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CHEMOSELECTIVITY IN THE REDUCTION OF ALDEHYDES AND KETONES WITH AMINE BORANES

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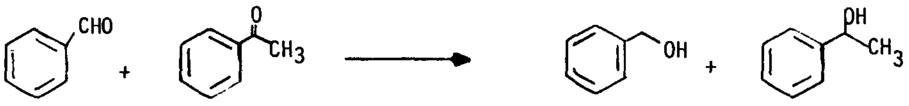
Abstract: Ammonia borane and primary amine boranes are highly chemoselective reducing agents for aldehydes and ketones.

There has been much recent interest in the development of chemoselective[1,2] reducing agents capable of distinguishing aldehyde and ketone functionality in a predictable manner.[3a-3i] While all of these reagents are capable of reducing an aldehyde in the presence of a methyl ketone, few[3a,3d,3e,3g,3i] have the ability to distinguish between an aldehyde and a more reactive ketone such as cyclohexanone. Of those capable of such discrimination all have serious drawbacks: limited availability and high cost (9-borabicyclo[3.3.1]nonane-pyridine complex,[3i] di-n-butyl-9-borabicyclo[3.3.1]nonane "ate" complex,[3a]), the need for the use of excess reagent, quenching of the reaction to avoid over-reduction (alkylthiol modified borohydride[3d]), and/or the requirement for reaction on a solid surface (isopropanol/alumina,[3h] tri-n-butyltin hydride/silica gel[3e]).

We wish to report that simple, commercially available amine borane reagents show high chemoselectivity in the reduction of a variety of aldehydes and ketones under mild conditions in most organic and protic solvents.[4,5,6,7]

The chemoselectivity in the competitive reduction of benzaldehyde (**1**) and acetophenone (**2**) with several amine boranes in protic and aprotic solvents is illustrated in Table I.

All reactions were run on 10-20 mmol scale using a 1/1/0.33 molar ratio of **1**/**2**/amine borane for 1 hr at the indicated temperature and analyzed by GLPC[8] after acid hydrolysis (2N HCl, 15 min, RT) of the intermediate borate esters. Reductions were normally complete in 10 min at 0° with ammonia borane and _t_-butylamine borane. Secondary amine boranes showed a marked decrease in both reactivity and chemoselectivity. Trimethyl amine borane was unreactive under these conditions of



1 2 3 4

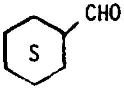
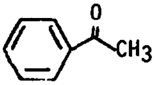
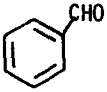
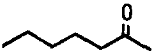
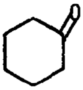
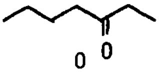
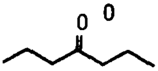
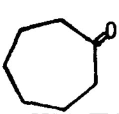
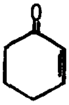
Table 1: The Reduction of 1:1 Molar Mixtures of Benzaldehyde and Acetophenone with Amine Borane Reagents

Reagent	Solvent	Temp.	Ratio 3:4	% Conversion 1→3
_t_-$C_4H_9NH_2 \cdot BH_3$	CH_3OH-H_2O (1-1)	0	98.2	81
"	THF	0	95:5	84
"	$CHCl_3$	0	97:3	87
"	$CH_3C_6H_5$	0	94:6	95
$NH_3 \cdot BH_3$	CH_3OH-H_2O (1-1)	0	97:3	97
$NH_3 \cdot BH_3$	CH_3OH/H_2O (1-1)	25	97:3	90
2,6-lutidine	$CHCl_3$	25	55:45	9
$C_5H_5N \cdot BH_3$	$CHCl_3$	25	35:65	11
$(CH_3)_3N \cdot BH_3$	$CHCl_3$	25	NR	NR

time and temperature. It should be noted that even in a protic solvent, all three hydrides of the amine borane were available for reaction, a mechanistically surprising result in view of earlier work on the reduction of ketones with tertiary amine boranes.[9] In the case of t-butylamine borane and ammonia borane excellent selectivity for reduction of the aromatic aldehyde is observed with high overall conversion.

The relative rates of reduction (obtained by competitive reduction in the presence of cyclohexanone) of several exemplary aldehydes and ketones are shown in Table 2. It is apparent that aliphatic and aromatic aldehydes may be reduced in the presence of cyclohexanone and other aliphatic and aromatic, acyclic and cyclic ketones. Cyclohexanone may be reduced selectively in the presence of aliphatic and aromatic acyclic ketones and cycloalkanones of 5 or 7 ring carbons. Aliphatic and aromatic acyclic ketones are reduced in the presence of cyclohexenone.[10] In contrast to the high chemoselectivity observed between 2-, 3-, and 4-heptanone in reductions with Yammamato's di-_n_-butyl-9-borabicyclo[3.3.1]nonane reagent, amine boranes show little differentiation in this electronically similar and sterically distinct series.[3a,11]

Table 2. The Relative Reactivity of Ketones and Aldehydes to $\underline{t}$-$C_4H_9NH_2 \cdot BH_3$ via Competitive Reductions versus Cyclohexanone[a]

Ketone or Aldehyde	R[b]	% Conversion[c]	Ketone or Aldehyde	R	% Conversion
	4.46	95		.06	90
	3.31	65		.05	90
	1.00	-		.06	91
	0.10	91		.04	89
	0.08	89		.01	95

a) Reactions were carried out on 10 mmol scale using a 1 1 0.33 molar ratio of substrate cyclohexanone and amine borane respectively at 0° in ethyl ether for 1 hr at 0°. Ratios were determined by GLPC analysis after quenching with 2N aqueous HCl.

b) Ratio of alcohol produced to cyclohexanol.[8] c) % reduction of the most reactive substrate in the mixture.

Ammonia borane and $\underline{t}$-butylamine borane are highly reactive members of the general class of amine borane reagents which exhibit chemoselective properties equal to or greater than previously reported reagents. In addition, they have the unique advantage of stability, convenience and commercial availability.

REFERENCES AND NOTES

1. The term "chemoselective" is used here as defined by Yamamoto[3a] to denote both the inter- and intra-molecular discrimination of a reagent to targets in a given structural unit or units.
2. B. M. Trost and T. N. Saltzmann, J. Amer. Chem. Soc., **95**, 6840 (1973).

3. (a) Y. Yamamoto, H. Toi, A. Sonoda, S. Murakashi, *J. Amer. Chem. Soc.*, 98 1965 (1976); (b) G. W. Gribble and D. C. Ferguson, *J. Chem. Soc.*, *Chem. Commun.*, 535 (1975); (c) J. M. Lalancette, A. Frêche, J. R. Brindle and M. Laliberté, *Synthesis*, 526 (1972); (d) Y. Maki, K. Kikuchi, H. Sugiyama and S. Seto, *Tetrahedron Lett.*, 263 (1977); (e) N.Y.M. Fung, P. deMayo, J. H. Schauble, and Alan C. Weedon, *J. Org. Chem.*, **43**, 3977 (1978); (e) R. O. Hutchins and D. Kandasamy, *J. Amer. Chem. Soc.*, **95**, 6131 (1973); (f) C. S. Sell, *Aust. J. Chem.*, **28**, 1383 (1975); (g) M. J. Chapdelaine, G. H. Posner and A. W. Runquist, *J. Org. Chem.*, **42**,1202 (1977); (h) P. Girard, H. B. Kagan and J. L. Namy, *Nouv. J. Chim*, **1**, 5 (1977); (i) H. C. Brown and S. U. Kulkarni, *J. Org. Chem.*, **42**, 4169 (1977); (j) M. M. Midland and A. Tramontano, *ibid.*, **43**, 1470 (1978).
4. G. C. Andrews and T. C. Crawford, Tetrahedron Letters, 0000, (1979).
5. Ammonia borane was obtained from Callery Chem., Co., as a white, crystalline, air stable compound soluble in water and methanol with limited solubility in THF, ethyl ether, chloroform and ethyl acetate.
6. *t*-Butylamine borane (mp 96°) was obtained from Aldrich Chem. Co., and is soluble in water, methanol and most organic solvents of greater polarity than hexane.
7. For a review of amine borane physical properties and reactivity see C. L. Lane, *Aldrich Chemica Acta* **6**, 21 (1973).
8. GLPC was accomplished on a 6 ft, 1/8" ID column, 20% Carbowax 20M on Chromasorb W, 80/100 mesh and ratios determined by peak areas using derived detector response factors.
9. T. Wolfe and H. C. Kelley, *J. Chem. Soc.*, *Perkin II*, 1948 (1973); S. S. White and H. C. Kelly, *J. Amer. Chem. Soc.*, **92**, 4203 (1972) and ref. cited therein.
10. Cyclohexenone and other ketones less reactive than cyclohexanone require greater than a 1:0.33 molar ratio of ketone to amine borane to afford complete reduction, especially in protic solvents where some hydrolysis of alkoxyborane reduction intermediates may occur.
11. The amine borane reagents appear less susceptible to steric interference as may be inferred from their high preponderance for axial hydride delivery in 4-*t*-butylcyclohexanone.[4]

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