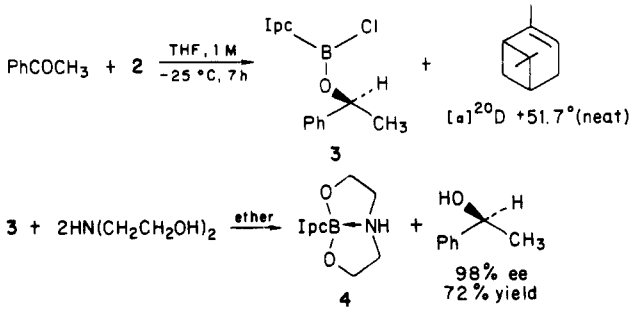
Scheme I



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.

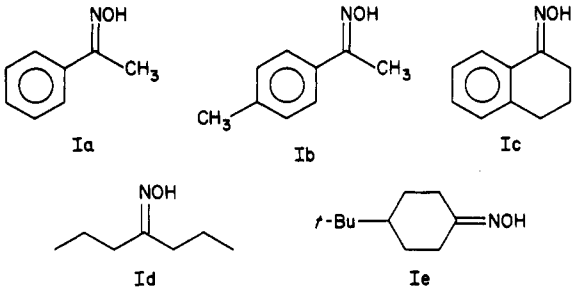
Sir: We would like to report the ability of hexamethylphosphoramide (HMPA) to divert the lithium aluminum hydride (LAH) reduction of oximes from its normal amine products. This results in a new method for the reversion of oximes to ketones and suggests the use of LAH/HMPA as a new, selective, reducing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

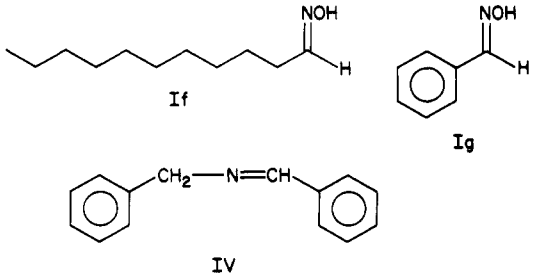
(1) (a) Lyle, R. E.; Troscianiec, H. J. *J. Org. Chem.* **1955**, *20*, 1757. (b) Rerick, M. N.; Trottier, C. H.; Daignault, R. A.; DeFoe, J. D. *Tetrahedron Lett.* **1963**, 629. (c) Graham, S. H.; Williams, A. J. S. *Tetrahedron* **1965**, *21*, 3263.
(2) For previous work in our laboratory on the 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



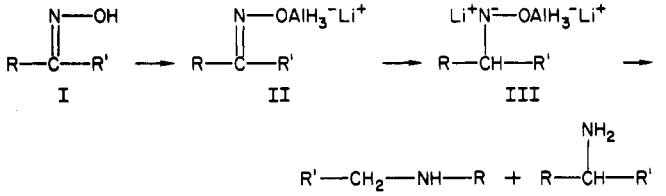
ever, LAH reduction (130 °C, 3 h) of these substrates in HMPA (*Caution*: carcinogen) yields only the ketone related to each oxime with no amine product. Ketones are not seen in the THF reductions.

Further investigation revealed the following. The conversion of oximes into ketones is independent of whether homogeneous solutions of LAH in HMPA are used or whether one uses a slurry of commercial LAH in HMPA.[3] The conversion of oximes into ketones can be done with only 10% HMPA (v/v) in THF if a high molar ratio (>10:1) of HMPA to LAH is maintained.[4] And finally, the reaction of LAH/HMPA with aldoximes gave strikingly different results. Reaction of If in LAH/HMPA for 6 h at 110 °C gave only undecanenitrile with no evidence of either amine or carbonyl product. Reaction of Ig at 95 °C for 20 min gave only benzaldehyde. When this reaction was allowed to proceed for 1 h it gave 76% IV and 24% benzaldehyde.

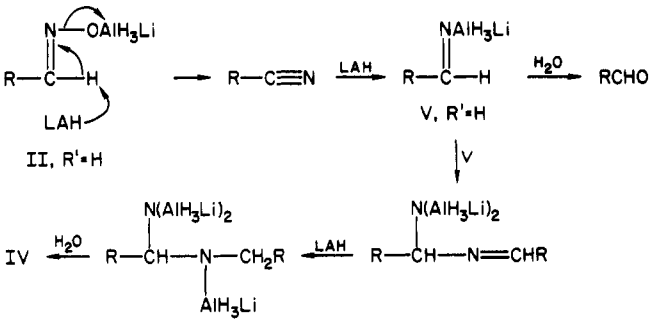


These findings represent a simple and efficient route for the reversion of oximes to ketones.[5] Furthermore, the limitations of the aldoxime system reveal a number of interesting features. The dehydration of aldoximes to nitriles in HMPA at 200 °C has been reported.[6] In LAH/HMPA (Scheme II) this dehydration proceeds at a lower temperature due to the basicity of the LAH. It is also this basicity that promotes removal of an α-proton from the incipient alkyl nitrile and prevents its further reduction.[7] Thus, in the case of benzaldoxime (Ig, no α-protons), the cyano group is reduced to imine V. This imine is the precursor to either carbonyl product on hydrolytic workup, or to dimer IV after coupling and reduction followed by hydrolysis.[8]

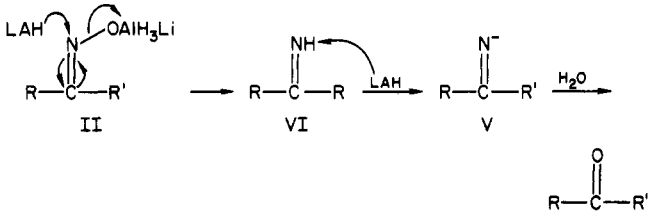
Scheme I



Scheme II



Scheme III



Further support for this scheme is provided by the reaction of benzaldoxime Ig in HMPA with lithium aluminum deuteride (LAD). This reaction gave no evidence of D incorporation into recovered Ig (partial reaction) and yet showed full deuteration (≥97%) of both the aldehydic proton of the benzaldehyde and the benzylic protons of IV. This is in contrast to the reaction of LAD with Ig in THF, where not only was benzylamine the only product, but it had precisely one H and one D in the benzylic position. This result precludes nitrile formation in THF. The deuterium content of IV also supports its formation from V (Scheme II).

Clearly, there are a number of ways in which HMPA alters the chemistry of LAH. In contrast to LAH/THF, LAH/HMPA allows imine V to survive without further reduction; it promotes the action of LAH as a base; and it induces the reductive hydrolysis of ketoximes to ketones. The ability of HMPA to allow V to resist reduction by LAH can be understood in terms of the Li complexing power of the HMPA and the resulting destabilization of anions in HMPA. Since hydride attack on V would lead to an amine dianion, this pathway is sufficiently retarded to allow V to survive and be hydrolyzed to a carbonyl on workup. However, the enhancement of LAH basicity and

(3) This was not true in ref 2. In that case, homogeneous and heterogeneous reactions gave different product distributions.

(4) The standard procedure for LAH/HMPA reduction of oximes used 10 mL of HMPA with 100–200 mg of LAH to reduce 50–150 mg (0.4–1.1 mmol) of oxime. After 3 h at 130 °C the carbonyl product could be isolated by a simple aqueous workup. Isolated yields of 82–92% of clean (by GC and NMR) ketone were obtained. We could substitute 10% HMPA in THF as the reaction solvent but were then limited to the reflux temperature of THF (66 °C) as the reaction temperature. For aryl ketoximes this necessitated reaction times of 16–24 h for complete conversion to ketone, and for alkyl ketoximes we could achieve no more than 50% conversion even after 48 h. Thus, while it is desirable to use less HMPA due to its carcinogenicity, this will require a higher boiling ether cosolvent.

(5) For other methods, see: Curran, D. P.; Brill, J. F.; Rakiewicz, D. M. *J. Org. Chem.* **1984**, *49*, 1654 and references therein. Barton, D. H. R.; Lester, D. J.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1212. Barton, D. H. R.; Motherwell, W. B.; Simon, E. S.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1984**, 337.

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the conversion of ketoximes to V require additional comment.

We suggest that in all solvents, the reaction of oximes with LAH initially forms II (Scheme I). Subsequent reaction of II to form dianion III is essential to the formation of amine products. Just as HMPA prevents hydride attack on imine V, it disfavors the hydride attack needed to transform II into III. There are then two alternative reaction pathways. When possible (Scheme II), elimination to a nitrile occurs. However, when both R and R′ are alkyl or aryl, hydride attack on nitrogen may occur. As shown in Scheme III, an addition–elimination sequence leads to VI, which is deprotonated to V. This pathway is enhanced both by HMPA destabilization of III and by the harder reagent that has been generated. In HMPA, disassociation of the Li from the aluminum hydride produces a more reactive, harder, hydride reagent. This hardness is manifest both in enhanced elimination (Scheme II) and in a shift from addition to carbon (a softer site) to attack on nitrogen[7] (the harder end of the C=N group). While there is precedent[9] for hydride attack on the N of an oxime, our results are the first suggestion that solvent may control the regiochemistry of this reaction.

Finally, the ability of HMPA to attenuate LAH reactivity is in contrast to the usual activation of nucleophilic reagents by dipolar aprotic solvents.[10] We are continuing to explore the scope of this reagent system for application to the selective reduction of other functional groups.

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Registry No. Ia, 613-91-2; Ib, 2089-33-0; Ic, 3349-64-2; Id, 1188-63-2; Ie, 4701-98-8; If, 2244-05-5; Ig, 932-90-1; IV, 780-25-6; IV-α,α-d_2, 38662-32-7; HMPA, 680-31-9; LAH, 16853-85-3; $PhCH(NH_2)CH_3$, 98-84-0; p-$MeC_6H_4CH(NH_2)CH_3$, 586-70-9; PhNHEt, 103-69-5; p-MeC_6H_4NHEt, 622-57-1; $CH_3(CH_2)_2CH(NH_2)(CH_2)_2CH_3$, 16751-59-0; PhAc, 98-86-2; p-MeC_6H_4C, 122-00-9; $CH_3(CH_2)_2C(O)(CH_2)_2CH_3$, 123-19-3; $CH_3(CH_2)_9CN$, 2244-07-7; PhCHO, 100-52-7; PhCDO, 3592-47-0; $PhCH_2NH_2$, 100-46-9; 1,2,3,4-tetrahydro-1-naphthalenamine, 2217-40-5; 2,3,4,5-tetrahydro-1*H*-2-benzazepine, 7216-22-0; 4-*tert*-butylcyclohexanamine, 5400-88-4; 3,4-dihydro-1(2*H*)-naphthalenone, 529-34-0; 4-*tert*-butylcyclohexanone, 98-53-3.

(9) We have found one literature example of hydride attack on the nitrogen of an oxime. It, however, required a special anthroquinone substrate: Costa, A.; Riego, J. M.; Garcia-Raso, A.; Sinisterra, J. V. *Liebigs Ann. Chem.* **1981**, 2085.

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