Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 11, pp. 3071-3074, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00400-4

Design, Synthesis and Applications of a Ketone Reduction Catalyst Containing a Phosphinamide Combined with a Dioxaborolidine Unit.

Mark P. Gamble,[a] John R. Studley[b] and Martin Wills.*[a]

a. Department of Chemistry, University of Warwick, Coventry, CV4 7AL, UK. email m.wills@warwick.ac.uk.

b. School of Chemistry, University of Bath, Claverton Down, Bath, BA7 2AY, UK.

Abstract: We have designed and prepared a catalyst for the asymmetric reduction of ketones which combines a phosphinamide and a boron-containing heterocyclic ring. The former group acts to direct and activated the borane, whilst the latter provides a well defined position for location of the ketone. The resulting reduction therefore takes place in a well-defined stereochemical environment. Enantiomeric excesses of up to 59%, in a predictable absolute sense, were achieved. Evidence that O- co-ordination of borane is important in the reduction mechanism is also presented

We have recently reported the preparation and use of chiral phosphinamides typified by the structure **1** as catalysts for the asymmetric reduction of ketones by borane.[1] Phosphinamides are generally easy to prepare, are robust and stable compounds and may be recovered and reused without appreciable decomposition or decrease in activity. Our studies have revealed that phosphinamides activate borane by donation of electron density, i.e. as Lewis bases (Figure 1). Whilst this effect generates high accelerations in the reductions, high enantiomeric excesses have been elusive with these compounds due to the conformational freedom allowed to the ketone in the transition state. We have recently discovered that the incorporation of a proximal hydroxyl group, as illustrated in **2**, provides a catalyst which gives dramatically improved enantiomeric excesses (up to 92%) yet retains the robustness common to other phosphinamide reagents.[2] It is believed that the hydroxyl group, upon reaction with borane, gives a complex with an electron-acceptor site for co-ordination of the ketone. Reduction of, for example, chloroacetophenone with this complex is believed to take place through a well defined transition state as depicted in Figure 2.[2] Buono has proposed a similar reduction complex in a closely related system[3] and Kellogg has also reported the use of related phosphorus-containing systems containing proximal hydroxyl groups but has given no details of the proposed reduction transition state.[4]

Figure 1

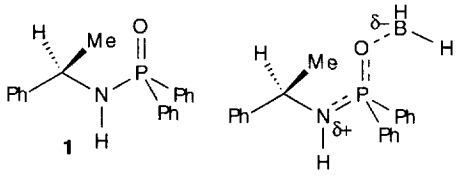
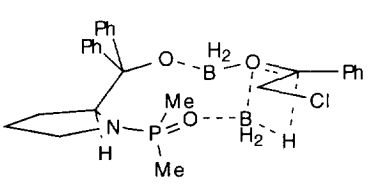


Figure 2



In order to improve the effectiveness of the 'ketone-location site' we wished to construct a more rigidly defined structure for this section of the catalyst. We believed that structure **3**, containing both a diol and a phosphinamide, would, upon reaction with borane, form a complex such as **4**. Assuming co-ordination of the lone pair of the ketone *trans* to the larger group (phenyl in the example of acetophenone shown) to boron in the ring, and activation of the borane by the phosphinamide on the top face of the heterocycle (Figure 3) then

delivery of hydride to the Re face of the ketone indicated would be predicted. In this example the reduction product of S- absolute configuration would be predicted to predominate. A weak interaction of the borane (supplying the hydride) with the oxygen atom in the dioxaborolidine, for which there is literature evidence,[5] may also contribute to the transition state structure. The alkyl group on the nitrogen atom may also be enantiomerically pure may provide a means for further improvement of asymmetric induction through 'matched' directing effects.

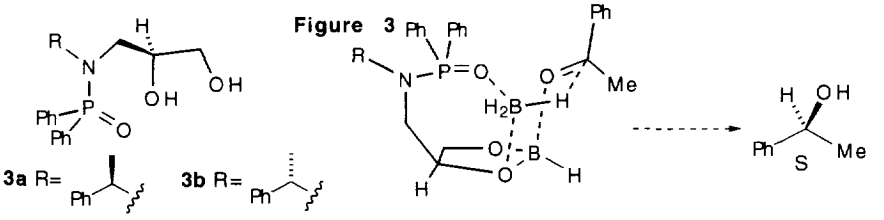
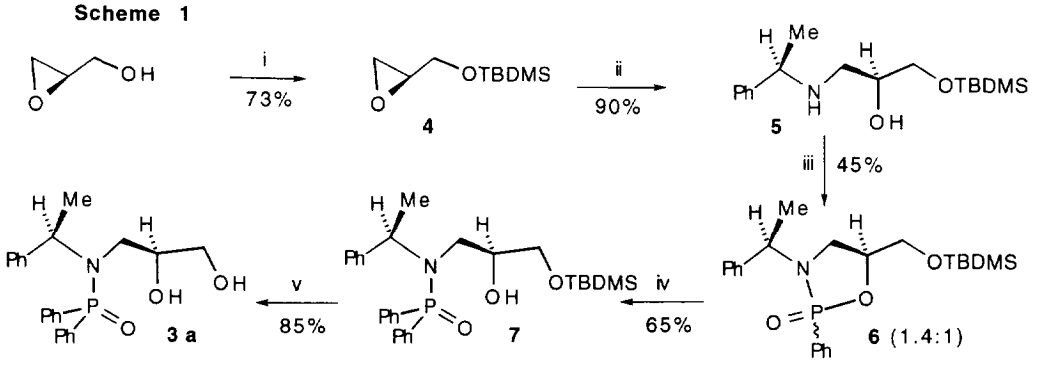


Figure 3

Our approach to compound **3a** is illustrated in Scheme 1. The reaction of R-glycidol with t-butyldimethylsilyl chloride gave the protected epoxide **4**. Reaction of **4** with R-(+)-α-methylbenzylamine in the presence of lithium perchlorate resulted in the formation of the ring-opened product **5** in 90% yield.[6] The choice of amine was dictated by the fact that phosphinamides derived from it furnish the S-reduction product of acetophenone and that, at least on the basis of this crude analysis, that it would therefore be 'matched' in stereodirecting terms to the dioxaborolidine. Incorporation of the phosphinamide group required the use of the procedure which we have already demonstrated[3] to solve the problems associated with competitive O-phosphorylation. Reaction of **5** with phenylphosphonic dichloride gave a 1.4:1 mixture of epimeric oxazaphospholidines **6** which were, without separation, treated with an excess of phenyl magnesium bromide to furnish the N-phosphinylated amino alcohol **7**. Finally deprotection using TBAF gave the catalyst **3a** as a single diastereoisomer.[7] Using an identical sequence of reactions but starting from S-(-)-α-methylbenzylamine, a sample of the diastereoisomeric compound **3b** was prepared with a corresponding level of efficiency.[7]

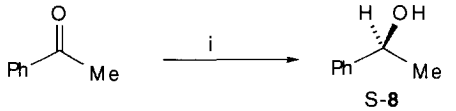
Scheme 1



Reagents and conditions: i) 1.1 eq. TBDMSCl, 1.2 eq. Et_3N, 0.05 eq. DMAP, CH_2Cl_2, rt. (ii) R-(+)-α-methylbenzylamine, 1.0 eq. $LiClO_4$, MeCN, rt. (iii) $PhP(O)Cl_2$, 2.2 eq. Et_3N, CH_2Cl_2, rt. (iv) 1.5 eq. MeMgBr, -30°C, THF. (v) 2 eq. TBAF, THF, 0°C.

Application of each catalyst to the reduction of acetophenone was then investigated (Scheme 2). Treatment of a catalytic amount (10 mol% relative to the ketone) of **3a** with an equimolar quantity of borane-dimethylsulphide complex (10M solution) for two hours at room temperature was first undertaken to allow the dioxaborolidine to form. Dry acetophenone was then added, followed by an equivalent of borane-dimethylsulphide solution. The latter was added dropwise at room temperature over a period of five minutes. After stirring for a total time of two hours (although TLC analysis indicated that the reaction was complete after 1 hour) 1-phenethyl alcohol **8** was obtained from the reaction in 88% yield and 59% e.e. in favour of the S- enantiomer. Enantiomeric excesses were calculated using chiral HPLC.[2] Although the predicted isomer was obtained, and the enantiomeric excess was significantly better than for simple phosphinamides, we found this catalyst rather more sensitive to moisture than most other related catalysts. However by ensuring that the ketone was dry (and by storing over 4Å molecular sieves) and the catalyst purified by recrystallisation, that this level of asymmetric induction was fully reproducible. In the case of the diastereoisomeric catalyst **3b**, the same reaction gave S-phenethyl alcohol **8** in 16% e.e. (84% yield). These results indicate that the dioxaborolidine structure has the dominant directing effect, which is matched to the R-configuration amine side chain in **3a**.

Scheme 2

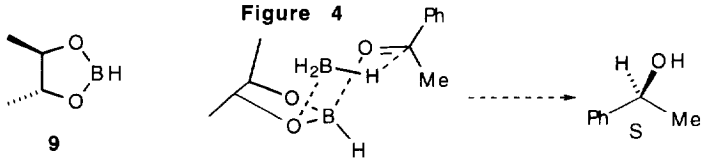


Conditions	Yield	e.e.
Using 10 mol% **3a**	88%	59%
Using 10 mol% **3b**	84%	16%
Using 100 mol% **9**	72%	41%
Using 100 mol% **9**/10 mol% **1**	88%	56%
Using 10 mol% **9**	20%	21%

Reagents and conditions: (i) 10 mol% **3a** or **3b** pretreated with 1 eq. $BH_3.SMe_2$, *or* 10 or 100 mol% **9**, then 1.0 eq. $BH_3.SMe_2$ (10M), r.t., 2 hr.

In an attempt to understand the process in more detail we examined the intermolecular combination of the directing groups used in our experiments. Reaction of RR-2,3-dihydroxybutane with an equivalent of $BH_3.SMe_2$ for twenty minutes was gave the borocycle **9** in situ (the structure is probably dimeric). Reaction of one equivalent of acetophenone with one equivalent of **9** gave no evidence of carbonyl reduction even over an extended time period (24 hours) as would be expected. However the slow addition of one further equivalent of $BH_3.SMe_2$, to a freshly prepared 1:1 solution of **9** and acetophenone in THF, resulted in reduction of the ketone to give S-**8** in 72% yield and 41% e.e. The reduction required between 3-4 hours to proceed to completion. When the same reaction was repeated using an additional 10 mol% of **1**, S-**8** of 56% e.e. was isolated in 88% yield within a reaction time of under 90 minutes. 'Matched' stereodirecting effects appear to be operating in the latter example. These results suggest that **9** directs the reduction *via* a transition state similar to that shown in Figure 4, itself very similar to that depicted for **3a** in Figure 3.[5a] In the case of **9** the borane supplying the hydride co-ordinates to an unhindered oxygen lone pair opposite the methyl group on the adjacent carbon atom. Hydride transfer *via* the depicted transition state would be predicted to give the S-enantiomer of product, as observed. If correct then this provides some indirect evidence that borane *O*-adducts can contribute to the reactivity of certain catalysts, as suggested by Katsuki.[5a] Using 100 mol% of **9**, all of the ketone will be fully complexed to the boron heterocycle, however using only 10 mol% of **9** as catalyst, S-**8** of 21% e.e. was obtained in low yield (20% after 12 hours, most of the ketone was recovered unchanged). In the catalyst **3a** the borane needs to co-ordinate to the lone pair adjacent to the substituent, a factor which may explain why higher selectivities were not obtained using this reagent.

Figure 4



9

Although we have not optimised this system, we have reported for the first time a phosphinamide reduction catalyst for which the sense of asymmetric induction can be predicted. Catalyst **3a** has given the highest asymmetric induction for a phosphinamide catalyst under the conditions quoted. There is literature evidence to suggest that, in common with oxazaborolidines, there is an optimum temperature for asymmetric reductions using borane-co-ordinating catalysts.[2,8,9] This may be due to either the existence of a non-productive dimer[8] at low temperature or may be due to accelerated breakdown of the reduction complex at high temperature, thus allowing the catalytic cycle to be propagated rapidly.[9] We are currently investigating methods for the improvement of asymmetric inductions using these novel catalysts.

Acknowledgements

We than the EPSRC for generous funding of this project. We also thank Dr J. Ballantine (EPSRC MS service, Swansea) for HRMS analyses of certain compounds.

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.

2) M. P. Gamble, J. R. Studley and M. Wills, *Tetrahedron Lett.*, 1996, **37**, 2853.

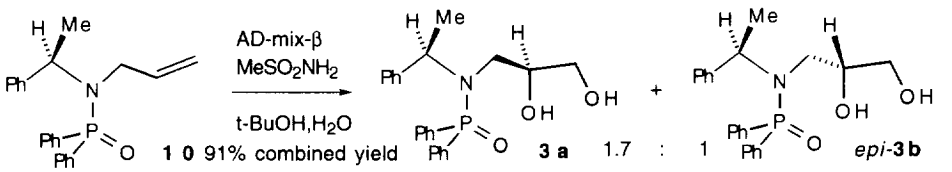
3) O. Chiodi, F. Fotiadu, M. Sylvestre and G. Buono, *Tetrahedron Lett.*, 1996, **37**, 39.

4) R. Hulst, H. Heres, N. C. M. W. Peper and R. M. Kellogg, *Tetrahedron: Asymmetry*, 1996, **7**, 1373.

5) (a) K. Otsuka, K. Ito and T. Katsuki, *Synlett.*, 1995, 429. (b) R. Berenguer, J. Garcia, M. Gonzalez and J. Vilarrasa, *Tetrahedron: Asymmetry*, 1993, **4**, 13.

6) (a) M. Canas, M. Poch, X. Verdaguer, A. Moyano, M. A. Pericas and A. Riera, *Tetrahedron Lett.*, 1991, **32**, 6931. (b) M. Meguro, N. Asao and Y. Yamamoto, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2597. (c) M. Chini, P. Crotti and F. Macchia, *Tetrahedron Lett.*, 1990, **31**, 4661.

7) In order to confirm the diastereoisomeric purity we compared the ^{1}H-NMR spectra with that of a 1.7:1 mixture of isomers of **3a:** *epi*-**3b** which had been prepared by the asymmetric dihydroxylation of **10** using AD-mix-β. This had been our original[10] approach to the synthesis of **3a**. It is noteworthy that this reaction, mediated by AD-mix-α or in the case of the omission of a chiral ligand, gave exactly the same mixture of products in each case, which suggests diastereoisomeric control entirely by the amine side chain.



8) J. M. Brunel, M. Maffei and G. Buono, *Tetrahedron: Asymmetry*, 1993, **4**, 2255.

9) (a) G. B. Stone, *Tetrahedron: Asymmetry*, 1994, **5**, 465. (b) A. W. Douglas, D. M. Tschaen, R. A. Reamer and Y.-J. Shi, *Tetrahedron: Asymmetry*, 1996, **7**, 1303, and references therein.

10) (a) P. J. Walsh, Y. L. Bennani and K. B. Sharpless, *Tetrahedron Lett.*, 1993, **34**, 5545.

(*Received in UK* 23 *August* 1996; *accepted* 8 *October* 1996)