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Anchoring Substitution in Acyclic 1,3-Amino Alcohols. Asymmetric Reductions with Chiral Modifications of Lithium Aluminum Hydride and Borane.

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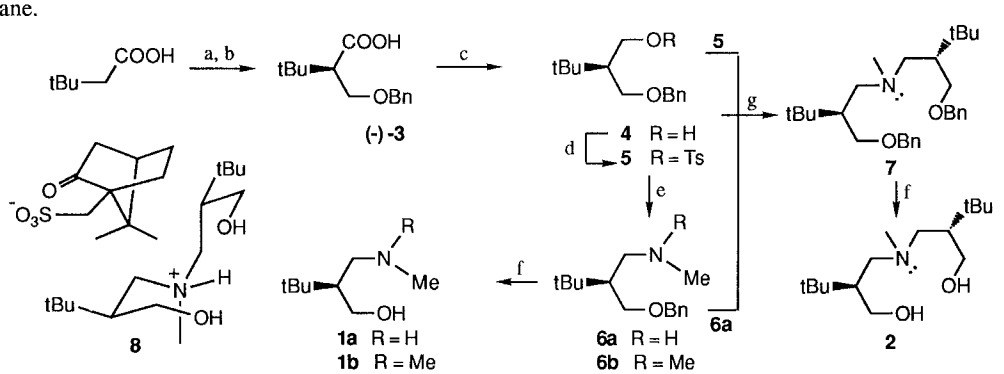
Abstract *: Chiral modifications of LAH and amino alcohols* ***1b*** *and* ***2*** *give erratic results in the asymmetric reduction of acetophenone. In the presence of chiral tetrahydro-1,3,2-oxazaborines, derived from* ***1a****, however, the borane reduction of acetophenone consistently leads to the (R)-carbinol in excess. The absolute configuration of the chiral ligands is determined via X-ray analysis of the ammonium (S)-(+)-10-camphorsulfonate salt* ***8****, derived from* ***2****.*

Recently we have been investigating the possibility of enforcing the proximity of functional groups in 1,3-disubstituted propane fragments by the incorporation of an anchoring substituent A, such as a *tert*-butyl group, in the 2-position.[2] In this context we wish to focus here on the chiral 1,3-disubstituted amino alcohols **1a**,**1b** and **2**, and on their potential as chiral ligands in modifications of lithium aluminum hydride (LAH) and borane.



[a] NaH, LDA; $ClCH_2OCH_2Ph$, THF (62 %); [b] (S)-PhCH(NH_2)Me; recrystallization in EtOAc; the acid is freed via 5 % HCl treatment and CH_2Cl_2 extraction; after 5 crystallizations the enantiomeric purity was >95 % as judged from ^1H NMR analysis of the corresponding methyl ester in the presence of the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene-(+)-camphorato] europium(III); [c] LAH, THF (92 %); [d] TsCl, pyridine (98 %); [e] for **6a** : $MeNH_2$ (40 % soln), THF, 100°C (90 %); for **6b** : Me_2NH (60 % soln), THF, 100°C (90 %); [f] Pd/C, H_2, (for **1a** : 90 %; for **1b** : 83 %; for **2** : 91 %); [g] MeOH, 90°C (77 %).

Scheme 1

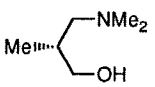
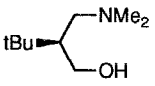
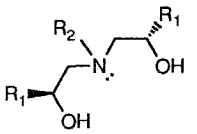
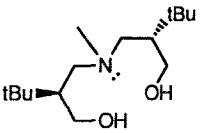
The synthesis of (+)-**1a**, (+)-**1b** and (+)-**2** is outlined in scheme 1.[3] It first involves the alkylation of the dianion of 3,3-dimethylbutanoic acid with chloromethyl benzyl ether, followed by the resolution of racemic (±)-**3** with (S)-(-)-α-methylbenzylamine. After reduction of enantiomerically pure acid (-)-**3**, the alcohol (-)-**4** is converted to tosylate (-)-**5**. Treatment of the latter with methylamine or dimethylamine leads to (+)-**6a** or (+)-**6b**, respectively. Debenzylation eventually yields the amino alcohols (+)-**1a** and (+)-**1b**, respectively. On the other hand, the coupling of amine (+)-**6a** with tosylate (-)-**5** in methanol at 90°C leads to the C_2-symmetrical tertiary amine (+)-**7**, which is eventually deprotected to diol (+)-**2**.

The shown absolute configuration of (+)-**2** (and hence of the starting acid (-)-**3**) was determined via X-ray diffraction analysis of the corresponding ammonium (S)-(+)-10-camphorsulfonate salt **8**.[4] As shown in scheme 2, the backbone adopts an overall staggered geometry with the (C-N) and (C-O)-bonds being roughly antiperiplanar to both *tert*-butyl groups.[5]

Among the relatively few 1,3-amino alcohols that have been used for the purpose of chirally modifying reducing agents,[6] an early and interesting example involves Mosher's use of Darvon alcohol with LAH.[7] The reduction of acetophenone gave either (R)-(+)- or (S)-(-)-1-phenyl ethanol in 60-70 % enantiomeric purity depending on the precise reaction conditions. Somewhat poorer results were obtained by Cohen when using structurally more simple amino alcohols such as e.g. **9** (table 1).[8] When reducing acetophenone with the complex obtained from LAH and chiral (+)-**1b** using Cohen's procedure the same (S)-(-)-carbinol was formed in excess (22 %); this result is surprising in view of the opposite stereogenicity of the stereocenters in **1b** and **9**.

A few tridentate 1,2-related aminodiols have also been used with the purpose of chirally modifying LAH. The tertiary amines **10** and **11** were reported by Morrison and Inanaga, respectively, to yield the (R)-(+)-carbinol upon acetophenone reduction (table 1).[9,10] Inanaga further studied a reagent system consisting of LAH-**11**-ROH, and observed the (S)-(-)-carbinol when ethanol was used as the modifier alcohol.[10]

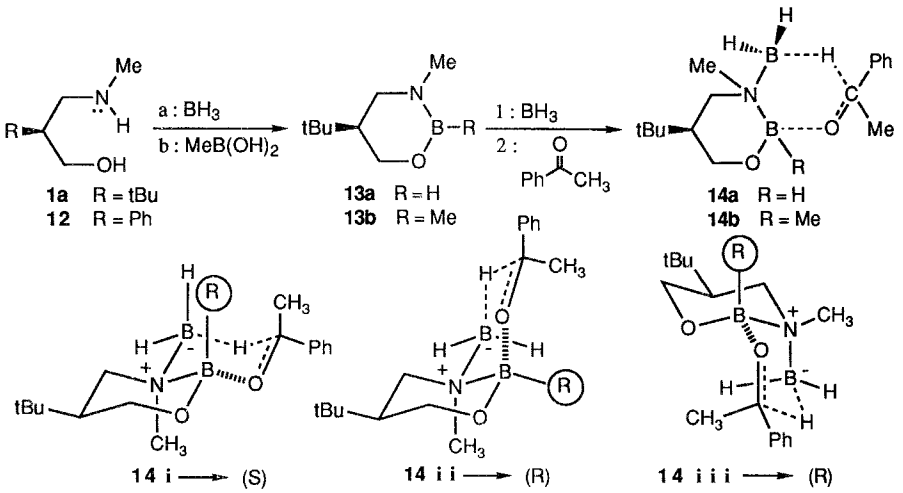
Table 1. Asymmetric reduction of acetophenone with chiral modifications of LAH (absolute configuration of 1-phenyl ethanol and enantiomeric excess).[a]

					
procedure[b]	**9**	**1b**	**10** (R_1=Me, R_2=Bu)	**11** (R_1=Ph, R_2=Me)	**2**
1	S(60)	S(22)			
2			R(44)[c]	R(20)	S(9)
3				S(88)	R(40)

[a] Determined by optical rotation and NMR analysis of MTPA esters obtained with (-)-Mosher's acid.

[b] Procedure 1 : (according to ref. 8). Slow addition of the amino alcohol (2.7 equiv.) in ether to a dilute solution of LAH in ether (1.2 equiv., 0.04 M) and addition of acetophenone in ether over 10' at -78°C. Stirring for 7 hrs at -78°C and water quenching at 25°C.
Procedure 2 : (according to ref. 10). Addition of a soln of LAH in ether (3.2 equiv., 1 M) to a cold soln of amino diol (3.5 equiv.) in ether, followed by stirring for 17 hrs at 25°C. Slow addition of acetophenone in ether at -100°C followed by stirring for 10 hrs at -100°C. Quenching with MeOH.
Procedure 3 : (according to ref. 10). Addition of a dilute soln of LAH in ether (5 equiv., 1 M) to a cold soln of aminodiol in ether (5 equiv.). After stirring for 5' dry EtOH (5 equiv) is added. The mixture is heated under reflux for 3 hrs. Slow addition of acetophenone in ether at -100°C, followed by stirring for 10 hrs. Quenching with MeOH.

[c] See ref. 9.



Scheme 2

Table 2. Asymmetric reduction of acetophenone with borane in the presence of chiral tetrahydro-1,3,2-oxazaborines **13a** (formed in situ) and **13b**.

procedure[a]	R	equivalents $PhCOCH_3$: ligand : BH_3	configuration (ee %)[b]
1	H (**13a**)	1.0 : 1.2 : 1.9	R(65)
2	Me (**13b**)	1.0 : 0.1 : 0.6	R(33)
		1.0 : 1.0 : 1.2	R(64)

[a] Procedure 1 (according to ref. 13). Addition of soln of BH_3 in THF (1.03 equiv.) to a soln of aminoalcohol (1.25 equiv.) in THF and stirring at 0°C overnight. Addition of acetophenone and stirring for 3 hrs. Procedure 2 (according to ref. 11). A soln of BH_3 in THF is added to a soln of **13b** in THF at 25°C. Addition of acetophenone, followed by stirring for 15' at 25°C.
[b] 1-phenyl ethanol, enantioselectivity determined by optical rotation

With the chiral *tert*-butyl derivative (+)-**2** the observed excesses were poor to almost non-existent and the sense of induction unpredictable. Clearly the obtained results can be considered erratic at best. We therefore turned our attention to a possibly more efficient and reproducible system based on borane as the hydride reagent.

As one of the superior methods in this field Corey and coworkers have recently described the highly efficient enantioselective borane reduction of ketones catalyzed by chiral 1,3,2-oxazaborolidines obtained e.g. from (S)-diphenyl prolinol and borane or methyl boronic acid.[11,12] In a similar way the chiral amino alcohol **1a** was treated with borane and methylboronic acid to yield the cyclic tetrahydro-1,3,2-oxazaborines **13a** and **13b**, respectively.[13] Upon further treatment with borane and acetophenone the (R)-carbinol was consistently obtained in excess (33-65 %) with reproducible chemical yield (~90 %). The results obtained with varying amounts of borane and catalyst are shown in table 2 (room temperature, THF). Whereas a faster reaction is observed than in the absence of the chiral boron derivative the enantiomeric excess drops when catalytic amounts are used. Very recently Didier et al. described the asymmetric reduction of acetophenone using the (S)-amino alcohol **12**; although the % ee was somewhat lower (30 %) the (R)-carbinol was also observed in excess.[14]

The transition state for reduction would involve the bicyclic system **14** for which 3 conformations **i-iii** need to be considered (scheme 2). The six-membered ring geometries would correspond to chair conformations

with in one ring the preferred equatorial position of the *tert*-butylgroup and in the second ring a preferred all staggered geometry. For each of the possible transition states is further indicated the expected absolute configuration of the resulting carbinol provided that the phenyl substituent adopts the equatorial orientation.[15] The observed formation of the (R)-carbinol may suggest a pathway via transition state **14ii** where the possibility exists for stabilization by anomeric effect. Future studies will tend to confirm this hypothesis.

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3. Satisfactory physical and spectral data were obtained for all compounds. Relevant ^{1}H NMR data (360 MHz) are as follows :
for **1a** ($CDCl_3$) : 3.92 (1H, ddd : 10.3, 3.3, 2.7 Hz), 3.67 (1H, t, 10.3 Hz), 3.05 (1H, ddd : 11.4, 2.7, 2.6 Hz), 2.59 (1H, t : 11.4 Hz), 2.40 (3H, s), 1.51 (1H, m), 0.89 (9H, s) ppm.
for **1b** (C_6D_6) : 4.06 (1H, dt : 10.2, 2.9 Hz), 3.72 (1H, t : 10.1 Hz), 2.32 (1H, t : 11.8 Hz), 2.17 (1H, dt : 12.0, 2.6 Hz), 1.90 (6H, s), 1.58 (1H, m), 0.73 (9H, s) ppm;
for **2** ($CDCl_3$) : 3.81 (2H, ddd : 11.1, 4.0, 1.0 Hz), 3.65 (2H, dd : 11.1, 6.5 Hz), 2.63 (2H, ~t : 12.0 Hz), 2.28 (2H, m), 2.28 (3H, s), 1.54 (2H, m), 0.93 (18H, s) pm.
4. $C_{25}H_{49}NO_6S$, mp 167°C (ethyl acetate). Mr = 491.1, monoclinic, $P2_1$, a = 9.287(2), b = 10.321(1), c = 15.193(1)Å, β = 103.43(1)°, V = 1416.4(3)Å^3, Z = 2, Dx 1.15 g.cm^{-3}, CuKα, λ = 1.5418Å, T = 291K, R = 0.084 for 3639 observed reflections.
5. The list of atomic coordinates and molecular dimensions has been deposited with the Cambridge Data Centre.
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11. We thank a referee for bringing to our attention that the enantioselective reduction of ketones by chiral oxazaborolidines from (S)-diphenyl prolinol was first described by U. Kroatz, German Patent DE 3609152A1 (**1987**).
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13. Tetrahydro-1,3,2-oxazaborine **13b** obtained from (+)-**1a** and methylboronine acid (CH_2Cl_2, 12 h, rt, mol. sieves 4A, Ar). Purification via distillation (130°C, 15 mm Hg) : 69 % yield. ^{1}H NMR analysis shows next to the expected **13b** also the presence of dimeric (?) derivative (ca 30 %). For **13b** ($CDCl_3$, 360 MHz) 3.98 (1H, ddd : 10.5, 3.4, 2.1 Hz), 3.55 (1H, t, 11 Hz), 2.82 (1H, t, 11.3 Hz), 2.70 (1H, ddd : 11.3, 5.2, 2. 0 Hz), 2.65 (3H, s), 1.70 (1H, tdd : 11.3, 5.2, 3.4 Hz) ppm.
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15. In 1-methyl-1-phenylcyclohexane there is an **axial** preference for phenyl of 1.4 kJ/mol. This apparent discrepancy in view of the A values for Me (7.5 kJ/mol) and phenyl (13 kJ/mol) is due to interactions with vicinal H's in the cyclohexane ring which are absent in **14**. For a discussion, see : Hodgson, D.J.; Rychlewska, U.; Eliel, E.L.; Manoharan, M., Knox, D.E.; Olefirowicz, E.M. *J. Org. Chem.* **1985**, *50*, 4838-4843.