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New Catalysts Containing an N-P=O Structural Unit for the Asymmetric Reduction of Ketones.

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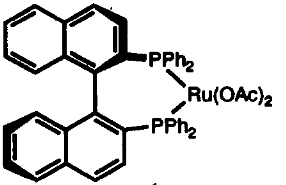
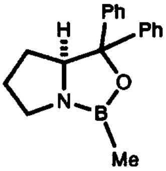
abstract; *New catalysts for the asymmetric reduction of ketones to chiral alcohols are described. Together they represent an entirely novel class of catalysts which have in common an N-P=O structural unit.*

The reduction of unsymmetrical ketones to chiral alcohols[1] is a pivotal reaction in organic synthesis. Although many efficient catalysts have been described for this transformation almost all fall into one of two major classes: a) transition metal catalysts modified by chiral phosphines such as **1**[2] or b) oxazaborolidine derivatives such as **2**.[3] The first class of catalyst furnish products of extremely high enantiomeric excess but are limited by the necessity for a nearby co-ordinating group in the substrate for optimum results. The second class of catalysts are effective for a broader range of substrates and also give very high enantiomeric inductions. However it is essential that they are prepared under conditions in which water is rigorously excluded for optimum effectiveness.[4] In this paper we introduce an entirely novel *class* of carbonyl reduction catalyst, represented by structures **3** to **5**, which give products of modest enantiomeric excess but at dramatically increased rates.



1



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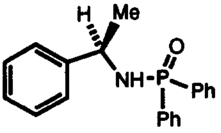
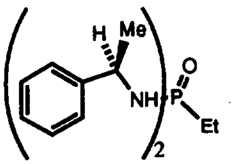
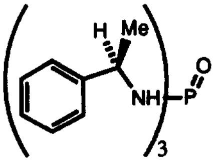


(+)-**3**



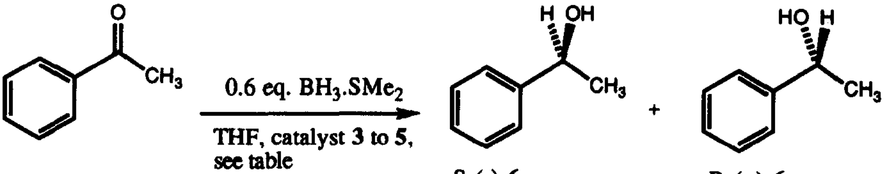
(+)-**4**



(+)-**5**

Compounds **3**-**5** were prepared by the reaction of R-(+)-α-methyl benzylamine with diphenylphosphinic chloride, ethylphosphonic dichloride and phosphorus oxychloride respectively. In all cases the yields were high (>80%) and the products stable solids easily purified by flash chromatography and recrystallisation. The use of compounds **3**-**5** as catalysts for the reduction of acetophenone by borane-dimethylsulphide complex was investigated using various quantities of catalysts relative to substrate (Scheme, Table). In all cases the reductions were complete (>98% conversion by HPLC) in under one hour even when only 2mol% of catalyst was employed. In contrast the uncatalysed reaction required an overnight reaction time to go to completion. The reduction products were isolated by flash chromatography followed by distillation (Khugelrohr). The enantiomeric excesses were modest, but the small difference between the value at the 2 and 10 mol% level in the case of **3** and **4** suggest that virtually all the reduction proceded through the catalysed pathway even at the lower level. In all cases the enantiomeric inductions were in the same sense. All of the catalysts could be recovered from the reaction in essentially quantitative yields by flash chromatography.

Scheme



S-(-)-**6** R-(+)-**6**

Table - asymmetric reductions of acetophenone using catalysts **3** to **5**.[6]

Catalyst	% catalyst	Temperature	Reaction time (98% reduction)	Yield **6** (isolated)	Major Enantiomer	Enantiomeric excess
none	-	r.t.	10 hrs	75%	-	-
3	2	r.t.	1.5 hr	75%	S	23%
3	10	r.t.	<1 hr	82%	S	27%
3	10	0°C	3 hrs*	75%	S	20%
4	2	r.t.	< 1 hr	76%	S	26%
4	2	0°C	3 hrs	78%	S	35%
4	10	r.t.	< 1 hr	88%	S	28%
4	20	r.t.	< 1 hr	82%	S	33%
5	10	r.t.	< 1 hr	70%	S	20%

*Catalyst partially precipitated from solution at this temperature

We are currently investigating the factors which influence the catalytic ability and the asymmetric inductions achieved with these promising new compounds with a view to producing an optimised catalyst, and our findings will be reported in due course.

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5. All new compounds gave satisfactory spectroscopic and analytical data.
6. The enantiomeric excess was determined by comparison of the optical rotation of **6** to the reported value[7] and by comparison of the integrals of the resolved methoxy peaks in 270 MHz ^{1}H-NMR spectra of the R-methoxyphenyl(trifluoromethane)acetate derivatives.[8]
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