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Synthesis of *P*-chirogenic diarylphosphinoacetic acids and their proline derivatives for palladium-catalysed allylic alkylation reactions

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Abstract—The synthesis of *P*-chirogenic diarylphosphinocarboxylic acids was achieved, from which a new class of amido- and amino-diphosphine ligands (PNP*) were derived, containing an L-proline backbone. The catalytic activities of the novel ligands were evaluated in the palladium-catalysed allylic alkylation reaction of 1,3-diphenylpropenyl acetate.

1. Introduction

There are very few reports of non-C_2 symmetrical phosphine ligands in asymmetric catalysis, especially those containing more than one stereogenic centre.[1]

Previously, we have reported novel classes of unsymmetrical, aminodiphosphine ligands derived from L-proline (Fig. 1), and their subsequent catalytic activity in the asymmetric palladium-catalysed allylic alkylation reaction.[2] In these studies, the pendant arm of the ligand attached to the pyrrolidinyl nitrogen was modified either by changing the nature of the nitrogen donor (**1** vs **2**), the pendant donor atom (**2** vs **4**) and/or by the introduction of an additional stereogenic carbon (**3** vs **4**). Herein, we report the synthesis and comparative catalytic activities of a related series of amido- and amino-diphosphine ligands **5** and **6** (Fig. 2), incorporating a stereogenic phosphorus donor on the pendant arm.

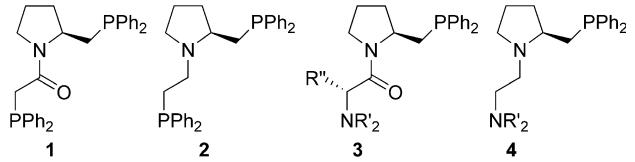

Figure 1. Proline-derived amido- and amino-phosphine ligands.

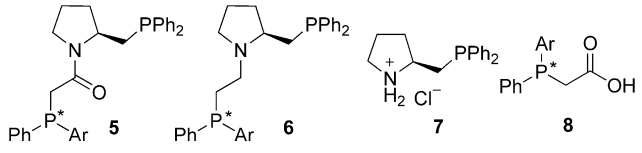

Figure 2. New classes of *P*-chirogenic ligands and their synthetic precursors.

2. Ligand synthesis

Adopting a convergent synthetic route previously established in our laboratory,[2] we envisaged that the ligands could be prepared by the coupling between **7** and the *P*-chiral phosphinocarboxylic acids **8**. Although synthetic methodologies for the preparation of *P*-chiral phosphinocarboxylic acid–boranes have been extensively developed by Imamoto and co-workers,[3] strategies to access diarylphosphinoacetic acids such as **8** are rare.[4] In this

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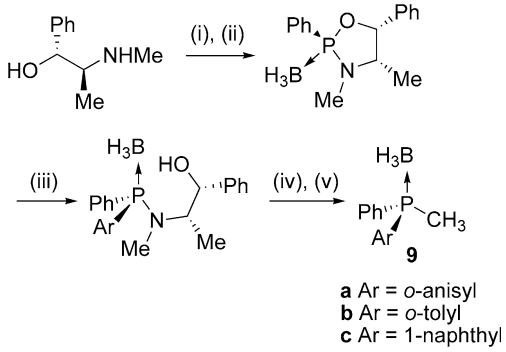


Scheme 1. Preparation of optically active diarylmethylphosphine–boranes **9a–c**: Reagents and conditions: (i) $PhP(NEt_2)_2$, PhMe, (ii) $BH_3{\cdot}SMe_2$, (iii) ArLi, −40 °C, THF; then H_2O, (iv) MeOH, H_2SO_4, (v) MeLi then H_2O.

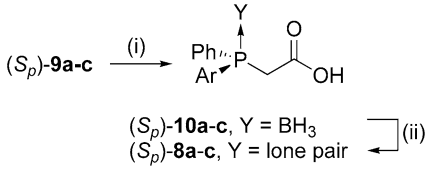
project, we have designed a synthetic route to these precursors. Based on a synthetic method pioneered by Jugé et al.,[5] successive stepwise chemo- and stereo-selective displacements of an ephedrine chiral auxiliary from a *P*-centre afforded three diarylmethylphosphine–borane adducts (*S*)-**9a–c** in good yields and excellent enantiopurities (Scheme 1).

Deprotonation of the methylphosphine–boranes **9** with *sec*-BuLi at −78 °C, followed by trapping with carbon dioxide at −40 °C, furnished *P*-chiral phosphinocarboxylic acid–boranes **10a–c** as white crystalline solids after acidic work up (Scheme 2).

The identity and absolute configuration (S_P) of the phosphinocarboxylic acid borane **10a** were established unequivocally by X-ray crystallography (Fig. 3).

The borane protecting group could be removed, with retention of configuration, by treatment with trifluoroacetic acid, to provide a new class of phosphinocarboxylic acid (PO) ligands **8a–c**, which were subsequently coupled with (*S*)-(−)-2-(diphenylphosphino)methylpyrrolidine, **7**, to afford the unsymmetrical amidodiphosphine ligands **5a–c** (Scheme 3). These amidodiphosphines displayed restricted rotation about the amide bond, giving rise to unequal rotamer populations.[6] Perhaps unsurprisingly, the distribution of the rotamers was dependent on the substitution of the pendant chirogenic phosphorus donor group, increasing in the following order: **1** (4.3:1) > **5c** (3.5:1) > **5b** (1.8:1) > **5a** (1.1:1).

Finally, reduction of the amide functionality and protection of the trivalent *N*- and *P*-donors were simul-



Scheme 2. Preparation of *P*-chiral phosphinocarboxylic acids: Reagents and conditions: (i) (a) *sec*-BuLi, −78 °C, (b) CO_2, −40 °C, (c) H_3O^+ (55–60%); (ii) (a) TFA, 0 °C, (b) aq NaOH (90–92%).

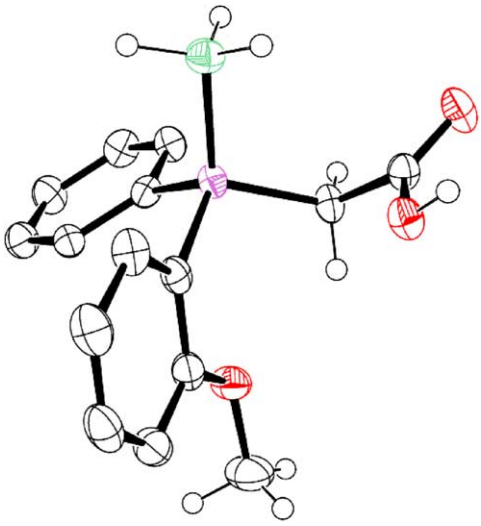
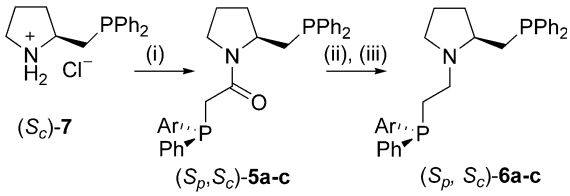


Figure 3. ORTEP representation of the molecular structure of **10a**, determined by X-ray crystallography. Aromatic hydrogens omitted for clarity.



Scheme 3. Preparation of *P*-chiral amido- and amino-diphosphines: Reagents and conditions: (i) (S_P)-**8**, DMAP, EDC, CH_2Cl_2, rt, 24 h (48–51%); (ii) $BH_3{\cdot}THF$; (iii) Et_2NH, Raney Ni, MeOH, reflux (50–60% over two steps).

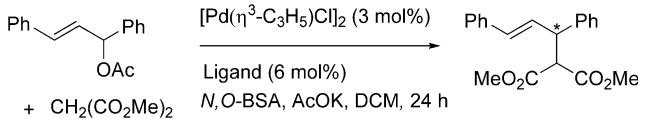
taneously achieved using $BH_3{\cdot}THF$, furnishing triborane adducts. Removal of the protecting groups from the *P*- and *N*-donor atoms was carried out in a one-pot procedure, using Raney Ni (cat.), Et_2NH and methanol,[2b] yielding the aminodiphosphine ligands **6a–c** as oils. Single sets of NMR resonances (^{31}P, ^{1}H and ^{13}C) confirmed that phosphines **5** and **6** were obtained as single diastereomers.

3. Catalytic studies

A number of phosphinocarboxylic acids have been employed in Pd-catalysed asymmetric allylic alkylation (AAA) reactions with good effect, but none of them contained a stereogenic phosphorus.[7]

To obtain a direct comparison, optimal conditions established in our previous work[2b] were employed to assess the catalytic performance of the *P*-chirogenic ligands **5**, **6** and **8** in the Pd-catalysed AAA of 1,3-diphenylpropenyl acetate with dimethyl malonate (Scheme 4, Table 1).

Using the *P*-chirogenic phosphinocarboxylic acids **8a** and **8c**, good conversion and enantioselectivity were obtained at ambient temperature (entries 1 and 2). The



Scheme 4. Palladium-catalysed allylic alkylation.

Table 1. Pd-catalysed asymmetric allylic alkylation (AAA) of 1,3-diphenylpropenyl acetate[a]

Entry	Ligand	T (°C)	t (h)	Conv. (%)[b]	ee/% (R/S)[c]
1[d]	**8a**	rt	24	100	63 (*R*)
2[d]	**8c**	rt	24	100	81 (*R*)
3	**1**	0	24	100	82 (*S*)
4	**5a**	0	48	—	—
5	**5b**	0	24	100	71 (*S*)
6	**5c**	0	24	100	27 (*S*)
7	**2**	0	2	100	80 (*S*)
8	**6a**	0	24	100	37 (*S*)
9	**6b**	0	24	100	23 (*S*)
10	**6c**	0	24	100	12 (*R*)

[a] Typical reaction conditions: see Ref. 8. Reaction times were unoptimised.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral HPLC.
[d] Ligand:metal ratio = 1:1.

naphthyl-substituted ligand afforded good enantioselectivity (81%) in favour of the *R*-enantiomer.

In comparison, the amido- and amino-diphosphine ligands **5** and **6** yielded the *S*-enantiomer as the major product (entries 3–10), except for the *P*-anisyl amido-diphosphine **5a**, which did not induce any catalytic activity at 0 °C (entry 4).

Cooperative effects between the ligand backbone and *P*-stereogenic centre have been previously observed in several asymmetric catalytic processes, including allylic alkylation, hydroboration, hydroformylation and hydrogenation reactions.[1b–e] In the present case, the introduction of the chirogenic *P*-donor in the pendant arm led to a decrease in the ee value. Replacement of the phenyl group of ligand **1** (entry 3) by *ortho*-substituted aryl groups (**5a**–**b**) or by a naphthyl moiety (**6c**) seemed to decrease the enantioselectivity of the reaction (entries 4–6), and a similar trend was observed for ligands **6a**–**c** (entries 7–10). Considering that the phosphinocarboxylic acids induce the formation of the opposite enantiomer (entries 1 and 2), we hypothesise that the beneficial effect induced by the chiral pyrrolidine backbone may be negated by the *P*-chiral pendant arm, playing an anti-cooperative effect. In the case of ligand **6c**, the stereoinduction imposed by the former is over-ridden by that of the stereogenic phosphorus centre.

4. Conclusion

In this letter, new mixed-donor unsymmetrical proline-derived amido- and amino-phosphines were prepared from *P*-chirogenic phosphinocarboxylic acids. Preliminary asymmetric catalytic results of these ligands were presented. The cooperative effects between *C*- and *P*-stereogenic centres will be examined in our future work.

Acknowledgements

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Supplementary data

Experimental procedures and characterisation data are available on-line. Crystallographic data (excluding structure factors) for compound **8a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 276442. 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]. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.09.136.

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6. For example, four singlets were observed in the ^{31}P NMR spectrum of phosphine **1**, at −13.7 (minor), −20.4 (minor), −17.3 (major) and −20.9 (major) ppm. Variable temperature ^{31}P NMR experiments revealed that these resonances coalesce at a temperature of 378 K, giving two broad singlets at −15.8 (P_B) and −19.0 (P_A).
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Umezu, Y.; Nishikawa, S.; Mori, R.; Nakayama, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 667–682.

8. *General catalytic procedure*:[2] To $[\eta^3\text{-}C_3H_5PdCl]_2$ (5.5 mg, 30 μmol, 3 mol %) was added a solution of the corresponding ligand (60 μmol) in DCM (5 mL). The suspension was degassed by three freeze-thaw cycles, then stirred at 50 °C for 2 h. The mixture was cooled to 0 °C, before the addition of a solution of (*rac*)*trans*-1,3-diphenylpropenyl acetate (126 mg, 0.5 mmol) in DCM (5 mL), dimethyl malonate (200 mg, 1.5 mmol), *N,O*-bis(trimethylsilyl)acetamide (370 μL, 1.5 mmol) and KOAc (0.75 mg). The reaction mixture was stirred for 24–48 h. Satd aq NH_4Cl solution (10 mL) was added to the reaction mixture, before extraction with diethyl ether (2×10 mL). The combined organic fractions were dried over $MgSO_4$, filtered, evaporated, and filtered through a short plug of silica to afford a viscous oil. Enantiomeric excess was determined by chiral HPLC using a Chiralpak AD column.