in recent years by organic chemists. Many interesting reagents have been developed, some of them achieving remarkable success.[2] For example, Noyori's Binal-H reduces several classes of prochiral ketones with high chiral induction.[3]

Trialkylboranes and borohydrides have also been applied as chiral reducing agents.[4] Of these, the Midland reagent, *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane (**1**) (Aldrich, *R*-Alpine-Borane) prepared from (+)-α-pinene has



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emerged as a very useful chiral reducing agent.[5] Midland and his co-workers initially reported that **1** reduces 1-deuterioaldehydes and α,β-acetylinic ketones in tetrahydrofuran (THF) at room temperature with excellent

(1) For a recent application, see: Rosen, T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 3731.
(2) "Asymmetric Synthesis", Vol. 2; Morrison, J. D., Ed., Academic Press: New York, 1983; Chapters 2, 3, and 4.
(3) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709, 6717.
(4) Reference 3, Chapter 2.
(5) (a) Midland, M. M.; Tramontano, A.; Zderic, S. A. *J. Organomet. Chem.* **1978**, *156*, 203. (b) The other isomer, *S*-Alpine-Borane, is obtained from (−)-α-pinene.

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Table I. A Comparison of Chiral Induction Obtained by Various Reagents in the Reduction of Representative Prochiral Ketones

ketone	% ee				
	Ipc_2BCl −25 °C	Alpine-Borane[a] 25 °C	Alpine-Borane[b] (high pressure)	Binal-H[c] −100 °C	NB-Enantride[d] −100 °C
2-butanone	4	43	(63)[e]	(24)[e]	76
3-methyl-2-butanone	32	62	90	*f*	68
3,3-dimethyl-2-butanone	95[g]	0.6		*h*	2
acetophenone	98	85	100	95	70

[a] From ref 8. [b] From ref 9. [c] From ref 3. [d] From ref 11. [e] Value for 2-octanone. [f] Data not available. [g] At room temperature. [h] Inert to the reagent.

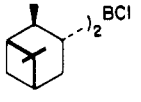
Table II. Chiral Reduction of Representative Aromatic Ketones with 2 in THF at −25 °C and a Comparison with Other Reagents

ketone	reactn time, h	isolated yield, %	$[\alpha]^{20}_D$, deg	% ee[a]	% ee by 1		% ee by Binal-H[d]
					neat conditn[b]	high pressure[c]	
acetophenone	7	72	−42.6	98[e] (97.4)[f]	85	100	95
2′-acetonaphthone	7	90	−41.1 (*c*, 6.03, EtOH)	98[g]			
3-acetylpyridine[h]	15	65	−43.2 (*c* 1.86, MeOH)	92[i] (92)	90	100	
2-acetylthiophene[h]	15	85	−22.5 (*c* 4.41, C_6H_6)	(91)			
butyrophenone	7	78	−45.6 (*c* 4.59, C_6H_6)	100.9[j] (98)			100
1-indanone	15	65		(97)			
isobutyrophenone	24	68	−19.2 (neat)	78[k]			71
pivalophenone	12 days[l]	45	+20.5 (*c* 1.9, C_6H_6)	79[m,n]			44

[a] Major isomer is the *S* alcohol. [b] From ref 7. [c] From ref 8. [d] From ref 3. [e] Based on −43.5° (neat).[12] [f] Values in parentheses are by capillary GC analyses of the (+)-α-methoxy-α-(trifluoromethyl)phenylacetates. [g] Based on −41.9° (*c* 4.92, EtOH).[13] [h] Employs 100% excess of the reagent; reaction too slow with stoichiometric amount of the reagent, presumably due to complex formation. [i] Based on +46.7° for 99% ee alcohol.[14] [j] Based on −45.2° (*c* 4.81, C_6H_6).[4] [k] Based on −24.6° (neat).[15] [l] Only 60% reaction is complete after 12 days at room temperature. [m] Based on 25.9° (*c* 2.2, C_6H_6).[16] [n] (+) Isomer has *R* configuration.[17]

asymmetric induction.[6] However, its reaction with less reactive ketones was very slow, accompanied by poor induction, presumably due to a competing achiral reduction process caused by the 9-BBN formed by the slow dissociation of **1**. For example, acetophenone could be reduced to (*S*)-1-phenylethanol in only 10% ee. However, it was later established that doing the reduction under neat conditions improves the rate as well as the chiral induction considerably.[7] Recently Midland and McLoughlin have further overcome the dehydroboration problem by applying very high hydrostatic pressures (6000 kbar) and obtained excellent chiral induction in the reduction of several representative prochiral ketones.[8]

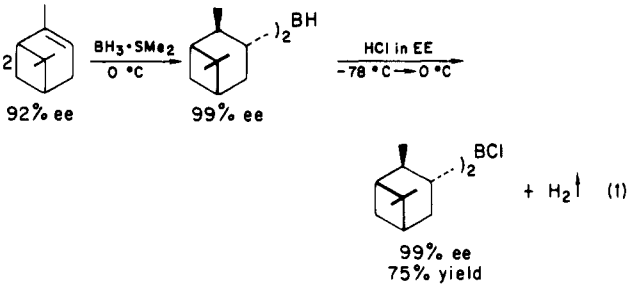
It occurred to us that a strategic modification of the electronic and steric environments of the boron in trialkylboranes might improve both the rate of reduction and the chiral induction. Introducing a halogen on the boron should increase the Lewis acidity of the boron, thereby facilitating its reaction with the carbonyl group. Since the 3-pinanyl group is a highly efficient chiral adjuvant, we decided to test diisopinocampheylchloroborane (**2**)



2

(Ipc_2BCl) derived from (+)-α-pinene as a chiral reducing agent. We applied **2** to the reduction of a standard series of ketones, 2-butanone, 3-methyl-2-butanone, 3,3-dimethyl-2-butanone, and acetophenone (Table I). A comparison of the data with those for some other important reagents revealed that **2** may be superior for aromatic and α-tertiary alkyl ketones. In this communication we disclose our results on the reduction of representative aromatic prochiral ketones with **2**.

2 could be readily prepared from commercially available (+)-α-pinene (92% ee) in high chemical and optical purities (99% ee) by hydroboration,[9] followed by treatment with dry hydrogen chloride in ethyl ether (EE) (eq 1).



2 reacts with ketones at convenient rates even at −25 °C in THF (1 M). The reaction cleanly stops with the elimination of 1 equiv of α-pinene. For example, acetophoneone could be reduced to (*S*)-1-phenylethanol in 98% ee and in 72% isolated yield. The isolation procedure involves a simple removal of the boron moiety by precipitation (**4**) with diethanolamine (Scheme I).

Incidentally, the α-pinene obtained as a byproduct exhibits a rotation comparable to the highest value previously reported[13] ($[\alpha]^{20}_D$ +51.7°). This reaction may be of value

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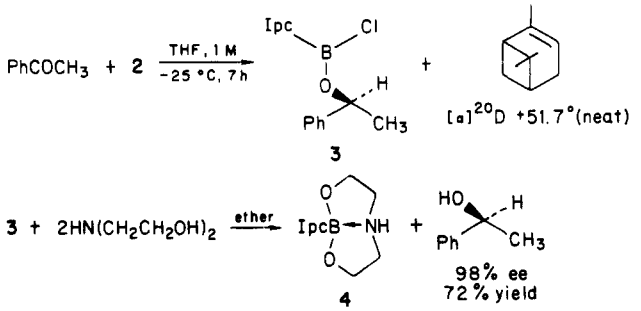
(7) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1985**, *50*, 1384.
(8) Midland, M. M.; McLoughlin, J. I. *J. Org. Chem.* **1984**, *49*, 1317.
(9) Brown, H. C.; Singaram, B. *J. Org. Chem.* **1984**, *49*, 945.
(10) The specific rotation obtained is comparable to the maximum value reported in the literature ($[\alpha]^{20}_D$ +51.6°) (Johnson, W. S.; Frei, B.; Gopalan, A. S. *J. Org. Chem.* **1981**, *46*, 1513).
(11) Midland, M. M.; Kazubski, J. *J. Org. Chem.* **1982**, *47*, 2496.
(12) MacLeod, R.; Welch, F. J.; Mosher, H. S. *J. Am. Chem. Soc.* **1960**, *82*, 876.
(13) Collyer, T. A.; Kenyon, J. *J. Chem. Soc.* **1940**, 676.
(14) Uskokovic, M. R.; Lewis, R. L.; Partridge, J. J.; Despreaux, C. W.; Pruess, D. L. *J. Am. Chem. Soc.* **1979**, *101*, 6742.

Scheme I



in obtaining α-pinene of very high optical purity.

We were highly encouraged by the nearly quantitative chiral induction achieved in the reduction of acetophenone. Hence, we studied the reduction of several representative aryl alkyl ketones (Table II). The data show that **2** can be successfully applied to a wide variety of such aromatic ketones. Thus, changing the aryl group from phenyl to 2-naphthyl does not affect the chiral outcome. 3-Acetylpyridine and 2-acetylthiophene are reduced to the corresponding alcohols in 92% and 91% ee. Increasing the chain length of the *n*-alkyl group has no detrimental effect on the chiral induction. Thus acetophenone and butyrophenone are both reduced in 98% ee. 1-Indanone is reduced in 97% ee. Branching the alkyl group in the aryl alkyl ketone decreases the asymmetric induction somewhat. Thus isobutyrophenone is reduced with 78% ee and phenyl *tert*-butyl ketone with 79% ee. Except for phenyl *tert*-butyl ketone where the *R* alcohol was the major isomer, in all other cases the *S* alcohol was obtained predominantly. *R*-Alpine-Borane (**1**) also gives the *S* alcohol predominantly. Consequently, our results can be explained by a model of the transition state similar to the one proposed earlier.[8] The opposite configuration obtained in the reduction of phenyl *tert*-butyl ketone is also in accord with this model.

It may be noted that Ipc_2BCl (**2**) has definite advantages as a chiral reducing agent for aromatic ketones. A comparison with other reagents (Table II) indicates that it is more efficient than Noyori's Binal-H and Alpine-Borane (without high pressure) and is close to the Alpine-Borane results with high pressure. It employs a far more available chiral auxiliary than Noyori's reagent, permitting large-scale reactions. The reduction rates are conveniently rapid.

In conclusion, Ipc_2BCl readily prepared from optically active α-pinene in high chemical and optical purities reduces aromatic prochiral ketones with excellent chiral induction. Further studies on the asymmetric reduction of other classes of prochiral ketones, such as α-tertiary alkyl ketones, are currently underway.

The following procedure is representative. All operations were carried out under nitrogen. Diisopinocampheylborane, prepared from (+)-α-pinene (230 mmol) and $BH_3{\cdot}SMe_2$ (100 mmol) in THF (96 mL) at 0 °C by the reported procedure[10] was suspended in EE (50 mL) at −78 °C. Dry hydrogen chloride in EE (1 equiv, calculated for the amount of Ipc_2BH) was added. After being stirred for 15 min at −78 °C, the reaction mixture was warmed to 0 °C and stirred at that temperature until all of the solid dissolved and gas evolution ceased (2 h). ^{11}B NMR showed a single peak at 74 ppm (relative to $BF_3{\cdot}OEt_2$). Upon removal of the ether solvent and cooling, **2** solidified (mp 54–56 °C after crystallization from pentane). The overall yield based on $BH_3{\cdot}SMe_2$ is 75%. To a solution of **2** (9.0 g, 28 mmol) in THF (20 mL) at −25 °C was added acetophenone (3.05 mL, 26 mmol) under a nitrogen atmosphere. A yellow color developed immediately. The reaction was complete after 7 h at −25 °C (followed by ^{11}B NMR after methanolysis of an aliquot). The volatiles were pumped off at aspirator pressure and the α-pinene was removed under reduced pressure (0.1 mmHg, 8 h). The residue was dissolved in EE (100 mL) and diethanolamine (2.2 equiv) was added. The separated solid was filtered off after 2 h and washed twice with pentane (~30 mL). The combined ether and pentane filtrates were concentrated. The residue, upon distillation (bp 118 °C (22 mmHg)) provided (*S*)-1-phenylethanol (2.3 g, 72% yield) ($[\alpha]^{20}_D$ −42.6° (neat)) after purification by preparative gas–liquid chromatography on Carbowax 20M; 98% ee based on −43.5° for maximum reported rotation.[12] GC analyis of its α-methoxy α-(trifluoromethyl)phenylacetate (made from (+)-MTPA chloride, Aldrich) on Supelcowax glass capillary column (15 m) showed a composition of 98.7% *S* + 1.3% *R* (i.e., 97.4% ee), in good agreement with the optical rotation measurement.

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The Reduction of Oximes by Lithium Aluminum Hydride in Hexamethylphosphoramide Solvent

Summary: A new approach to the control of LAH reductions is illustrated by the reversion of oximes to ketones in LAH/HMPA.

Sir: We would like to report the ability of hexamethylphosphoramide (HMPA) to divert the lithium aluminum hydride (LAH) reduction of oximes from its normal amine products. This results in a new method for the reversion of oximes to ketones and suggests the use of LAH/HMPA as a new, selective, reducing medium.

The reduction of oximes by LAH in ether solvents gives[1] a mixture of amine products (Scheme I). We reasoned that formation of dianion III would be unfavorable in the presence of HMPA.[2] We therefore compared the LAH reduction of representative ketoximes in tetrahydrofuran (THF) and in HMPA.

The reductions of Ia,b,c (LAH/THF, reflux, 3–8 h) each give a mixture of both primary amine and the secondary amine resulting from aryl migration from C to N. The ratios of primary to secondary amine are 80/20, 63/37, and 69/31, respectively. Id,e give only primary amine. How-

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(2) For previous work in our laboratory on the ability of HMPA to divert reactions involving anionic intermediates, see: Wang, S. S.; Sukenik, C. N. *J. Org. Chem.* **1985**, *50*, 653.

0022-3263/85/1950-5448$01.50/0