Asymmetric Reduction of Aromatic Ketones with Chiral Alkoxy-amine-borane Complexes

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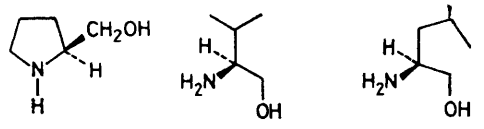
Summary Asymmetric reduction of prochiral aromatic ketones with chiral alkoxy-amine-borane complexes afforded the corresponding aromatic secondary alcohols in as much as 60% enantiomeric excess.

AMINE-BORANE complexes have been extensively studied as reducing agents for functional groups such as alkenes, carbonyls, and imines.[1] Their remarkable stability (both thermal and hydrolytic), solubility in a wide variety of

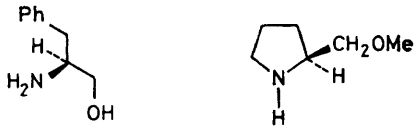
protic and aprotic solvents, and handling convenience makes them attractive reagents in organic syntheses. Furthermore, it has recently been reported that ammonia- and primary amine-boranes are highly chemoselective reducing agents for aldehydes and ketones under mild conditions.[2,3]

Application of the complexes to asymmetric reduction was first reported by Fiaud and Kagan who used borane-chiral amine complexes derived from ephedrine in the reduction of ketones and obtained poor optical yields (3·6—5·0%).[4] Attempts have been made to use the borane complexes with (*R*)-(+)-, (*S*)-(−)-α-methylbenzylamine,[5,6] or α-amino-esters in the presence of BF_3–Et_2O[7] in asymmetric reductions of ketones but limited success has attended these attempts at selectivity so far (*ca.* 20% optical yield).

We report the asymmetric reduction of aromatic ketones utilizing borane complexes with chiral amino-alcohols (**1**)—(**4**) derived from α-amino-acids which gives the corresponding secondary alcohols with up to 60% stereoselectivities.



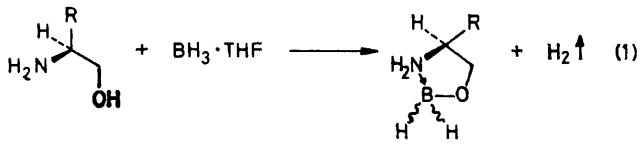
(1) (2) (3)



(4) (5)

A typical procedure is illustrated by the asymmetric reduction of propiophenone with (*S*)-(−)-2-amino-3-methylbutanol (**2**)-borane in tetrahydrofuran (THF) at 30 °C. A dry 50 ml flask equipped with a side arm covered with a rubber stopper and a magnetic stirrer bar was flushed with nitrogen. The flask was charged with solid (**2**)-borane (1·15 g). Then dry THF (20 ml) was added to dissolve the complex and was followed by a solution of propiophenone (1·06 g) at 30 °C, over 5 min. The resulting clear, transparent solution was stirred at 30 °C for 60 h. The usual work-up gave a pale yellow oil which was purified by t.l.c. and further by bulb-to-bulb distillation to give (*R*)-(+)-1-phenylpropan-1-ol, $[\alpha]_D^{20}$ +27·93° (*c* 4·40, Me_2CO), which was characterized by n.m.r. spectroscopy and was homogeneous on g.l.c. and t.l.c. This represents a 60% excess of the (*R*)-(+)-enantiomer based on the known maximum rotation, $[\alpha]_D^{20}$ −47·03° (Me_2CO).[8]

Amino-alcohols are generally allowed to react with borane to form alkoxy-amine-borane complexes.[1] All the chiral amino-alcohols examined, (**1**)—(**4**), liberated 1 equiv. of hydrogen rapidly at −70—0 °C to produce optically active alkoxy-amine-borane complexes which were isolated and used in the reduction. The resulting complexes are proposed to contain a relatively rigid five-membered ring system (equation 1).



As can be seen from the Table, substantial stereoselectivities in the order of 37—60% are obtained in the reduction of propiophenone with the complexes derived from (**1**)—(**4**) (runs 1, 8, 10, and 11). Of the complexes tested, the highest selectivity was observed with the (**2**)-borane complex (run 8). Other aromatic ketones such as acetophenone and β-naphthyl methyl ketone were reduced with

TABLE. Asymmetric reduction of aromatic ketones with chiral alkoxy-amine-borane complexes at 30 °C for 60 h.[a]

				Alcohol produced			
Run	Amino-alcohol	Ketone	Solvent	Yield/%[b]	$[\alpha]_D^{20}$/°	Optical yield/%	Absolute configuration
1	(**1**)	EtCOPh	THF	99	+20·74[d]	44	(*R*)
2[c]	(**1**)	EtCOPh	THF	93	+21·49	46	(*R*)
3	(**1**)	EtCOPh	C_6H_6	100	+ 3·41	7·3	(*R*)
4	(**1**)	EtCOPh	MeOH–H_2O (2:1)	100	+ 7·80	17	(*R*)
5	(**1**)	EtCOPh	$CHCl_3$	88	− 8·29	18	(*S*)
6	(**1**)	MeCOPh	THF	98	+23·30[e]	44	(*R*)
7	(**2**)	MeCOPh	THF	99	+25·60	49	(*R*)
8	(**2**)	EtCOPh	THF	99	+27·93	60	(*R*)
9	(**2**)	β-Naphthyl methyl ketone	THF	100	+21·56[f]	52	(*R*)
10	(**3**)	EtCOPh	THF	100	+19·08	41	(*R*)
11	(**4**)	EtCOPh	THF	100	+17·59	37	(*R*)
12	(**5**)	EtCOPh	THF	99	+ 7·43	16	(*R*)

[a] Conditions: alkoxy-amine-borane complex, 10 mmol; ketone, 8 mmol; total volume of solvent, 20 ml. The ratio of [complex]:[ketone] was 1:0·8. [b] Based on relative peak areas of alcohol and unchanged ketone in g.l.c. [c] Reaction was carried out at 0 °C for 170 h. [d] Optical yield was calculated from optical rotation. Maximum value for 1-phenylpropan-1-ol $[\alpha]_D^{20}$ −47·03° (Me_2CO) (see ref. 8). [e] Maximum value for $[\alpha]_D^{23}$ −52·5° (*c* 2·27, CH_2Cl_2) (see U. Nagai, T. Shishido, R. Chiba, and H. Mitsuhashi, *Tetrahedron*, 1965, **21**, 1701). [f] Maximum value for $[\alpha]_D^{20}$ −41·9° (*c* 5, EtOH) (see S. R. Landor, B. J. Miller, and A. R. Tatchell, *J. Chem. Soc.*, 1966, 2282).

the same complex to give the corresponding alcohols in reasonably good optical yields (44—52%) (runs 6, 7, and 9). In each case the (*R*)-enantiomer of the secondary alcohol was formed preferentially.

In the case of the (**1**)-borane complex, the maximum asymmetric induction was obtained in THF, while benzene and a mixture of methanol and water were much less effective (runs 3 and 4). Interestingly, the opposite alcohol enantiomer was found to predominate in $CHCl_3$ (run 5).

The reduction of propiophenone with (**1**)-borane is slow at −30 °C in comparison with that at 30 °C and can be completely accomplished in 170 h. The optical yield, however, was little affected by lowering the temperature (runs 1 and 2).

Finally, it should be noted that when the methyl ether of (S)-(−)-pyrrolidine-2-methanol (**5**) was used, the enantiomeric purity was significantly lower than that obtained for the (**1**)-borane complex. This suggests that the OH group in the complex plays an important role in the stereoselective process.

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[1] A. Pelter and K. Smith, in 'Comprehensive Organic Chemistry,' ed. D. N. Jones, Pergamon, Oxford, 1979, vol 3, pp. 687—940.
[2] G. C. Andrews and T. C. Crawford, *Tetrahedron Lett.*, 1980, 693.
[3] G. C. Andrews, *Tetrahedron Lett.*, 1980, 697.
[4] J. C. Fiaud and H. B. Kagan, *Bull. Soc. Chim. Fr.*, 1969, 2742.
[5] R. F. Borch and S. R. Levitan, *J. Org. Chem.*, 1972, **37**, 2347.
[6] D. G. McCleery, Research Thesis, New University of Ulster, Coleraine, N. Ireland, 1976.
[7] M. F. Grundon, D. G. McCleery, and J. W. Wilson, *Tetrahedron Lett.*, 1976, 295.
[8] H. Kwart and D. P. Hoster, *J. Org. Chem.*, 1967, **32**, 1867.