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TETRAHEDRON: *ASYMMETRY*

Dramatic reversal of enantioselection in a palladium catalysed allylic substitution by choice of nitrogen substituents in a N–P chiral ligand

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Abstract

Two chiral chelate nitrogen–phosphorus ligands derived from (*S*)-valine, with the potential for stereogenic nitrogen donors, gave dramatically different enantioselectivities, ranging from 92% *ee* (*R*) to 83% *ee* (*S*), in the palladium catalysed allylic substitution reaction.

The design of chiral ligands for asymmetric catalysis is in most cases an empirical and iterative process. In order to facilitate the rational design of chiral ligands we have investigated the effect of nitrogen substituents in chiral chelate ligands for asymmetric catalysis. We have reported that allowing the nitrogen donor in simple chiral nitrogen–sulfur chelate ligands to become configurationally fixed and stereogenic gave higher enantioselectivities in the asymmetric addition of diethylzinc to aromatic aldehydes when compared to achiral nitrogen donors of the same ligand system.[1] This has been achieved by the correct choice of nitrogen substituents and by chelation to a metal ion. The ligand systems have been prepared from readily available (*S*)-valine, and the results rationalised on the basis of chirality transfer.[2] We reasoned that as nitrogen–phosphorus chelate ligands are amongst the most successful ligands in the palladium catalysed asymmetric allylic substitution reaction,[3] we should investigate the diphenylphosphine analogues of our amino sulfide ligands[4] (Fig. 1). In effect, we have looked at chiral nitrogen versions of valphos **3** and wish to report that changes of the potentially stereogenic nitrogen donors can reverse the sense of enantioselection in this reaction.

The ligands were all synthesised from (*S*)-*N*-phenyl-2-amino-3-methylbutan-1-ol,[2] itself derived from (*S*)-valine in good yield (Scheme 1). Valphos **3** was synthesised according to the procedure of Hayashi et al.[5] The effectiveness of these ligands was then investigated using the standard palladium catalysed substitution of 1,3-diphenyl-2-propenyl acetate **9** with dimethylmalonate. Two common procedures were used that involved either the generation of the nucleophile in situ, using dimethyl malonate (3 equiv.)

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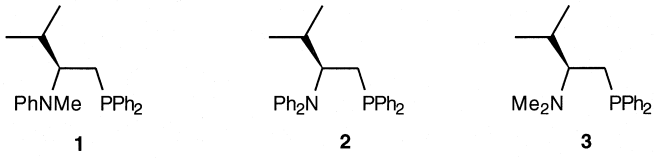
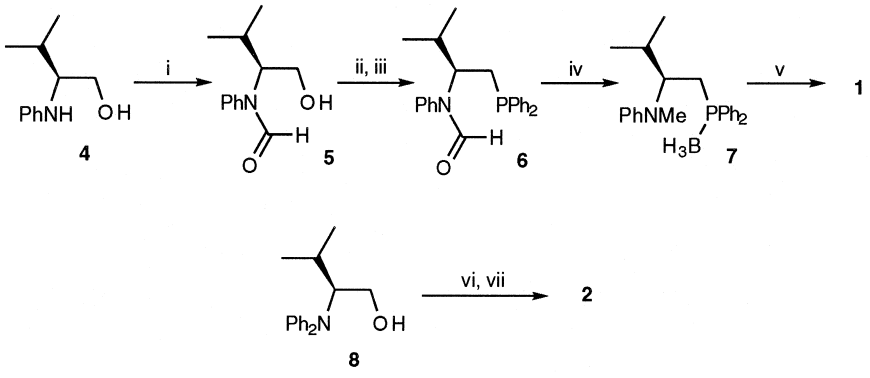
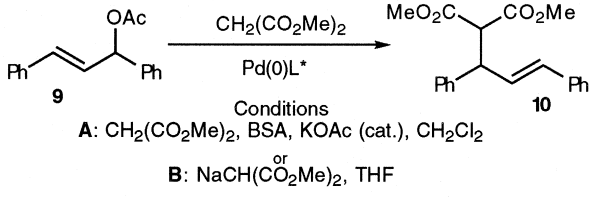


Figure 1.



Scheme 1. (i) 2.6 equiv. Ac_2O, 3.2 equiv. HCO_2H, THF, 60°C, 2 h then add **4**, rt, 5 h, 94%;[5] (ii) 1 equiv. $SOCl_2$, CH_2Cl_2, rt, 30 min, 76%;[6] (iii) 1 equiv. $HPPh_2$, 1.5 equiv. KO^{t}Bu, THF, rt, 2 h, 85%; (iv) 2 equiv. $BH_3 \cdot DMS$, THF, rt, 14 h, 90%;[7] (v) 1 equiv. DABCO, PhMe, 40°C, 14 h, 95%;[8] (vi) 1 equiv. MsCl, 2 equiv. Et_3N, CH_2Cl_2, 0°C, 1 h, 60%; (vii) 0.9 equiv. $HPPh_2$, 1.8 equiv. KO^{t}Bu, THF, rt, 14 h, 60%[9]

and *N*,*O*-bis(trimethylsilyl)acetamide (BSA, 3 equiv.) with catalytic potassium acetate (3 mol%) in dichloromethane, or the use of preformed nucleophile, sodium dimethylmalonate (1.5 equiv.) in THF. The palladium catalyst (5 mol%) was formed by mixing the allyl palladium chloride dimer with two molar equivalents of the chiral ligand in the reaction solvent for 15 minutes at room temperature.



In general, our best results (Table 1) show that in both reactions ligands **1** and **2**, which possess the potential for a stereogenic nitrogen atom, both give higher *ee*s than valphos **3**. In particular, ligand **2** gives the highest *ee* (92%) of the substituted product **10** in 94% yield compared to a 91% yield and 62% *ee* for ligand **3** under exactly the same reaction conditions. It is striking that despite each ligand possessing identical backbone chirality, ligand **1** gives (*S*)-**10** while ligands **2** and **3** both give (*R*)-**10** under each of the reaction conditions.

The enantioselection of heterobidentate nitrogen–phosphorus chiral ligands has been reported to be due to the difference in electronic character of the two donor atoms which may exert a stereoelectronic bias upon intermediate π-allyl complexes.[4,10] Stereoelectronically, the palladium–allyl terminus bond opposite the more powerful acceptor atom (phosphorus) will be longer and hence more susceptible to cleavage as a result of nucleophilic attack.[11] Such physical attributes have been verified by NMR and X-ray studies and are claimed to control enantioselection.[8f,12,13]

Considering this evidence and to offer a hypothesis for the dramatic reversal of enantioselection, we

Table 1
Allylic alkylation of **9** with $CH_2(CO_2Me)_2$ catalysed by Pd–chiral ligand complexes

Entry	Ligand	Conditions	t	Yield[a] **10** [%]	*ee* [%][b]
1	**1**	**A**	96 h	94	83 (*S*)
2	**1**	**B**	96 h	89	73 (*S*)
3	**2**	**A**	48 h	96	80 (*R*)
4	**2**	**B**	72 h	94	92 (*R*)
5	**3**	**A**	48 h	93	60 (*R*)
6	**3**	**B**	96 h	91	62 (*R*)

a Isolated yield. *b* Determined by iH NMR using gniral shift reagent $Eu(hfc)_3$

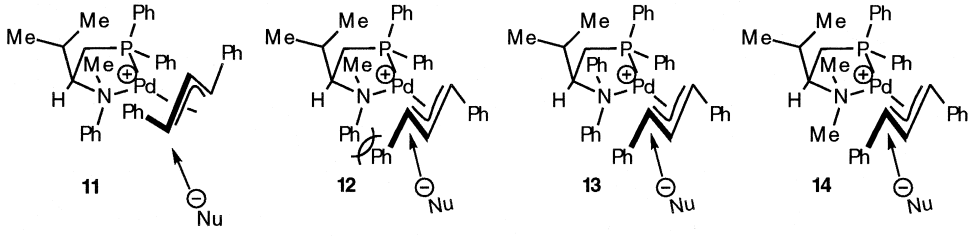


Figure 2. Possible intermediate π-allyl complexes

examined the possible conformation of the allyl intermediates for this reaction which could lead to the observed enantiomer of the product **10**. Fig. 2 shows the possible intermediates (**11**, **13** and **14**) that explain the sense of enantioselection for ligands **1**, **2** and **3**, respectively. This is assuming the ligands chelate the reactive intermediate responsible for enantioselection, which follows closely the good evidence we have for the mechanism of our analogous imine–sulfide ligands.[14] Ligand **1** should orientate the allyl group in the 'W' conformation due to the avoidance of a destabilising steric interaction between the *N*-phenyl group and the allyl phenyl group which would arise if the allyl group were orientated in the 'M' conformation (**12**, Fig. 2). We propose, for ligands **2** and **3**, that the intermediates **13** and **14** are responsible for the observed enantioselection. The 'M' conformation of the allyl group is preferred as the 'W' conformation would engender a more severe steric buttressing between the allyl phenyl group and the β-*N*-substituent of the chelate ring. Both these intermediates (**13** and **14**) lead to the opposite enantiomer of the product (*R*) to that which would arise from **11** (*S*). The orientation of the β-phenyl ring in **13**, which is dictated by the backbone *iso*-propyl group, must be such that it is more sterically demanding than the α-phenyl group. To account for the increase in enantiomeric excess for ligand **2** over **3** we propose that the stereo-inducing power of the backbone chiral centre is enhanced by the presence of phenyl rather than methyl substituents. This assumes the conformation of the phosphorus phenyl substituents are constant for each ligand system.

In summary, we have shown that the choice of nitrogen substituents in this simple ligand system can have a dramatic effect upon the sense and efficiency of enantioselectivity in this particular palladium catalysed allylic substitution reaction. Although our ligands do not give the highest recorded enantioselectivities for this particular reaction, the fact that such a small change in donor ligands can completely reverse enantioselection is highly interesting. As an explanation for our results we have forwarded a hypothesis which has not discussed the concept of preferential rotation.[10c,12c,15] A firm explanation and understanding of the subtle effects of this ligand system awaits the completion of ongoing structural and mechanistic studies.

Acknowledgements

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References

1. Anderson, J. C.; Harding, M. *Chem. Commun*. **1998**, 393.
2. Anderson, J. C.; Cubbon, R.; Harding, M.; James, D. S. *Tetrahedron: Asymmetry* **1998**, *9*, 3461.
3. (a) Sprinz, J.; Helmchen, G. *Tetrahedron Lett*. **1993**, *34*, 1769. (b) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl*. **1993**, *32*, 566. (c) Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett*. **1993**, *34*, 3149.
4. Anderson, J. C.; James, S. D.; Mathias, J. P. *Tetrahedron: Asymmetry* **1998**, *9*, 753.
5. Krishnamurthy, S. *Tetrahedron Lett*. **1982**, *23*, 3315.
6. Hayashi, T.; Konishi, M.; Fukushima, M.; Kanehira, K.; Hioki, T.; Kumada, M. *J. Org. Chem*. **1983**, *48*, 2193.
7. We believe the boron is coordinated to the phosphorus atom due to the NMR characteristics of **7** and **1**. ^{1}H NMR *N*-Me **7** δ 2.31, **1** δ 2.49; ^{31}P NMR **7** δ 15.6 (br), **1** δ −20.8
8. Brisset, H.; Gourdel, Y.; Pellon, P.; Le Corre, M. *Tetrahedron Lett*. **1993**, *34*, 4523.
9. Sakuraba, S.; Okada, T.; Morimoto, T.; Achiwa, K. *Chem. Pharm. Bull*. **1995**, *43*, 927.
10. (a) Yang, H.; Khan, M. A.; Nicholas, K. M. *Organometallics* **1993**, *12*, 3485. (b) von Matt, P.; Loiseleur, O.; Koch, G.; Pfaltz, A.; Lefeber, C.; Fuecht, T.; Helmchen, G. *Tetrahedron: Asymmetry* **1994**, *5*, 573. (c) Brown, J. M.; Hulmes, D. I.; Guiry, P. J. *Tetrahedron* **1994**, *50*, 4493. (d) Burckhardt, U.; Hintermann, L.; Schnyder, A.; Togni, A. *Organometallics* **1995**, *14*, 5415.
11. (a) Åkermark, B.; Hansson, S.; Krakenberger, B.; Vitagliano, A.; Zetterberg, K. *Organometallics* **1984**, *3*, 679. (b) Åkermark, B.; Hansson, S.; Vitagliano, A. *J. Am. Chem. Soc*. **1990**, *112*, 4587. (c) Åkermark, B.; Krakenberger, B.; Hansson, S.; Vitagliano, A. *Organometallics* **1987**, *6*, 620.
12. (a) Sprinz, J.; Kiefer, M.; Helmchen, G.; Reggelin, M.; Huttner, G.; Walter, O.; Zsolnai, L. *Tetrahedron Lett*. **1994**, *35*, 1523. (b) von Matt, P.; Lloyd-Jones, G. C.; Minidis, A. B. E.; Pfaltz, A.; Macko, L.; Neuburger, M.; Zehnder, M.; Rüegger, H.; Pregosin, P. S. *Helv. Chim. Acta* **1995**, *78*, 265. (c) Togni, A.; Burckhardt, U.; Gramlich, V.; Pregosin, P. S.; Salzmann, R. *J. Am. Chem. Soc*. **1996**, *118*, 1031.
13. Steinhagen, H.; Reggelin, M.; Helmchen, G. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2108.
14. Adams, H.; Anderson, J. C.; Cubbon, R.; James, D. S.; Mathias, J. P., submitted for publication.
15. (a) Dierkes, P.; Ramdeehul, S.; Barloy, L.; De Cian, A.; Fischer, J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Osborn, J. A. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 3116. (b) Ramdeehul, S.; Dierkes, P.; Aguado, R.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Osborn, J. A. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 3118. (c) Boog-Wick, K.; Pregosin, P. S.; Trabesinger, G. *Organometallics* **1998**, *17*, 3254.