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Diazaborolidines, a New Class of Enantioselective Organoboron Catalytic Agents.

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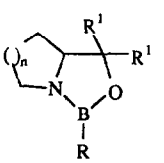
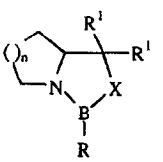
Abstract: *Diazaborolidines 6 and 9, derived from 2-aminomethyl-piperidine, have been prepared in an optically pure form from 2-cyano-6-phenyl oxazolopiperidine 3. The best results for the asymmetric reduction of acetophenone (yield>95%, 72% ee) have been obtained with $BH_3.Me_2S$ in the presence of 9a as a chiral catalyst.*

In the last few years, remarkable achievements have been made in the area of enantioselective reduction of prochiral ketones to optically active alcohols [1] using stoichiometric borane in the presence of catalytic amounts of chiral oxazaborolidines **1**. These ligands were first developed by Itsuno[2], then fully identified by Corey[3] and then characterized by ^{1}H NMR, ^{11}B NMR and mass spectrometry [3a,4]. B-Unsubstituted oxazaborolidines (**1**, R=H) are both air and moisture sensitive ; B-alkyloxazaborolidines (**1**, R=Me, Bu) are more stable and have been obtained by reaction of aminoalcohols and alkylboronic acids[5] or trialkylboroxine[6]. The enantioselectivity observed during reduction catalysed by compounds **1** is thought to be controlled by steric factors ; it has been proposed that reduction proceeds via a six-membered cyclic transition state [4,7]. Recently, oxazaborolidines have been looked at by Quantum Mechanical Methods[8] and an investigation into the origins of the enantioselectivity was carried out using molecular orbital methods[9].



1

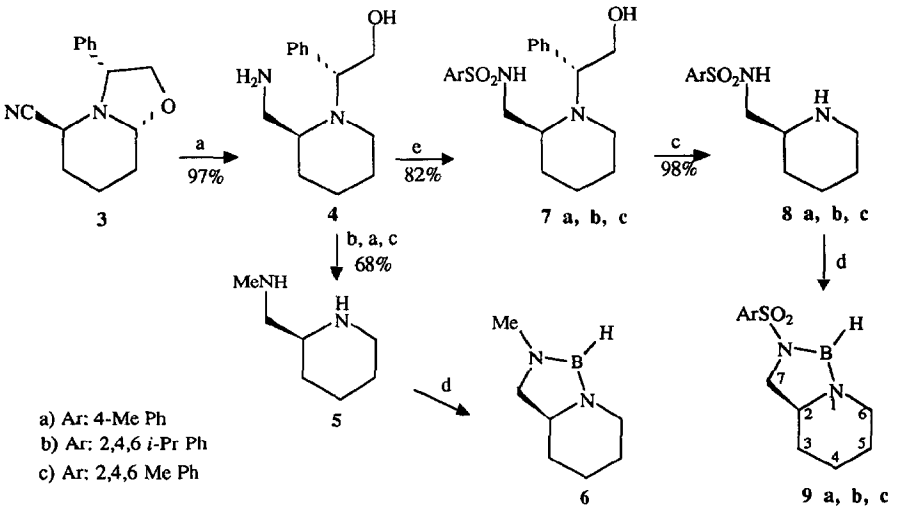


2

Despite the versatility of this reaction, there is still a need for new types of catalysts with general application to reduce keto-esters, enones or ketones having similar steric bias. Surprisingly, for many of the new catalysts described[1a] only β-aminoalcohols have been used for their preparation, which could be due to the difficulty of access to starting materials in an optically pure form, although analogs of type **2** (X= N, S...) leading to the same type of process can be envisaged. Oxazaphospholidine-borane complex have been reported[10];

Midland[11] has synthesized 1,2-azaboracyclohexanes as a new class of reducing agents but these compounds cannot be used in catalytic quantities. Nevertheless, it is obvious that new types of catalysts would be of great importance for the deduction of the mechanisms involved during the catalytic process. In the course of a program aimed at the asymmetric synthesis of vicinal diamines[12] we envisioned the preparation of diazaborolidines **2** (X=NR). We wish to present here our first results concerning the ability of these new catalysts to induce asymmetric reduction of prochiral ketones.

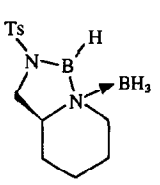
$LiAlH_4$ reduction of synthon **3**[13] afforded aminoalcohol **4**, the key intermediate for the synthesis of **6** and **9**. In a first experiment 1,2-diamine **5**[12b] was treated with 1 equivalent of $BH_3.Me_2S$ complex in Me_2S at reflux for 1h to give **6**. The ^{11}B NMR spectrum of crude **6** exhibited a single resonance (δ 32.3 ppm), which can be compared to the values previously reported[6] (δ 34.3 ppm) for an oxazaborolidine.



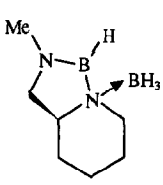
Reagents : a) $LiAlH_4$, Et_2O, rt; b) $ClCO_2Me$, $CHCl_3$, NaOH; c) H_2, Pd/C, MeOH; d) $BH_3.Me_2S$ in Me_2S, 1h, 100°C; e) $ArSO_2Cl$, NEt_3, CH_2Cl_2, rt

The homogenous reduction of acetophenone with this diazaborolidine catalyst (10 mol %) and $BH_3.Me_2S$ as a reducing agent gave complete reduction of the ketone in 1h. Optically active 2-phenyl ethanol was isolated in excellent chemical yield (95 %) and moderate optical yield (40 % determined by optical rotation and chiral HPLC analysis). This first result prompted us to study the role of the nitrogen basicity in order to increase the selectivity of the new type of catalyst. By adding $BH_3.Me_2S$ to a solution of **6** in THF, two new resonances appeared in the ^{11}B NMR spectrum (δ -20.3 and -13.5 ppm). These signals were analyzed as quartets in a non-decoupling experiment, indicating the presence of two different species **11a** and **11b**. This hypothesis was confirmed by the observation of two BH signals at δ 32.8 and 37.0 ppm. The poor enantiomeric excess could be explained by the presence of these two different species which result from the equivalence of the two amine functions. We reasoned that a compound in which these functions are differentiated could be a better candidate for asymmetric control. To verify this postulate the N-tosyl derivative **8a** was prepared. Diaminoalcohol **4** was first tosylated, then deprotected (H_2, Pd/C) to furnish compound **8a** as a crystalline product ($[\alpha]^{20}_D$ +26 c=1.0, MeOH; mp :

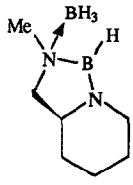
92°C, MeOH/ Et_2O) in 78% yield from synthon 3. Treatment of **8a** with 1 equivalent of $BH_3.Me_2S$ solution in Me_2S led to **9a** as a stable liquid after removal of the solvent. Compound **9a** was fully characterized by NMR (^1H, ^{13}C and ^{11}B) and mass spectrometry[14]. In this case, addition of 1 equivalent of $BH_3.Me_2S$ produced a single adduct **10a** as indicated by ^{11}B NMR, where a quadruplet was observed at δ -19.3 ppm.



10a



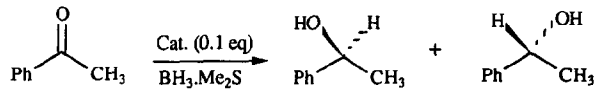
11a



11b

Reduction of acetophenone[15] with $BH_3.Me_2S$ (0.7 eq.) complex in the presence of **9a** (0.1 eq) afforded chiral 2-phenylethanol with reasonably good ee depending upon experimental conditions (see table). The chemical yield of the chiral alcohol was > 95 %, isolated after filtration on silica gel. The (*R*)-enantiomer was formed preferentially with the best ee (72%) in THF at rt, as previously observed for oxazaborolidines[3a]. In each case the diamine **8** was easily recovered by acido-basic treatment.

Table : Reduction of acetophenone with $BH_3.Me_2S$ in the presence of diazaborolidine.

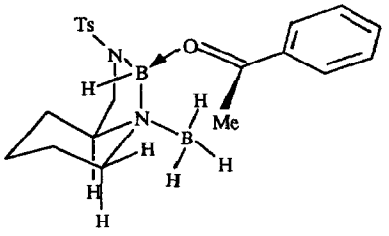


Catalyst	Solvent	Temp, °C	t (hr)	Yield (%)	ee (%)[a]
9a	Toluene	rt	1	> 95	30 (R)
"	THF	-78	12	35	20 (R)
"	"	-20	12	50	37 (R)
"	"	0	12	75	43 (R)
"	"	rt	1	> 95	72 (R)
"	THF/toluene	"	1	"	70 (R)
9b	THF	"	1	"	60 (R)
9c	THF	"	1	"	70 (R)

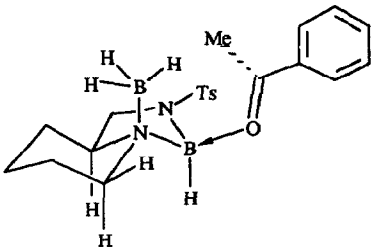
a) Determined by HPLC using a chiral column (Chiracel OD).

By analogy with the proposed mechanism[4] two models (cis and trans-diazaborolidine) can be imagined depending on the stereochemistry of the ring junction. In both cases the reduction occurs via a six-membered transition state and leads to the (*R*)-enantiomer regardless of the preferred transition state structure. On the basis of such a model we expected that the reduction should proceed at an even higher level of stereoselection if the

catalyst had a more sterically demanding arylsulfonamide group. Sulfonamides **8b** and **8c** were prepared but no increase of ee was observed in reductions carried out in the presence of these compounds (Table).



cis -diazaborolidine



trans -diazaborolidine

These preliminary results show that diazaborolidine complex constitute a new class of enantioselective catalysts. The influence of the substitution on C-7, of the group attached to the oxazaborolidine boron and of the size of the ring is actually studying and will be reported in due time.

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(14) **Preparation of chiral diazaborolidine 9a.** A 2M Me_2S solution of $BH_3.Me_2S$ complex (0.75 mmol) was added at rt to diamine **8a** (0.2 g, 0.75 mmol). The reaction mixture was heated for 1h at 100°C in a Schlenk apparatus, then evaporated under reduced pressure for 1h. MS (electrospray) : 278. ^1H NMR (C_6D_6) δ : 0.5-1.4 (6H), 1.83 (s, Me), 2.27 (td, J= 12.2, 3.2 Hz, H-6ax), 2.65 (dddd, J= 11.7, 9.0, 6.3, 3.4 Hz, H-2), 2.88 (dd, J= 9.7, 6.3 Hz, H-7), 3.06 (br d, J= 12.2 Hz, H-6eq), 3.42 (dd, J= 9.7, 9.0 Hz, H-7), 6.71 (d, J= 8.2Hz, 2H ar), 7.8 (d, J= 8.2 Hz, 2H ar). ^{13}C NMR (C_6D_6) δ : 20.74 (Me), 23.45, 26.58, 32.79 (C-3, C-4, C-5), 44.94, 52.51 (C-6, C-7), 58.04 (C-2). ^{11}B NMR (C_6D_6) δ : 27.62
15) Diazaborolidine **9a** was used without further purification. In a typical procedure, to a solution of the catalyst **9a** (0.22 g, 0.81 mmol) and $BH_3.Me_2S$ complex (2M in Me_2S, 5.6 mmol) in THF (8mL) was slowly added acetophenone (0.85 mL, 8.1 mmol). After stirring for 1h at rt, 5N HCl (2mL) was added. The resulting mixture was extracted with CH_2Cl_2 furnishing optically active alcohol after classical work-up. The diamine **8a** could be recycled from the aqueous phase after basic treatment.