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Enantioselective Reduction of Ketones by Borane Catalysed by Oxazaphospholidine Oxides

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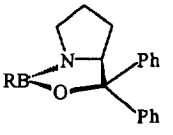
Abstract : New enantioselective catalysts for the asymmetric reduction of ketones by borane are described. Easily prepared by oxidation of chiral oxazaphospholidines, these compounds increase sensitively the reduction rate of numerous ketones and induce ee's up to 94% in the case of the 2-chloroacetophenone.

Based on the pioneering research of Itsuno,[1] Corey discovered that the reduction of ketones by borane is strongly catalysed by the chiral oxazaborolidine **1** and provides alcohols with excellent enantioselectivity and predictable stereochemistry.[2] Since this discovery, numerous applications have appeared and new efficient oxazaborolidines as catalysts have been reported.[3, 4]

We have found that the oxazaphospholidine borane complex **2** can also be used as a catalyst in enantioselective reduction of ketones by borane. Indeed we obtained enantioselectivity ranging from 33 to 92% and quantitative conversion at 110°C by using 2, whereas the reduction proceeded with 99% enantiomeric excess under stoichiometric conditions.[5]

These recent results open the way to the design of new chiral organophosphorus catalysts. Recently, Wills *et al.* have described a new class of asymmetric ketones reduction catalysts containing a N-P=O structural unit such as **3**.[6] Although these catalysts are very active and dramatically increase reduction reaction rates, asymmetric inductions remain modest.



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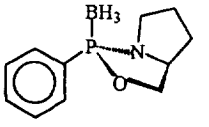

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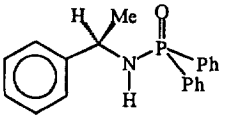

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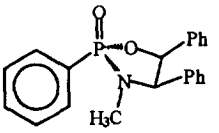
In this letter we wish to report the enantioselective reduction of ketones by borane catalysed by oxazaphospholidine oxides **4-6**. These compounds can be easily prepared quantitatively by oxidation of the corresponding oxazaphospholidines by a cyclohexane solution of *tert*-butyl hydroperoxide.[7] The chiral oxazaphospholidines were synthesised by the exchange reaction between phenyl bis(dimethylamino)phosphine and enantiomerically pure amino alcohols.[8] In these reactions only one diastereoisomer was obtained, in which the P-phenyl group is in an *anti* position with respect to the oxazaphospholidine ring substituents (R_P configuration for **4**, and S_P configuration for **5** and **6**).



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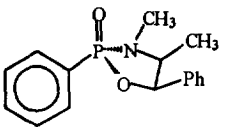

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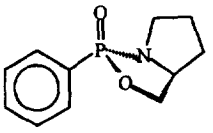

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The oxazaphospholidine oxides have been tested as catalysts (2 mol. %) in the enantioselective reduction of acetophenone by a THF solution of BH_3:SMe_2 (Table 1).[9]

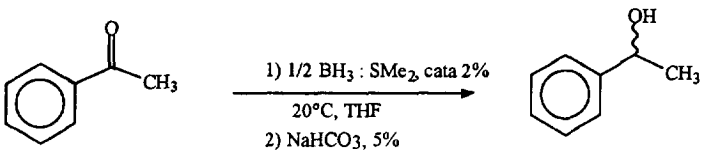


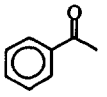
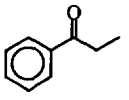
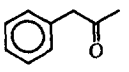
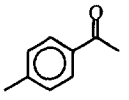
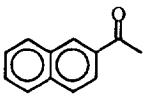
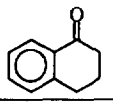
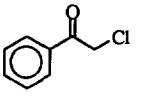
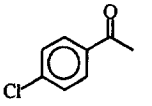
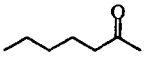
Table 1. Reduction of Acetophenone Catalysed by 4, 5, 6.

Catalyst	ee (%)	Abs. Conf.
4	23	*S*
5	30	*R*
6	40	*R*

After one hour, the reaction was complete and the alcohol isolated in 85% yield. The most satisfactory results were obtained with **6** as a catalyst. Catalyst **4** afforded alcohol of opposite configuration. As with oxazaphospholidine borane complex **2**,[5] the enantioselectivity increased with the temperature : at 60°C with **6** as a catalyst, (*R*)-1-phenylethanol was obtained in 70% enantiomeric excess, compared to 40% at 20°C.

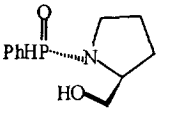
Different ketones have been reduced at 60°C under similar conditions.[9] The results are reported in Table 2. Catalyst **6** is very active. The alcohols were isolated in 70-90% yields and 25-94% enantiomeric excesses, depending on their structure. The major enantiomers had always the same relative configurations. This catalyst revealed very high enantioface-differentiating ability in the reduction of 2-chloroacetophenone : indeed, the chiral isolated chlorohydrin was obtained in 92% yield and 94% ee (Table 2, entry 7). The enantioselective reduction of this chloroketone thus constitutes an easy pathway to homochiral phenyloxirane.

Table 2. Enantioselective Reduction of Ketones Catalysed by 6 at 60°C[9]

Entry	Ketones	ee (%)	Abs. Conf.[d]
1		70 [a]	*R*
2		50 [a]	*R*
3		64 [a]	*R*
4		70 [a]	*R*
5		40 [c]	*R*
6		33 [c]	*R*
7		94 [a]	*S*
8		49 [b]	-
9		25 [b]	*R*
10		49 [b]	*R*
11		35 [b]	*R*

Enantiomeric excess measurement : (a) the alcohol was esterified by trifluoroacetic anhydride and the ester was injected on a chiral GC column Lipodex E. *(b)* e.e. of the alcohol was determined by HPLC analysis using a Chiracel OJ column with hexane/iPrOH 9:1 as eluent. *(c)* the alcohol was converted into carbamate with (*R*)- phenylethylisocyanate for analysis by GC on a SE 30 column. *(d)* The absolute stereochemistry was determined by comparison of the optical rotation with the reported values.[11]

For the moment we are unable to propose a mechanism. Nevertheless, as shown by ^{31}P NMR spectroscopy, under these experimental conditions, the five membered oxazaphospholidine ring was opened in all the cases, but the P-N bond was conserved.[10] The enantioselective reduction process seems thus to involve different catalytic species : the oxazaphospholidine oxide **6** and borane complexes of (2*S*)-hydroxymethyl 1-P-phenylphosphinic amide pyrrolidine **7**, resulting from **6** opening. In order to verify this assumption, we prepared borane complexes of **7** by action of an excess of borane on **6**. They showed efficient enantioselective reduction catalysts : in a test run without any optimisation, chloroacetophenone was reduced into the corresponding chlorhydrine in 95% yield and 80% ee at 60°C in the presence of 2 mol. % of catalyst.



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These promising preliminary results illustrate the interest and potentialities of organophosphorus compounds as catalysts in the enantioselective reduction of ketones by borane. Investigations for further improvements in the enantioselectivity and mechanistic studies are currently underway.

REFERENCES AND NOTES

1. (a) Hirao, A.; Itsuno, S.; Nakahama, S.; Yamazaki, Y. *J. Chem. Soc., Chem. Commun.* **1981**, 315-317. (b) Itsuno, S.; Hirao, A.; Nakama, S.; Yamazaki, Y. *J. Chem. Soc., Chem. Commun.* **1983**, 1673-1676. (c) Itsuno, S.; Ito, K. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2887-2893.
2. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551-5552. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925-7926. (c) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861-2863.
3. (a) Singh, V. K. *Synthesis* **1992**, 605-617. (b) Deloux, A.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763-784.
4. (a) Quallich, G. J.; Woodall, T. M. *Tetrahedron Lett.* **1993**, *34*, 4145-4148. (b) Quallich, G. J.; Woodall, T. M. *Synlett.* **1993**, *12*, 929-30. (c) Quallich, G. J.; Blake, J. M.; Woodall, T. M. *J. Am. Chem. Soc.* **1994**, *116*, 8516-8525.
5. (a) Brunel, J. M.; Pardigon, O.; Faure, B.; Buono, G. *J. Chem. Soc., Chem. Commun.* **1992**, 287-288.(b) Buono, G.; Brunel, J-M.; Faure, B.; Pardigon, O. *Phosphorus, Sulfur, and Silicon* **1993**, *75*, 43-46.
6. (a) Burns, B.; Studley, J. R.; Wills, M. *Tetrahedron Lett.* **1993**, *34*, 7105-7106. (b) Burns, B.; King, N. P.; Studley, J. R.; Tye, H.; Wills, M. *Tetrahedron: Asymmetry* **1994**, *5*, 801-804.
7. Compound **6** can alternatively be obtained according to Koizumi's method : (*S*)-prolinol reacts with phenylphosphonic dichloride to afford a mixture of diastereoisomeric bicyclic oxazaphospholes in 80-90% yield, easily separated by flash chromatography. Koizumi, T.; Yanada, R.; Takagi, H.; Hirai, H.; Yoshii, E. *Tetrahedron Lett.* **1981**, 571-572.
8. Cros, P.; Buono, G.; Peiffer, G.; Denis, D.; Mortreux, A.; Petit, F. *New J. Chem.*, **1987**, *11*, 573-579.
9. Typical reduction procedure : a solution of 0.01 mol of ketone in 12 ml of THF and 2 mol. % of catalyst are introduced in a 50 ml round bottom flask. The mixture is stirred at the temperature indicated before. The borane dimethyl sulfide complex is then added slowly dropwise via a syringe. When the reaction is finished the mixture is cooled to 5°C and slowly hydrolysed by an aqueous 5% $NaHCO_3$ solution. The crude product is extracted with ether and dried over anhydrous $MgSO_4$. After removing of the solvent, the pure alcohol is obtained by distillation on a Kugelrohr apparatus.
10. The ^{31}P -NMR spectra clearly indicates the formation of different borane complexes derived from **7** : the peak at 38 ppm corresponding to **6** disappeared and new signals at 80-100 ppm were detected.
11. See : Jacques, J.; Gros, C.; Boursier, S. *Stereochemistry, vol. 4 "Absolute Configurations. One Asymmetric Carbon"*. Kagan, H. B. Ed; Georg Thieme Verlag Publishers : Stuttgart 1977.

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