Enantiocontrolled Reduction of Prochiral Aromatic Ketones with Borane using Diastereoisomeric Secondary Aminoalcohols as Chiral Catalysts

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Exo- and *endo*-2-hydroxy-3-(1-methyl-2-pyrrolyl)methylaminobornanes were found to be efficient catalysts for enantioselective borane reduction of prochiral aromatic ketones with predictable absolute stereochemistry.

Asymmetric synthesis using chiral ligands is a topic of considerable current interest.[1] In many of these syntheses, it is difficult to synthesize both enantiomers of a product because both antipodes of a ligand are not always readily available. If the products could be prepared in both optical forms without tedious resolution from the single chiral auxiliary that is commercially available and cheap, and the reactions could proceed with predictable absolute stereochemistry, this method would be most attractive and desirable from a synthetic viewpoint.

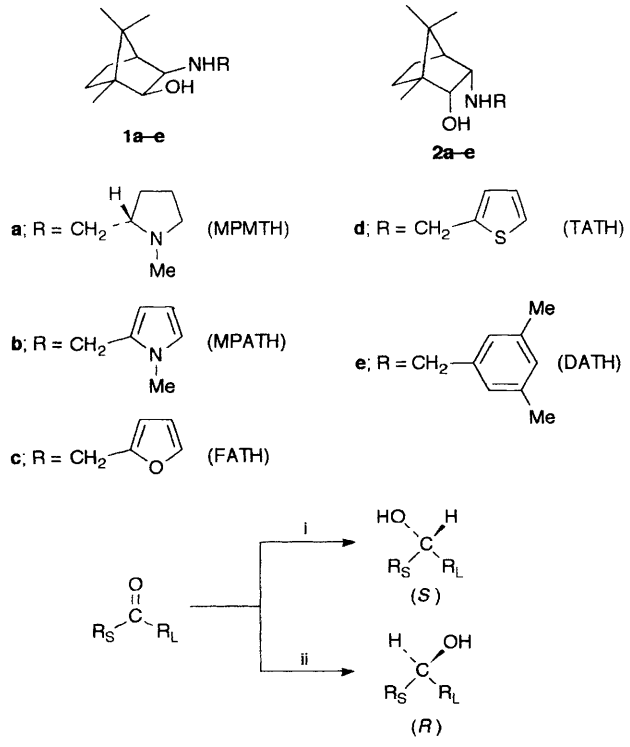
Recently we reported the enantiocontrolled addition of diethylzinc to aldehydes using chiral ligands such as *exo*- and *endo*-3-amino-2-hydroxybornanes **1a** and **2a**,[2] which could be readily prepared from D-camphor.[3] A similar control of the stereochemistry was observed in the asymmetric synthesis of (*R*)- and (*S*)-muscone by conjugate addition of chiral methylcuprate to (*E*)-2-cyclopentadecen-1-one using these secondary aminoalcohols as chiral ligands.[3]

We have now found the first case of enantiocontrolled reduction of prochiral aromatic ketones catalysed by dia-

Table 1 Enantiocontrolled reduction of prochiral ketones

			Alcohol			
Ketone	Chiral ligand		Yield (%)	$[\alpha]_D^{23}$ (*c*, solvent)	E.e. (%)	Configuration
PhCOMe	*exo*-MPATH	**1b**	68	−33.4 (2.99, MeOH)[a]	73	*S*
PhCOMe	*endo*-MPATH	**2b**	62	+33.1 (2.98, MeOH)	73	*R*
PhCOEt	*exo*-MPATH	**1b**	71	−33.4 (1.12, Me_2CO)[b]	77	*S*
PhCOEt	*endo*-MPATH	**2b**	65	+35.8 (1.10, Me_2CO)	79	*R*
PhCOEt	*exo*-FATH	**1c**	71	−6.0 (1.07, Me_2CO)	13	*S*
PhCOEt	*endo*-TATH	**2d**	64	+23.3 (1.00, Me_2CO)	50	*R*
PhCOEt	*exo*-DATH	**1e**	64	−1.1 (1.07, Me_2CO)	2	*S*
$PhCOPr^n$	*exo*-MPATH	**1b**	96	−32.0 (1.99, benzene)[c]	71	*S*
$PhCOPr^n$	*endo*-MPATH	**2b**	93	+34.2 (2.99, benzene)	76	*R*
$PhCOCH_2Ph$	*exo*-MPATH	**1b**	78	+40.4 (1.41, EtOH)[d]	72	*S*
$PhCOCH_2Ph$	*endo*-MPATH	**2b**	79	−41.8 (1.65, EtOH)	75	*R*

[a] Based on the maximum $[\alpha]_D^{25}$ −45.5 (*c* 3.0, MeOH).[7] [b] Based on the maximum $[\alpha]_D^{25}$ −47.0 (*c* 1.0, Me_2CO).[7] [c] Based on the maximum $[\alpha]_D^{25}$ −45.2 (*c* 3.0, benzene).[7] [d] Based on the maximum $[\alpha]_D^{18}$ +55.9 (*c* 1.4, benzene).[8]



Scheme 1 i, **1**–BH_3; ii, **2**–BH_3

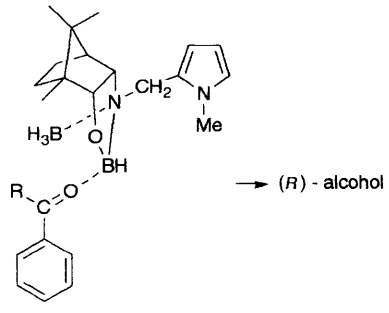


Fig. 1

stereoisomeric ligands. The reduction was carried out by employing borane[4] and ligands **1** or **2** according to the procedure developed by Itsuno[5] and Corey.[6] Thus, the reduction of propiophenone in the presence of 5 mol% *exo*-ligand **1b** afforded (*S*)-1-phenylpropanol in 77% enantiomeric excess (e.e.) (Scheme 1). It is of particular interest that in the presence of diastereoisomeric *endo*-ligand **2b**, the stereoselectivity is reversed, and (*R*)-alcohol was obtained in 79% e.e. With (−)-*N*-(1-phenylethyl)-3,5-dihydrodinaphthazepine–borane complex devised recently, however, the asymmetric reduction proceeds in 11–57% e.e.,[7] producing only the *R*-configuration of secondary alcohols. A similar stereocontrolled reduction was observed by using other ligands **1c**, **1e** and **2d**, although the enantioselectivity was moderate to low as shown in Table 1. The enantiocontrolled reduction observed here can be visualized by the mechanism shown in Fig. 1, similar to that for oxazabolidines advanced by Corey and coworkers.[6] The transition state in which the aromatic ketone is attached on its *si* face leading to *R*-alcohol is sterically favoured over the diastereoisomeric transition state, which suffers steric repulsion between the phenyl group on the ketone and the camphor skeleton.†

The fact that both (*S*)- and (*R*)-secondary alcohols are available with predictable absolute stereochemistry from aromatic prochiral ketones by using diastereoisomeric catalysts prepared from D-camphor makes this reaction especially attractive.‡ The scope of the enantiocontrolled reactions using diastereoisomeric ligands are now being investigated.

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† The mechanism for the *endo*-MPATH was illustrated as a representative example. With *exo*-MPATH, the oxygen atom of the ketone interacts with boron in order to minimize the steric congestion betweeen the phenyl group and the *N*-methylpyrrole moiety, so that the addition of borane on the *re* face of the ketone affords *S*-alcohol.

‡ The following experimental procedure was used for the catalytic reduction of ketones: a 100 ml, round-bottomed flask equipped with a Claisen adapter, a rubber septum, and a magnetic sitrrer was flashed with argon and charged with 5 ml of THF solution of *exo*-MPATH **1b** (66 mg, 0.25 mmol). The Claisen adapter was fitted with a ball condenser and a three-way stopcock connected to a mercury bubbler to maintain 100 mmHg of positive gas pressure. The above solution was added 0.75 ml of BH_3·THF (1.0 mol dm^{-3}). After having been refluxed for 2 days, the reaction mixture was diluted with 80 ml of THF. To this solution was added 0.5 ml of BH_3·THF (1.0 mol dm^{-3}). A solution of 670 mg (5 mmol) of propionoaldehyde in 5 ml of THF and 2.5 ml of BH_3·THF (1.0 mol dm^{-3}) were added. After having been stirred for 5 h at room temperature, the reaction mixture was decomposed by addition of 0.73 ml of methanol. To the resulting mixture was added 100 ml of 10% HCl and the mixture was extracted with ethyl acetate (2 × 80 ml). The extracts were washed successively with brine, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and evaporated to give a pale-yellow oil. The crude product was chromatographed on silica gel with hexane–ethyl acetate (7 : 1 v/v) as eluent to give 1-phenylpropan-l-ol (490 mg, 71%), which was identified by analysis of spectral data (IR and ^1H NMR) and by comparison with the reported data.