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Synthesis and Applications of a New Class of C2 Symmetric Phosphorus Donor Ligand for Asymmetric Catalysis.

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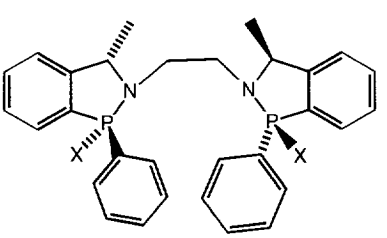
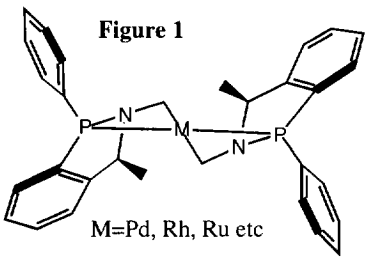
Abstract: A novel class of C2-symmetric ligand has been prepared using an intramolecular cyclisation reaction of a diazaphosphole borane complex. Preliminary results of its application to the asymmetric catalysis of hydrogenation, hydrosilylation and allylic substitution reactions are described. Copyright © 1996 Elsevier Science Ltd

As a part of an ongoing programme of research directed at the development of a versatile class of chiral ligands for asymmetric synthesis[1] we wished to prepare and test the C2 symmetric benzazaphosphole dimer **1** (the *(SpS)(SpS)*- isomer is illustrated). When complexed to a suitable metal, we propose that the chiral environment of the four aromatic rings in **1** (X=lone pair) proximal to the reaction centre (Figure 1) would closely resemble the array generated by similar complexation of C2 symmetric diphosphines such as chiraphos, DiPAMP and BINAP.[2] If this was the case then **1** may be capable of the generation of high enantiomeric excesses in several classes of organotransition metal catalysed reactions.[3] It should also be noted however that **1** is electronically distinct from other phosphine ligands, which may have a great bearing on its reactivity profile.

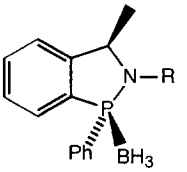
Figure 1



(SpS)(SpS)-**1** (X=BH_3 or lone pair)



M=Pd, Rh, Ru etc



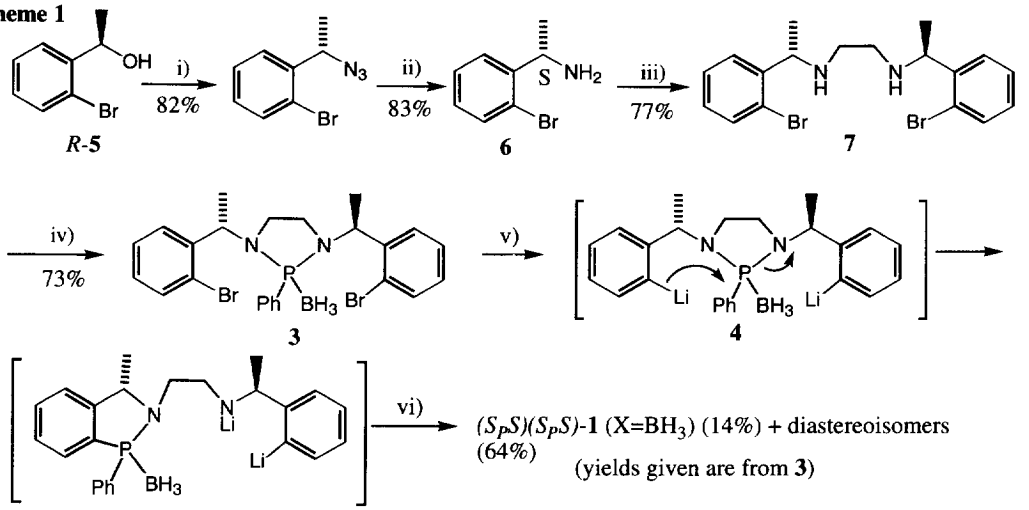
2a (R=H)
2b (R=Me)
2c (R=CH_2Ph)
2d (R=$CH_2CH{:}CH_2$)
2e (R=Si(t-Bu)Ph_2)

Our initial approach to **1** was *via* the coupling of two molecules of **2a**, a diastereoisomerically pure material, the synthesis of which we have already reported.[1] The borane serves to protect the phosphorus atom during chemical manipulations, and may be removed immediately before the reactions to which the ligands are applied.[1] Alkylation of **2a** may be achieved using powerful electrophiles such as methyliodide, benzylbromide and allylbromide in combination with sodium hydride to give the derivatives **2b** to **2d** in good yields. However, despite a lengthy series of investigations, we were unable to dimerise **2a** by alkylation with biselectrophiles under any conditions.[4]

We envisaged that an alternative approach to **1** (Scheme 1) might be through the intramolecular cyclisation of a suitable precursor such as **3** using lithium/bromide exchange followed by trapping of the intermediate dianion **4** with dichlorophenylphosphine and borane. A drawback of this approach is that a

mixture of diastereoisomers is likely to be formed, however the method would serve to provide sufficient material, after chromatographic separation, for initial investigations of its utility. The synthesis of **3** (Scheme 1) was achieved by the reaction of homochiral alcohol **5**[5] with diphenylphosphoryl azide,[6] reduction to the amine **6** and dimerisation via reaction with 1,2-dibromoethane to **7**. Reaction of **7** with dichlorophenylphosphine followed by borane gave **3**.

Scheme 1

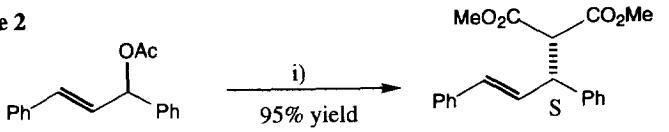


Reagents: i) $(PhO)_2P(O)N_3$, DBU, THF, rt o/n then 45°C, 4 hrs, ii) $SnCl_2.H_2O$, THF/H_2O, iii) 0.5 eq. $ClCH_2CH_2Cl$, 100°C, o/n, iv) $PhPCl_2$, THF, Et_3N, then $BH_3.SMe_2$, then recrystallisation, v) 4.0 eq. t-BuLi, Et_2O, -78°C, vi) $PhPCl_2$, -78°C, then $BH_3.SMe_2$, then flash chromatography.

Treatment of **3** with 4 equivalents of *t*-butyllithium at low temperature as described above resulted in formation of a mixture of diastereoisomeric products from which a single C2-symmetric isomer *(SpS)(SpS)*-**1** could be separated by flash chromatography in 14% yield. The remaining material consisted of an inseparable mixture of the alternative C2 symmetric product and the mixed *trans/cis* diastereoisomer. The relative stereochemistry of the stereocentres in *(SpS)(SpS)*-**1** was assigned on the basis of the coupling of the benzylic proton of the heterocyclic ring to the phosphorus atom which was identical to that we have previously observed (and proved by X-ray crystallography) for the *trans/cis* (phenyl/methyl) monomeric diastereoisomer.[7] Although the synthesis of *(SpS)(SpS)*-**1** is illustrated in Scheme 1, a quantity of its enantiomer *(RpR)(RpR)*-**1** was prepared by an analogous method from commercially available *S*-**5**.[5]

We have already demonstrated that the monomeric ligand **2e** is an excellent directing ligand for asymmetric palladium-catalysed allylic substitution reactions.[1] Application of **1** to a typical prototype reaction resulted in a good rate of acceleration - complete conversion was observed within four hours at room temperature (Scheme 2), however the product was of modest enantiomeric excess. Although not explicitly shown, deboration of **1** was achieved prior to this and other reactions using morpholine as previously described.[1] In view of the large number of highly effective ligands available for this reaction[8] we did not seek to optimise this application.

Scheme 2

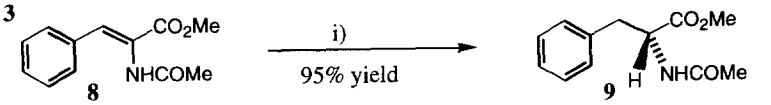


54% e.e.

Reagents: i) 2.5 mol% *(RPR)(RPR)*-**1**, 1 mol% $[(C_3H_5)PdCl]_2$, 1.1.eq.$MeO_2CCH_2CO_2Me$, 1.1.eq. (TMS)NCO(TMS)Me, cat. KOAc, CH_2Cl_2, r.t.

Asymmetric hydrogenation of the α-acylaminoacrylate **8** using 12 mol% of ligand and 5% ruthenium catalyst (Scheme 3) proved to be a slow reaction and gave the product **9** in only 33% enantiomeric excess.[11] Although a number of reactions were attempted under different conditions no improvement to the selectivity could be achieved. This result clearly demonstrates the importance of the electronic properties in the control of the enantioselectivity in asymmetric catalytic reactions.

Scheme 3

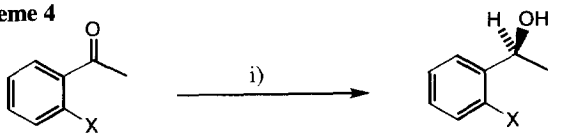


33% e.e.

Reagents: i) 12 mol% *(SPS)(SPS)*-**1**, 5 mol% $[(COD)Rh(I)Cl]_2$, 1 atm H_2, CH_2Cl_2, MeOH, 48 hrs.

We found **1** to be an effective ligand for asymmetric hydrosilylation reactions (Scheme 4); the results for a number of representative aromatic ketone reductions are given below. Diphenylsilane was employed as hydride source in all the examples, and the work-up procedure featured the use of hydrolysis by dilute HCl to free the alcohol product. Removal of by-products from the silane was achieved by the use of Khugelrohr distillation. Enantiomeric excesses in all cases were measured by HPLC on a chiral column and absolute configurations were assigned by the direction of optical rotation.[9]

Scheme 4



Product	Yield	e.e.
10a, (X=H).	84%	37%
10b, (X=Cl)	86%	59%
10c, (X=Br)	75%	84%

Reagents: i) 6 mol% *(SPS)(SPS)*-**1**, 2.5 mol% $[(COD)RhCl]_2$, Ph_2SiH_2, 0°C , 1-4 hrs. ii) HCl/H_2O.

Although the e.e for the synthesis of 1-phenethanol (**10a**) was modest, a better result was obtained for the same reaction of *o*-chloro and bromo substituted substrates. In the latter case the e.e. obtained is competitive with other reported methods. In all cases good results were obtained at the 5 mol% catalyst level and loadings of as low as 1.25% gave similar inductions (35% e.e. in the reduction to give **10a**) within short reaction times. Reduction of 1-acetonaphthone gave a product of low e.e. (14%) under the same conditions, which suggests that a secondary interaction of a coordinating side-chain group to the substrate may be important to the enantiocontrol in the reaction.

In summary we have demonstrated the asymmetric synthesis of a novel C2 symmetric phosphorus donor ligand *via* an intramolecular cyclisation followed by trapping with a phosphine dichloride and chromatographic resolution. The ligand has been shown to be capable of the catalysis of asymmetric hydrogenation, allylic substitution and hydrosilylation reactions, although it appears to have most promise in the latter application. We are currently investigating methods for the optimisation of the ligand and the conditions of the reactions to which it is applied.

Acknowledgements

We thank the EPSRC and SmithKline Beecham Pharmaceuticals (Harlow) for a CASE award (to GB), for supplying a quantity of *S*-**5** for ligand synthesis and use of HPLC facilities with the help of Dr David Guest. Thanks also to Dr Ray Jones and Neil Wallis of Zeneca FCMO for assistance with chiral HPLC analysis of hydrosilylation products and Dr J. Ballantine (EPSRC Mass Spectrometry Service) for HRMS analyses on certain compounds.

References

1) (a) G. Brenchley, E. Merifield, M. Wills and M. Fedouloff, *Tetrahedron Lett.*, 1994, **35**, 2791. (b) G. Brenchley, M. Fedouloff, M. F. Mahon, K. C. Molloy and M. Wills, *Tetrahedron*, 1995, **51**, 10581.

2) The significance of the array of four aromatic rings has been addressed in detail, for example; (a) R. Noyori, *Chem. Soc. Rev.*, 1989, **18**, 225. (b) R. Noyori, *Tetrahedron*, 1994, **50**, 4259. (c) D. Seebach, E. Devaquet, A. Ernst, M. Hagakawa, F. N. M. Kuhnle, W. B. Schweiser and B. Weber, *Angew. Chem. Int. Edn. Engl.*, 1995, **78**, 1636 and references therein. See also reference 3.

3) For excellent recent surveys see (a) R. Noyori, "Asymmetric Catalysis in Organic Synthesis", John Wiley and Sons Ltd, NY, 1994. (b) I. Ojima, "Catalytic Asymmetric Synthesis", VCH Press, Berlin, 1993.

4) The following are representative of the methods we attempted; 1,2-dibromoethane in THF, DMF or DMSO using sodium hydride (with and without added silver salts or 18-crown-6), butyllithium. potassium carbonate, P4 superbase; also with sodium hydride as base in THF: ethane-1,2-diol(bis)trifluorosulfonate, 1,2 diiodoethane, 1,3 dibromopropane, oxalyl chloride; ethane-1,2-diol with triphenylphosphine and DEAD.

5) A sample of *S*-**5** was generously provided by SmithKline Beecham, however for the synthesis of the antipodal diphosphine ligand it was necessary to prepare *R*-**5** by the asymmetric reduction of *o*-bromoacetophenone using the method reported by Evans; D. A. Evans, S. G. Nelson, M. R. Gagne and A. R. Muci, *J. Am. Chem. Soc.*, 1993, **115**, 9800.

6) A. S. Thompson, G. R. Humphrey, A. M. Demarco, D. J. Mathre and E. J. J. Grabowski, *J. Org. Chem.*, 1993, **58**, 5886.

7) The methine protons in **2a** and **2e** appear as quartets at δ4.98 and 5.52 ppm respectively. Their *cis*-diastereoisomers have corresponding resonances at δ4.86 and 5.08 ppm (multiplet and sextet respectively). The same pattern is repeated in a derivative of **2a** containing a 2-pyrollidylethyl group in the nitrogen atom, the relative configuration in which, like **2e**, has been confirmed by X-ray crystallography. Compound *(SPS)(SPS)*-**1** displayed a quartet at δ4.63 ppm for the methine resonance.

8) For an excellent recent review see B. M. Trost, *Chem. Rev.* 1996, **96**, 395.

9) Determination of enantiomeric excesses: Allylic ligand by NMR shift reagent.[1] Hydrogenation product **9**: chiral HPLC on Chiralcel OJ column; M. J. Burk, J. E. Feaster, W. A. Nugent and R. L. Harlow, *J. Am. Chem.Soc.*, 1993, **115**, 10125. **10a** - **10c**: Chiral HPLC, Chiralcel OD column, 1.0-8% isopropanol (depending on sample) in hexane containing 0.1% diethylamine. 1-(1-Naphthyl)ethanol; chiral HPLC on Chiralcel OJ column using 8% isopropanol in hexane containing 0.1% diethylamine. Flow rates of 0.5-1ml/min give excellent separations although exact elution times and efficiency of separation depend on exact column dimensions and history. Further details will be given in a full paper. Absolute configurations confirmed for **10a** to **10c** and 1-(1-naphthyl)ethanol by optical rotation sign as given in ref. 5 and (a) M. B. Carter, B. Schiott, A. Gutierrez and S. L. Buchwald, *J. Am. Chem. Soc.*, 1994, **116**, 11667, (b) G. B. Jones and S. B. Heaton, *Tetrahedron: Asymmetry*, 1993, **4** 261.

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