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Stereoelectronic Requirements for a New Class of Asymmetric Ketone Reduction Catalysts Containing an N-P=O Structural Unit.

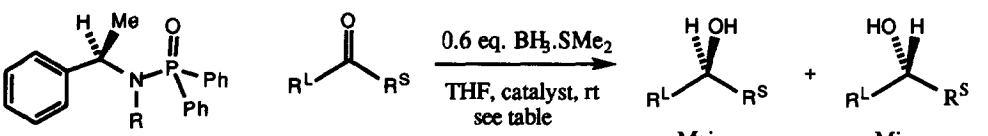
Barry Burns, N. Paul King, John R. Studley, Heather Tye and Martin Wills.*

School of Chemistry, University of Bath, Claverton Down, Bath, BA2 7AY.

abstract; *A number of new catalysts for the asymmetric reductions of ketones by borane are described. The highest accelerations are achieved by catalysts in which the phosphinamide (R_2NPO) unit can adopt a planar geometry. This observation has provided an insight into the mechanism of catalysis.*

We recently reported that chiral phosphinamides such as **1** are efficient catalysts for the asymmetric reduction of ketones by borane.[1] As well as dramatically increased reaction rates, modest asymmetric inductions may be achieved at catalyst levels as low as 2 mol%. In this paper we report further results from an on-going systematic examination of the scope of this process with respect to the structure of the substrate, and the stereoelectronic requirement of the catalyst.

Scheme



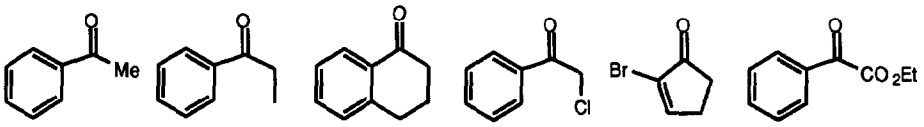
(+)-**1** R=H
(+)-**12** R=Me

Major

Minor

R^L = Large group (Ph, Ar,α-Br in **6**)
R^S = Small group (Me, CH_2Cl, CO_2Et))

The reduction of ketones **2** - **7** may be achieved using borane with 10 mol% of phosphinamide **1** as catalyst (Scheme, Table). Reduction of ketones **3** - **5** gave high yields of the corresponding alcohols with asymmetric excesses (e.e.s) similar to that recorded for **2**, which has already been reported by us.[1] The α-bromo enone **6** gave a product of slightly higher e.e. but in disappointing yield whilst the α-keto ester **7** was reduced in very low e.e. to the diol.[2] In the case of ketones **2** - **6** the enantioselectivity appears to be determined on the basis of the relative size of the ketone substituents, hydride being delivered in the absolute sense illustrated in the Scheme.[3a,b] On this basis **7** would have been predicted to give the opposite enantiomer, however it is likely that in this case a competitive co-ordination with the ester group may have modified the borane reactivity. Several of these compounds, or close relatives, have been used in the asymmetric synthesis of complex natural products or physiologically important compounds.[3c-3e]



2 3 4 5 6 7

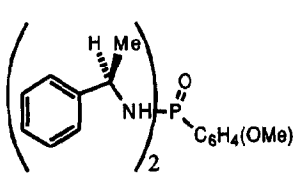
Table: Asymmetric ketone reductions using phosphinamide catalysts [1]

Ketone	Catalyst	% catalyst	Reaction time (98% reduction)	Yield of alcohol (isolated)	Major Enantiomer	Enantiomeric excess
2	none	-	ca. 10 h	75%	-	-
2	**1**	10	<1 h	82%	S-(-)	27%
3	**1**	10	<1 h	88%	S-(-)	23%
4	**1**	10	<1 h	97%	S-(+)	21%
5	**1**	10	<1 h	83%	R-(-)	22%
6	**1**	10	<1 h	46% [2]	S-(-)	46%
7	**1**	10	<1 h	80% [3]	S-(-)	5%
2	**8**	5	15 min.	95%	S-(-)	24%
2	**9**	10	3 h	90%	-	-
2	**10**	10	4 h	85%	R-(+)	35%
2	**11**	10	3 h	81%	S-(-)	4%
2	**12**	10	<1 h	90%	S-(-)	10%

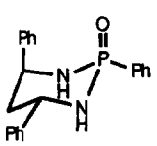
[1] All reactions were carried out at r.t. using borane-dimethylsulphide complex in THF solution.
[2] The reaction was carried out at 0°C. [3] The diol was formed.

As part of an investigation into the importance of electronic factors on the activity of phosphinamide catalysts we prepared derivative **8** which contains an electron-rich aromatic substituent.[4] In the presence of 10mol% of **8**, the reduction of acetophenone was complete within 15 minutes at room temperature[5] and the e.e. of the product was similar to that obtained using **1**. This result suggests that the donation of electron-density to the phosphinamide system is beneficial for catalysis, although it does not appear to improve the asymmetric induction.

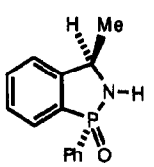
In order to probe the importance of the conformation of the R_2N-P=O system in the catalytic process we investigated three catalysts, **9** - **11**, in which the conformational freedom of this group was restricted.[6] The preparation of the amine precursor to **9** has been reported and to date we have only investigated the racemic modification.[7] Dihydrobenzazaphosphole oxide **10**, for which the relative stereochemistry has been confirmed by an X-ray crystal structure, has been reported by us in a previous communication.[8] Compound **11** was prepared in enantiomerically pure form from the commercially available precursor diamine.[6]



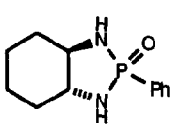
R,R-(+)-**8**



9 (racemic)



$S_{(P)}$R-(-)-**10**

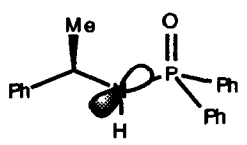


R,R-(+)-**11**

Remarkably each of the compounds **9** to **11** proved to be a poor catalyst for the reduction acetophenone by borane, a reaction time in excess of three hours being required for the reactions to proceed to *exactly* 98% completion in each case (Table).[5] The e.e. of the reduction product using catalyst **11** was very low, whilst that achieved with **10** was also modest.

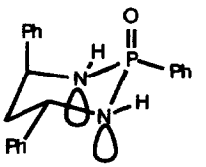
The observations above suggest that the optimum geometry for catalytic activity is that in which the 'R_2NPO' system can lie in a single plane and therefore electron donation from the nitrogen lone pair to the P=O bond is maximised. This suggestion is supported by observations in X-ray crystal structures in which nitrogen is shown to be rehybridised to an sp^2 geometry in this geometry, which suggests a high degree of overlap (Figure 1).[9,10] In contrast X-ray structures of compounds structurally related to **9**, in which such coplanarity cannot be attained contain essentially sp^3 hydridised nitrogen atoms,[9,11] suggesting that electron donation to the P=O bond is a minimum (Figure 2). However this interaction is much weaker than the corresponding effect in carbonyl amides, and the energetic benefit can be outweighed by crystal packing effects in some cases.[9] In the case of compounds **9** - **11**, which are poor catalysts, the coplanar geometry cannot be achieved whilst in contrast the catalysts **1** and **8**, which generate the highest accelerations in reduction rate, may readily achieve this. Additional electron donation from, for example, an electron-rich aromatic group as in **8** further increases the effectiveness of the catalyst by increasing the electron density in the phosphinamide (N-P=O) system.

Figure 1



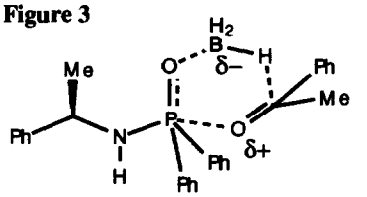
Orbital overlap in a good catalyst

Figure 2



Orbital overlap not possible in a poor catalyst

Figure 3



Proposed mechanism of catalysis

On the basis of the observations above we propose that catalysis of the reduction reaction is achieved by activation of borane by a strong donation from the oxygen atom of the N-P=O system coupled with a weaker interaction of the substrate carbonyl lone pair with the phosphorus atom (Figure 3). The initial borane co-ordination is important because it increases the electrophilicity of the phosphorus atom, which would not normally be considered to be a Lewis acid of appreciable strength. The means by which asymmetric induction is achieved is not clear at this stage and is the subject of ongoing investigations. In order to confirm that a hydrogen bond between catalyst and substrate was not a prerequisite for catalysis we prepared compound **12** by methylation of **1** (NaH/MeI in THF at room temperature). Phosphinamide **12** was as active a catalyst as **1** and gave of product of 10% e.e. in favour of the S- enantiomer at the 10mol% level. The catalysts appear to be robust with respect to moisture. In a reaction in which one equivalent of water (relative to catalyst **1**) was added to a mixture of acetophenone and **1** prior to addition of borane, the rate of the reduction was as fast as under 'dry' conditions and a product of essentially identical e.e. (26%) was obtained.[12]

Acknowledgments

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References and notes

1. B. Burns, J. R. Studley and M. Wills, *Tetrahedron Lett.*, **1993**, *34*, 7105.
2. The ketone is reduced first, then the alcohol directs reduction of the ester, for example see S. Saito, T. Hasegawa, M. Inaba, R. Nishida, T. Fujii, S. Nuzumi and T. Moriwake, *Chem. Lett.*, **1984**, 1389.
3. (a) Enantiomeric excesses of reduction products were determined by comparison of the optical rotation value to the published values in the case of the reduction of **1**[1] and **6**[3b] or the values of a sample provided by Aldrich Chemical Company (**5**, **7**) or Fluka (**3**, **4**). The value in the case of **2** was also confirmed by HPLC analysis of a chiral ester derivative.[1] (b) E. J. Corey and K. S.Rao, *Tetrahedron Lett.*, **1991**, *32*, 4623.(c) E. J. Corey and J. O. Link, *Tetrahedron Lett.*, **1990**, *31*, 601. (d) T. K. Jones, J. J. Mohan, L. C. Xavier, T. J. Blacklock, D. J. Mathre, P. Sohar, E. T. T. Jones, R. A. Reamer, F. E. Roberts and E. J. J. Grabowski, *J. Org.Chem.*, **1991**, *56*, 763. (e) E. J. Corey, C. P. Chen and G. A. Reichard, *Tetrahedron Lett.*, **1989**, *30*, 5547.
4. Compound **8** was prepared by the reaction of phosphorus oxychloride with two equivalents of α-methyl benzylamine followed by reaction with *p*-methoxyphenyl magnesium bromide. This compound gave satisfactory spectroscopic and analytical data.
5. Progress of the reaction was followed by HPLC analysis using a uv detection system. Acetophenone has an extinction coefficient ca. 50 times that of 1-phenyl ethanol therefore the method is very sensitive for the dissappearance of the ketone. Reaction completion to the extent of 98% is conveniently indicated by the detection of a 1:1 ratio of ketone and alcohol by uv. In the presence of 10 mol% of catalysts **1**, **8** and **12** essentially *no ketone* could be detected after one hour. In the absence of catalyst the reduction was ca. 35% complete after hour. Oxazaborolidines are somewhat faster than our catalysts, times of as little as one minute being sufficient for acetophenone reduction at the 10 mol% level at room temperature: For a summary see S. Wallbaum and J. Martens, *Tetrahedron: Asymmetry*, **1992**, *3*, 1481.
6. Compounds **9** -**11** were prepared in high yield by the reaction between the corresponding diamine and phenylphosphonic dichloride in dichloromethane, using triethylamine as base. All three compounds are crystalline solids, stable to air and moisture and were purified by flash chromatography. All new compounds gave satisfactory spectroscopic and analytical data.
7. S. E. Denmark and J.-H. Kim, *Synthesis*, **1992**, 229.
8. B. Burns, E. Merifield, M. F. Mahon, K. C. Molloy and M. Wills, *J. Chem. Soc., Perkin Trans 1*, **1993**, 2243.
9. A phosphonamide containing a chiral centre at phosphorus has been reported: T. A. Hamor, W. B. Jennings, C. J. Lovely and K. A. Reeves, *J. Chem. Soc., Perkin Trans 1*, **1992**, 843. In an X-ray structure of this phosphinamide the unit cell contains two molecules which differ with respect to the conformation of the R_2N unit relative to the P=O bond. The molecule in which these are perpendicular contains an sp^3 hydridised nitrogen atom whilst the molecule in which they are close to planarity contains an essentially sp^2 hydridised nitrogen atom.
10. D. Barr, W. Clegg, R. E. Mulvey and R. Snaith, *J. Chem. Soc., Chem. Commun.*, 1984, 79.
11. (a) S. E. Denmark and R. L. Dorow, *J. Am. Chem. Soc.*, 1990, **112**, 864. (b) S. E. Denmark, P. C. Miller and S. R. Wilson, *J. Am. Chem. Soc.*, 1991, **113**, 1468.
12. J. R. Studley and M. Wills, unpublished result.

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