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The Use of Phosphinamide N-Protecting Groups in the Diastereoselective Reduction of Ketones.

Matthew J. Palmer,[a] John R. Studley,[a] Tim C. Walsgrove[b] and Martin Wills.[a*]

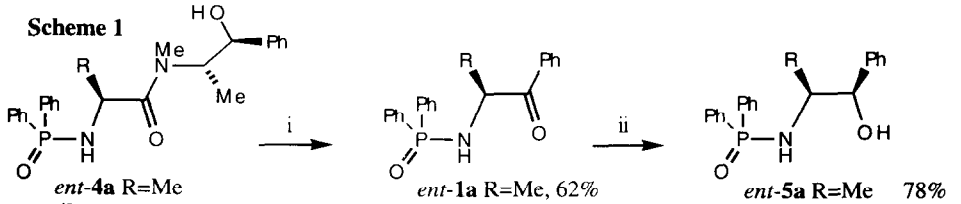
a Department of Chemistry, University of Warwick, Coventry, CV4 7AL.

b SmithKline Beecham Pharmaceuticals. Old Powder Mills, Nr Leigh, Tonbridge, Kent, TN11 9AN.

abstract; *The phosphinamide N-protecting group is demonstrated to be an effective directing group for the diastereoselective reductions of proximal ketones.* © 1997 Elsevier Science Ltd.

We have recently reported the preparation and use of phosphinamides as catalysts for asymmetric reductions of ketones by borane.[1] However the use of phosphinamides as amine protecting groups[2] has been little exploited in synthetic chemistry. We wished to explore whether the phosphinamide group in protected α-amino ketones such as **1** could direct the stereochemical course of the reduction of α -amino ketones.

Scheme 1



ent-**4a** R=Me
4b R=CH(Me)$_2$
4c R=CH$_2$Ph

ent-**1a** R=Me, 62%
1b R=CH(Me)$_2$, 33%
1c R=CH$_2$Ph, 79%

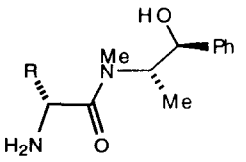
ent-**5a** R=Me 78%
5b R=CH(Me)$_2$ 90%
5c R=CH$_2$Ph 72%

Reagents and conditions; i) 5 eq.PhLi, THF, -78-0°C, 6 hr (**4b**) or 5 eq. PhMgBr, THF, -78°C to rt, 12 hrs (**4a, c**). ii) 1.1 eq. $BH_3.SMe_2$, THF, 3 hrs.

We first prepared a sample of the stereoselectively methylated derivative **2** of (1S,2S)-(+)-psuedoephedrine glycinamide **3** (73% yield).[3] Phosphinylation of **2** was then carried out in 64% yield to give *ent*-**4a** which was subsequently converted to the ketone *ent*-**1a** by treatment with an excess of phenyl magnesium chloride (Scheme 1). Reaction of *ent*-**1a** with a stoichiometric quantity of $BH_3.SMe_2$ complex resulted in rapid and complete reduction to give alcohol *ent*-**5a** as a 10:1 ratio of diastereoisomers. The assignment of the relative configurations of the chiral centres in the major isomer of *ent*-**5a** as (1S,2R) was confirmed by direct N-phosphinylation of a sample of (1S,2R)-(+)-norephedrine (85%) to give a product with identical spectroscopic characteristics. The observation that the optical rotation values of the two samples of *ent*-**5a** thus produced were essentially identical provided good evidence that no epimerisation had occured during the preparation of the ketone. However in order to confirm this each sample was independently converted to the corresponding Mosher ester derivative, which were also identical in all respects.

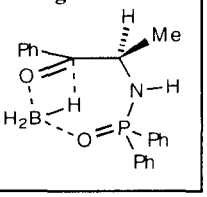
In view of the results of our previous studies it would be logical to assume that the phosphinamide promotes and directs the reduction *via* a donation of electron density from the oxygen atom to the borane[1] within a transition state similar to that shown in Figure 1. Evidence for this proposed nucleophilic catalysis

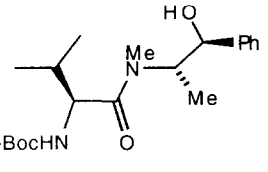
was provided by the observation that sodium borohydride, which cannot benefit from electron donation from the phosphinamide, reduced *ent*-**1a** to give only a 2:1 mixture of *ent*-**5a** and its diastereoisomer. The reduction of the *t*-butoxycarbamate protected analogue of *ent*-**1a** proceeded with a selectivity of only 3.8:1 under the same conditions (70% yield), again emphasising the importance of the phospinamide directing group effect.



3 R=H
2 R=Me

Figure 1





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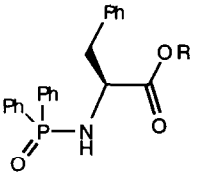

7, R=Me
8, R=H

In order to demonstrate that amino acid derivatives may be employed as precursors we also prepared the α-amino ketones derived from valine and phenylalanine, **1b** and **1c** respectively. A different route was employed in each case. The former, **1b**, by coupling of t-Boc protected valine with (1S,2S)-(+)-psudoephedrine[4] to give **6** followed by protecting group exchange and reaction with phenyllithium (33% yield). Ketone **1c** was obtained *via* the hydrolysis of the phosphinylated phenylalanine methyl ester **7** to acid **8**.[2] The latter was then coupled to (1S,2S)-psuedoephedrine to give **4c** (71% yield) and subsequently converted to **1c**.[4]. The reduction of both **1b** and **1c** (Scheme 1) proved to be even more selective than that of *ent*-**1a**. In each case only one diastereoisomer, assigned the stereochemistry depicted in **5b** and **5c** respectively, was obtained. The reaction appears to be particularly effective for aromatic ketones; a complex mixture of products was obtained in low yield when aliphatic ketones were employed as substrates.

In conclusion we have demonstrated that the diphenylphosphinyl group may be employed both as an amine protecting group and as a directing and activating group for the stereoselective reduction of adjacent ketones by borane. In view of the known ease of removal of the diphenylphosphinyl group[2] this represents a valuable new approach to the stereoselective synthesis of chiral amino alcohols.

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References

1. (a) B. Burns, J. R. Studley and M. Wills, *Tetrahedron Lett.*, 1993, **34**, 7105. (b) B. Burns, N. P. King, J. R. Studley, H. Tye and M. Wills, *Tetrahedron: Asymmetry*, 1994, **5**, 801. (c) M. P. Gamble, J. R. Studley and M. Wills, *Tetrahedron Lett.*, 1996, **37**, 2853. (d) M. P. Gamble, J. R. Studley and M. Wills, *Tetrahedron: Asymmetry*, 1996, **7**, 3071.
2. (a) G. W. Kenner, G. A. Moore and R. Ramage, *Tetrahedron Lett.*, 1976, 3623. (b) R. Ramage, D. Hopton, M. J. Parrott, G. W. Kenner and G. A. Moore, *J. Chem. Soc., Perkin Trans. I*, 1984, 1357. (c) R. Ramage, B. Atrash, D. Hopton and M. J. Parrott, *J. Chem. Soc., Perkin Trans. I*, 1985, 1217.
3. (a) A. G. Myers and T. Yoon, *Tetrahedron Lett.*, 1995, **36**, 9429. (b) A. G. Myers, T. Yoon and J. L. Gleason, *Tetrahedron Lett.*, 1995, **36**, 4555. (c) A. G. Myers, B. H. Yang and D. J. Kopecky, *Tetrahedron Lett.*, 1996, **37**, 3623. (d) A. G. Myers, J. L. Gleason and T. Yoon, *J. Am. Chem. Soc.*, 1995, **117**, 8488. (e) A. G. Myers, B. H. Yang, H. Chen and J. L. Gleason, *J. Am. Chem. Soc.*, 1994, **116**, 9361.
4. We found that this was best achieved via the formation of the mixed anhydride derived from pivaloyl chloride.[3b] In our hands **4c** was formed in 71% yield from the corresponding acid and **4b** was formed in 31% overall yield from the t-Boc protected valine (4 processes in two pots).

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