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ENANTIOSELECTIVE REDUCTION OF KETONES WITH BORANE, CATALYZED BY (*S*)-(-)-PROLINE OR (*S*)-(+)-PROLINOL.

Jean Michel Brunel, Michel Maffei and Gérard Buono*

E.N.S.S.P.I.C.A.M., URA 1410 Réactivité Catalyse, Université Aix-Marseille III, Avenue Escadrille Normandie Niemen, 13397 Marseille Cedex 13, France.

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Abstract : The enantioselective reduction of ketones by borane in the presence of catalytic amounts of (*S*)-(-)-proline or (*S*)-(+)-prolinol as chiral auxiliaries has been investigated. The alcohols possess all the (*R*) configuration, and are obtained in good enantiomeric excess. A mechanistic rationale is proposed, involving an oxazaborolidine formed from (*S*)-(+)-prolinol and borane.

Efficient enantioselective reduction of ketones has recently been achieved with optically active catalysts[1]. One of the most important examples is the homogeneous catalytic hydrogenation of a wide range of functionalized ketones using as catalyst (BINAP-Ru(OAc)$_2$)[2]. Several reports describe the enantioselective reduction of ketones by a wide variety of reagents prepared by mixing aluminum or boron hydrides with various chiral diols or aminoalcohols[3]. Among these catalysts, Corey[4] used oxazaborolidines from α,α-diphenyl-2-pyrrolidine methanol in borane reductions, leading to the formation of chiral secondary alcohols with 84-100% enantiomeric excess (e.e.).

It was shown that the sodium (*S*)-prolinate-borane complex[5] reduces ketones to the corresponding alcohols with e.e. up to 62%. Furthermore, a chiral reducing reagent, synthesized from (*S*)-N-acylproline has been applied to the enantioselective reduction of prochiral cyclic imines[6].

The borane reduction of ketones implying merely (*S*)-(-)-proline **1** or (*S*)-(+)-prolinol **2** as chiral auxiliaries has never been reported; we wish to describe herein our preliminary studies on this reaction (Scheme I).

1 R = COOH

2 R = CH_2OH

Scheme I

Thus, acetophenone was reduced with BH_3:THF and (*S*)-(-)-proline at room temperature to yield (*R*)-1-phenyl ethanol in low enantiomeric excess, i.e. 8% and 15% respectively, with 2 and 10 mol % of 1. However, enantioselectivity was found to increase with the temperature (Table 1). The best result was obtained by running the reaction in refluxing toluene (110°C), where (*R*)-1-phenyl ethanol was isolated in 59% and >95% e.e. respectively, with 2 and 10 mol % of 1.

Temperature (°C)	E.e. (%)
25	8
35	37
66	42
110	59

Table 1. Effect of the Temperature on the Enantioselective Reduction of Acetophenone to (*R*)-1-Phenyl Ethanol by Borane in the Presence of 2 mol % of (*S*)-(-)-Proline.

The above optimized conditions were applied to different ketones, leading to the corresponding (*R*)-alcohols in good enantiomeric excess (Table 2). Chemical yields usually range from 63 to 84%.

Ketone	E.e. (%)	
	2 mol % 1	10 mol % 1
$PhCOCH_3$	59	>95
$tBuCOCH_3$	36	>95
$PhCH_2COCH_3$	24	81
2-furylCOCH$_3$	41	83
$iPrCOCH_3$	27	90

Table 2. Enantioselective Reduction of Ketones with Borane in the Presence of (*S*)-(-)-Proline in Refluxing Toluene (110°C).

Trying to establish the nature of the active species, we found out that proline is actually reduced to prolinol by borane. Furthermore, the use of (*S*)-(+)-prolinol as chiral auxiliary in borane reduction of acetophenone leads essentially to the same results as with (*S*)-(-)-proline : (*R*)-1-phenyl ethanol was obtained with 63%, 89% and >95% ee respectively, with 2, 4 and 10 mol % of (*S*)-(+)-prolinol.

One explanation for the performance of (*S*)-(-)-proline in borane reductions could be the formation of the corresponding oxazaborolidine, by analogy with Corey's results[4].

Even though a reasonable mechanism[4] has been suggested for the oxazaborolidine catalysis, and quantum modeling of chiral oxazaborolidine was investigated[7], the relation between increasing temperature and enantioselectivity has not yet been taken into consideration. Recently, it has been shown that oxazaborolidines derived from N-methyl ephedrine dimerize when treated with an excess of borane[8]. Several related structures have been studied with 2-alkyl-1,2-azaborolidines[9]. For his part, Corey[4] observed by ^{11}B NMR analysis that the proportion of dimer increases with decreasing temperature. Recently, Mathre[10] isolated this dimer by adding excess BH_3:SMe_2 to a solution of α,α-diphenyl-2-pyrrolidine methanol in toluene at room temperature. Following this procedure, we were able to isolate dimer 3 as a white solid. Its structure was determined by ^1H and ^{11}B NMR, taking into account NMR data already reported and collected in Table 3.

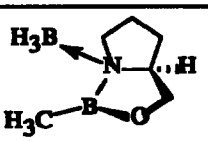
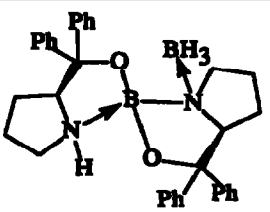
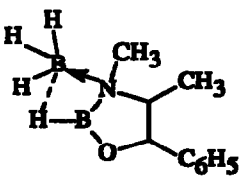
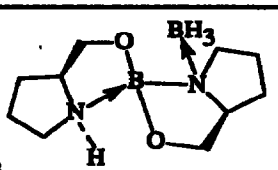
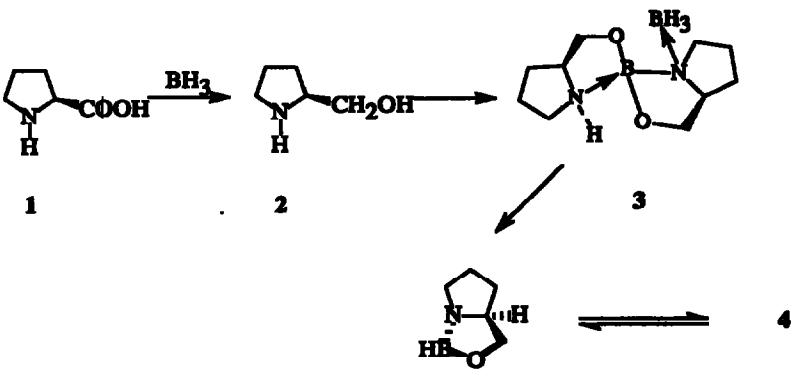
Compounds	^{11}B NMR (N-BH_3)	^{11}B NMR (oxazaborolidine nucleus)	Reference
	-14.5 -12.87	34.5 40.47	10 11
	-14.4	10.4	10
	-20.8 (erythro) -23.1 (threo)	6.0 1.47	8
 3	-19.37	5.41	This study

Table 3. Selected ^{11}B NMR data for Several Borane-Amino alcohol complexes.

Refluxing a solution of 3 in toluene for 15 min. led to a new compound 4[12] since ^{11}B NMR displayed two peaks (δ = 10.09 ppm, singulet and δ = 0.31 ppm, triplet, $^{1}J_{BH}$ = 112 Hz). These signals can be attributed to a trisubstituted boron atom and a N-BH_2 moiety, respectively.

Our proposed rationale is that enantioselective reductions proceed through the oxazaborolidine 5 derived from (*S*)-(+)-prolinol following Corey's mechanism[4]. This oxazaborolidine is obtained *via* the dimeric structure 3, which we suppose to be inactive towards the reduction since the Lewis acid character of the boron atom is decreased by the strong oxygen and nitrogen donors, and is in equilibrium with 4 (Scheme II).



Scheme II

In refluxing toluene, this equilibrium should be shifted towards a predominance of the monomer 5, which would be responsible for the high e.e. encountered ; then, the increasing amount of the dimer 4 at lower temperatures could explain the decrease in enantioselectivity since the competing uncatalyzed reduction takes place to a higher extend. Due to steric effects, the influence of the temperature seems to be more important in our case than that Corey's oxazaborolidine. Indeed, the presence of two aryl groups in this latter reduces its ability to dimerize, comparing to 5.

Finally, we decided to run the reductions at lower temperatures with preliminary preparation of the catalyst in refluxing toluene. Thus, an equimolar mixture of BH3:THF and proline was heated to reflux, then cooled to a specified temperature before adding the ketone followed by BH3:THF.

The insignificant change in e.e. compared to those obtained without prior heating (Table 1) is consistent with a rapid equilibrium between 4 and 5, where the latter is favored at high temperatures. Therefore, it is necessary to carry out the whole reduction in refluxing toluene to get the highest e.e.s.

In summary, (*S*)-(-)-proline or (*S*)-(+)-prolinol used in catalytic amounts constitute efficient chiral auxiliaries in the enantioselective reduction of ketones by borane at elevated temperatures. Thus, the present results complement precedent reports in this area, namely the recently discovered oxazaborolidine catalysts in the so-called CBS reductions. Although the mechanism of these reductions remains obscure and the experimental conditions are not tolerable with highly

functionalized molecules, the ready availability and low cost of these auxiliaries may lead to their application in synthesis.

We are currently studying the structure of the different species involved in order to get a more detailed rationale.

Experimental

^{11}B NMR spectra were recorded on a Bruker MC 400 spectrometer with BF_3 etherate as external standard. The e.e.s of the isolated alcohols were measured by ^{31}P NMR using the recently developped derivatizing agent (4R,5R)-Dicarboisopropoxy 2-Chloro 1,3,2-dioxaphospholane[13].

Typical procedure for reduction of ketones : The reactions were run under a nitrogen atmosphere in a three necked round bottom flask, equipped with an efficient reflux condenser, a rubber septum, and a dropping funnel. To a stirred suspension of (*S*)-(-)-Proline (85.0 mg; 0.83 mmol) in toluene (7 mL) was added at room temperature a 1 M solution of BH_3: THF (0.83 mL; 0.83 mmol) via syringe. After stirring for a further 10 min., the mixture was heated to reflux (110°C). Acetophenone (1.0 g; 8.3 mmol) was added via syringe, followed by dropwise addition of a further amount of 1 M solution of BH_3: THF (1 equiv., based on the ketone) over 15 min, and reflux was maintained for 15 min. After cooling to room temperature, ether (10 mL) was added and the mixture was quenched by cautious addition of saturated aqueous $NaHCO_3$ (5 mL). The organic layer was separated, dried ($MgSO_4$), filtered and the solvents were removed *in vacuo*. The resulting oil was purified by Kugelrohr distillation (150°C/20 mm Hg, air bath temperature) to afford 773 mg of (*R*)-1-(+) phenyl ethanol (76% yield, >95% e.e.).

Preparation of dimer 3 : A 1M solution of BH_3:THF (10 mL, 2 equiv.) was added dropwise with stirring to a solution of (S)-(+)-prolinol (500 mg) in toluene (5 mL) at room temperature and stirring was continued for two hours. After removal of the solvents *in vacuo*, dry hexane (10 mL) was added, and the mixture was cooled to -20°C overnight. Standard Schlenck filtration under nitrogen afforded 3 in quantitative yield as a white solid (m.p. 80°C) after drying over P_2O_5 .
^1H NMR (100 MHz, $CDCl_3$) : 0.80-1.42(m, 2H); 1.80-2.06(m, 10H); 2.77-3.05(m, 7H); 4.07-4.32(m, 3H).
^{11}B NMR (128.4 MHz , $CDCl_3$) : -19.37 (q, J = 84 Hz, N-BH_3); 5.41 (s, oxazaborolidine nucleus).

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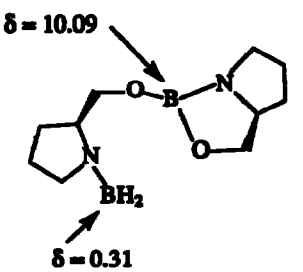
12. Further studies are in progress to confirm our proposed structure 4.



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