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Chiral Ligands Containing Heteroatoms. 15.[1] Cyclic β-Amino Alcohols as Chiral Inductors for Enantioselective Reductions of Ketones

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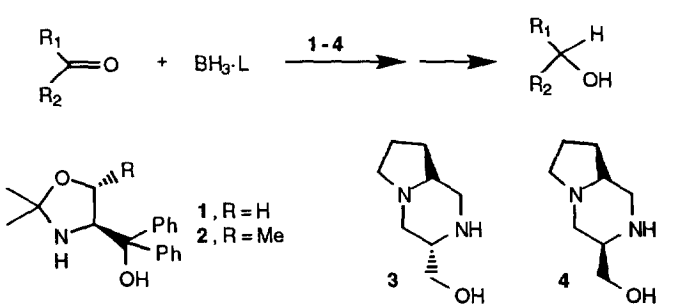
Abstract: Cyclic β-amino alcohols **1-4** derived from natural α-amino acids were used as chiral ligands in oxazaborolidine reduction of ketones. The processes were carried out in the presence of various achiral tertiary amine: better resuts are achieved by *N,N*-diethylaniline.

Enantioselective reduction and alkylation of carbonyl groups have received considerable attention during recent years. In particular, reducing agents, prepared from aluminum and boron hydrides and a variety of ligands, exhibit diverse degrees of enantioselectivity. Chiral oxazaborolidine-borane adducts have been shown to be highly effective for the catalytic enantioselective reduction of many prochiral ketones.[2] Different kinds of inductors were used derived from amino acids,[3] bornane derivatives[4], ephedrine[5] and so on. Such a diversity indicates that finding highly selective inductors of broad applicability is still a worthwhile objective.

Scheme 1



Recently we have described new families of ligands having rigid structures with more than 2 heteroatoms built in, such as 1,3-oxazolidinyl methanols **1**, **2**[1] and chiral piperazinic alcohols **3** and **4**.[6] A common feature for both these classes of ligands is the capability of enantioselective induction in the addition of diethyl zinc to benzaldehyde, even if with different degrees of success, the piperazinic alcohols giving generally low selectivities.[6] In this context, it appeared interesting to test the efficiency of these tridentate aminoalcohols as inductors in the reduction of some ketones by boron hydrides.

Initially, the diborane-THF complex was treated with a benzene solution of the ligands **1-4** and the resulting mixture was heated for 3 h. The mixture was cooled at 0°C and again BH_3·THF was added. It was found that these reagents afford reasonable conversion ratios only at 50°C with low enantioselectivities.

It was then found, according to other authors,[7] that the use of the *N,N*-diethylaniline-BH_3 complex gives better results than the corresponding THF complex. Therefore, we carried out several experiments: the chosen ligand was treated with a benzene solution of BH_3·THF and then the amine was added and the mixture refluxed for 4h. Again, BH_3·THF was added followed by the ketone and the reaction mantained at 20°C. The reagent so prepared reduces ketones quantitatively.

Table 1. Enantioselective reductions of ketones with BH_3 Using Ligands 1-4[a]

			carbinol	
entry	ligand	ketone	Conv. (%)[b]	e.e.%[c]
1	**1**	acetophenone	100	49(*R*)
2	**1**	ethyl phenyl ketone	98	20(*R*)
3	**1**	*i*-propyl phenyl ketone	98	2(*S*)
4	**1**	2-acetonaphtone	98	37(*R*)
5	**2**	acetophenone	100	5(*R*)
6	**2**	ethyl phenyl ketone	99	4(*R*)
7	**2**	*i*-propyl phenyl ketone	80	3(*R*)
8	**2**	2-acetonaphtone	99	14(*R*)
9	**3**	acetophenone	100	13(*R*)
10	**3**	ethyl phenyl ketone	96	78(*S*)
11	**3**	*i*-propyl phenyl ketone	95	27(*R*)
12	**3**	2-acetonaphtone	90	13(*R*)
13	**4**	acetophenone	86	79(*S*)
14	**4**	ethyl phenyl ketone	97	58(*S*)
15	**4**	*i*-propyl phenyl ketone	81	29(*R*)
16	**4**	2-acetonaphtone	90	62(*S*)

[a] Reactions carried out in benzene with a molar ratio BH_3/ketone/ligand/amine = 6.6/5/1/1. [b] GLC yields of the crude products. [c] Determined by specific rotations and confirmed by GLC on chiral column.

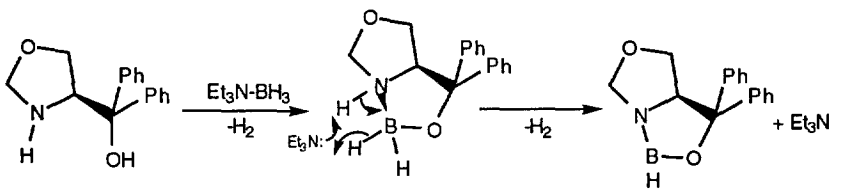
The data obtained are summarized in Table 1. The carbinols were obtained in good chemical yields, within 18 h, as the main products. In the majority of the runs we have performed, the conversions exceed 90%, while the enantioselectivity ranges from moderate to poor, reaching maximum values when ligand **4** is employed as inductor (runs 13-16). It is however interesting to note that the β-amino alcohol **1**, having diphenyl groups at the α-position, affords carbinols with low enantiomeric excess, contrary to what observed with the structurally similar α,α-diphenylpyrrolidinyl methanol.[8] This behaviour is different from that observed with the same couple of ligands in the enantioselective addition of diethylzinc to aldehydes.[1] The stereoselectivity of the reduction is then dramatically lowered on passing from ligand **1** to ligand **2**: in this last case, the second stereogenic centre at the 5-position probably has a mismatch effect on the total stereoselection. Moreover these results are in contrast with what is generally accepted on the presence of aromatic groups on the inductors in order to obtain higher enantioselectivities.[9]

On the contrary, the possibilities offered by totally aliphatic inductors are still to be largely explored. In this context, the results obtained with constrained aliphatic ligands, such as **3** and **4**, need to be considered. The ligand **4** is generally a better enantioselective catalytic inductor than the diastereomeric ligand **3**. Moreover, whereas in all the cases examined (Table 1) the enantioselectivity of the reduction decreases on increasing the complexity of the alkyl substituent on the aromatic ketone, in the reductions carried out with the inductor **3**, the ee reaches the maximum value with the ethyl phenyl ketone coupled with a reversal of stereochemistry (run 10).

A reverse stereochemical trend was noted in the reduction of *i*-propyl phenyl ketone (run 15) by the oxaborolidine derived from ligand **4**.

However, judging from the results of the Table, it is the structure of the ligand which plays an important role in determining the asymmetric induction. Some authors have noted the effect of *N,N*-diethylaniline or triethylamine addition as contributing to an increase in the ee of the reductions. Using oxaborolidines for reducing ketones, in some cases two H atoms can act, the second transfer being less stereoselective (Scheme 2). The current opinion is that the tertiary amine functionality may prevent the second hydride transfer by removing one of the reactive hydrogens from the catalyst, so favoring the ring fusion.

Scheme 2



In this respect, it appeared interesting to check further the effect of the nature of a tertiary amine on the enantioselectivity of the reduction process. The results obtained on adding diverse amines to the reduction of acetophenone with borane, in the presence of ligand **4** are reported in Table 2.

Examination of the data reported confirms the strong influence of a tertiary amine on the stereoselectivity of the reduction. It is of note that, contrary to other authors, triethylamine has not the same behaviour as *N,N*-diethylaniline, and the enantioselectivity of the reduction drops from run 13 to run 21. Actually, the enantioselectivity of the reaction is related to the base strength of the tertiary amine and the ee appears to decrease on passing from *N,N*-diethylaniline to triethylamine: DMAP does not fit this scale, probably owing the presence of two possible coordinating nitrogen atoms. Unfortunately no direct relationship can be draw, as no value of pK_b of the amines exist related under the reaction conditions and any consideration has to be based on the aqueous values.

Table 2. Enantioselective reductions of acetophenone with BH_3 Using Ligand 4 in the presence of different amines[a]

		optically active carbinol	
entry	amine	Conv. (%)[b]	e.e.%[c]
13	*N,N*-dimethylaniline	86	79(*S*)
17	*N*-methylmorpholine	100	70(*S*)
18	pyridine	100	62(*S*)
19	2,6-lutidine	95	57(*S*)
20	*N,N*-di-*i*-propylethylamine	97	56(*S*)
21	triethylamine	80	44(*S*)
22	DMAP	99	32(*S*)
23	none	87	4(*S*)

[a]) Reactions carried out in benzene with a molar ratio BH_3/ketone/ligand/amine = 6.6/5/1/1. [b]) GLC yields of the crude products.[c]) Determined by specific rotations and confirmed by GLC on chiral column.

However, all these data seem to confirm undoubtedly the mechanism of the formation of the reactive oxaborolidine complex.

Experimental Section

Bulb to bulb distillations were carried out with a Büchi GRK-51 apparatus equipped with a vacuum controller Büchi B-168. Optical rotations were measured with a Perkin-Elmer 241 automatic polarimeter in a 1 dm tube. GC analyses of the reaction products were carried out on a Perkin-Elmer 8600 gas chromatograph on fused silica megabore column (15 m x 0.53 mm) SUPELCOWAX (Supelco), operating with an He flow rate of 9 mL/min, enantioseparations of reduction carbinols were carried out on fused silica megabore columns (30 or 60m x 0.53 mm) BETA-DEX-120 (Supelco). Optical purity of the carbinols was determined also by direct comparison of optical rotations, which, when possible, was carefully done with the synthetic and authentic resolved matherials. All reactions were carried out at least in duplicate and under argon atmosphere: all reagents and solvents employed were reagent grade matherials purified by standard methods and distilled before use. Optically active (*S*)-diphenyl-(2,2-dimethyl-1,3-oxazolidin-4-yl)-methanol {**1**, mp 135°C, $[\alpha]_D^{25}$ -72.8 (c 0.6, $CHCl_3$)}, (4*S*,5*R*)-diphenyl-(2,2-dimethyl-5-methyl-1,3-oxazolidin-4-yl)-methanol {**2**, mp 92°C, $[\alpha]_D^{25}$ -160 (c 2, $CHCl_3$)} having ee ≥97% were prepared as reported in ref. 1. Optically active (2*S*,5*S*)-2-hydroxymethyl-1,4-diaza[4.3.0]bicyclononane {**3**, bp 112°C/0.5 mBar, $[\alpha]_D^{25}$ +14.56 (c 1, $CHCl_3$)} and (2*R*,5*S*)-2-hydroxymethyl-1,4-diaza[4.3.0]bicyclononane {**4**, bp 125-130°C/0.5 mBar, $[\alpha]_D^{25}$ +7.77 (c 1.9, $CHCl_3$)} were prepared as reported in ref. 6.

Asymmetric Reduction of Ketones by Using Ligand/Borane/Amine Complexes. General procedure: a solution of the ligand (1 mmol) and tertiary amine (1 mmol) in benzene (10 mL) was cooled at 0°C and THF·BH_3, (3 mL, 3.3 mmol, 1.1 *M*) was added. The resulting solution was then refluxed for 3 h; after cooling at 0°C, a further addition of THF·BH_3, (3 mL, 3.3 mmol, 1.1 *M*) was made, followed by the addition of the ketone (5 mmol) in benzene (5mL). The mixture was stirred at room temperature for 12-18 h (sometimes the reaction course was followed by GLC). The reaction mixture was quenched with ether (10 mL) and 10% H_2SO_4 (10 mL) then extracted with ether (10 mL) and the organic layer washed with 10% H_2SO_4, saturated $NaHCO_3$ (10 mL) and dried (Na_2SO_4). The crude product was bulb to bulb distilled and, if necessary, purified by flash chromatography to afford pure (GLC) carbinol.

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