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Examining the effect of hemilabile donor groups in non-C_2 symmetrical terdentate ligands

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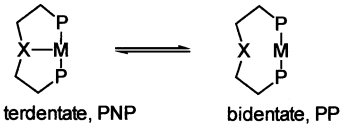
Abstract—The type and position of donor atoms in proline-derived, non-C_2 symmetric, terdentate ligands are found to have significant effects on the enantioselectivity of the palladium-catalysed allylic substitution reaction.

A majority of non-C_2 symmetrical ligands used in asymmetric catalysis are mixed-donor, bidentate systems.[1–4] In contrast, there are scarcely any reports of non-C_2-symmetrical terdentate ligands in catalysis. Previously, we described the synthesis of phosphorus–nitrogen–phosphorus (PNP) ligands[5] and their coordination chemistry with palladium and ruthenium complexes.[6,7] By placing a hemilabile donor (X) strategically between two strong (phosphorus) donors, the ligand is able to switch between PNP and PP coordination modes (Scheme 1).[6]

Since the dissociation is a facile intramolecular process, we predicted that this will improve the activity and stability of the metal catalyst. Indeed, subsequent investigations found the metal complexes of a class of phosphorus–nitrogen–phosphorus ligands to be generally more robust and efficient than conventional monodentate and/or bidentate phosphorus ligands in a number of catalytic reactions.[7–9]

In this paper we report the synthesis and catalytic activity of a class of chiral, *non-C_2 symmetric* ligands **1**, **2** and **3** (Fig. 1). Based on the same ligand backbone, yet differing in the type and nature of donor ligands, their comparative activities are examined. The effect of the nature and position of the hemilabile site on enantioselectivity constitutes a particularly important aspect in our investigation.



Scheme 1. Hemilabile behaviour of PXP ligands (X = hemilabile site).

Aminodiphosphine ligand **1** (PNP) was prepared in five steps (Scheme 2): Proline methyl ester **4** was alkylated with methyl bromoacetate, and then subsequently reduced to the hygroscopic amino diol **6**. The unstable amino dimesylate **7** was generated and treated immediately with potassium diphenylphosphide at −78°C. The amino diphosphine was subsequently protected as a borane complex **8** prior to isolation and purification.

Colourless crystals of **8** suitable for X-ray analysis were obtained (Fig. 2). The structure was completely resolved with the expected configuration at C-2.

A *syn* relationship between the BH_3 and CH_2PPh_2 substituents gives the compound an exclusive (1*R*,2*S*)-configuration. It is believed that in this arrangement both CH_2PPh_2 and $CH_2CH_2PPh_2$ occupy conformationally favourable (equatorial) positions. In similar

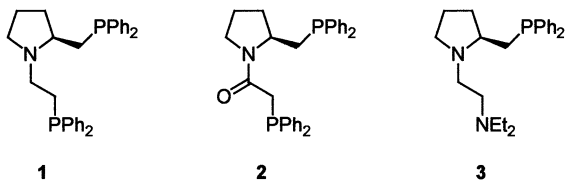


Figure 1.

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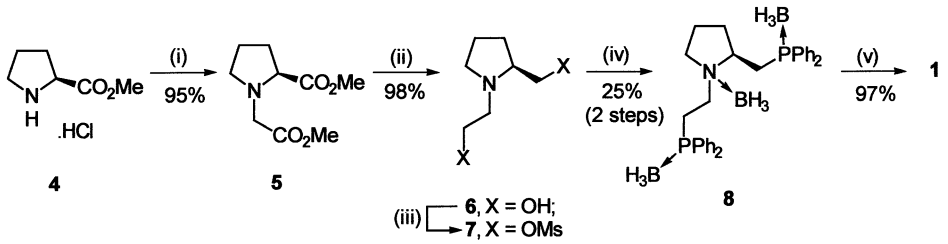


Scheme 2. *Reagents and conditions*: (i) $BrCH_2CO_2Me$, Na_2CO_3, MeOH, reflux; (ii) $LiAlH_4$, THF, reflux; (iii) MsCl, NEt_3, –78°C, toluene; (iv) (a) 2 $KPPh_2$, THF; (b) $BH_3{\cdot}SMe_2$; (v) Raney Ni, cat. Et_2NH, MeOH.

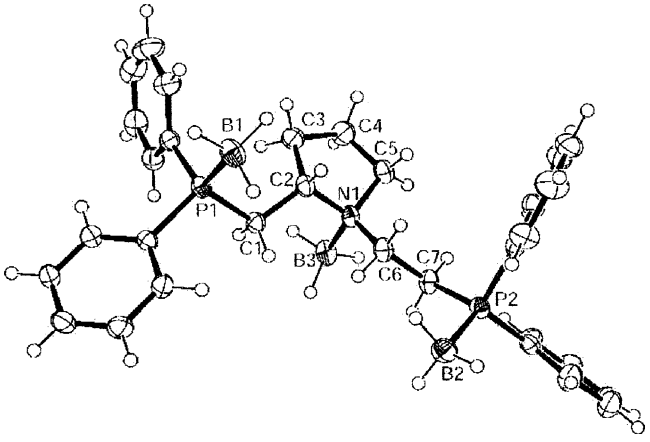
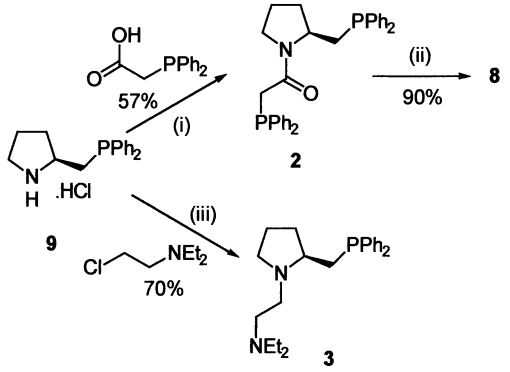


Figure 2. ORTEP structure of (1*R*,2*S*)-aminodiphosphine triborane **8**.

systems, the origin of such stereoselectivity has been attributed to the longer N→B bond being more able to adopt 1,2-eclipsing interactions with adjacent substituents on the pyrrolidine ring.[10]

Decomplexation of the borane protecting group from phosphorus and nitrogen was achieved by modifying a procedure for the deprotection of amine–boranes.[11] By adding diethylamine to a mixture of the borane complex **8** and a catalytic amount of Raney nickel in MeOH, the protecting groups can be removed cleanly in one-pot, quantitatively.[12]

Ligands **2** (POP)[13] and **3** (PNN)[14] were prepared subsequently by the reaction of aminophosphine **9**[15] with diphenylphosphinoacetic acid and *N*,*N*-diethyl-2-chloroethylamine, respectively (Scheme 3).



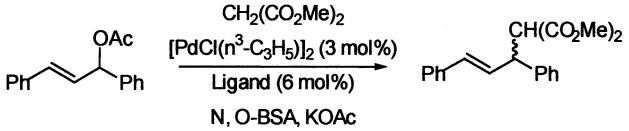
Scheme 3. Preparation of ligands **2** and **3**. *Reagents and conditions*: (i) DCC, DMAP, CH_2Cl_2; (ii) $BH_3{\cdot}SMe_2$; (iii) NaI, K_2CO_3, MeCN.

Compounds **1**–**3** were subsequently used as ligands in the palladium-catalysed asymmetric allylic substitution reaction of 1,3-diphenyl-2-propenyl acetate by dimethylmalonate.

The catalysts generated from ligands **1**–**3** display excellent activity (Scheme 4, Table 1). Complete conversions were achieved, even at 0°C, in relatively short periods of time (no starting material detectable by HPLC). A respectable ee of 74% was achieved by the PNP ligand **1** at 25°C within 2 h. When the nitrogen donor is replaced by an amide, a decrease in selectivity resulted (entries 3 and 4). Lowering the reaction temperature led to an expected rise in ee value to >80%, but has a bigger beneficial effect on the system catalysed by ligand **2** (entries 2 and 4). Removal of the pendant phosphine arm, or a change to an amino group led to a sharp fall in the enantioselectivity (entries 5 and 6).

Reactions involving two terminal phosphorus donor groups are selective for the (*S*)-isomer (entries 1–4), whereas ligands **3**, **9** (entries 5 and 6) and analogous ligands **10** (Fig. 3, where R = benzyl/benzoyl derivatives) induce the opposite stereoselectivity.[16,17] This is particularly interesting as it suggests that the stereoselectivity of the reaction is dependent on the nature of the terminal donor group of these ligands and not on the central hemilabile group—the latter appears to have a bigger role in the stability of reaction intermediates, as indicated by the better maintenance of ee values at higher temperatures by ligand **1**.

This work demonstrates that non-C_2 symmetric terdentate ligands can form highly active catalysts, given the right combination of donor groups, which are also crucial for high enantioselectivity. Although the ee values are currently lower than the best of the bidentate ligands for the system, we believe the activity and selectivity of ligands **1** and **2** are among the highest achieved by non-C_2 symmetrical terdentate ligands.



Scheme 4. Palladium-catalysed allylic substitution reaction.

Table 1. Asymmetric palladium-catalysed allylic substitution of 1,3-diphenyl-2-propenyl acetate by dimethyl malonate[a]

Entry	Ligand	T (°C)	Time (h)	% Conv.	% ee (R/S)
1	**1**	25	2	100	74 (S)
2	**1**	0	24	100	80 (S)
3	**2**	25	24	100	64 (S)
4	**2**	0	24	100	82 (S)
5	**3**	25	2	100	18.5 (R)
6	**9**	25	20	100	5 (R)

[a] All reactions were duplicated to within ±1%. Reaction times are unoptimised. % ee determined by chiral HPLC (Chiralpak AD column).

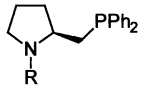


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Figure 3.

Further development of these ligands, as well as optimisation of the associated catalytic chemistry, will be reported in due course.

Supplementary material

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 182801. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

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12. **Deprotection of aminophosphine borane**: A suspension of Raney nickel (10 mg) in dry methanol (10 mL) was added to a mixture of aminodiphosphine borane **8** (160 mg, 0.31 mmol) in Et_2NH (5 mL). After heating at 55°C overnight, the solution was filtered through a pad of Celite. The filtrate was evaporated in vacuo to afford a residue, which was subjected to flash chromatography (basic alumina). The aminodiphosphine **1** was isolated as its HCl salt by adding 1 M HCl solution in ether.
13. Under Ar, a solution of diphenylphosphino acetic acid (688 mg, 2.84 mmol) in dry CH_2Cl_2 (5 mL) was added slowly to a solution of DCC (643 mg, 3.12 mmol) and DMAP (694 mmol, 5.68 mmol) in CH_2Cl_2 (10 mL) at 0°C. After stirring for 1 h, a suspension of the aminophosphine **9** (860 mg, 2.84 mmol) in CH_2Cl_2 (10 mL) was added slowly. The reaction mixture was left to warm to room temperature. After stirring overnight, degassed water (10 mL) was added and the suspension was left to stir for another hour. The precipitated urea was removed by filtration through a pad of Celite, before the solvents were removed in vacuo. The oily residue was then purified by flash chromatography to afford the amidophosphine **2** as a viscous colourless oil (800 mg, 57%).
14. Under a N_2 atmosphere at ambient temperature, a mixture of aminophosphine **9** (400 mg, 1.3 mmol), finely ground K_2CO_3 (2.0 g, 19 mmol) and 2-*N*,*N*-diethylaminoethyl chloride·HCl (200 mg, 1.2 mmol) were stirred in CH_3CN (30 mL) for 30 min, before the addition of potassium iodide (5 mg, 0.30 mmol). The reaction mixture was stirred for a further 4 h, before it was filtered. The filtrate was evaporated and purified by column chromatography to afford ligand **3** as a colourless oil (300 mg, 70%).
15. The ligand was prepared from L-proline according to a reported procedure: Kanai, M.; Nakagawa, Y.; Tomioka, K. *Tetrahedron* **1999**, *55*, 3843–3854.
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