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New Chiral Phosphinamide Catalysts for Highly Enantioselective Reduction of Ketones.

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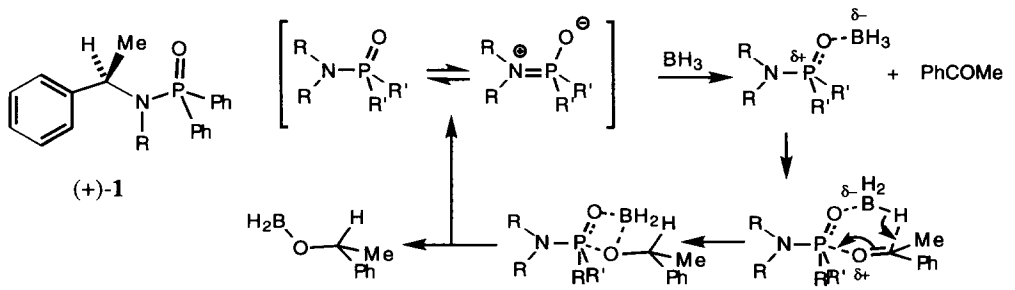
abstract; *A novel class of recoverable and highly stable phosphinamide catalysts for the asymmetric reduction of ketones by borane is described. Enantiomeric excesses of up to 92% have been obtained using 10 mol% of the optimum catalyst.* Copyright © 1996 Elsevier Science Ltd

We recently reported that chiral phosphinamides such as **1** are efficient catalysts for the asymmetric reduction of ketones by borane.[1,2] 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 our recent results from our studies of improved phosphinamide catalysts which give enantiomeric excesses of up to 92%.

Our initial studies of reduction catalysts have allowed the requirements for an effective catalyst to be defined. In particular it is essential that the 'N-P=O' structural unit can adopt a conformation in which the lone pair on nitrogen can effectively donate electron density to the d-orbitals of the P=O bond.[2] We have speculated that the mechanism of the reduction reaction is as illustrated in Scheme 1, where the first step of the catalytic cycle is co-ordination of the phosphinamide oxygen atom to a molecule of borane. This is then followed by an interaction of a lone pair from the ketone with the electron-deficient phosphorus atom. Rapid hydride transfer within this chelated structure is then followed by dissociation of the alkoxyborane complex and release of the phosphinamide into another catalytic cycle.

Scheme 1: Catalytic cycle for carbonyl reduction with borane/phosphinamide

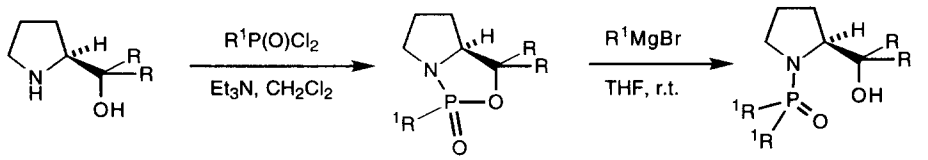


Detailed synthetic and computational[3] studies on reported[2] and unreported phosphinamides suggested that whilst the phosphinamide - borane interaction was very strong within the proposed catalytic cycle, the subsequent ketone interaction was much weaker, probably due to the high level of steric congestion around the

phosphorus atom. This led us to the conclusion that an effective catalyst might be constructed by combining the phosphinamide with a second functional group capable of providing an alternative electrophilic site for ketone co-ordination. An alcohol could provide such a site upon reaction with borane therefore, given the requirement for a rigid structure, we chose to study phosphinamide derivatives of L-prolinol, and closely related compounds **2** - **5**.

Phosphinamides **2** - **5** were prepared from commercially available L-proline derivatives *via* the oxazaphospholidine intermediates **6**[4] as illustrated in Scheme 2, a sequence developed in our laboratories which avoids the problem of competing O-phosphinylation when direct preparation from prolinol was attempted.[5,6] The oxazaphospholidine intermediates were generally formed as a mixture of diastereoisomers and the relative configuration of the major product was not determined in any of these examples. The reaction of methylmagnesium bromide with **6b** gave a small amount (7%) of the corresponding phosphinamide which decomposed rapidly during storage. This may have been precipitated by intramolecular transfer of the $Me_2P(O)$ unit from the nitrogen to oxygen atom, which would be less likely to take place in the case of the more hindered diphenyl substituted reagent.

Scheme 2



6a (R=H, R^1=Ph) 64% (4:1 mixture)
6b (R=H, R^1=Me) 15% (single isomer)
6c (R=Ph, R^1=Ph) 70% (single isomer)
6d (R=Ph, R^1=Me) 74% (1:1 mixture)

2 (R=H, R^1=Ph) 76% from **6a**
3 (R=H, R^1=Me) 7% from **6b**
4 (R=Ph, R^1=Ph) 33% from **6c**
5 (R=Ph, R^1=Me) 71% from **6d**

Phosphinamides **2**, **4** and **5** thus prepared were stable crystalline compounds and proved to be effective catalyst for ketone reduction by borane. Each compound was fully stable to the reaction conditions and could be recovered and reused after the reaction. The results of our studies are shown in Scheme 3 and the Table. Using catalyst **2** and acetophenone as substrate we initially carried out reductions at room temperature in THF solution, however under these conditions the enantiomeric excess of the product did not exceed 19%, even when a stoichiometric amount of catalyst was employed (entries 1 and 2).

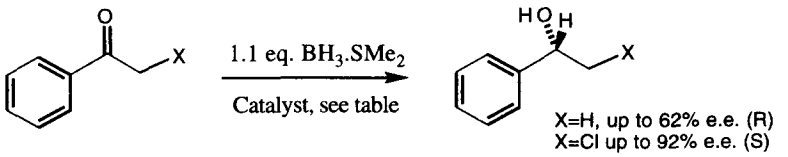
Buono has recently shown that reductions of ketones with certain catalysts[7,8] at 110°C in toluene can in some cases give higher asymmetric inductions than the room temperature reaction. Following this precedent we found a similar trend with catalyst **2** (entries 3 and 4), which gave e.e.s of up to 48% when 1 equivalent of catalyst was utilised.[9] A similar pattern of selectivity was observed when catalyst **5**, which benefits from a much lower level of steric hinderance at phosphorus, was employed (entry 5). Using chloroacetophenone as the substrate further improvements to the e.e.s were observed (entries 6 to 8), peaking at 92% when 10 mol% of catalyst **5** was used. It appears that the introduction of two phenyl groups into the prolinol unit, whilst essential for phosphinamide stability, is detrimental to the selectivity.

In all cases reduction of acetophenone gave the R enantiomer of product and chloroacetophenone the S enantiomer. This selectivity corresponds to the same sense of hydride addition with respect to the size of substituents attached to the carbonyl group, suggesting that the reduction selectivity is essentially sterically

defined. The reason for the improved selectivity in reduction of chloroacefophenone is not readily apparant but may involve a secondary interaction of a lone pair on the chlorine atom with part of the catalyst structure.

A further variation on catalyst structure could be provided by introduction of a chiral centre at the phosphorus atom. By way of a preliminary investigation of this we prepared **7**, as a single diastereoisomer, by the reaction of **6c** with methyl magnesium bromide.[4] Compound **7** also proved to be an effective catalyst for ketone reduction (entries 9-12) and gave reduction enantioselectivities intermediate between **4** and **5**. Whether this is due to an unmatched set of directing effects or is simply due to the level of steric hinderance at phosphorus is unclear and is the subject of ongoing studies.

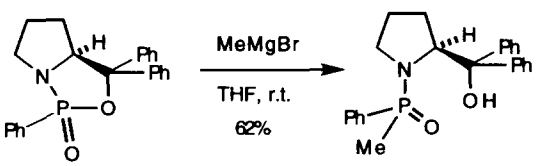
Scheme 3



Table

Entry	Ketone	Catalyst	Mol% catalyst	Solvent	Temp. °C	Yield %	e.e. %	R/S
1	PhCOMe	**2**	10	THF	r.t.	75	8	R
2	PhCOMe	**2**	100	THF	r.t.	79	19	R
3	PhCOMe	**2**	10	Toluene	110°C	84	24	R
4	PhCOMe	**2**	100	Toluene	110°C	81	48	R
5	PhCOMe	**5**	10	Toluene	110°C	90	62	R
6	$PhCOCH_2Cl$	**2**	100	Toluene	110°C	72	70	S
7	$PhCOCH_2Cl$	**4**	100	Toluene	110°C	69	24	S
8	$PhCOCH_2Cl$	**5**	10	Toluene	110°C	81	92	S
9	PhCOMe	**7**	10	Toluene	110°C	84	55	R
10	$PhCOCH_2Cl$	**7**	2	Toluene	110°C	75	62	S
11	$PhCOCH_2Cl$	**7**	10	Toluene	110°C	70	83	S
12	$PhCOCH_2Cl$	**7**	100	Toluene	110°C	84	82	S

Scheme 4



6c single diastereoisomer — **7** single diastereoisomer

The results suggest that the level of steric hinderance at the phosphorus atom is important; reduction of this may result in closer association of the catalyst with the borane and hence the reaction proceeds *via* a better defined transition state. Although the full course of the mechanism requires further study, it is likely that the initial reaction of the above catalysts with borane leads to formation of a complex such as **8**, and that the subsequent reduction transition state involves interactions of both donor and acceptor groups in this complex with the corresponding complementary reagents, as illustrated in Figure 1. In a very recent report[10] on the use of

cyclic oxazaphospholidine oxide **6a** for carbonyl reduction, Buono has suggested that the actual catalytic species may be the P-O cleaved product **9** (or the borane derivative thereof).[8] Compound **6a** gives a very similar pattern of reduction selectivities to those observed with our structurally related catalysts which strongly supports Buono's proposition, however unlike our catalysts, neither **6a** nor **9** cannot be recovered and reused after the reaction.

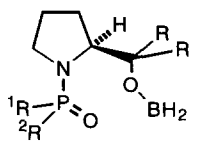


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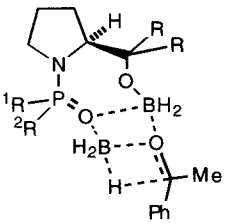
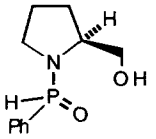
Figure 1





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In conclusion we have demonstrated that chiral phosphinamides are capable of control of the asymmetric reduction of unsymmetrical ketones in high enantiomeric excess. We expect work in this field to expand greatly in the near future and shall be reporting further and full details of our ungoing studies shortly.

Acknowledgments

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References and notes

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2. B. Burns, N. P. King, J. R. Studley, H. Tye and M. Wills, *Tetrahedron: Asymmetry*, 1994, **5**, 801.
3. I. H. Williams, L. Linney and M. Wills, *unpublished results.*
4. The oxazaphospholidine ring opening reaction of related compounds has been reported to proceed with retention of configuration at phosphorus, for example: J. M. Brown, J. V. Carey and M. J. H. Russell, *Tetrahedron*, 1990, **46**, 4877.
5. (a) H. M. I. Osborn, J. B. Sweeney and B. Howson, *Synlett.*, 1994, 145. (b) H. M. I. Osborn, A. A. Cantrill, J. B. Sweeney and B. Howson, *Tetrahedron Lett.*, 1994, **35**, 3159.
6. The reaction between prolinol and diphenylphosphinic chloride, in the presence of triethylamine and in dichloromethane solvent gave a large quantity of O-phosphinylated material. However the same reaction using diphenylprolinol gave mainly the N-phosphinylated product in 56% yield.
7. (a) J.-M. Brunel, O. Pardigon, B. Faure and G. Buono, *J. Chem. Soc., Chem. Commun.*, 1992, 287. (b) G. Buono, J.-M. Brunel, B. Faure and O. Pardigon, *Phosphorus, Sulfur and Silicon*, 1993, **93**, 43.
8. J.-M. Brunel, M. Maffei and G. Buono, *Tetrahedron: Asymmetry*, 1993, **4**, 2255.
9. In a typical procedure borane-dimethylsulfide complex (1.1 mmol) and catalyst (0.1 mmol) are dissolved in dry toluene (5 ml) and heated to 110°C. A solution of the ketone (1.0 mmol) in toluene (1 ml) is then added dropwise over 5 minutes. The reduction is essentially complete within a few minutes of the completion of the addition, however all reactions were heated for 90 minutes to ensure full conversion. The reaction is allowed to cool to room temperature, water (5 ml) is added and the product is extracted using dichloromethane (3 x 10 ml). After solvent removal the alcohol and the phosphinamide may be isolated by flash chromatography on silica gel. Enantiomeric excesses were measured by HPLC using a chiralcel OD column with 3 - 5% isopropanol in hexane, and 0.1% diethylamine as mobile phase.
10. O. Chiodi, F. Fotiadu, M. Sylvestre and G. Buono, *Tetrahedron Lett.*, 1996, **37**, 39.

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