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Enantioselective Reductions of Aromatic Ketones with Ammonia–Borane Complexes of Chiral Tetraphenyl-18-crown-6 Derivatives

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Enantioselective reductions of prochiral aromatic ketones with adducts formed between ammonia–borane and (2*R*,3*R*,11*R*,12*R*)- and (2*S*,3*S*,11*S*,12*S*)-tetraphenyl-1,4,7,10,13,16-hexaoxacyclo-octadecane, (*RRRR*)-(**3**) and (*SSSS*)-(**3**), have afforded the corresponding (*S*) and (*R*) aromatic secondary alcohols with enantiomeric excesses of 20—67%.

Although NH_3BH_3, RNH_2BH_3, and R_2NHBH_3 adducts exhibit[1,2] excellent (>90%) chemo- and diastereo-selectivities in their reductions of RCHO and R_2CO substrates, high enantiomeric excesses (e.e.s) in the reductions of RCOR′ substrates with $R^*NH_2BH_3$ adducts have been much more elusive. Thus, the rather low e.e.s (≤5%), obtained[3—5] when BH_3 was bound to $PhCH_2C^*HMeNRR'$ and PhC^*HMeNH_2, were only slightly improved upon (to *ca.* 21%) by BF_3 activation[6] of the RCOR′ substrates, and (to *ca.* 33%) by employing[5] $RC^*H(CO_2Me)NH_2$ as the chiral auxiliaries instead of R^*NH_2. More recently, $RC^*H(CH_2OH)NH_2$ auxiliaries have afforded[7] e.e.s approaching 100% and RNH_2BH_3, $RR'NHBH_3$, and $R_2R'NBH_3$ adducts modified[8] with axially chiral 2,2′-dihydroxy-6,6′-dimethylbiphenyl are almost (e.e.s ≤84%) as good. However, in all these reagents, the chiral auxiliary is covalently bonded to the boron atom and

Table 1. Reductions of aromatic ketones with NH_3BH_3 adducts of 18-crown-6 (**1**), the (2*R*,3*R*,11*S*,12*S*)-tetraphenyl-18-crown-6 derivative (**4**), and the (2*R*,3*R*,11*R*,12*R*)- and (2*S*,3*S*,11*S*,12*S*)-tetraphenyl-18-crown-6 derivatives, (*RRRR*)-(**3**) and (*SSSS*)-(**3**).[a]

Run	Crown ether (C.E.)	NH_3BH_3:C.E.	Ketone	Solvent	Time /h	% Yield[b]	$[\alpha]_D$ /°	Optical yield[c] (%)	E.e.[d] (%)	Absolute configuration
1	(**1**)	1:1	PhCOMe	PhMe	16	80	0	0	0	–
2	(**4**)	2:1	PhCOMe	PhMe–CH_2Cl_2 (9:1)	16	80	0	0	0	–
3	(*RRRR*)-(**3**)	1:1	PhCOMe	PhMe	1	70	–	–	28	(*S*)
4	(*RRRR*)-(**3**)	2:1	PhCOMe	PhMe	16	70	–	–	26	(*S*)
5	(*SSSS*)-(**3**)	1:1	PhCOMe	PhMe–CH_2Cl_2 (3:2)	16	70	–	–	20	(*R*)
6	(*RRRR*)-(**3**)	1:1	PhCOEt	PhMe	1.25	63	−12.7	28[e]	22	(*S*)
7	(*SSSS*)-(**3**)	1:1	PhCOPr^i	PhMe	1.25	71	+33.9	71[f]	67	(*R*)
8	(*SSSS*)-(**3**)	1:1	PhCOBu^t	PhMe	1.25	73	+17.8	59[g]	64	(*R*)
9	(*SSSS*)-(**3**)	2:1	PhCOBu^t	PhMe	1.25	70	–	–	62	(*R*)

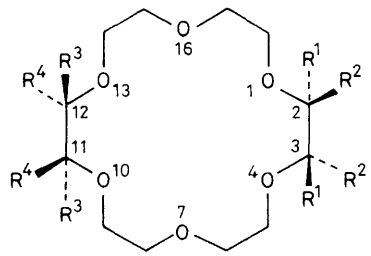
[a]Conditions illustrated by reference to run 3. To a stirred solution of (NH_3BH_3)·(*RRRR*)-(**3**) (0.35 mmol) in dry PhMe (10 ml) under N_2 at −78 °C were added PhCOMe (0.43 mmol) and distilled BF_3·Et_2O (0.35 mmol). The reaction mixture was stirred for 1 h, H_2O was added, and the organic products were isolated and chromatographed (SiO_2, CH_2Cl_2–n-pentane, 4:1, then MeOH) to separate PhCHOHMe from (*RRRR*)-(**3**). The alcohol was converted into the menthoxyacetate ester in the standard manner. The diastereoisomeric ratios were determined by ^1H n.m.r. spectroscopy after addition of $Eu(hfbc)_3$. [b]All yields quoted refer to *isolated* yields. In the case of $(NH_3BH_3)_2$·(**4**) (0.5 mol. equiv.), the progress of reaction with PhCOMe (1.0 mol. equiv.) was monitored by g.l.c. After 75 min, conversion into PhCHOHMe was found to be quantitative. [c]The optical yields were calculated from the optical rotations of the alcohols. [d]The enantiomeric excesses (e.e.s) of the alcohols were deduced from the diastereoisomeric ratios of their menthoxyacetate esters estimated by ^1H n.m.r. spectroscopy (*cf.* footnote a). [e]Based on the reported (R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, 1914, 1115) value of $[\alpha]_D$ +45.45° (*c* 5.15, $CHCl_3$) for (*R*)-PhCHOHEt. [f]Based on the reported (P. A. Levene and L. A. Mikeska, *J. Biol. Chem.*, 1926, **70**, 355) value of $[\alpha]_D^{20}$ + 47.66° (*c* 6.8, Et_2O) for (*R*)-PhCHOHPr^i. [g]Based on the reported (S. Winstein and B. K. Morse, *J. Am. Chem. Soc.*, 1952, **74**, 1133) value of $[\alpha]_D^{20}$ +30.6° (*c* 3.64, Me_2CO) for (*R*)-PhCHOHBu^t.

hence not easily recycled. Here, we describe the first examples of chiral reagents where the reducing agent is bound non-covalently to the chiral auxiliaries.

Our observations[9] that NH_3BH_3 forms crystalline 1:1 and 2:1 complexes, respectively, with 18-crown-6 (**1**) and its octamethyl derivative (**2**) led us to establish conditions (run 1 in Table 1) for the reduction of PhCOMe. Since the use of 18-crown-6 derivatives incorporating carbohydrate residues[10] as chiral auxiliaries in the reduction of this prochiral ketone with NH_3BH_3 gave[11] disappointingly low e.e.s (*ca.* 10%), we decided to evaluate the tetraphenyl-18-crown-6 derivatives[12—15] (*RRRR*)-(**3**) and (*SSSS*)-(**3**) as chiral auxiliaries. The indirect synthetic approach,[12] relying upon reaction of (±)-hydrobenzoin and $Ts(OCH_2CH_2)_2OTs$ (Ts = *p*-$MeC_6H_4SO_2$) in dioxane with NaOH as base gave a crude product which, on treatment[16] with methanolic NH_3BH_3, afforded the 2:1 crystalline adduct† $(NH_3BH_3)_2$·(**4**), m.p. 210—220 °C, with the *trans–syn–trans* configuration‡ in 31% yield. Single crystals suitable for *X*-ray crystallography§ were grown from CH_2Cl_2–n-pentane. An *X*-ray structural analysis (Figure 1) confirmed the existence of a 2:1 adduct in which the two equivalent NH_3BH_3 guest molecules approach opposite faces of (**4**). Comparison with the published[14] *X*-ray structure of uncomplexed (**4**), which adopts a conformation closely paralleling that of (**1**), shows that the formation of the centrosymmetric 2:1 NH_3BH_3 adduct with (**4**) causes the host molecule to revert to a conventional all-*gauche* conformation with pseudo D_{3d} symmetry for the ring ignoring the four equatorial phenyl substituents. Reduction of PhCOMe with 0.5 mol. equiv. of $(NH_3BH_3)_2$·(**4**) to give (*RS*)-PhCHOHMe in quantitative yield (footnote b relating to run 2 in Table 1) established that, in 2:1 adducts, both NH_3BH_3 guests can provide (*cf.* refs. 2 and 6) at least one hydride ion each. Our failure‡ to obtain a crystalline adduct of (±)-*trans–anti–trans*-tetraphenyl-18-crown-6 (±)-(**3**) with NH_3BH_3 from the above reaction persuaded us to resolve hydrobenzoin and convert[12,13] the (*R*)-(+)- and (*S*)-(−)-isomers separately into (*RRRR*)-(**3**), m.p. 113—116 °C, $[\alpha]_D$ +8.2°, $[\alpha]_{436}$ +25° (*c* 0.87, $CHCl_3$) and (*SSSS*)-(**3**), m.p. 110—111 °C, $[\alpha]_D$ −7.6°, $[\alpha]_{436}$ −24° (*c* 0.74, $CHCl_3$). Recrystallisation of (*RRRR*)-(**3**) from CH_2Cl_2–n-pentane afforded single crystals suitable for *X*-ray analysis and the structure is currently being investigated. In contrast with the *trans–syn–trans* isomer (**4**), the chiral *trans–anti–trans* isomers, (*RRRR*)-(**3**) and (*SSSS*)-(**3**), formed 1:1 adducts with NH_3BH_3 in CH_2Cl_2–n-pentane: (NH_3BH_3)·(*RRRR*)-(**3**), m.p. 150—155 °C, and (NH_3BH_3)·(*SSSS*)-(**3**), m.p. 152—157 °C were isolated† in 69 and 62% yields, respectively. Single crystals of the former were suitable for *X*-ray crystallography.§ The structural analysis (Figure 2) shows that, despite the 1:1 stoicheiometry of the adduct and the fact that two of the four phenyl substituents are axial, the macrocyclic ring still adopts an all-*gauche* conformation approximating to local pseudo D_{3d} symmetry, *i.e.* a stable chiral NH_3BH_3 adduct is formed. Runs 3—9 in Table 1 demonstrate that, even in solution, the chiral tetraphenyl-18-crown-6 derivatives (*RRRR*)-(**3**) and (*SSSS*)-(**3**) bind NH_3BH_3 and serve as chiral auxiliaries for enantioselective reductions of prochiral PhCOR (R = Me, Et, Pr^i, or Bu^t) substrates by NH_3BH_3. The following comments can be made and conclusions drawn.

(i) Compared with the only other previous report[17] on asymmetric borohydride ($NaBH_4$) reduction of aromatic ketones in the presence of chiral 18-crown-6 derivatives (the highest e.e. observed was 8.1%) the enantioselectivities recorded in Table 1 are encouragingly high, given that the only substrate binding to the chiral NH_3BH_3 adduct is probably restricted to that associated with the reduction, *i.e.* the transfer of H^- ion from the BH_3 group in (NH_3BH_3)·(**3**) to the CO group in the PhCOR substrate.

(ii) The e.e.s obtained (compare runs 3 and 4, and 8 and 9) with 2:1 adducts are almost as high as those obtained with 1:1 adducts.



	R^1	R^2	R^3	R^4
(**1**)	H	H	H	H
(**2**)	Me	Me	Me	Me
(*RRRR*)-(**3**)	Ph	H	Ph	H
(*SSSS*)-(**3**)	H	Ph	H	Ph
(**4**)	H	Ph	Ph	H

† All new adducts gave satisfactory analytical data.

‡ The free crown (**4**), m.p. 190—191 °C, $M^{\cdot+}$ 568 (electron impact mass spectrum), $[M + NH_4]^+$ 586 (chemical ionisation with NH_3 as carrier gas), was obtained (89% yield) after treatment of $(NH_3BH_3)_2$·(**4**) with Me_2CO–$CHCl_3$ and column chromatography on SiO_2 ($CHCl_3$–MeOH, 9:1): ^{1}H n.m.r. data: δ($CDCl_3$, 400 MHz) 3.59, 3.59, 3.75, and 3.90 (16H, 4 × ABCD system, 4 × OCH_2CH_2O), 4.52 (4H, s, 4 × PhC*H*O), and 6.90—7.16 (20H, m, 4 × Ph). Although t.l.c. and ^{1}H n.m.r. spectroscopy indicated that the crude reaction mixture contained (±)-(**3**) in addition to (**4**), these diastereoisomeric 18-crown-6 derivatives could only be separated efficiently by column chromatography on an analytical scale. Also, all attempts to obtain a crystalline adduct of (±)-(**3**) with NH_3BH_3 were unsuccessful. The free chiral crowns, (*RRRR*)-(**3**) and (*SSSS*)-(**3**) {$[M^{\cdot+}$ 568 (electron impact), $[M + NH_4]^+$ 586 (chemical ionisation with NH_3 as carrier gas)}, obtained (*cf.* ref. 12) in 27 and 36% yields from (*R*)-(+)- and (*S*)-(−)-hydrobenzoins, respectively by stereospecific synthesis [$Ts(OCH_2CH_2)_2OTs$, NaOH, dioxane, 80 °C, 16 h] afforded identical ^{1}H n.m.r. spectra: δ($CDCl_3$, 400 MHz) 3.60, 3.70, 3.77, and 3.86 (16H, 4 × ABCD system, 4 × OCH_2CH_2O), 4.55 (4H, s, 4 × PhC*H*O), and 6.90—7.15 (20H, m, 4 × Ph). This ^{1}H n.m.r. spectrum was identical with that obtained at 400 MHz for the analytical sample of (±)-(**3**) dissolved in $CDCl_3$.

§ *Crystal data:* for $(NH_3BH_3)_2$·(**4**), $C_{36}H_{52}B_2O_6N_2$, M = 630.4, triclinic, space group $P\bar{1}$, a = 7.270(1), b = 8.489(1), c = 16.023(3) Å, α = 78.80(1), β = 82.20(1), γ = 75.04(1)°, U = 933 Å^3, Z = 1, D_c = 1.12 g cm^{-3}. R = 0.042, R_w = 0.058 for 1812 independent observed reflections [θ ≤50°, $|F_o| > 3\sigma(|F_o|)$]; preliminary results for (*RRRR*)-(**3**), $C_{36}H_{40}O_6$, M = 568.7, monoclinic, space group $P2_1$, a = 8.835(2), b = 23.419(5), c = 16.939(6) Å, β = 96.51(2)°, Z = 4; structure determination is continuing; for (NH_3BH_3)·(*RRRR*)-(**3**), $C_{36}H_{46}BO_6N$·0.25H_2O, M = 604.0, orthorhombic, space group $P2_12_12_1$, a = 8.166(2), b = 13.588(6), c = 32.420(8) Å, U = 3597 Å^3, Z = 4, D_c = 1.12 g cm^{-3}. R = 0.046, R_w = 0.050 for 2239 independent observed reflections [θ ≤58°, $|F_o| > 3\sigma(|F_o|)$].

In all cases, data were measured on a Nicolet R3m diffractometer with graphite-monochromated Cu-K_α radiation using the ω-scan routine. The structures of $(NH_3BH_3)_2$·(**4**) and (NH_3BH_3)·(*RRRR*)-(**3**) were solved by direct methods and the non-hydrogen atoms refined anisotropically. The NH_3 and BH_3 hydrogen atom positions were obtained from ΔF maps and the groups refined as rigid bodies. The atomic co-ordinates for $(NH_3BH_3)_2$·(**4**) and (NH_3BH_3)·(*RRRR*)-(**3**) are available from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation of this communication.

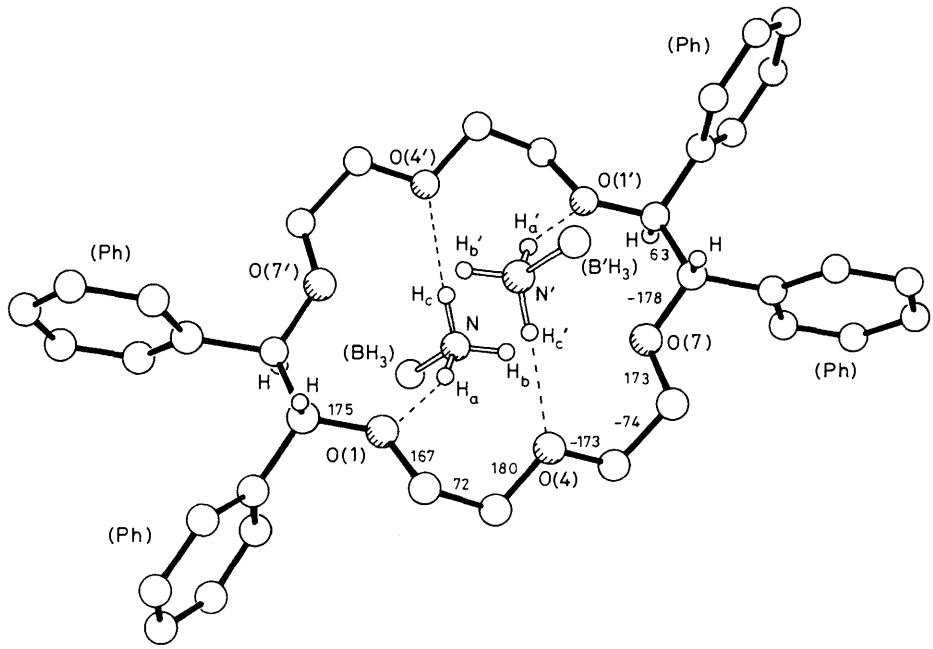


Figure 1. The supramolecular structure of $(NH_3BH_3)_2$·(**4**). The torsional angles (°) around the macrocycle are shown beside the relevant bonds. The ring experiences four [N–H · · · O] contacts within hydrogen bonding distance: *R*[N · · · O], *R*[H · · · O](Å), angles (θ_N and θ_H°) between COC planes and (a) NO vectors and (b) HO vectors, N–H · · · O angles (°) at H atoms: [N · · · O(1)] 3.07, [H_a · · · O] 2.15, (a) 4.2, (b) 5.1, H_a 161; [N · · · O(4')] 3.06, [H_c · · · O] 2.11, (a) 9.2, (b) 7.7, H_c 173. Non-bonded N · · · O(7) distance, 3.55 Å. Distance of N from mean plane of six O atoms, 1.78 Å. The B–N bond is inclined by 24° to the normal to this plane.

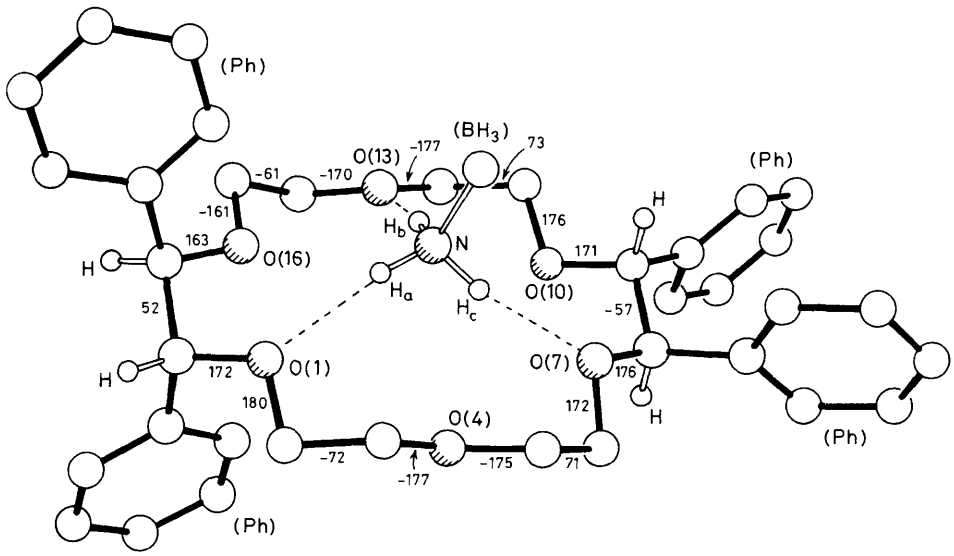


Figure 2. The supramolecular structure of (NH_3BH_3)·(*RRRR*)-(**3**). The torsional angles (°) around the macrocyclic ring are shown beside the relevant bonds. Hydrogen bond distances; *R*[N · · · O], *R*[H · · · O](Å), angles (θ_N and θ_H°) between COC planes and (a) NO vectors and (b) HO vectors, N–H · · · O angles (°) at H atoms: [N · · · O(1)] 3.07, [H_a · · · O] 2.12, (a) 15, (b) 11, H_a 168; [N · · · O(7)] 3.00, [H_c · · · O] 2.05, (a) 14, (b) 17, H_c 167; [N · · · O(13)] 2.94, [H_b · · · O] 1.98, (a) 20, (b) 18, H_b 172. Distance of N from mean plane of six O atoms, 1.24 Å. The B–N bond is inclined by 13° to the normal to this plane.

(iii) Solvent has a small influence on the observed e.e.s (compare runs 3 and 5); toluene is the preferred choice.

(iv) Without exception, the chiral auxiliaries (*RRRR*)-(**3**) and (*SSSS*)-(**3**) lead to (runs 3—9) the (*S*) and (*R*) alcohols, respectively.

(v) For the prochiral PhCOR substrates, much higher e.e.s are obtained when R is Pr^i or Bu^t (runs 7—9) than when R is Me or Et (runs 3—6).

We have been encouraged by these observations to synthesise other chiral 18-crown-6 derivatives (a) with bulkier

aromatic substituents and (b) with aromatic substituents carrying functional groups for attachment to solid supports for catalytic purposes.[12]

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