Tetrahedron Letters, Vol.27, No.5, pp 635-638, 1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

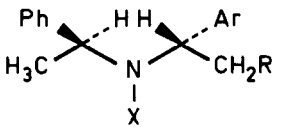
ENANTIOSELECTIVE REDUCTION OF ACETOPHENONE BY BORANE.CHIRAL AMINE COMPLEXES

M.B. Eleveld and H. Hogeveen*
Department of Organic Chemistry, University of Groningen,
Nijenborgh 16, 9747 AG Groningen,
The Netherlands

Abstract: The enantioselective reduction of acetophenone by the borane.chiral amine complexes BH_3.1a - BH_3.1d affords 1-phenyl-1-ethanol with o.y. up to 42%.

In the enantioselective reduction of prochiral ketones the use of chirally modified metal hydrides has extensively been studied. Especially lithium aluminum hydride modified by optically active alcohols or amines give high enantioselective reductions.[1] Although borane.achiral amine complexes have been intensively investigated as reducing agents for functional groups such as alkenes, carbonyls and imines,[2] only a few reports exist on the use of borane.chiral amine complexes; the most successful complexes have proven to be the ones with the following amines: (S)-α-methylbenzylamine,[3] (S)-1,2-diphenylethylamine,[4] (S)-valinol[5] and (S)-2-amino-3-methyl-1,1-diphenylbutan-1-ol[6] which reduce acetophenone in an o.y. of 21%,[3b] 25%,[4] 49%[5] and 94%,[6] respectively.

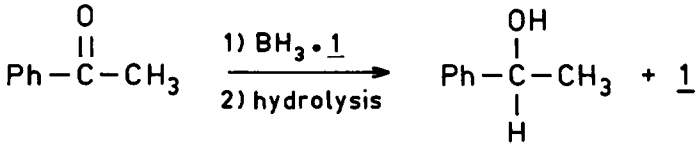
In our investigations of the applicability of some novel chiral amines (1) and chiral lithium amides (2)[7] in stereoselective synthesis we have investigated the potentiality of BH_3.1 to reduce acetophenone in an enantioselective way. The BH_3.1 complexes were made by



1 X = H
2 X = Li

a Ar = phenyl , R = H
b Ar = 2-pyridyl , R = H
c Ar = o-methoxyphenyl, R = H
d Ar = phenyl , R = OCH_3
e Ar = phenyl , R = OX

ligand exchange on treating a solution of 1 with BH_3.THF in THF (BH_3 coordinates more strongly with amines than with ethers). It was not possible to isolate the BH_3.1 complexes in pure form due to decomposition and therefore they were used *in situ*.[8] Although BH_3.amine complexes, such as BH_3.$N(CH_3)_3$ and BH_3.pyridine[9] do not reduce acetophenone in THF as



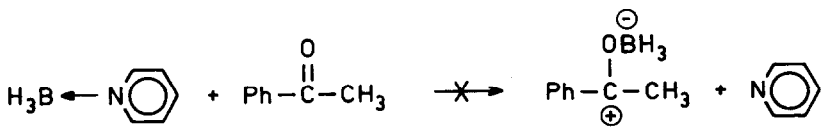
solvent, the BH_3.1a complex reduces it with an o.y. of 18% (Table, run 1). This difference can be explained by the assumption that in BH_3.1a the BH_3 is more loosely complexed to 1a than it is to trimethylamine and pyridine in $BH_3.N(CH_3)_3$ and BH_3.pyridine, respectively (attributed to a steric repulsion of the BH_3 group with the phenylgroups of 1a as shown in a CPK model of BH_3.1a). This makes the complexation of BH_3 with the carbonylgroup of

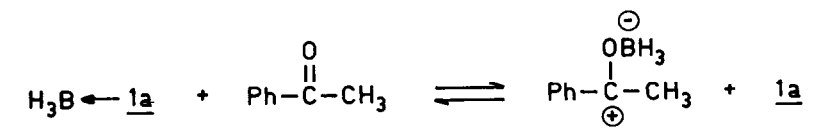
Table: Reduction of acetophenone to (S)-1-phenyl-1-ethanol by BH_3.1 complexes[a] in the presence of $BF_3.OEt_2$ (THF solution)

run	ligand	c.y.[b] (%)	o.y.[c] (%)
1[d]	1a	70	18
2	1a	76	42
3[e]	1a	58[f]	41
4[g]	1a	75	39
5[h]	1a	80	42
6	1c	77	38
7	1d	73	41
8	1b	66	0

[a] Ratio acetophenone:BH_3.1:$BF_3.OEt_2$ is 1:2:1.
[b] Chemical yields not optimalized.
[c] Optical yields calculated on basis of the highest value reported. in literature: $[\alpha]_D^{23}$ = -52.5 (c 2.3, CH_2Cl_2); reference 6a.
[d] Without $BF_3.OEt_2$.
[e] Ratio acetophenone:BH_3.1a:$BF_3.OEt_2$ is 1:1:1.
[f] Still 10% of acetophenone present in the crude reaction mixture.
[g] Ratio acetophenone:BH_3:1a:$BF_3.OEt_2$ is 1:4:2:1.
[h] Et_2O as solvent.

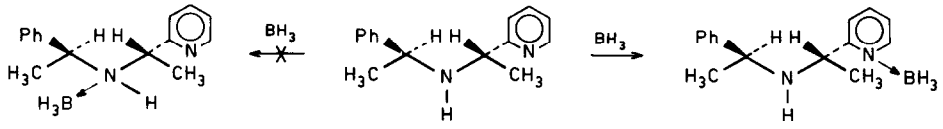
acetophenone to compete effectively with that of amine 1a, allowing the reduction to take place (the latter complexation is proposed as the first step in the uncatalyzed BH_3 reduction[10]).





On addition of $BF_3.OEt_2$ to the reaction mixture (which causes a stronger polarization of the carbonylbond[11]) an o.y. of 42% was obtained (Table, run 2). This result compares favourably with that obtained with the BH_3.(S)-α-methylbenzylamine complex (o.y. 14%).[3b] When the reaction was performed with an additional two equivalents of BH_3.THF the optical yield was hardly lowered (runs 2 and 4). This implies that the rate of reduction with BH_3.1a is considerably faster than with BH_3.THF as reducing agent. Using diethylether instead of THF as solvent did not alter the enantioselectivity (o.y. 42%, run 5), which differs from the results found for other borane.chiral amine complexes.[3b]

The replacements of ligand 1a by an amine with an additional methoxy group (ligands 1c and 1d) did not increase the optical yield (38% and 41%, respectively; runs 6 and 7).[13] This contrasts sharply with the effect observed for the corresponding lithium amides (2a-2d) in the nBuLi addition to benzaldehyde.[7a] The difference can be explained by the fact that in the former case the boron atom is coordinatively saturated after complexation with the amine, leaving no capacity for an additional internal ligation with the methoxy group. The complexes BH_3.1a, BH_3.1c and BH_3.1d are sterically very similar and as a consequence the same degree of enantioselectivity is to be expected. The fact that BH_3.1b gave no optical induction (run 8) is understandable when the assumption is made that BH_3 has a preference for complexation with



the aromatic nitrogen rather than with the aliphatic nitrogen atom of 1b which may bring the BH_3 moiety too far away from the chiral environment in order to cause enantioselectivity. The preference of the BH_3 group for complexation with the pyridine nitrogen is in agreement with the already mentioned steric repulsion between the BH_3 and the two phenyl groups in complex BH_3.1a.[14]

It is worthwhile to note that in all experiments the amines 1a-1d could be recovered easily in >90% yield without any loss of optical activity.

Acknowledgement: This investigation was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for the Advancement of Pure Research (ZWO).

References and Notes

1. See e.g. S. Terashima, N. Tanno, K. Koga, Chem. Lett, 1980, 981; R. Noyori, I. Tomino, Y. Tanimoto, J. Am. Chem. Soc. 1979, **101**, 3129; M. Asami, T. Mukaiyama, Heterocycles, 1979, **12**, 499; T. Sato, Y. Gotoh, T. Fujisawa, Tetrahedron Lett. 1982, 4111; S. Yamaguchi, H.S. Mosher, J. Org. Chem. 1973, **38**, 1870.

2. A. Pelter and K. Smith in "Comprehensive Organic Chemistry", D.N. Jones (Ed.), Pergamon, Oxford, 1979, Vol. 3, p. 687-940.
3. a) R.F. Borch, S.R. Levitan, J. Org. Chem. 1972, **37**, 2347; b) M.F. Grandon, D.G. McCleery, J.W. Wilson, J. Chem. Soc., Perkin Trans I, 1981, 231.
4. T. Yamashita, H. Mitsai, H. Watanabe, N. Nakamura, Makromol. Chem., 1980, **181**, 2563.
5. A. Hirao, S. Itsuno, S. Nakahama, N. Yamazuki, J. Chem. Soc., Chem. Commun., 1981, 315.
6. a) S. Itsuno, A. Hirao, S. Nakahama, N. Yamazuki, J. Chem. Soc., Perkin Trans I, 1983, 1673; b) S. Itsuno, K. Ito, A. Hirao, S. Nakahama, J. Org. Chem., 1984, **49**, 555.
7. a) M.B. Eleveld and H. Hogeveen, Tetrahedron Lett, 1984, 5187; b) M.B. Eleveld and H. Hogeveen, submitted for publication; c) H. Hogeveen and W.M.P.B. Menge, to be published; d) M.B. Eleveld, H. Hogeveen and E.P. Schudde, forthcoming paper.
8. The enantiomers of the amines used in these experiments are also easily accessible because compounds 1a-1e are prepared starting from α-methylbenzylamine which is commercially available in both enantiomeric forms.[7d]
9. a) C.L. Lane, Aldrichimica Acta, 1977, **10**, 41; b) R.P. Baines, J.H. Graham, M.D. Taylor, J. Org. Chem., 1958, **23**, 1561.
10. W.M. Jones, J. Am. Chem. Soc., 1960, **82**, 2528; H.C. Brown, H.I. Schlesinger, A.B. Burg, J. Am. Chem. Soc., 1939, **61**, 673.
11. This stronger polarization may have as consequence that the reduction can take place by a direct nucleophilic attack of the BH_3.amine to the carbonyl bond. See e.g. U. Nagai, T. Shishito, R. Chiba and M. Mitsuhashi, Tetrahedron, 1965, **21**, 1701.
12. When 1 eq. of BH_3.1a instead of 2 eq. was used (see runs 2 and 3) the same o.y. was found but the reaction mixture still contained 10% of unreacted acetophenone; hence in all other runs 2 equivalents of BH_3.1 were used.
13. The BH_3.1c and BH_3.1d complexes can both exist as a diastereomeric pair because a new chiral center (the nitrogen atom) is created. The effect of this extra chiral center has not been investigated because separation of the diastereomers will be very difficult due to the observed instability of this type of complexes in the solid phase.
14. Attempts to reduce acetophenone by reagents derived from 1e with 1 eq. as well as with 2 eq. of BH_3 failed under conditions where (S)-valinol with BH_3 gives complete reaction with acetophenone.[5] Even addition of 1 eq. of $BF_3.OEt_2$ did not lead to reaction.

(Received in UK 11 November 1985)