

New Chiral Oxazaphospholidine Oxides as Highly Efficient Catalysts in the Enantioselective Reduction of Ketones

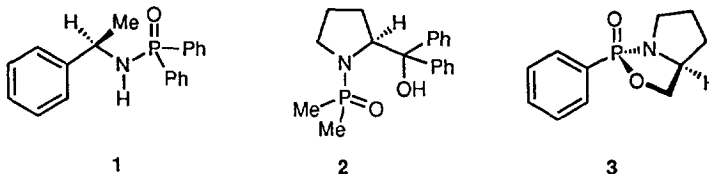
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Abstract: New catalysts **4-10** for the asymmetric reduction of the two model ketones **13** and **14** by borane are described. These catalysts are easily prepared by reaction of the corresponding β -amino alcohols with phenylphosphonic dichloride or alternatively by oxidation of the chiral 1,3,2-oxazaphospholidines. Enantiomeric excesses of 96% in the case of the ω -chloroacetophenone have been obtained using only 1 mol% of the optimum catalyst. Copyright © 1996 Elsevier Science Ltd

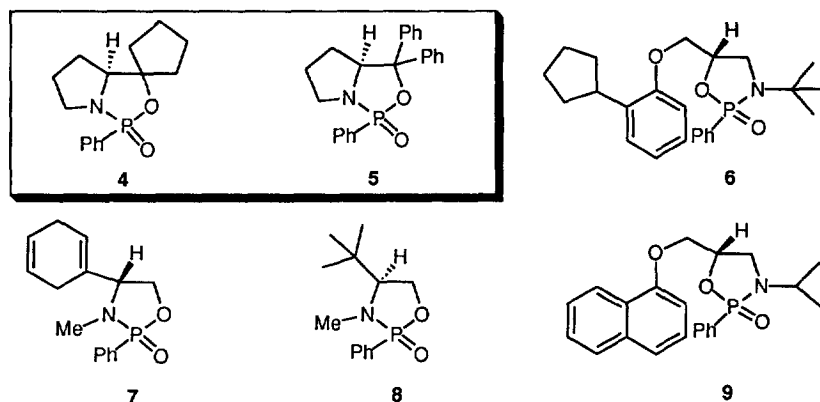
The reduction of unsymmetrical ketones to chiral alcohols using an asymmetric catalyst is an important reaction in organic synthesis.¹ Almost all of those catalysts fall into one of two major classes: 1) transition metal catalysts modified by chiral phosphines² or 2) oxazaborolidines developed by *Itsuno* and other authors.³ Some asymmetric ketone reduction catalysts do not belong to these both major classes.⁴

Organophosphorus compounds such as **1-3** are interesting new catalysts for the asymmetric reduction of ketones by borane. Although the catalyst **1** is very active and dramatically increases reaction rates, asymmetric inductions remain modest.⁵ Recently, the reduction of ω -chloroacetophenone in the presence of 10 mol% of the chiral phosphinamide **2** was reported to give the 2-chloro-1-phenylethanol with 92%*ee*.⁶ If 2 mol% of the oxazaphospholidine oxide **3** was used the 2-chloro-1-phenylethanol was obtained in 94%*ee*.⁷

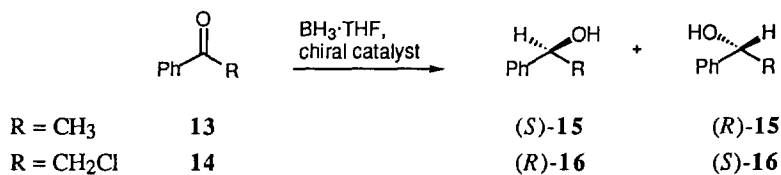


In this paper we wish to report our results about the enantioselective reduction of the two model ketones **13** and **14** by borane catalysed by the oxazaphospholidine oxides **4-10**.⁸ These compounds are easily prepared by reaction of the corresponding β -amino alcohol with phenylphosphonic dichloride. The resulting mixture of diastereomeric oxazaphospholidine oxides was separated by column chromatography (eluant: ethyl acetate). It

may be noted that the oxazaphospholidine oxides **6** and **9** were prepared from active pharmaceutical ingredients (**6**: from (*S*)-penbutolol; **9**: from (*R,S*)-propranolol^{9a}, resolution as described in the literature^{9b}). The compound **10a** can also be prepared by oxidation of the corresponding 1,3,2-oxazaphospholidine **12** by a toluene solution of *tert*-butyl hydroperoxide (Scheme 2). The 1,3,2-oxazaphospholidine **12** was synthesised by the exchange reaction between phenylbis(diethylamino)phosphine and the enantiomerically pure β -amino alcohol **11**.¹⁰ In these reaction only one diastereomer was obtained.^{4c}



One diastereomer each (the configuration at the phosphorus atom was not yet determined) of the compounds **4** and **5**¹¹ has been tested as catalyst in the enantioselective reduction of acetophenone **13** and ω -chloroacetophenone **14** by borane. After maximally 30 min (in the case of 0.1 mol% of catalyst **5**), the reaction was complete and the secondary alcohol isolated in chemical yields up to 95%. In the case of compound **4** (10 mol%) the enantioselectivity increases with increasing temperature (78%*ee* at 20°C but 90%*ee* at 62°C with acetophenone as model ketone to (*R*)-**15**). Whereas, the temperature not particularly influence the enantioselectivity if compound **5** (10 mol%) was used as catalyst (97%*ee* at 19°C and 95%*ee* at 62°C with acetophenone to (*R*)-**15**). Using ω -chloroacetophenone further improvements to the enantiomeric excesses were observed (Figure 1), up to >99% when 10 mol% of catalyst **5** was used.



Scheme 1: Enantioselective catalytic reductions of prochiral ketones with the oxazaphospholidine oxides **4-10** and excess borane in THF¹²

Very interesting is the result that a decreasing amount of catalyst **5** not considerable decreases the enantioselectivity. Using only 1 mol% of the catalyst **5** the (*S*)-2-chloro-1-phenylethanol (*S*)-**16** was obtained with 96%*ee* (Figure 1).

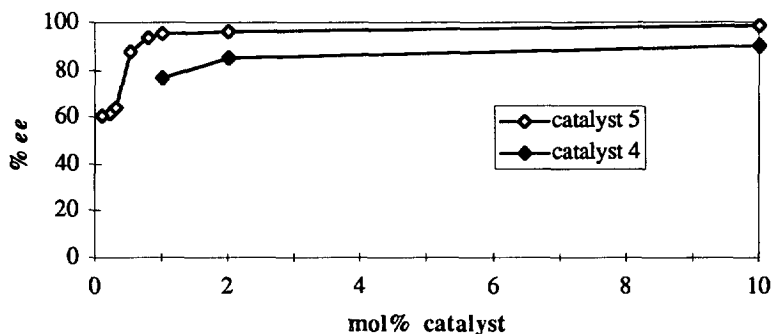
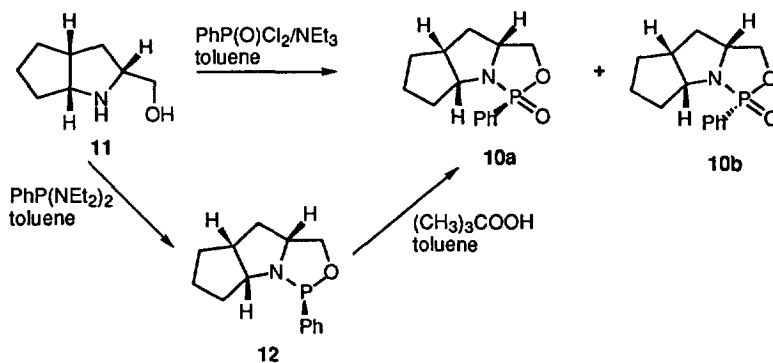


Figure 1: Enantioselective catalytic reduction of ω -chloroacetophenone with catalyst 4 at 62°C and catalyst 5 at 20°C to (*S*)-16.¹³

We have also tested both diastereomers (R_P^* and S_P^*) of the compounds 6-9 as catalysts (2 and 10 mol%) in the enantioselective reduction of acetophenone and ω -chloroacetophenone by borane. After 15 min, the reaction was complete and the secondary alcohol isolated in chemical yields up to 93%. However, the highest *ee*-value were only 11% with 10 mol% of compound (*S*, R_P^*)-9b⁸ and acetophenone as model ketone.

Using the tricyclic catalyst 10a an increase in the enantiomeric excess of the phenyl alcohol (Scheme 1) was obtained. A variation of the temperature has indicated that the best *ee*-value could be observed at room temperature. In the presence of 10 mol% 10a as inductor we obtained the (*S*)-1-phenylethanol with an enantioselectivity of 39%. The reduction of ω -chloroacetophenone with 10 mol% of catalyst 10a has afforded the (*R*)-2-chloro-1-phenylethanol with 54%*ee*.



Scheme 2.

In conclusion we have demonstrated that chiral oxazaphospholidine oxides such as 4, 5 and 10a are very efficient catalysts for the asymmetric reduction of ketones by borane. Further investigations of the catalytic ability and the asymmetric induction in the enantioselective reductions of achiral ketones are still in progress and our findings will be reported in due course.

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- Some analytical data of the new compounds: **4**: M.p. 97°C.– $[\alpha]_D^{20} = -1.9$ ($c = 2.36$, MeOH).– **5**: M.p. 153°C.– $[\alpha]_D^{20} = -235.6$ ($c = 1.15$, CHCl₃).– (*S*, *S*_P^{*})-**6a**: M.p. 113°C.– $[\alpha]_D^{20} = +9.4$ ($c = 1.04$, CHCl₃).– (*S*, *R*_P^{*})-**6b**: M.p. 108°C.– $[\alpha]_D^{20} = -56.8$ ($c = 1.71$, CHCl₃).– (*R*, *S*_P^{*})-**7a**: M.p. 98°C.– $[\alpha]_D^{20} = -60.8$ ($c = 1.87$, CHCl₃).– (*R*, *R*_P^{*})-**7b**: yellow oil.– $[\alpha]_D^{20} = +26.7$ ($c = 2.38$, CHCl₃).– (*S*, *S*_P^{*})-**8a**: M.p. 86°C.– $[\alpha]_D^{20} = +15.7$ ($c = 2.01$, CHCl₃).– (*S*, *R*_P^{*})-**8b**: yellow oil.– $[\alpha]_D^{20} = -47.5$ ($c = 4.10$, CHCl₃).– (*S*, *S*_P^{*})-**9a**: M.p. 126°C.– $[\alpha]_D^{20} = +13.9^\circ$ ($c = 3.47$, CHCl₃).– (*S*, *R*_P^{*})-**9b**: M.p. 94°C.– $[\alpha]_D^{20} = -100.2^\circ$ ($c = 3.79$, CHCl₃).– **10a**: M.p. 126°C.– $[\alpha]_D^{20} = -129.8$ ($c = 1.33$, CHCl₃).– **10b**: M.p. 174°C.– $[\alpha]_D^{20} = -1.1$ ($c = 1.67$, CHCl₃).–
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- The oxazaphospholidine oxide **5** was mentioned by Wills et al. (see footnote 6), but wasn't tested as catalyst in the enantioselective reduction of ketones by borane.
- Typical reduction procedure see: V. Peper, J. Martens, *Chem. Ber.* **1996**, *129*, 691. The enantiomeric excess was determined by GC analysis using a SGE Cydec-B as chiral column with *n*-hexane as eluant.
- Catalyst **4**: 10 mol% (91%ee), 2 mol% (86%ee) and 1 mol% (77%ee). Catalyst **5**: 10 mol% (>99%ee), 2 mol% (97%ee), 1 mol% (96%ee), 0.8 mol% (94%ee), 0.5 mol% (88%ee), 0.3 mol% (64%ee), 0.2 mol% (62%ee) and 0.1 mol% (61%ee). Reduction procedure: see footnote 12.