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Unsymmetrical terdentate phosphorus-nitrogen-nitrogen (PNN) ligands: effect of the M/L ratio and the pendant group on stereoselectivity

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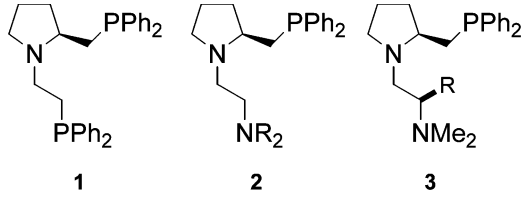
Abstract—Twelve novel, unsymmetrical terdentate pyrrolidine-based phosphorus-nitrogen ligands were prepared. These ligands promoted very high catalytic activity in the palladium-catalysed allylic substitution reactions of 1,3-diphenylpropenyl acetate with malonate esters (100% conversion at 0°C in <2 h). Enantioselectivities up to 94% were attained. An unusual effect of metal-to-ligand ratio was observed. Various structural features affecting the enantioselectivity and stereoinduction were examined and discussed.

1. Introduction

The discovery of phosphinooxazolidine ligands that can promote highly efficient and enantioselective catalysis[1,2] constituted an important breakthrough and has created significant impetus in the study of chiral non-C_2 symmetrical mixed-donor ligands for asymmetric synthesis.

Previously, we reported a novel class of unsymmetrical, proline-derived, terdentate phosphine ligands **1** and **2** (R = Et) and their catalytic activity in the asymmetric palladium-catalysed allylic alkylation reaction.[3] Prior to our study, there were very few reports of non-C_2 symmetrical terdentate phosphine ligands in asymmetric catalysis. To date, there are still only limited examples.[4,5] Herein we report the preparation and catalytic activity of a novel series of aminophosphine ligands **1**–**3** (Fig. 1). In these examples, the pendant arm of the ligand (attached to the pyrrolidinyl nitrogen) was modified, either by the introduction of different substituents on the nitrogen donor atom **2**, or by the introduction of an additional stereogenic centre **3**. Their reactivity is compared with a few structurally related ligands.



1 2 3

Figure 1.

2. Results and discussion

2.1. Ligand syntheses

2.1.1. *N*-Substitution. Ligands **2b** and **2c** were prepared by the direct *N*-alkylation of (*S*)-(−)-2-(diphenylphosphino)methyl-pyrroline **4**[6] with the corresponding 2-*N*,*N*-substituted-aminoethyl chloride or tosylate (Scheme 1, Method A). However, this procedure was not always successful. An alternative procedure (Scheme 1, Method B) involves amide coupling of the aminophosphine **4** with corresponding *N*,*N*-disubstituted glycines. The resultant amides **5** were reduced to the triborane complexes **6**, which were not isolated but subjected to decomplexation in situ using a one-pot procedure, to give the aminophosphines **2a** and **2d**.[3] This latter procedure also provided amidophosphine ligands **5a** and **5d**.

2.1.2. Additional stereogenic centre. On the other hand, enantiomerically pure 1-substituted-2-chloroethyl-*N*,*N*-dimethylamine hydrochloride salts **7** may be derived

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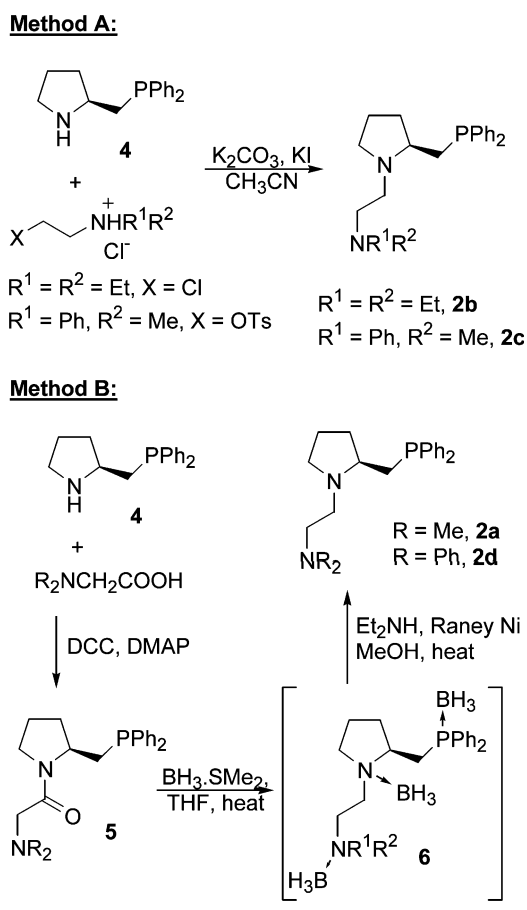
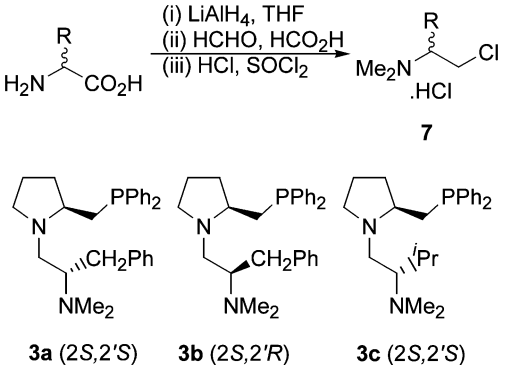


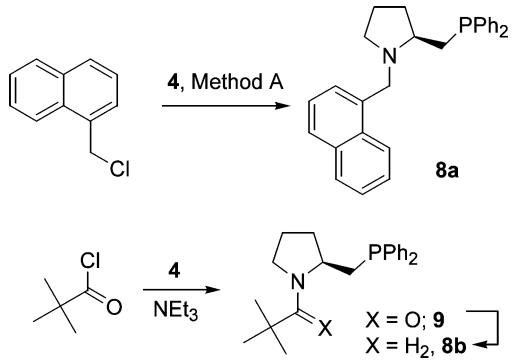
Scheme 1. Synthesis of ligands **2**.

from corresponding phenylalanine (both D and L isomers) and L-valine through a series of functional group transformations.[7] These were used to prepare ligands **3a**–**3c**, incorporating a second stereogenic centre, via Method A (Scheme 2).



Scheme 2.

2.1.3. Amino and amido-phosphine (PN) ligands without pendant arms. To assess the significance of the pendant arm and donor group, ligands **8a** and **8b** were synthesised from 1-naphthylmethylchloride and pivaloyl chloride via Methods A and B, respectively (Scheme 3). Similar amido and amino phosphine ligands have also

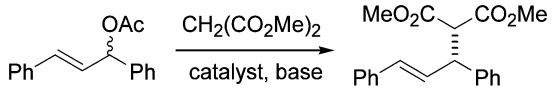


Scheme 3.

been reported independently by groups of Hiroi[8] and Tomioka.[6]

2.2. Catalytic reactions

All of the ligands prepared above were evaluated in the palladium-catalysed allylic substitution reaction of 1,3-diphenyl-2-propenyl acetate with dimethylmalonate (Scheme 4). Catalytic precursors were generated in situ by mixing $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ with the ligand in dichloromethane prior to the introduction of the substrates. The most popular reaction conditions were initially adopted: 1.5 mol% of the π-allylpalladium precursor, with 3 equiv. of *N*,*O*-bis(trimethylsilyl)-acetamide (BSA) and catalytic amount of potassium acetate as bases.



Scheme 4. Palladium-catalysed allylic alkylation reaction.

2.2.1. Metal-to-ligand ratio. We found that the stereoselectivity of the reaction was extraordinarily dependent on the metal-to-ligand (M/L) ratio (Table 1). Adopting the conventional ratio of 1:2, the enantioselectivity achieved by ligand **2b** was initially unpromising (entry 1, 18%). However, a dramatic improvement was observed when the amount of ligand used was reduced (entries 2–5). By using slightly less than 1 equiv. of the ligand **2b** (M/L = 1:0.9) the optimal e.e. value of 82% can be realised. This effect of the M/L ratio on the enantioselectivity was also mirrored by ligands **2a** (entries 8 and 9), **2c** (entries 10 and 11) and **2d**. In the latter case, an enhancement as much as 60% was observed by lowering the M/L ratio by just 0.1 (entries 14 and 15).

These observations led us to postulate that the coordination of these PNN ligands to palladium is very sensitive to the metal-to-ligand ratio.

Preliminary NMR experiments supported the above conjecture. A solution containing the palladium complex $[(\eta^3\text{-}C_3H_5)_3PdCl]_2$ and 2 equiv. (per palladium) of ligand **2b** gave rise to a complex mixture of resonances

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

Entry	Ligand	M:L[b]	T (°C)	% e.e.[c,d]
1	**2b**	1:2	25	18
2	**2b**	1:2	0	41
3	**2b**	1:1	0	66
4	**2b**	1:0.5	0	82
5	**2b**	1:0.9	0	82
6	**2b**	1:0.9	−20	80
7	**2b**	1:0.9	−20	89[e]
8	**2a**	1:1	0	54
9	**2a**	1:0.9	0	70
10	**2c**	1:1	0	74
11	**2c**	1:0.9	0	86
12	**2c**	1:0.9	−20	86
13	**2c**	1:0.9	−20	92[e]
14	**2d**	1:1	0	27
15	**2d**	1:0.9	0	87
16	**2d**	1:0.9	−20	86
17	**2d**	1:0.9	−20	94[e]

[a] Reaction conditions are given in Section 4. All reactions were complete (100% conversion, TLC analysis) in 16 h (unoptimised, vide infra).
[b] Metal-to-ligand ratio
[c] Determined by chiral HPLC (Chiralpak AD column)
[d] Absolute stereochemistry was found to be *R*, by comparison of the specific rotation to literature values.
[e] BSA added over a period of 8 h.

in the ^{31}P spectrum, including the resonance signal of the uncoordinated phosphine ligand (δP −19.6 ppm). When the experiment was repeated with equivalent amounts of the palladium complex and **2b**, only two major ^{31}P resonance peaks were observed (δP +34.3 and 32.6 ppm). ^{1}H NMR spectrum exhibited a significant downfield shift and broadening of the *N*-ethyl resonances, suggesting the coordination of the pendant nitrogen donor. In addition, we also observed a sharp ABX spin system in the region corresponding to the presence of an η^1-allyl fragment (δ 5.5–6.5 ppm). Based on these observations, we tentatively propose an equilibrating mixture of η^1- and η^3-allyl complexes in the stoichiometric mixture (Fig. 2), with the pyrrolidinyl nitrogen donor acting as the hemilabile site. Similar hemilabile behaviour has been previously proposed in analogues C_2-symmetrical PNP ligands.[9]

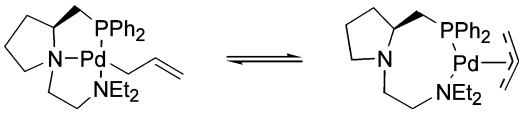


Figure 2.

A sub-stoichiometric amount of the ligand (with respect to palladium) is therefore essential for the formation of a single selective catalytic precursor. A slight excess will generate highly competitive catalytic species that compromises the enantioselectivity of the process. This effect has been previously noted for the Pd-catalysed allylic substitution reaction in a system utilising phosphine oxazoline ligands.[10]

2.2.2. Effect of the *N*-substituent and kinetic control. The nature of the nitrogen pendant arm affects the stereoselectivity of the reaction, and the following trend was observed: **2a**<**2b**<**2c**<**2d** (Table 1, entries 5, 9, 11 and 15), i.e. an increase in steric bulk of the *N*-substituent led to an enhancement in the enantioselectivity, with the diphenyl-substituted ligand **2d** affording the highest e.e. (87%).

Optimal enantioselectivity was reached at 0°C. Lowering the temperature further to −20°C did not appear to affect the enantioselectivity (entries 5, 6, 11, 12, 15 and 16). We postulate that this is because the rate of the formation of the active catalytic precursor has become comparable with the rate of the stereo-defining step at this temperature. To test this hypothesis, we performed the reaction by adding BSA slowly via a syringe pump over 8 h at −20°C (effectively decreasing the concentration of the nucleophile, and hence the rate of the stereo-defining step). Indeed, subjecting the catalytic reaction to such kinetic control led to e.e. enhancements of roughly 10% (entries 7, 13 and 17)—with ligand **2d**, an excellent e.e. of 94% may be attained.

Even though the slow addition has a beneficial effect on the enantioselectivity, this was not applied in subsequent catalytic studies, due to the rather inconvenient set-up.

2.2.3. The pendant donor group and the sense of stereoinduction. If the pendant nitrogen donor group is absent, as in ligands **8a** and **8b**, the enantioselectivity of the allylic substitution reaction was found to be in favour of the (*R*)-enantiomer, and is also dependent on the nature of the pyrrolidinyl nitrogen substituent (Table 2, entries 4 and 6), as was observed with analogous ligands.[8] However, what was not reported before was the effect of the M/L ratio, which we found to be crucial in maintaining high enantioselectivity (Table 2, entries 2–4, 5 and 6). Once again, a slightly less than stoichiometric amount was essential for optimal e.e.s. With ligand **8a**, the sense of stereoinduction was dependent on the M/L ratio (entries 2 and 4).

Table 2. Effect of the pendant donor[a]

Entry	Ligand	M:L	T (°C)	% e.e.[c,d]
1	**1**	1:1[b]	0	80 (*S*)
2	**8a**	1:2	0	11 (*S*)
3	**8a**	1:1	0	20 (*R*)
4	**8a**	1:0.9	0	74 (*R*)
5	**8b**	1:1	0	13 (*R*)
6	**8b**	1:0.9	0	46 (*R*)
7	**9**	1:0.9	0	18.5 (*R*)
8	**5a**	1:0.9	0	36 (*R*)
9	**5d**	1:0.9	0	22 (*R*)
10	**3a** (2*S*,2′*S*)	1:0.9	0	47 (*R*)
11	**3b** (2*S*,2′*R*)	1:0.9	0	72 (*R*)
12	**3c** (2*S*,2′*S*)	1:0.9	0	42 (*R*)

[a] Reaction conditions as before.
[b] M/L ratio has no effect on the e.e.
[c] Determined by chiral HPLC (Chiralpak AD column)
[d] By comparison of the specific rotation to literature values.

The enantioselectivity attained by ligands **9**, **5a** and **5d** (Table 2, entries 7–9) were much lower than their amine analogues **8b**, **2a** and **2d** (Table 2, entry 6; Table 1, entries 9 and 15, respectively), thus providing further evidence of the involvement of a centrally placed hemilabile site for the preservation of a well-defined coordination environment for stereo-discrimination.

Under the optimised M/L ratio (1:0.9), the sense of stereoinduction remained the same in all these studies. These observations were significant when compared to the result reported with the PNP ligand **1** (Table 2, entry 1), where the (*S*)-isomer was obtained in 80% e.e.[3] This is somewhat surprising, considering ligands **1** and **2d** are identical except for the pendant donor group (N versus P).

All of the above observations suggest that the nature of the pendant arm is at least as important as the stereogenic centre on the pyrrolidine ring, in determining the stereochemical outcome and stereoinduction of these allylic alkylation reactions.

2.2.4. Additional stereogenic centre. Introduction of a stereogenic centre next to the pendant dimethylamino donor group led to interesting 'match' and 'mismatch' effects (Table 2, entries 10–12).

The presence of a benzyl group with an (*S*)-configuration resulted in lower enantioselectivity (entry 10, 47% e.e.), but its presence in the (*R*)-configuration led to a slight enhancement of the enantioselectivity (entry 11, 72% e.e.). Changing the substituent from a benzyl **3a** to an isopropyl **3c** group caused a drop in the enantioselectivity (entry 12).

Interestingly, the sense of stereoinduction may be reversed with ligand **10**—the amide synthetic precursor of ligand **3c**. Containing amide functionality and a second stereogenic centre (Fig. 3), this ligand induced a small e.e. in favour of the *S*-isomer (compared to Table 2, entry 12).

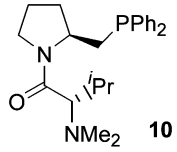


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Figure 3.

2.2.5. Rate and stereochemical pathway. The rates and selectivities of the reactions catalysed by ligands **2b** and **2d** were also compared. In this study, aliquots of reaction mixtures were extracted periodically and analysed for % conversion (^{1}H NMR) and enantioselectivity (chiral HPLC). The result clearly showed that these catalysts are not only highly selective, but are also highly active (Fig. 4). Complete conversions were achieved within 2 h at 0°C, placing these systems among some of the most active catalysts reported to date.

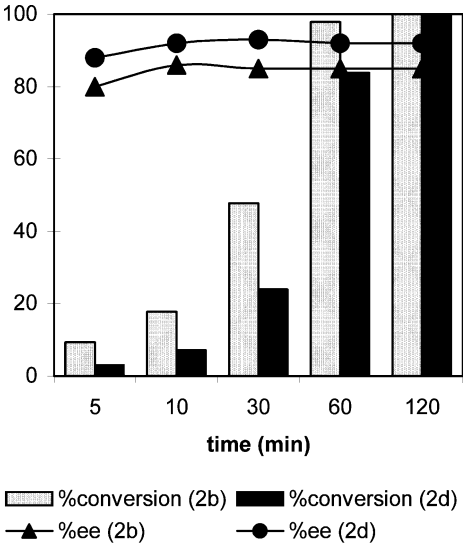
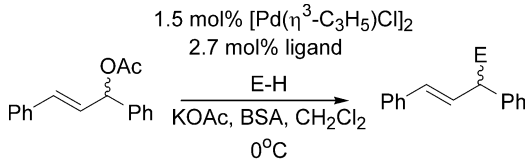


Figure 4.

Comparison between the runs showed that the less selective ligand **2b** induced faster catalytic turnover than ligand **2d**. The optimal e.e. values were established at the beginning and were maintained during the course of the reactions.

2.2.6. Varying the malonate ester. Different malonate esters were also evaluated as substrates (Table 3). The reactivity and selectivity of the addition were essentially unchanged by adopting the bulkier *tert*-butyl ester (entries 1–4). However, enantioselectivity decreased when methyl malonate ester was used (entries 5–8). Ligand **2d** achieved the highest enantioselectivities, 87 and 75%, respectively, in both cases (entries 4 and 8).

Table 3. Reaction with different electrophiles[a]



Entry	Electrophile	Ligand	% e.e.
1	$CH(CO_2^tBu)_2$	**2a**	63 (*R*)
2		**2b**	80 (*R*)
3		**2c**	81 (*R*)
4		**2d**	87 (*R*)
5	$CMe(CO_2Et)_2$[b]	**2a**	60 (*S*)
6		**2b**	65 (*S*)
7		**2c**	60 (*S*)
8		**2d**	75 (*S*)

[a] Reaction conditions are given in Section 4. All reactions were complete (100% conversion, TLC analysis) in 16 h (unoptimised).
[b] Determined by NMR using $Eu(hfc)_3$ as chiral resolving agent.

3. Conclusion

In summary, a series of novel PN(N) ligands have been synthesised with systematic variations at the *N*-donor group(s). These ligands effect high activity and enantioselectivities in palladium-catalysed asymmetric allylic alkylation reactions. The metal-to-ligand ratio was found to affect the enantioselectivity of these ligands in a profound way. In addition, there are clearly synergic effects between the nature of the pendant donor group, the central amine/amide functionality and the presence of an additional stereogenic centre on the stereoselectivity of the catalysed reaction. This supports our belief that unsymmetrical terdentate ligands provide new possibilities and opportunities in asymmetric catalysis by offering several possible tunable sites for the optimal control of reactivity and stereoselectivity.

4. Experimental

4.1. General

All reactions were carried out under an inert atmosphere of nitrogen or argon using standard Schlenk line techniques. Solvents were purified by standard procedures. (*R*) and (*S*)-2-*N*,*N*-Dimethylamino-3-phenyl-1-propylchloride hydrochloride, (*S*)-(+)-2-*N*,*N*-dimethylamino-3-methyl-1-butylchloride hydrochloride[7] and (*S*)-(−)-2-[(diphenylphosphino)methyl]pyrroline **4**[8] were prepared following reported procedures. Unless otherwise stated, all other reagents were procured from Avocado, Lancaster or Aldrich chemical companies and used as received. ^{31}P, ^{1}H and ^{13}C NMR spectra were recorded using Bruker AVANCE 360, 400 or 500 MHz instruments with TMS (^{1}H and ^{13}C) and 85% H_3PO_4 (^{31}P) as external standards. Mass spectrometry facilities were provided by the University of London MS Service. Elemental analyses were performed at London Metropolitan University. HPLC were performed on a Gilson instrument.

4.2. Ligand synthesis

4.2.1. Method A. Ligands **2b**, **2c**, **3a**, **3b** and **3c** were prepared by the alkylation of (*S*)-(−)-2-[(diphenylphosphino)methyl]pyrroline **4** with the corresponding *N*,*N*-disubstituted-aminoalkylchlorides or tosylate. A general procedure is described below for the synthesis of **(2*S*)-(−)-1-[2-(*N*,*N*-diethylamino)ethyl]-2-[(diphenylphosphino)methyl]pyrroline, 2b**: A mixture of (*S*)-(−)-2-[(diphenylphosphino)methyl]pyrroline **4** (0.40 g, 1.31 mmol), 2-(*N*,*N*-diethylamino)ethylchloride hydrochloride (0.20 g, 1.16 mmol) and K_2CO_3 (2.0 g) were dissolved in degassed CH_3CN (30 ml). The mixture was stirred for 30 min before the addition of KI (0.05 g, 0.30 mmol). Stirring was continued overnight at rt. The reaction mixture was then filtered via cannula and the residue was washed with degassed diethyl ether. The combined filtrate was evaporated under reduced pressure and subjected to column chromatography (neutral Al_2O_3, Et_2O:hexane:Et_3N, 20:78:2), furnishing the product as a colourless liquid. Yield 0.30 g, 70%. Anal. calcd for $C_{23}H_{33}N_2P$: C, 74.97; H, 9.03; N, 7.60%. Found C, 74.61; H, 9.00; N, 7.54%. ^{31}P NMR (145 MHz, $CDCl_3$) δ: −19.7. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.93 (t, 6H, J=7.2 Hz), 1.50–1.79 (m, 3H), 1.83–1.96 (m, 2H), 2.01–2.12 (m, 2H), 2.19–2.29 (m, 1H), 2.41–2.52 (m, 7H), 2.83–2.92 (m, 1H), 3.04–3.10 (m, 1H), 7.22–7.39 (m, 10H). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 11.9, 22.6, 23.9 (d, J=8 Hz), 34.2 (d, J=13 Hz), 47.8, 52.2, 52.8, 54.5, 63.0 (d, J=19 Hz), 128.1–140.2 (Ph). HRMS (FAB): exact mass calcd for $C_{23}H_{34}N_2P$ (MH^+) 369.2460, found 369.2468. IR (cm^{-1}, thin film, NaCl discs) ν: 2965, 2798, 1585, 1433, 1069, 738, 696. $[\alpha]_D^{25}$ = −121.4 (*c* 1.13, EtOH).

(2*S*)-(−)-1-[2-(*N*-Methyl-*N*-phenyl)aminoethyl]-2-[(diphenylphosphino)methyl]-pyrrolidine, 2c was prepared from 2-(*N*-methyl-*N*-phenyl)aminoethyl tosylate[11] and **4**. Colourless liquid. Yield: 75%. Anal. calcd for $C_{26}H_{31}N_2P$: C, 77.58; H, 7.76; N, 6.96%. Found C, 77.60; H, 7.63; N, 6.79%. ^{31}P NMR (145 MHz, $CDCl_3$) δ: −20.1. ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.45–1.79 (m, 3H), 1.81–1.98 (m, 2H), 2.04–2.20 (m, 2H), 2.25–2.40 (m, 1H), 2.38 (dt, 1H, J=3.4, 13.2 Hz), 2.82 (s, 3H), 2.80–2.89 (m, 1H), 3.10–3.20 (m, 1H), 3.24 (m, 1H), 3.38 (ddd, 1H, J=5.0, 9.9, 14.8 Hz), 6.39–7.62 (m, 15H). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 23.0, 32.0 (d, J=7 Hz), 34.6 (d, J=13 Hz), 39.0, 50.9, 52.3, 54.6, 62.9 (d, J=19 Hz), 112.3–149.4 (Ph). HRMS (FAB): exact mass calcd for $C_{26}H_{32}N_2P$ (MH^+), 403.2303, found 403.2322. IR (cm^{-1}, thin film, NaCl discs) ν: 3067, 2959, 2795, 1599, 1505, 1103, 746, 694. $[\alpha]_D^{25}$ = −144.5 (*c* 1.05, EtOH).

(2′*S*,2*S*)-1-[2-(*N*,*N*-Dimethylamino)-3-phenyl)]-2-[(diphenylphosphino)methyl]pyrrolidine, 3a. From (*S*)-(+)-2-*N*,*N*-dimethylamino-3-phenyl-1-propylchloride hydrochloride and **4**. Colourless oil. Yield: 65%. Anal. calcd for $C_{28}H_{35}N_2P$: C, 78.11; H, 8.19; N, 6.51%. Found C, 77.96; H, 8.31; N, 6.57%. ^{31}P NMR (145 MHz, $CDCl_3$) δ: −20.0. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 150–1.78 (m, 3H), 1.88–1.96 (m, 2H), 2.08–2.14 (m, 1H), 2.26 (dd, 1H, J=5.8, 12.4 Hz), 2.30 (s, 6H), 2.29–2.68 (m, 1H), 2.38 (m, 1H), 2.61–2.68 (m, 2H), 2.74 (dd, 1H, J=6.3, 13.9 Hz), 2.85–2.92 (m, 1H), 3.12–3.18 (m, 1H), 7.32–7.43 (m, 15H). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 22.9, 31.9 (d, J=8 Hz), 33.9, 34.3 (d, J=13 Hz), 41.2, 54.6, 54.9, 62.9 (d, J=19 Hz), 65.7, 125.9–142.1. HRMS (FAB): exact mass calcd for $C_{28}H_{36}N_2P$ (MH^+) 431.2616, found 431.2629. IR (cm^{-1}, thin film, NaCl discs) ν: 3053, 2935, 2776, 1601, 1584, 1433, 738, 696. $[\alpha]_D^{25}$ = −83.1 (*c* 1.09, EtOH).

(2′*R*,2*S*)-(−)-1-[2-(*N*,*N*-Dimethylamino)-3-phenyl)]-2-[(diphenylphosphino)methyl]-pyrrolidine, 3b. From (*R*)-(−)-2-*N*,*N*-dimethylamino-3-phenyl-1-propylchloride hydrochloride and **4**. Yield: 80%. Anal. calcd for $C_{28}H_{35}N_2P$: C, 78.11; H, 8.19; N, 6.51%. Found C, 78.27; H, 8.24; N, 6.48%. ^{31}P NMR (145 MHz, $CDCl_3$) δ: −19.1. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 1.37–1.53 (m, 2H), 1.56–1.85 (m, 4H), 1.88–1.99 (m, 1H), 2.03–2.25

(m, 2H), 2.28 (s, 6H), 2.39 (dd, 1H, $J=3.2$, 13.0 Hz), 2.72–2.89 (m, 3H), 2.91–2.99 (m, 1H), 7.03–7.37 (m, 15H). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 23.1, 32.8 (d, $J=7$ Hz), 34.0, 34.6 (d, $J=13$ Hz), 41.7, 54.9, 55.6, 63.9 (d, $J=19$ Hz), 65.6, 126.1–133.5. HRMS (FAB): exact mass calcd for $C_{28}H_{36}N_2P$ (MH^+) 431.2616, found 431.2603. IR (cm^{-1}, thin film, NaCl discs) ν: 3054, 2934, 1602, 1584, 1433, 738, 697. $[\alpha]_D^{25}=-160.0$ (c 1.18, EtOH).

(2′*S*,2*S*)-(−)-1-[2-(*N*,*N*-Dimethylamino)-3-methyl]butyl-2-[(diphenylphosphino)methyl]-pyrrolidine, 3c. The compound was synthesised from (*S*)-(+)-2-*N*,*N*-dimethylamino-3-methyl-1-butylchloride hydrochloride and **4**. Colourless liquid. Yield: 54%. Anal. calcd for $C_{24}H_{35}N_2P$: C, 75.36; H, 9.22; N, 7.32%. Found C, 75.33; H, 9.27; N, 7.32%. ^{31}P NMR (145 MHz, $CDCl_3$) δ: −19.1.^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.84 (d, 3H, $J=6.9$ Hz), 0.89 (d, 3H, $J=6.8$ Hz), 1.35–1.69 (m, 3H), 1.70–1.90 (m, 3H), 1.93–2.10 (m, 2H), 2.18 (s, 6H), 2.11–2.25 (m, 2H), 2.48 (dt, 1H, $J=3.4$, 13.1 Hz), 2.61 (dd, 1H, $J=7.3$, 12.1 Hz), 3.02–3.18 (m, 1H), 7.21–7.42 (m, 10H). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 20.6, 21.4, 22.7, 29.4, 32.1 (d, $J=7$ Hz), 34.3 (d, $J=13$ Hz), 42.1, 52.2, 54.5, 63.2 (d, $J=19$ Hz), 67.4, 128.7–133.5. HRMS (FAB): exact mass calcd for $C_{24}H_{36}N_2P$ (MH^+) 383.2616, found 383.2599. IR (cm^{-1}, thin film, NaCl discs) ν: 3053, 2953, 2775, 1585, 1456, 1433, 1026, 737, 696. $[\alpha]_D^{25}=-132.6$ (c 1.08, EtOH).

(2*S*)-(−)-1-(1-Naphthylmethyl)-2-[(diphenylphosphino)-methyl]-pyrrolidine, 8a. Prepared from 1-naphthylmethylchloride and **4**. White solid. Yield: 60%. Mp 75–76°C. Anal. calcd for $C_{28}H_{28}NP$: C, 82.12; H, 6.89; N, 3.42%. Found C, 82.17; H, 7.00; N, 3.32%. ^{31}P NMR (145 MHz, $CDCl_3$) δ: −19.6. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 1.61–1.80 (m, 3H), 2.02–2.28 (m, 3H), 2.50–2.64 (m, 1H), 2.76 (dt, 1H, $J=3.5$, 13.1 Hz), 2.81–2.89 (m, 1H), 3.53 (d, 1H, $J=12.9$ Hz), 4.55 (d, 1H, $J=12.9$ Hz), 7.23–8.50 (m, 17 H). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 22.5, 32.4 (d, $J=7$ Hz), 34.4 (d, $J=13$ Hz), 54.6, 57.0, 63.1 (d, $J=19$ Hz), 124.8–139.8. HRMS: exact mass calcd for $C_{28}H_{29}NP$ (MH^+) 410.2038, found 410.2050. IR (cm^{-1}, Nujol, NaCl discs) ν: 2927, 1459, 1376, 1139, 733. $[\alpha]_D^{25}=-154.8$ (c 1.08, EtOH).

4.2.2. Method B. General procedure is described for the synthesis of **(2*S*)-1-[2-(*N*,*N*-dimethylamino)]acetyl-2 (diphenylphosphinomethyl)-pyrrolidine, 5a**. A mixture of 2-(*N*,*N*-dimethylamino)acetic acid hydrochloride (0.56 g, 4.0 mmol), **4** (1.10 g, 3.6 mmol), DMAP (1.46 g, 12 mmol) and DCC (1.24 g, 6.0 mmol) in CH_2Cl_2 (20 ml) was stirred at 30°C overnight. The reaction mixture was then extracted with 1N aq. HCl (25 ml). The aqueous layer was neutralised by the addition of 30% aq. NaOH (4 ml) at 0°C, before extraction with *n*-hexane (30 ml). The combined organic layers were washed repeatedly with water, then evaporated to dryness. The residue was subjected to column chromatography (SiO_2, toluene:EtOAc:NEt_3, 90:8:2) to give the amide as a colourless oil. Yield: 0.65 g 51%. Anal. calcd for $C_{21}H_{27}N_2OP$: C, 71.16; H, 7.68; N, 7.90%. Found C, 71.29; H, 8.06; N, 8.09%. HRMS (FAB): exact mass calcd for $C_{21}H_{28}N_2OP$ (MH^+) 355.1939, found 355.1951. IR (cm^{-1}, thin film, NaCl discs) ν: 3051, 2944, 1654, 1428, 1170, 740, 700. A mixture of rotamers were observed in the NMR spectra of the compound in solution: Major rotamer (78%): ^{31}P NMR (145 MHz, $CDCl_3$,) δ: −21.1. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 1.13–127 (m, 1H), 1.39–1.58 (m, 2H), 1.65–1.88 (m, 2H), 2.13 (s, 6H), 2.59 (s, 2H), 2.98–3.23 (m, 1H), 4.11–4.29 (m, 1H), 7.18–7.64 (m, 10H). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 24.9, 30.7 (d, $J=8$ Hz), 33.5 (d, $J=14$ Hz), 45.8, 46.8, 56.1 (d, $J=20$ Hz), 64.1, 125.2–141.0 (Ph), 168.3. Minor rotamer (22%). ^{31}P NMR (145 MHz, $CDCl_3$) δ: −20.2. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 1.27–1.38 (m, 2H), 1.39–1.58 (m, 2H), 1.94 (s, 6H), 2.20–2.30 (m, 2H), 2.64 (d, 1H, $J=13.9$ Hz), 2.72 (d, 1H, $J=13.9$ Hz), 3.20–3.50 (m, 2H), 4.00–4.10 (m, 1H), 7.18–7.64 (m, 10H). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 22.0, 31.8 (d, $J=8$ Hz), 35.3 (d, $J=16$ Hz), 45.7, 45.9, 55.7 (d, $J=23$ Hz), 61.4, 125.2–141.0, 167.9. $[\alpha]_D^{25}=-94.5$ (c 1.24, EtOH).

One-pot reduction and decomplexation to **(2*S*)-(−)-1-(2-*N*,*N*-dimethylamino)ethyl-2-[(diphenylphosphino)-methyl]pyrrolidine, 2a**. After the dropwise addition of BH_3 (1.5 M in THF, 4.2 ml, 6.8 mmol) to a solution of **5a** (0.30 g, 0.85 mmol) in THF (10 ml) at rt, the reaction mixture was refluxed gently for 8 h. The solution was then cooled in ice-bath, and methanol (2 ml) was added carefully. When the effervescence ceased, the solvents were removed in vacuo. Degassed pyrrolidine (6 ml), methanol (20 ml) and Raney Nickel (0.1 g) were then added and the reaction mixture was allowed to reflux overnight. The solvent was then removed in vacuo and the residue extracted with Et_2O (2×20 ml). The combined organic extracts were evaporated and the residue was purified by column chromatography (neutral Al_2O_3, Et_2O:hexane:NEt_3, 40:58:2) to afford a colourless oil. Yield: 0.18 g, 61%. Anal. calcd for $C_{21}H_{29}N_2P$: C, 74.09; H, 8.59; N, 8.32%. Found C, 73.99; H, 8.68; N, 8.42%. ^{31}P NMR (145 MHz, $CDCl_3$) δ: −19.7. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 1.44–1.78 (m, 3H), 1.84–2.08 (m, 4H), 2.13 (s, 6H), 2.17–2.32 (m, 3H), 2.46 (dt, $J=3.3$, 13.1 Hz), 2.83–2.91 (m, 1H), 3.06 (br t, 1H, $J=8.4$ Hz), 7.21–7.39 (m, 10H). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 22.6, 32.0 (d, $J=7$ Hz), 34.2 (d, $J=13$ Hz), 46.3, 52.8, 54.5, 58.9, 63.0 (d, $J=19$ Hz), 128.7–139.8 (Ph). HRMS (FAB): exact mass calcd for $C_{21}H_{30}N_2P$ (MH^+) 341.2147, found 341.2158. IR (cm^{-1}, thin film, NaCl discs) ν: 3069, 2942, 2756, 1585, 1433, 738, 769. $[\alpha]_D^{25}=-118.2$ (c 1.12, EtOH).

(2*S*)-(−)-1-[2-(*N*,*N*-Diphenylamino)acetyl]-2-(diphenyl-phosphinomethyl)-pyrrolidine, 5d. The compound was recrystallised from methanol. Yield: 59%. Mp 125–126°C. Anal. calcd for $C_{31}H_{31}N_2OP$: C, 77.80; H, 6.53; N, 5.85%. Found C, 77.72; H, 6.59; N, 5.75%. HRMS (FAB): exact mass calcd for $C_{31}H_{32}N_2OP$ (MH^+) 479.2252, found 479.2266. IR (cm^{-1}, Nujol, NaCl discs) ν: 2921, 1646, 1459. Major rotamer (73%): ^{31}P NMR (145 MHz, $CDCl_3$) δ: −21.3. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 1.77–2.12 (m, 5H), 2.82 (dt, 1H, $J=3.8$, 13.0 Hz), 3.24–3.45 (m, 2H), 4.19 (d, 1H, $J=16.9$ Hz),

4.17–4.26 (m, 1H), 4.29 (d, 1H, $J=16.9$ Hz), 6.80–7.50 (m, 20H). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 25.0, 30.1 (d, $J=9$ Hz), 32.4 (d, $J=14$ Hz), 46.7, 55.7, 56.4 (d, $J=19$ Hz), 121.1–148.3, 167.8. Minor rotamer (27%): ^{31}P NMR (145 MHz, $CDCl_3$,) δ: −20.7. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 1.77–2.12 (m, 5H), 2.12–2.22 (m, 1H), 3.24–3.45 (m, 2H), 3.62–3.78 (1H, m), 3.90 (s, 2H), 6.80–7.50 (m, 20H). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 21.8, 32.1 (d, $J=7$ Hz), 35.6 (d, $J=16$ Hz), 46.0, 54.2, 55.1 (d, $J=21$ Hz), 121.1–148.3, 167.8. $[\alpha]_D^{25}=-67.8$ (*c* 1.06, EtOH).

(2*S*)-(−)-1-(2-*N*,*N*-Diphenylamino)ethyl-2-(diphenylphosphinomethyl)-pyrrolidine, 2d. Colourless oil. Yield: 82%. Anal. calcd for $C_{31}H_{33}N_2P$: C, 80.14; H, 7.16; N, 6.03%. Found C, 80.04; H, 7.05; N, 5.94%. HRMS (FAB): exact mass calcd for $C_{31}H_{34}N_2P$ (MH^+) 465.2460, found 465.2479. ^{31}P NMR (145 MHz, $CDCl_3$) δ: −20.1 Hz. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 1.54–1.78 (m, 3H), 1.80–1.96 (m, 2H), 2.10 (dd, 1H, $J=8.6$, 17.1 Hz), 2.22–2.48 (m, 3H), 2.93–3.01 (m, 1H), 3.07–3.12 (m, 1H), 3.68–3.75 (m, 2H), 6.83–7.43 (m, 20H). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 23.1, 32.0 (d, $J=7$ Hz), 34.6 (d, $J=13$ Hz), 51.6, 51.8, 54.7, 62.8 (d, $J=19$ Hz), 121.1–148.1. IR (cm^{-1}, thin film, NaCl discs) *v*: 3053, 1588, 1496, 1361, 1154, 747, 695. $[\alpha]_D^{25}=-102.1$ (*c* 1.05, EtOH).

(*S*)-(−)-1-(2,2-Dimethylpropionyl)-2-(diphenylphosphinomethyl)-pyrrolidine, 9.[6] Pivoyl chloride (0.41 ml, 3.3 mmol) was added dropwise to a solution of **4** (0.60 ml, 2.2 mmol) and triethylamine (1.2 ml) in CH_2Cl_2 (12 ml) at 0°C. The reaction mixture was stirred for 30 min, then diluted with CH_2Cl_2 (20 ml), washed with water (2×10 ml) and dried over Na_2SO_4. After filtration and concentration, the residue was passed through a silica column (hexane:EtOAc, 4:1) to afford 0.69 g of white solid. Yield: 88% (lit.[6] 68%). Mp 96–97°C (lit.[6] 97–97.5°C). Anal. calcd for $C_{22}H_{28}NOP$: C, 74.76; H, 7.99; N, 3.96%. Found C, 74.64; H, 8.06; N, 3.85%. ^{31}P NMR (145 MHz, $CDCl_3$) δ: −19.9. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 1.11 (s, 9H), 1.68–1.73 (m, 1H), 1.80–2.00 (m, 4H), 2.84–2.94 (m, 1H), 3.40–3.44 (m, 1H), 3.62–3.66 (m, 1H), 4.21–4.27 (m, 1H), 7.16–7.56 (m, 10H). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 25.9, 27.9, 29.9 (d, $J=10$ Hz), 33.0 (d, $J=13$ Hz), 39.4, 48.4, 57.5 (d, $J=18$ Hz), 128.7–137.7, 176.7. HRMS (FAB): exact mass calcd for $C_{22}H_{29}NOP$ (MH^+) 354.1987, found 354.1983. IR (cm^{-1}, Nujol, NaCl discs) *v*: 2928, 1615, 1466, 1407, 746. $[\alpha]_D^{25}=-71.6°$ (*c* 1.70, EtOH). lit.[6] −67.3 (*c* 1.45, $CHCl_3$).

Compound **9** was then reduced with borane, as described above to give **(2*S*)-(−)-1-(2,2-dimethyl)-propyl-2-(diphenylphosphinomethyl)-pyrrolidine, 8b** as a colourless liquid. Yield: 81%. Anal. calcd for $C_{22}H_{30}NP$: C, 77.84; H, 8.91; N, 4.13%. Found C, 77.91; H, 9.03; N, 4.06%. ^{31}P NMR (145 MHz, $CDCl_3$) δ: −19.2. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.80 (s, 9H), 1.32–1.43 (m, 1H), 1.50–1.70 (m, 2H), 1.78–1.92 (m, 2H), 1.93 (d, 1H, $J=13.3$ Hz), 2.09–2.16 (m, 1H), 2.25–2.35 (m, 1H), 2.29 (d, 1H, $J=13.3$ Hz). 2.42 (dt, 1H, $J=3.5$, 13.2 Hz), 3.10–3.17 (m, 1H), 7.21–7.29 (m, 10H). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 23.6, 29.0, 31.9 (d, $J=7$ Hz), 33.0, 35.1 (d, $J=13$ Hz), 57.9, 64.4 (d, $J=20$ Hz), 68.1, 128.6–140.1. HRMS (FAB): exact mass calcd for $C_{22}H_{31}NP$ (MH^+) 340.2194, found 340.2207. IR (cm^{-1}, thin film, NaCl discs) *v*: 3053, 2950, 2805, 1585, 1433, 1360, 1108, 737, 695. $[\alpha]_D^{25}=-152.1$ (*c* 1.01, EtOH).

(2′*S*,2*S*)-(−)-1-[2-(*N*,*N*-Dimethylamino)-3-methyl]-butyryl-2-(diphenylphosphinomethyl)-pyrrolidine, 10. Synthesised via the coupling between (*S*)-(+)-*N*,*N*-dimethyl valine and **4**, and was obtained as a colourless liquid. Yield: 71%. Anal. calcd for $C_{24}H_{33}N_2OP$: C, 70.17; H, 8.41; N, 3.90%. Found C, 70.26; H, 8.45; N, 3.83%. HRMS: exact mass calcd for $C_{24}H_{34}N_2OP$ (M^++1) 397.2409, found 397.2411. A mixture of rotamers were observed in the NMR spectra of the compound in solution: Major rotamer (75%): ^{31}P NMR (145 MHz, $CDCl_3$) δ: −20.3. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.90 (d, 3H, $J=6.6$ Hz), 1.03 (d, 3H, $J=6.6$ Hz), 1.62–2.10 (m, 5H), 212–2.22 (m, 1H), 2.39 (s, 6H), 2.96 (d, 1H, $J=10.1$ Hz), 3.12–3.18 (m, 1H), 3.42–3.65 (m, 2H), 4.32–4.45 (m, 1H), 7.28–7.73 (m, 10H). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 20.1, 20.2, 24.7, 28.8, 30.2 (d, $J=9$ Hz), 31.8 (d, $J=14$ Hz), 41.8, 47.7, 55.6 (d, $J=21$ Hz), 71.1, 128.7–139.8, 170.8. Minor rotamer (25%): ^{31}P NMR (145 MHz, $CDCl_3$) δ: −19.8. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.61 (d, 3H, $J=6.6$ Hz), 0.75 (d, 3H, $J=6.6$ Hz), 1.62–2.10 (m, 3H), 2.35 (s, 6H). 2.00–2.40 (m, 5H), 3.42–3.65 (m, 2H), 3.70–3.90 (m, 1H), 7.28–7.73 (m, 10H). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 19.4, 20.2, 22.1, 29.1, 31.1 (d, $J=9$ Hz), 34.5 (d, $J=14$ Hz), 42.2, 45.3, 55.3 (d, $J=21$ Hz), 70.3, 128.7–139.8, 172.3. IR (cm^{-1}, thin film, NaCl discs) *v*: 3051, 2954, 1633, 1449, 739, 695. $[\alpha]_D^{25}=-78.8$ (*c* 1.24, EtOH).

4.3. General catalytic procedure

The appropriate ligand (27 μmol, 2.7 mol%) and $[PdCl_2(\eta^3\text{-}C_3H_5)]_2$[12] (15 μmol, 1.5 mol%) were placed into a Young's tube reaction tube, which was purged and filled with argon successively. CH_2Cl_2 (2 ml) was then added and catalytic solution was refluxed for 2 h, then cooled down to 0°C. It was then treated with a solution of (*rac*)-diphenylpropen-2-yl acetate (0.5 mmol), CH_2Cl_2 (0.5 ml), dimethyl malonate (1.5 mmol), *N*,*O*-BSA (1.5 mmol) and KOAc (0.75 mg). The reaction mixture was then stirred overnight (16 h) at 0°C. It was quenched by the addition of a saturated solution of NH_4Cl. After separation, the organic layer was washed successively with an aq. $NaHCO_3$, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was then passed through a short silica column to afford the product as a colourless oil. The e.e. and the conversion of the reaction were determined by chiral HPLC using a Chiralpak AD column (Daicel Industries): 10% ^{i}PrOH in *n*-hexane, 1 ml/min, $t_R=11.1$ min, $t_S=15.1$ min.

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