Asymmetric Reduction of Prochiral Aromatic Ketones by Borane–Amine Complexes in the Presence of Chiral Amine–BF_3 Catalysts

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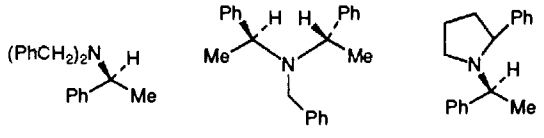
The borane complexes of (*S*)-(−)-*N*,*N*-dibenzyl-1-phenylethylamine **1**, (*S*,*S*)-(−)-*N*,*N*-bis(1-phenylethyl)-1-phenylethylamine **2**, (−)-2-phenyl-1-(1-phenylethyl)pyrrolidine **3**, (−)-7-(1-phenylethyl)-4,5-dihydro-3*H*-dinaphth[2,3-*c*;2′,3′-*e*]azepine **4** and 1-(1-phenylethyl-3,4-diphenylpyrrolidine **5** have been prepared and used to reduce prochiral aromatic ketones to alcohols in 10–57% e.e. in the presence of BF_3·OEt_2. The complex **4**·BF_3 catalyses asymmetric reduction of acetophenone by *N*,*N*′-diethylaniline–BH_3 to give 1-phenylethyl alcohol in 51% e.e. A transition state consisting of a chiral amine·BF_3·BH_3 complex and the ketone is proposed to explain the transformation.

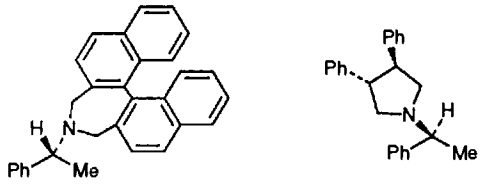
Chiral amine·BH_3 complexes are promising reagents for asymmetric reduction of prochiral compounds since the chiral amine can be readily recovered and recycled.[1-3] Although (*R*)-(+) and (*S*)-(−)-1-phenylethylamine–borane complexes reduce prochiral ketones to alcohols at reflux temperatures the latter are obtained in only low (1–3%) enantiomeric excess.[4] In contrast, borane complexes of 1-phenylethylamine and *N*,*N*-dimethyl-1-phenylamine fail to reduce ketones at room temperature in benzene,[5] although in the presence of 1 equiv. of BF_3·OEt_2 they do so in 0.5 h at 0 °C, to give the alcohols in up to 13% e.e.[5] More recently, the chiral bis(1-phenylethyl)-amine·BH_3 complex has been reported to reduce acetophenone with 42% e.e. in the presence of BF_3·OEt_2.[6] Here we describe a detailed investigation of this transformation undertaken both in order to understand its mechanism and also to select a chiral amine system that would give good results.

Results and Discussion

Synthesis of the Chiral Amines **1–5**.—The parent amines of 1 and 2 have been prepared by following closely related procedures.[7,8] The amines **3**, **4** and **5** have been prepared as outlined in Scheme 1.[9-12]

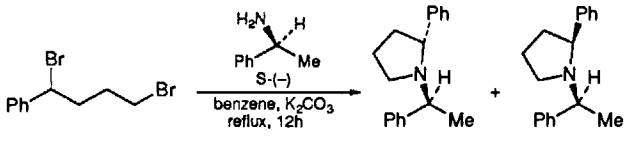


1 **2** **(−)-3**



(−)-4 **(−)-5**

The amine–borane derivatives of (*S*)-**1**, (*S*,*S*)-**2** and (−)-**3** prepared using (*S*)-(−)-1-phenylethylamine, (−)-**4** prepared using (R)-(+)-1-phenylethylamine and (−)-**5** prepared using (*S*)-(−)-1-phenylethylamine (Scheme 1) were utilized for reductions. Initially, we carried out the investigations utilizing the amine system (−)-**4**. The borane complex of the chiral amine (−)-**4** was prepared by bubbling an excess of diborane gas through a benzene solution of (−)-**4**, the IR spectrum of which showed strong BH absorption at 2400 cm^{-1}. Attempted reduction of acetophenone using this borane complex in benzene gave recovery of acetophenone even after the mixture had been stirred for 24 h at room temperature. A similar reaction conducted in the presence of BF_3·OEt_2 gave 1-phenylethanol in 51% e.e. (Scheme 2).



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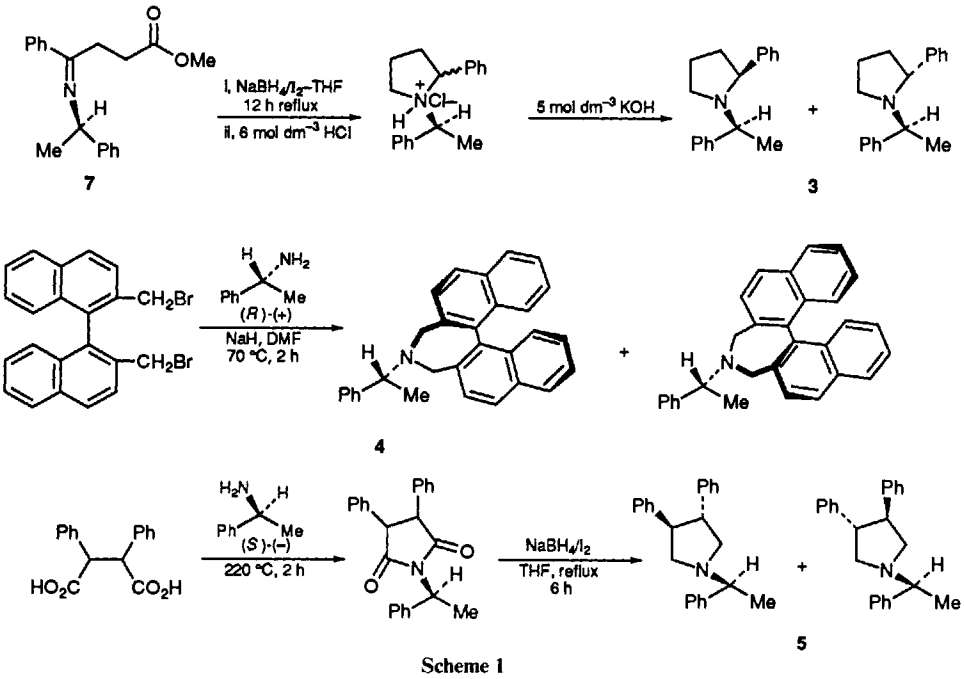
Results for the reduction of other ketones with this complex in the presence of BF_3·OEt_2 are summarized in Table 1. The configurations of the products are consistently *R* with the optical induction decreasing with increasing chain length of the alkyl moiety.

Although the role of BF_3·OEt_2 in these reductions is not understood, Grundon *et al.* suggested a mechanism involving hydrogen-transfer followed by fluorine-transfer (Scheme 3).[5]

We have carried out further investigations in order to understand the role of BF_3·OEt_2 in this reaction. It is known that BF_3·OEt_2 liberates diborane from amine·BH_3 and, also, that diborane does not displace BF_3 from amine·BF_3 adducts.[13] Accordingly, the formation of an amine·BF_3 complex as an intermediate cannot be ruled out. In any case, it was of interest to prepare the amine·BF_3 complex and examine whether it would catalyse the asymmetric reduction of acetophenone by an achiral Lewis base–borane complex such as *N*,*N*-diethylaniline–borane.

The chiral amine·BF_3 complex was prepared by the addition of a stoichiometric amount of BF_3·OEt_2 to the chiral amine (−)-**4** in dry ether under nitrogen. The ether was pumped off under dry nitrogen to give the amine·BF_3 complex, to which *N*,*N*-diethylaniline–borane complex (1 equiv.) in dry benzene followed by acetophenone (1 equiv.) were added. Work-up gave the alcohol product in 51% e.e. The result is similar to that obtained following the earlier procedure. We carried out experiments using various amounts of chiral amine·BF_3 complex in the reduction of acetophenone by *N*,*N*-diethylaniline·BH_3 or triethylamine·BH_3 the results for which are summarized in Table 2.[10] They indicate that although the

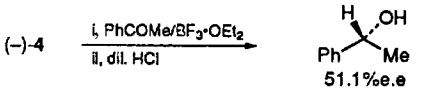


Scheme 1

Table 1 Reduction of prochiral ketones using amine (−)-4-borane complex[a]

Substrate RCOR′	Product[b]	Yield[c] (%)	$[\alpha]_D^{25}$ (*c*, solvent[d])	E.e.% (Configuration)
R = Ph, R′ = Me		82	+23 (3, MeOH)[e]	51(*R*)
R = Ph, R′ = Et		81	+20 (1, Me_2CO)[f]	41(*R*)
R = Ph, R′ = Pr		80	+5 (2, benzene)[g]	11(*R*)
R = 1-naphthyl, R′ = Me		78	+45 (2, MeOH)[h]	57(*R*)

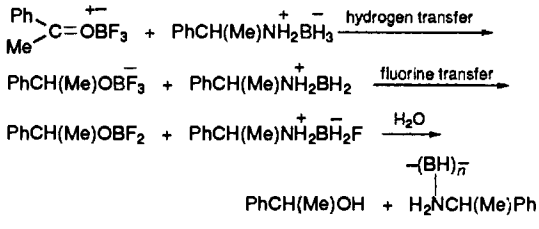
[a] All reactions were carried out at 0 °C with 10 mmol each of amine·BH_3, ketone and BF_3·OEt_2 in benzene. The experiments were run at least twice in each case. [b] Products were identified by analysis of spectral data (IR, ^1H NMR) and comparison with the reported data. [c] Yields are of isolated, chromatographed and distilled products. [d] Optical rotations were measured with an Autopol-II automatic polarimeter (observed rotation accuracy 0.01). Throughout, $[\alpha]_D$ values are quoted in units of 10^{-1} deg cm^2 g^{-1}. [e] Based on the maximum $[\alpha]_D^{25}$ −45.5 (*c* 3, MeOH)[16]. [f] Based on the maximum $[\alpha]_D^{25}$ −47.03 (*c* 1, Me_2CO) (R. H. Pickard and K. Kenyon, *J. Chem. Soc.*, 1914, **105**, 115). [g] Based on the maximum $[\alpha]_D^{25}$ +45.2 (*c* 3, benzene (see ref. in footnote *f*). [h] Based on the maximum $[\alpha]_D^{25}$ −78.9 (*c* 3, MeOH).[13]



Scheme 2

asymmetric inductions are decreased very little by a 50% reduction in the concentration of chiral amine·BF_3 complex, any further reduction has a significant effect. This may result from competitive uncatalysed reduction of the ketone by the *N*,*N*-diethylaniline·BH_3 complex. We found that in the absence of amine·BF_3 acetophenone reacts with the *N*,*N*-diethylaniline·BH_3 complex at 0 °C over 3 h to give the corresponding alcohol in 30% yield.

In order to examine both whether such a catalytic process is a general one and its structural aspects, we have carried out similar experiments using amines **1**, **2**, **3** and **5**. The results are summarized in the Table 3.



Scheme 3

It is clear from these results that the asymmetric inductions are at best, modest. However, the mechanism of the catalytic reduction by amine·BF_3 in intriguing since there is no free coordination site available on the boron for further complexation with the ketone. The nature of the actual reactive species may be deduced from the results summarized in Tables 1–3. The

Table 2 Catalytic reduction of acetophenone in the presence of the chiral amine (−)-**4**·BF_3 complex[a]

Ketone–amine·BF_3 (mol. equiv.)	Reaction time (h)	External reducing agent	Yield[b] (%)	$[\alpha]_D^{25}$ (C3, CH_3OH)	E.e.%[c]
1:1	3	$PhEt_2N{\cdot}BH_3$	81	+23	51.1
1:1	15	$Et_3N{\cdot}BH_3$	80	+22	48.9
1:0.75	3	$PhEt_2N{\cdot}BH_3$	82	+23	51.1
1:0.5	3	$PhEt_2N{\cdot}BH_3$	80	+22	48.9
1:0.5	15	$Et_3N{\cdot}BH_3$	80	+22	48.9
1:0.4	3	$PhEt_2N{\cdot}BH_3$	80	+19	42.2
1:0.25	3	$PhEt_2N{\cdot}BH_3$	75	+9	20.0

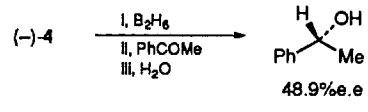
[a] Reactions were carried out with the ketone (10 mmol) and the amine·BH_3 (10 mmol) at 0 °C. The experiments were run at least twice in each case. [b] Yields are of isolated, chromatographed and distilled products. [c] Enantiomeric excess based on the maximum[16] $[\alpha]_D^{25}$ −45.5 (*c* 3, MeOH).

Table 3 Reduction of prochiral ketones using amine-borane complexes[a]

Substrate RCOR′	Amine·borane complex	Product[b] 	Yield (%)[c]	E.e. (%) (Config. all *R*)
R = Ph, R′ = Me				
	(−)-**1**	R = Ph, R = Me	80	24[d]
	(−)-**2**	R = Ph, R = Me	82	48
	(−)-**3**	R = Ph, R = Me	73	53
	(−)-**5**	R = Ph, R = Me	86	17
R = Ph, R′ = Et				
	(−)-**1**	R = Ph, R′ = Et	87	22[e]
	(−)-**2**	R = Ph, R′ = Et	78	37
	(−)-**3**	R = Ph, R′ = Et	70	41
	(−)-**5**	R = Ph, R′ = Et	84	10
R = Ph, R′ = Pr				
	(−)-**1**	R = Ph, R′ = Pr	80	6[f]
	(−)-**2**	R = Ph, R′ = Pr	75	10
	(−)-**3**	R = Ph, R′ = Pr	65	15
R = 1-naphthyl, R′ = Me				
	(−)-**1**	R = 1-naphthyl, R′ = Me	75	39[g]
	(−)-**2**	R = 1-naphthyl, R′ = Me	70	52
	(−)-**3**	R = 1-naphthyl, R′ = Me	71	56

[a] All reactions were carried out at room temp. for 6 h with amine·BH_3 (10 mmol) ketone (10 mmol) and BF_3·OEt_2 (10 mmol) in benzene. The experiments were run at least twice in each case. [b] Products were identified by analysis of the spectral results (IR, ^1H NMR) and comparison of these with those already reported. [c] Yields are of isolated, chromatographed and distilled products. [d] Based on the maximum $[\alpha]_D^{25}$ −45.5 (*c* 3, MeOH). [e] Based on the maximum $[\alpha]_D^{25}$ −47.03 (*c* 1, Me_2CO).[14] [f] Based on the maximum $[\alpha]_D^{25}$ +45.2 (*c* 3, benzene).[16] [g] Based on the maximum $[\alpha]_D^{25}$ −78.9 (*c* 3, MeOH) (see ref. in footnote *f*, Table 1).

reaction of $R_3N{\cdot}BH_3$ with $BF_3{\cdot}OEt_2$ is expected to give $R_3N{\cdot}BF_3$ and borane. Since the diborane is not liberated, the >B–H unit must be present in an associated form along with the $R_3N{\cdot}BF_3$ to provide the reactive intermediate. Also, the same reactive intermediate would have been formed in the reaction of chiral $R_3N{\cdot}BF_3$ with $PhEt_2N{\cdot}BH_3$ or $Et_3N{\cdot}BH_3$. In order to gain further information about the reactive species, we prepared chiral amine·BF_3 using the amine **4** as described above. This was dissolved in dry benzene and diborane gas was bubbled through the solution. The IR spectrum of the solution exhibits strong >B–H absorption at 2450 cm^{-1}. Since diborane cannot displace BF_3 from the $R_3N{\cdot}BF_3$ complex, the >B–H must be present in an associated form with $R_3N{\cdot}BF_3$. Addition of triphenylphosphine to this gave, after work-up, a solid product along with the chiral amine. The ^{11}B NMR spectrum of this compound was found to be the same as that of $PPh_3{\cdot}BH_3$. The associated complex prepared in this way reduced acetophenone to the corresponding alcohol in 48.9% e.e. (Scheme 4).



Scheme 4

Initially, it was thought that since this catalysis might be explained in terms of displacement of one of the fluorides by the ketone oxygen to give a reactive intermediate, the amine·BF_3 should also catalyse other ketone reactions. For example, if this amine·BF_3 species can activate an α,β-unsaturated carbonyl group, it should catalyse certain Diels–Alder reactions. In the event Diels–Alder additions of dienes and dienophiles normally catalysed by a Lewis acid failed to react in the presence of the amine·BF_3 species. Since $R_3N{\cdot}BF_3$ catalyses, then, only borane reductions, the results can be best explained in terms of the transition state outlined in Fig. 1. In order to investigate this species, we carried out similar experiments with triethylamine which, although forming a strong complex with borane, failed to reduce acetophenone at 0 °C. However, in the presence of $BF_3{\cdot}OEt_2$ (1 equiv.) the reduction is complete in 8 h at 0 °C to give 1-phenylethanol (85%). Similarly, acetophenone gave 1-phenylethanol (84%).

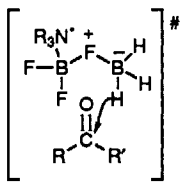


Fig. 1

Experimental

The chiral amine **1** was prepared through benzylation of (*S*)-(−)-1-phenylethylamine in the presence of KOH, benzyl bromide and sodium iodide.[7] The amine **2** has been synthesized by benzylation of the corresponding secondary amine which can be readily prepared using (*S*)-(−)-1-phenylethylamine following a reported method.[8] The diastereoisomeric amines of **3** have been prepared from the dibromide **6** or the imine **7** as outlined in Scheme 1.[9] The diastereoisomeric amines **4** and **5** were also prepared as outlined in Scheme 1.[10-12] These diastereoisomers were separated by chromatography on neutral alumina column utilizing hexane–ethyl acetate as eluent. The amines eluted first in each case were obtained in pure form and utilized for this study (Tables 1–3).

Reduction of Acetophenone with a Chiral Amine (−)-**4**•*borane Complex in the Presence of* BF_3•OEt_2.—Diborane gas (20 mmol) generated through the slow addition of I_2 (5.2 g, 20 mmol) in diglyme (25 cm^3) to $NaBH_4$ (1.6 g, 40 mmol) in diglyme (10 cm^3) at room temperature, was bubbled slowly into a benzene solution of (−)-7-(1-phenylethyl)-4,5-dihydro-3*H*-dinaphthazepine (3.99 g, 10 mmol) during 2 h. Acetophenone (1.2 g, 10 mmol) was added at 0 °C to the reaction mixture which was then stirred for 2 h at 0 °C. The reaction was quenched with water and the organic layer was separated, washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The amine present in the mixture was precipitated with BF_3•OEt_2 in ether as a BF_3 salt. The ether layer was decanted and concentrated to give the crude alcohol product which was purified first by column chromatography on silica gel with hexane–ethyl acetate (90:10) as eluent and then by distillation under reduced pressure; the product (1.0 g, 82%) had b.p. 80 °C at 6 mmHg, {lit.,[15] 203 °C (at 760 mmHg), $[\alpha]_D^{25}$ +23 (*c* 3, MeOH); lit.,[16] $[\alpha]_D^{25}$ −45.5 (*c* 3, MeOH)}; ν_{max}(neat)/cm^{-1} 3350, 3050 and 1600; δ_H(100 MHz, $CDCl_3$) 1.4 (d, 3 H), 2.9 (br s, 1 H), 4.8 (q, 1 H) and 7.3 (m, 5 H).

Reduction of Acetophenone with a N,N-*Diethylaniline–Borane Complex in the Presence of a Chiral Amine* (−)-**4**•BF_3 *Complex as Lewis Acid Catalyst.*—To a solution of the chiral amine **4** (3.99 g, 10 mmol) dissolved in dry ether (20 cm^3) was added BF_3•OEt_2 (1.42 g, 10 mmol) at 0 °C. The chiral amine•BF_3 complex was precipitated and the solvent was pumped off under nitrogen atmosphere. Into a two-necked septum flask *N*,*N*-diethylaniline (1.49 g, 10 mmol) was dissolved in benzene (40 cm^3) and diborane gas (20 mmol) was bubbled into the solution at 10 °C during 3 h. The *N*,*N*-diethylaniline–borane thus prepared was transferred to the flask containing the chiral amine•BF_3 complex under a nitrogen atmosphere and this was followed by acetophenone (1.2 g, 10 mmol) added at 0 °C. The mixture was stirred for 3 h after which the reaction was quenched with water (5 cm^3). The organic layer was separated and washed with 3 mol dm^{-3} HCl (3 × 10 cm^3) to remove *N*,*N*-diethylaniline after which the chiral amine was removed as its BF_3 complex to give the amine-free reduced product. The alcohol was purified by column chromatography over silica gel using hexane–ethyl acetate (90:10) as eluent and by distilation under reduced pressure; the product (1.0 g, 82%) had $[\alpha]_D^{25}$ +23 (*c* 3, MeOH).

Acknowledgements

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