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THE SYNTHETIC UTILITY OF AMINE BORANE REAGENTS IN THE REDUCTION OF ALDEHYDES AND KETONES

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Abstract: Primary and secondary amine boranes have been shown to be mild, efficient, and stereoselective reducing agents for aldehydes and ketones in protic or non-protic solvents with reactivity patterns different than diborane or sodium borohydride.

During the course of our studies on new stereo- and chemo-selective reducing agents we have found that the reactivity and stereoselectivity of amine borane reagents is highly dependent on the nature of the amine used in the amine borane complex. In fact, contrary to much of the literature, commercially available ammonia borane and primary and secondary amine borane reagents are versatile, efficient and reactive reducing agents for aldehydes and ketones.[1]

While amine boranes have been extensively studied as carbonyl reducing agents both mechanistically[2a-e] and in synthetic applications,[3a-c] they have failed to gain widespread use in synthetic chemistry in spite of their remarkable stability (both thermal[4] and hydrolytic),[2a,2c] solubility in protic and aprotic solvents,[4] and handling convenience. The relative disuse of amine boranes is a result of the conclusions of previous work, primarily[5] with tertiary amine boranes (trimethyl amine borane,[2a,2e,2b,3d] N-phenylmorpholine borane[2b-e]) and pyridine borane.[3a] These studies show that in the absence of Lewis acid catalysis,[2c,2e,5a] tertiary amine boranes react with ketones and aldehydes only sluggishly, at elevated temperatures,[3a,3b] transferring only one of the three available hydride equivalents.

Table 1 shows the relative reactivity of several amine boranes in the reduction of 4-*t*-butyl-cyclohexanone (1). Reductions were accomplished with a 1:1 molar ratio of ketone to amine-borane.[6] Primary and unhindered amine boranes afforded high stereoselectivity and rapid reduction. Tertiary amine boranes were unreactive even at pH 2.0. The stereoselectivity observed decreased with decreasing reactivity and was temperature dependent, illustrated by the fact that NH_3BH_3 afforded a 96:4 ratio of 2:3 at -50° in 87% isolated yield.[3] This contrasts markedly with the moderate stereoselectivity and harsh conditions previously reported for the Me_3NBH_3 reduction of 1 (2:3::86:14 in 55% conversion after 3 days at 100°).[3b]

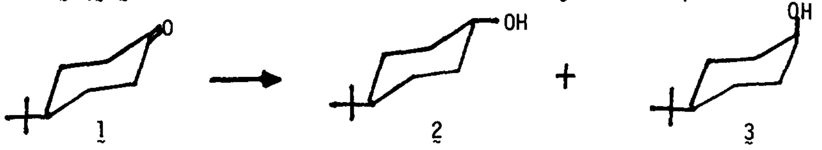
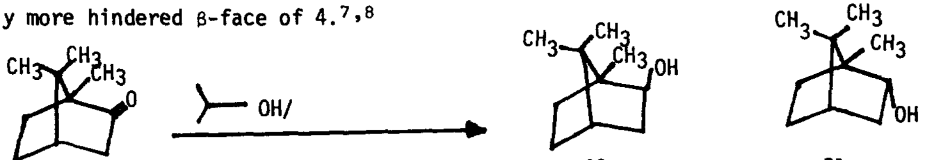


Table 1. The Relative Reactivity of Amine Boranes in the Reduction of 4-t-butylcyclohexanone in CH_3OH/H_2O (2/1) at RT

Reagent	Time					
	15 min		85 min		18 hr	
	2:3	2+3	2:3	2+3	2:3	2+3
$NH_3\cdot BH_3$	91:9	>99%	--	--	--	--
t-$C_4H_9NH_2\cdot BH_3$	92:8	>99%	--	--	--	--
$(CH_3)_2NH\cdot BH_3$	90:10	73	92:8	>99%	--	--
2,6-lutidine$\cdot BH_3$	82:18	33	85:15	42	86:14	>99
pyridine$\cdot BH_3$	-	0	-	-	81:19	29*
$(CH_3)_3NBH_3$	-	0	-	0	80:20	6
N-phenylmorpholine$\cdot BH_3$	-	0	-	0	--	<1

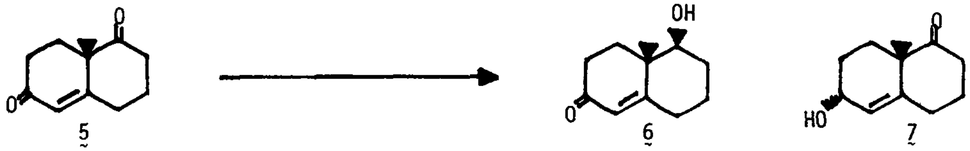
The high selectivity observed for axial hydride delivery in this sterically biased cyclohexanone system suggests amine boranes may be less susceptible to non-bonded steric interactions than traditional hydride and borane reductants. This premise is supported by a comparison of $NaBH_4$, and NH_3BH_3 in the reductions of camphor (4). Ammonia borane affords reduction at a significantly greater rate than $NaBH_4$ and with a higher percentage of hydride delivery across the sterically more hindered β-face of 4.[7,8]



4

NH_3BH_3/7 hrs/ >99% conversion (93% isolated yield)	49	:	51
$NaBH_4$/7 days/ 53% conversion	85	:	15

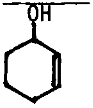
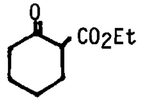
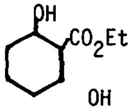
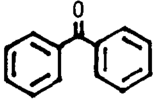
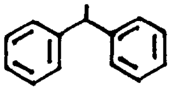
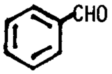
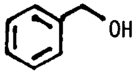
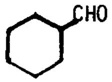
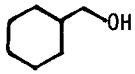
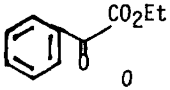
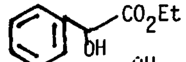
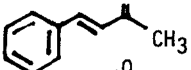
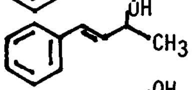
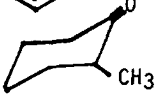
There appear to be major electronic differences in the reactivity of amine borane reagents and diborane. The reduction of 9-methyl-$\Delta^{5(10)}$-octaline-1,6-dione 5, ammonia borane affords the C-1 reduced enone, 6, while BH_3 primarily reduces the more electron rich C-6 enone carbonyl.[9]



	6	7
B_2H_6/0°/THF	28	72
NH_3BH_3/0°/CH_3OH	98	2
$NaBH_4$/0°/CH_3OH	99	-[9]

We have examined the synthetic utility of ammonia and t-butylamine borane reagents in the reduction of several different carbonyl containing molecules. In the cases reported, excess hydride reagent (1.1→3 hydride equivalents) was utilized for convenience, and the reactions quenched witl aqueous 2N HCl or H_2SO_4. Reduction yields in Table 2 are of isolated, distilled or crystallized products.

Table 2: Reduction of Ketones and Aldehydes with Amine Borane Reagents

Substrate	Amine Borane	Solvent	/ Conditions	Product	Yield (%)
	t-$C_4H_9NH_2BH_3$	Et_2O	RT (16 hr)		87[10]
 CO2Et	t-$C_4H_9NH_2BH_3$	Et_2O	RT (16 hr)		65[11]
	NH_3BH_3	CH_3OH/H_2O	RT (1 hr)		85
	NH_3BH_3	CH_3OH/H_2O	0° (10 min)		83[12]
	t-$C_4H_9NH_2BH_3$	$CHCl_3$	0° (10 min)		92[12]
	NH_3BH_3	Et_2O	RT (4 hr)		84
	t-$C_4H_9NH_2BH_3$	$CHCl_3$	RT (1 hr)		79[10]
	NH_3BH_3	Et_2O	0° (1 hr)		87[13]

Thus primary and secondary amine boranes are efficient and stereoselective carbonyl reducing agents with reducing properties unique from diborane and hydridoborate reagents. Amine boranes represent a major class of reducing agents which heretofore have not generally been recognized and should prove to be an important addition to the family of reducing agents generally used by the practicing organic chemist. Our further studies of the utility of amine boranes in the reductions of carbohydrates in aqueous media, their chemoselectivity, use in reductive aminations, and in the reduction of other functional groups will be reported in due course.

REFERENCES AND NOTES

1. Amine borane reagents utilized are available from Callery Chemical Co. or Aldrich Chem. Co.

2. (a) G. Ryschkewitsch, J. Amer. Chem. Soc., 82 3290 (1960); (b) S. S. White and H. C. Kelly, ibid, 90, 2009 (1968); (c) S. S. White and H. C. Kelly, ibid, 92, 4203 (1970); (d) T. C. Wolfe and H. C. Kelly, J. Chem. Soc., Perkin II, 1948 (1973); (e) H. C. Kelly, M. B. Guisto and F. R. Marchelli, J. Amer. Chem. Soc., 86, 3883 (1964).

3. (a) R. Barnes, J. H. Graham and M. D. Taylor, J. Org. Chem., 23, 1561 (1958); (b) W. M. Jones, J. Amer. Chem. Soc., 82, 2528 (1959); (c) H. Noth and H. Beyer, Chem. Ber., 93, 1078 (1960); (d) W. C. Perkins and D. H. Wadsorth, J. Org. Chem., 37, 800 (1972).

4. (a) H. Noth and H. Beyer, Chem. Ber., 93, 928 (1960); (b) see C. L. Lane, Aldrich Chemica Acta, 6, 21 (1973) for a list of amine borane physical properties and solubilities.

5. Primary and secondary amine boranes have been used at elevated temperatures in the reductions of aldehydes and ketones by Noth and Beyer.^{3c} Optically active phenethylamine boranes and amine boranes derived from amino-acid methyl esters have been used recently for asymmetric reduction: M. F. Grundon, D. G. McCleery and J. W. Wilson, Tetrahedron Letters, 295 (1976); (b) J. Fraud and H. Kagan, Bull. Soc. Chim. Fr., 2742 (1969); (c) R. F. Borch and S. R. Levitan, J. Org. Chem., 37, 2347 (1972).

6. The use of 1.0 hydride equivalent (.33 molar equivalent of amine borane) afforded a 76% yield in the reduction of 1 with ammonia borane under these conditions. In aprotic solvents hydride utilization is nearly quantitative. Epimer ratios are not significantly altered with respect to reductions using excess reductant.

7. Ratios were determined by GLPC analysis versus internal standards.

8. H. C. Brown and J. Muzzio, J. Amer. Chem. Soc., 88, 2011 (1966).

9. CBC Boyce and J. S. Whitehurst, J. Chem. Soc., 2680 (1960); see also M. Sefanovic and S. Lajsic, Tetrahedron Letters, 1977 (1967).

10. Conjugate reduction of cyclohexenone also occurs, the ratio of 2-cyclohexenol:cyclohexanol being 95:5. No conjugate addition was observed in the reduction of 4-phenyl-3-butone-2-one.

11. Ratio of *cis* and *trans* 2-carbethoxy-1-cyclohexanol was 65:35.

12. Under these conditions, with reactive aldehyde substrates, reductive amination of the borane amine with the substrate yields minor side product removed during acid extraction of the reduction mixture. In the reduction of benzaldehyde in refluxing ether with t-$C_4H_9NH_2BH_3$, 3% of t-$C_4H_9NHCH_2C_6H_5$ is formed.

13. Ratio of *cis* and *trans* 2-methylcyclohexanol was 30:70.

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