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Investigation of the importance of nitrogen substituents in a N–P chiral ligand for enantioselective allylic alkylation

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Abstract—The synthesis of three chiral chelate nitrogen–phosphorus (*S*)-valine derived ligands with the potential for stereogenic nitrogen donation is described. In palladium catalysed allylic substitution reactions the ligands induced varying enantioselectivities ranging from 92% e.e. of the (*R*)-enantiomer to 83% e.e. of the (*S*)-enantiomer. Structural and spectroscopic investigations into the origin of this effect were conducted, but were inconclusive. However, the importance of the consideration of *N*-substituents in such systems is highlighted.

1. Introduction

We have reported that allowing the nitrogen donor in simple nitrogen–sulfur chelate ligands to become configurationally fixed and stereogenic (**1**, Fig. 1) gave higher enantioselectivities in the asymmetric addition of diethylzinc to aromatic aldehydes when compared to achiral nitrogen donors of the same ligand system.[1] While the corresponding sulfide ligands **2** were ineffective for the asymmetric palladium catalysed allylic substitution reaction,[2] the corresponding imine-sulfides **3** were shown to be excellent as chiral ligands in this reaction[3] and the mechanism of chirality transfer was deduced.[4] As nitrogen–phosphorus chelate ligands are amongst the most successful in the palladium catalysed asymmetric allylic substitution reaction,[5] we investigated the diphenylphosphine analogues **4** of our amino sulfide ligands **2** and found a dramatic reversal in the sense of enantioselection by simply altering the nitrogen substitution pattern.[6] Ligands **4** are essentially chiral N versions of valphos **5**. Herein, we detail the synthesis of these ligands and further studies into the origin of this pronounced selectivity effect.

2. Design and synthesis of ligands

An essential feature of the molecular architecture of these ligands is the potential for the transmission of chirality inherent to the backbone of the ligand to the stereogenic nitrogen atom. This should place an asymmetric environment close to the reaction sphere. We were interested in synthesising three sterically and electronically different ligands **6**–**8** (Scheme 1) for our studies. To create a suitably large disymmetric environment around the nitrogen donor of **4** we chose the methyl and phenyl substitutents (A values: Me = 1.7;[7] Ph = 3.0[8]) to give ligand **6**. In order to try and assess whether the donor ability of the nitrogen lone pair and the three-dimensional shape of the amine could be compromised by the delocalising effect of the phenyl substituent, we decided to synthesise ligand **7**. The

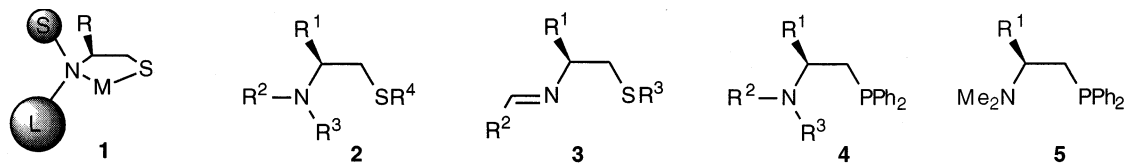

Figure 1.

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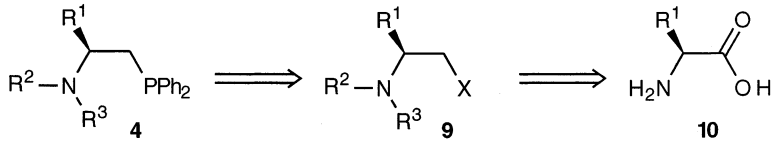


6 R^1=^{i}Pr, R^2=Me, R^3=Ph
7 R^1=^{i}Pr, R^2=Me, R^3=^{i}Pr
8 R^1=^{i}Pr, R^2, R^3=Ph

Scheme 1.

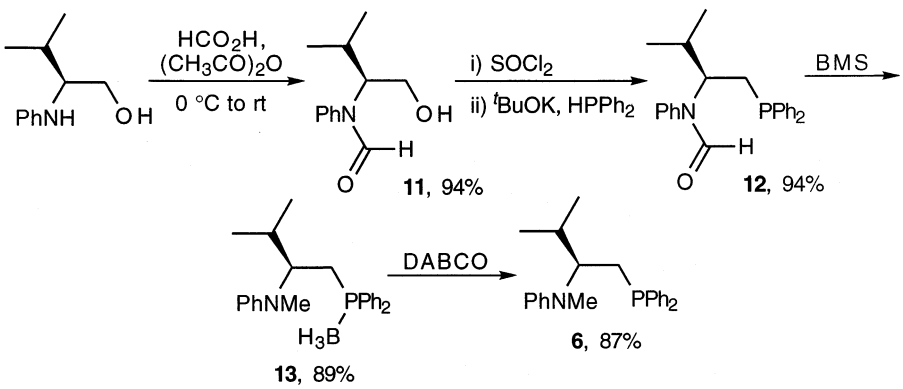
N-iso-propyl substituent removes the possibility of any delocalisation effect with only a small compromise in size differential between the *iso*-propyl and methyl substituents (A values: Me = 1.7;[7] ^{t}Pr = 2.7[7]). The two phenyl substituents of ligand **8** give a nitrogen donor possessing different orientations of its aromatic rings. The rotational freedom of the β-phenyl ring will be restricted by the proximity of the backbone chiral centre. The orientation of this phenyl ring will affect that of the α-phenyl ring and render the nitrogen atom stereogenic.[9]

Our retrosynthetic analysis for the target ligands **4** is outlined in Scheme 1. It was decided to introduce the phosphine group late in the synthetic scheme in order to minimise problems associated with oxidation. We planned to achieve this by displacement of a suitable leaving group X on precursor **9** using a phosphine anion. This precursor was seen to be accessible via functional group interconversions of amino acid **10**. A flexible synthetic route to ligands **4** was required to permit access to a variety of structural and electronic analogues. We chose to base our ligands on valinol and although this retrosynthesis treats the ligands as being similar to **2**, their synthesis proved to be notably more difficult. We were aware that internal displacement of leaving groups by the nucleophilic nitrogen atom could potentially lead to other products and loss of stereochemical integrity via the formation of aziridinium ions.[1b] In the synthesis of valphos[10] this is avoided by generating the hydrochloride salt of *N,N*-dimethyl valinol before conversion of the hydroxyl function to a chloride leaving group for displacement with potassium diphenylphosphine. In analogous syntheses of our ligands the prerequisite *N,N*-disubstituted valinols of ligands **6–8** did not give the desired nitrogen–phosphine chelates upon sequential treatment with HCl; $SOCl_2$; $KPPh_2$.[10]

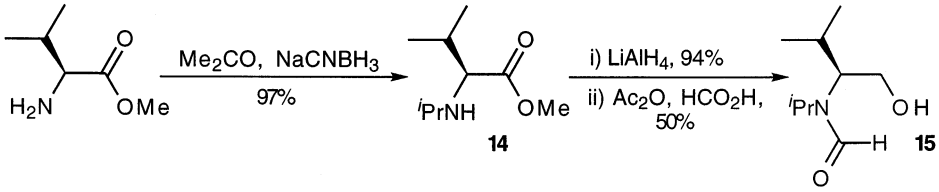
The synthesis of ligand **6** was achieved by using an *N*-formyl group as a latent methyl group. Reaction of (*S*)-*N*-phenyl-2-amino-3-methylbutan-1-ol[1b] with in situ generated formic–acetic anhydride[11] at ambient temperature led to the *N*-formyl derivative **11** (94%, Scheme 2). Subsequent introduction of the diphenylphosphine group by the literature method proceeded in good overall yield to give **12** (67%, two steps). Failure of DIBAL to effect the desired reduction of **12** to the *N*-methyl derivative led us to use borane–dimethylsulfide (BMS) complex, which served a dual purpose. Reduction with this reagent proceeded in 89% yield and gave the protected phosphine-borane complex **13** of ligand **6**; the reported sensitive nature of phosphines led us to use **13** for storage purposes and, when required, ligand **6** was formed cleanly by treatment with DABCO.[12]

Based on NMR evidence we believe the borane in **13** is coordinated to phosphorus in preference to the possible amino-borane intermediate. The ^{31}P NMR spectrum of **13** exhibited a broad signal at 15.6 ppm, characteristic of phosphine-boranes.[13] The phosphorus resonance in **6** appears at −20.8 ppm. Also in the ^{1}H NMR spectrum the protons adjacent to phosphorus in **13** [2.47 (1H, ddd) and 2.68–2.86 (1H, m)] exhibit an upfield shift in decomplexed **6** [2.27 (1H, ddd) and 2.46–2.55 (1H, m)].

As the Kumada type synthesis[10] of ligand **7** from *N-iso*-propyl-*N*-methylvalinol was unsuccessful, we attempted to carry the methyl substituent through as a



Scheme 2.



Scheme 3.

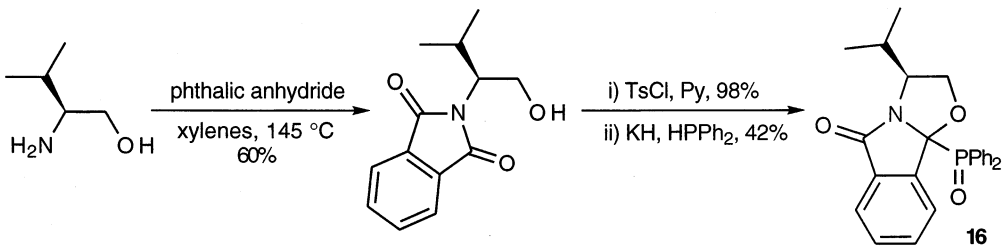
formyl group by a similar strategy to that used for ligand **6** (Scheme 2). The *N-iso*-propyl group was introduced by reductive alkylation of the (*S*)-valine methyl ester to give **14** in a 97% yield (Scheme 3). Reduction to the corresponding amino alcohol with $LiAlH_4$ (94%) was followed by selective formylation to give **15** in moderate yield (50%). Alcohol **15** was seemingly inert to thionyl chloride.

At this stage an attempt to protect the nitrogen of **15** as its phthalimide derivative and displacement of tosylate by a phosphinyl anion was attempted (Scheme 4). This led to the rearranged product **16** which has literature precedence;[14] its congener was observed in an attempted synthesis of a phenylalanine derived primary amino phosphane ligand.[15]

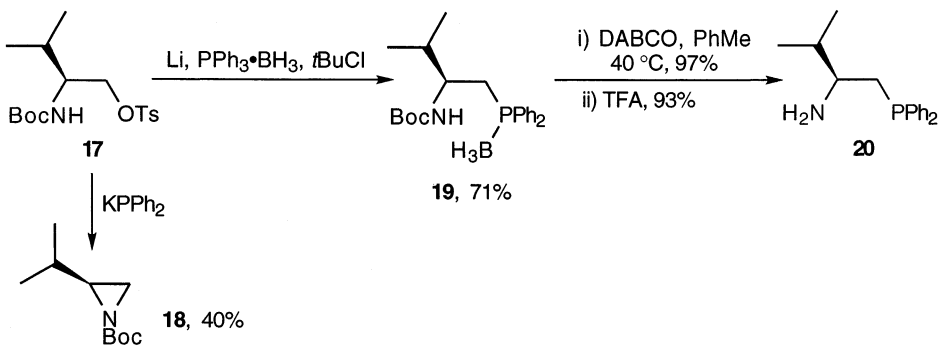
A successful strategy we have used for the synthesis of analogous amino sulfide ligands involved protection of the primary amine function of valinol with a Boc group.[4] Treatment of **17**[16] with potassium diphenylphosphine at low temperature resulted only in the isolation of aziridine **18** in 40% yield (Scheme 5). All attempts to alter the course of this reaction by varying solvent, temperature and counterion failed.[17] It has been reported that anions of phosphine-boranes are less basic than those of free phosphines.[12] Treatment of **17** with lithium diphenylphosphine–borane complex under optimised reaction conditions gave a 71% yield of the desired **19**, which is protected at both ends of the chelate structure. It would have been desirable to retain the borane protection throughout the remainder of the synthesis to prevent possible oxidation to the phosphine oxide, but initial attempts to remove the *N*-Boc group with trifluoroacetic acid (TFA) led to a mixture of compounds, one of which showed loss of phosphine complexed borane. In order to avoid such complications it was decided to remove the borane prior to further manipulations. Treatment with DABCO in warm toluene gave the free phosphine (97%), which was further deprotected by treatment with TFA to afford **20** in 93% yield. Chiral amino-phosphines based on an amino acid template may be interesting as chiral ligands for other metal catalysed reactions. Their synthesis has proved unsuccessful to date[15] and this synthetic route will enable these materials to be prepared efficiently.

Introduction of the *iso*-propyl substituent required a two-step procedure whereby the isolated acetone-imine was reduced with $LiAlH_4$ to give the secondary amine **21** in 69% yield over two steps (Scheme 6). The *N*-methyl substituent was similarly introduced as before to give the required ligand **7** in 80% yield over two steps.

The *N,N*-diphenylated ligand **8** was easily synthesised in the light of the experiences above. Mesylation of

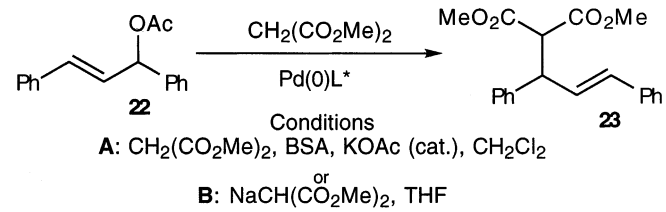


Scheme 4.



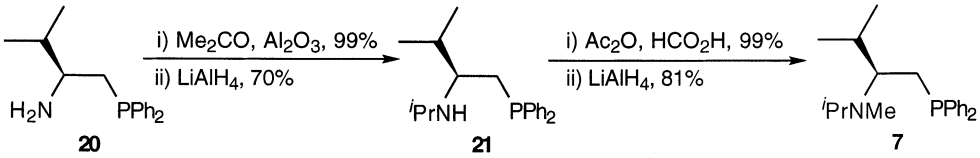
Scheme 5.

Table 1. Allylic alkylation of **22** with $CH_2(CO_2Me)_2$ catalysed by Pd–chiral ligand complexes



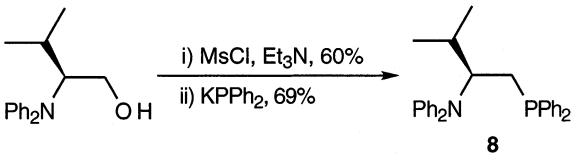
Entry	T (°C)	Conditions	Ligand (L*)											
			6 (-NPhMe)			**7** (-N^{i}PrMe)			**8** (-NPh_2)			Valphos (-NMe_2)		
			t[a]	Yield[b] **23** (%)	e.e. (%)[c]	t[a]	Yield[b] **23** (%)	e.e. (%)[c]	t[a]	Yield[b] **23** (%)	e.e. (%)[c]	t[a]	Yield[b] **23** (%)	e.e. (%)[c]
1	rt	**A**	1 m	98	50 (*S*)	–	–	–	15 m	97	20 (*R*)	–	–	–
2	rt	**B**	15 m	89	33 (*S*)	–	–	–	15 m	89	54 (*R*)	15 m	90	54 (*R*)
3	0	**A**	1.5 h	98	50 (*S*)	–	–	–	5 h	91	32 (*R*)	10 m	97	61 (*R*)
4	0	**B**	14 m	85	45 (*S*)	1 h	82	11 (*R*)	50 m	83	68 (*R*)	15 m	91	54 (*R*)
5	−20	**B**	12 h	85	47 (*S*)	–	–	–	4.5 h	90	80 (*R*)	12 h	91	69 (*R*)
6	−30	**A**	12 h	91	73 (*S*)	–	–	–	12 h	93	70 (*R*)	12 h	97	54 (*R*)
7	−35	**B**	2.5 d	93	65 (*S*)	–	–	–	12 h	94	85 (*R*)	2.5 d	95	59 (*R*)
8	−50	**B**	4 d	89	73 (*S*)	24 h	89	56 (*S*)	3 d	94	92 (*R*)	4 d	91	62 (*R*)
9	−65	**A**	4 d	94	83 (*S*)	–	–	–	2 d	96	80 (*R*)	2.5 d	93	60 (*R*)

[a] m = minute, h = hour, d = day.
[b] Isolated yield.
[c] Determined by ^{1}H NMR using chiral shift reagent $Eu(hfc)_3$.



Scheme 6.

(*S*)-*N*,*N*-diphenylvalinol[1b] gave a stable derivative in 60% yield, which was treated with potassium diphenylphosphine to give the ligand **8** in 69% yield (Eq. (1)).



(1)

3. Asymmetric alkylation

The effectiveness of these ligands for chirality transfer was then investigated using the standard palladium catalysed substitution of 1,3-diphenyl-2-propenyl acetate **22** with dimethyl malonate. As a reference our ligands were surveyed against valphos,[10] which does not have the potential for a stereogenic nitrogen atom when chelated. Two common procedures were used which involved either the generation of the nucleophile in situ, using dimethyl malonate (3 equiv.) and *N*,*O*-bis(trimethylsilyl)acetamide (BSA, 3 equiv.) with catalytic potassium acetate (3 mol%) in dichloromethane or the use of a preformed nucleophile, sodium dimethyl malonate (1.5 equiv.) in THF. The palladium catalyst (5 mol%) was formed by mixing the allyl palladium chloride dimer with 2 molar equivalents of the chiral ligand in the reaction solvent for 15 minutes at room temperature. The results of the reactions carried out at progressively lower temperatures, in terms of yield and enantioselectivity for the substituted product **23**, are summarised in Table 1. Ligand **7**, which was the most difficult to synthesise, was only used in two cases and showed no results to justify the synthesis and testing of further quantities.

The most intriguing aspect of these results is the reversal of selectivity exhibited by ligand **6** compared to ligand **8**, when both possess identical backbone chirality. They both perform substantially better than valphos (compare entries 8 and 9), which supports our hypothesis that a potentially stereogenic nitrogen donor can lead to enhanced enantioselectivity. Ligand **7** was assayed to determine whether *N*-lone pair delocalisation into an *N*-phenyl substituent had any detrimental effect. At room temperature ligand **7** exhibited very poor (*R*)-selectivity of 11%, but at lower temperatures gave a product with a greatly improved e.e. of 56% for the (*R*)-enantiomer and 62% for the (*S*)-enantiomer. This is comparable with the results obtained using valphos.

From the limited examples we have it would seem that a nitrogen donor in this ligand system with two identical substituents selects for the (*R*)-enantiomer of **23**, whereas a nitrogen donor with two unlike substituents selects for the (*S*)-enantiomer. Based upon our characterisation of a structurally similar imine-sulfide chelate ligand in the same reaction,[4] we offered a hypothesis involving the conformation of the possible π-allyl palladium intermediates in this reaction.[6] The result from use of ligand **7** fits this proposed model. Enantioselection by heterobidentate nitrogen–phosphorus chiral ligands has been reported to be a result of the difference in electronic character of the two donor atoms, which may exert a stereoelectronic bias upon intermediate π-allyl complexes.[3,18] 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.[19] Such characteristics have been verified by NMR and X-ray studies and are claimed to control enantioselection.[18c,20,21] To explain the sense of enantioselection with ligands **6**–**8** and valphos, assuming the ligands chelate the reactive intermediate responsible for enantioselection and that the conformation of the phosphorus phenyl substituents are constant for each ligand system, we arrived at the intermediates in Fig. 2. Ligands **6** and **7** with two different sized *N*-substituents should orientate the allyl group in the 'W' conformation **24** due to the avoidance of a destabilising steric interaction between N–R_L and the allyl phenyl group, which would arise if the allyl group were orientated in the 'M' conformation **25** (Fig. 2). We propose for ligands **8** and valphos, which possess two identical *N*-substituents, that the

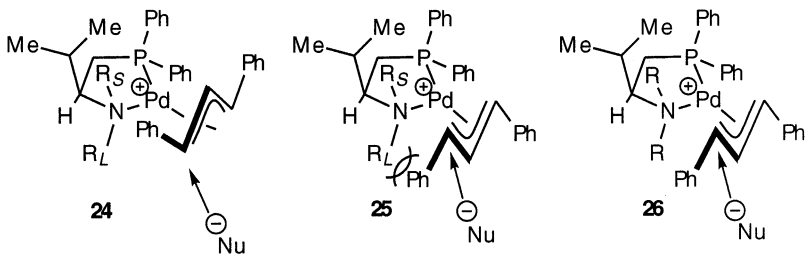
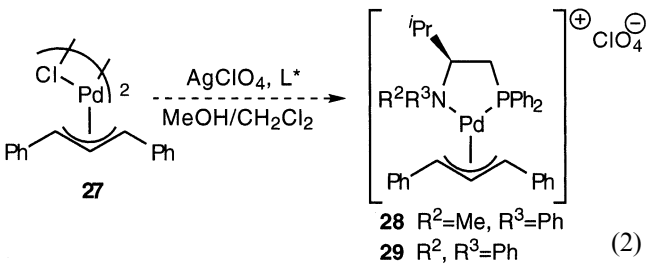


Figure 2.

intermediate **26** may be responsible for enantioselection. For this intermediate to be more stable we must assume that the backbone chirality pushes the *N*-β-substituent into the reaction sphere making it more sterically demanding than the *N*-α-substituent. Intermediate **26** would lead to the opposite (*R*)-enantiomeric product to that which would arise from **24**.

4. Structural studies of π-allyl intermediates

As a starting point we assumed that the major diastereoisomer of the intermediate π-allyl complex would lead to the major enantiomer observed for the product.[22] Analogously to previous studies[4,22] we attempted to form a complex between chiral ligands **6** and **8** and the *trans*-1,3-diphenylpropenyl palladium chloride dimer **27**[23] in an attempt to obtain a crystalline sample of the π-allyl intermediate (Eq. (2)). The yellow–orange solid **28** obtained with ligand **6** gave broad signals in its ^{1}H NMR spectrum (CD_2Cl_2, rt), which indicates fluctionality, but it could be seen that there were two distinct sets of doublets for the *iso*-propyl group. Originally it was thought that these signals arose from two possible conformations of the allyl-palladium–ligand complex. The ^{31}P NMR spectrum in deuterochloroform at room temperature revealed eight signals. Two ($\delta_P = 26.0$ and 35.0) were significantly more intense than the others, did not show phosphorus–phosphorus coupling, and are in the typical range of phosphorus chelates in five-membered rings.[24] These could arise from two different conformations of the π-allyl complex. However, FAB mass spectroscopy failed to reveal a mass peak for such a π-allyl complex, instead a signal was detected corresponding to two ligands and one palladium. If a ligand dimer did exist in solution there would have to be two symmetrical complexes to account for the lack of phosphorus–phosphorus coupling.[25] The NMR studies proved inconclusive and attempts to obtain crystals suitable for X-ray analysis failed.



(2)

The formation of an allyl-palladium–ligand complex with **8** was performed as before. The orange–red solid **29** gave broad signals in its ^{1}H NMR spectrum in CD_2Cl_2 at room temperature, suggesting that more than one species were in dynamic equilibrium. Two sets of *iso*-propyl signals could be identified, but these were much broader than before. The ^{31}P NMR spectrum proved more revealing. The major signals were those of an AB spin system ($\delta_A = 15.9$, $\delta_B = 18.4$, $^2J_{P\text{-}P} = 57$ Hz), indicating a palladium species bound by two phosphorus atoms that were in chemically different environments. The chemical shifts suggest that the ligands are non-chelating monophosphine donor ligands.[24] The other weaker signals present in the spectrum were two broad peaks at 24.1 and 30.6 ppm, which are typical values for chelating phosphines in five-membered ring environments.[24] These latter signals could arise from the *exo* and *endo* conformations of the desired allyl complex **28** in flux. Low temperature NMR studies on this complex did not lead to any usable information. The FAB mass spectrum revealed a 100% abundance mass peak at 772, which corresponds to the cationic fragment of **29**. A mass signal for a ligand:palladium ratio of 2:1 was not observed. Attempts to obtain crystals of suitable quality for X-ray analysis were unsuccessful. It would appear that for both complexes the mass spectral data are in direct contradiction of the tentative NMR data. It is clear that there is no single distinct π-allyl intermediate present in solution and an explanation of enantioselection is much more complex than in our previous systems.[4]

A number of studies have reported differing results when using different sources of palladium for standard allylic substitution reactions.[26] In general the presence of chloride ions, commonly arising from the catalyst precursor $[Pd(\eta^3\text{-}C_2H_5)Cl]_2$, had positive effects on enantioselectivity (Reference 25b is an exception) when compared to reactions performed using a non-chloride containing source of palladium(0) [commonly $Pd(dba)_2$ or $Pd_2(dba)_3{\cdot}CHCl_3$]. In order to investigate this effect we repeated the sodiomalonate (procedure B) reactions at –20°C, an intermediate temperature that gave moderate enantioselectivities and good yields. The non-chloride source of catalyst $Pd(dba)_2$ was used with all ligands **6**–**8** and valphos. An extended reaction time of up to 4 days was allowed, but only the valphos ligand led to considerable product formation. In 12 hours valphos gave a 78% yield of (*R*)-**23** with 63% e.e. [Table 1: entry 5, 12 h, 91% yield, 69% e.e. (*R*)-enantiomer]. It would appear that valphos is little affected by the presence of chloride ions, but ligands **6**–**8** require chloride ions to act efficiently.

We were also interested in the binding mode of these ligands. The structural studies had suggested the existence of complexes possessing a ligand:palladium ratio of 2:1 and that the ligands were acting as non-chelating monophosphine donors. Our experiments to date had all involved the use of two equivalents of ligand to palladium in order to ensure complete cyclisation. Control reactions were performed using the two sources of palladium catalyst [$[Pd(\eta^3\text{-}C_2H_5)Cl]_2$ and $Pd(dba)_2$] and only one equivalent of ligand:palladium, again at –20°C, using the sodiomalonate nucleophile (procedure B) with extended reaction times. None of the ligands gave good conversion with $Pd(dba)_2$. Only **8** and valphos gave any appreciable conversion with the allyl-palladium chloride dimer [ligand **8**, 91% yield, 83% e.e. (*R*); valphos, 84% yield, 73% e.e. (*R*)-enantiomer] and the results were similar to those obtained in the original assay with two equivalents of ligand to palladium. These results suggest that ligands **6** and **7** may be monodentate in the active catalytic complex. Potentially ligand **8** may be acting as a chelate ligand, but only in the presence of chloride ions. Valphos also may act as a bidentate ligand, but requires chloride ions to do so efficiently with only one equivalent of ligand.

5. Conclusions

Three new enantiomerically pure N–P ligands have been synthesised with the specific design element of creating a disymmetric environment around the nitrogen atom. Ligands **6** and **8**, which possess phenyl, methyl and diphenyl nitrogen substituents, respectively, both perform substantially better than valphos in the palladium catalysed allylic substitution reaction between dimethyl malonate and *trans*-1,3-diphenylpropenyl acetate. The most intriguing aspect of these results is that ligand **6**, with two unlike *N*-substituents, selects for the (*S*)-enantiomer of the product **23**, whereas ligand **8**, with two identical *N*-substituents, selects for the (*R*)-enantiomer. This is despite both ligands possessing identical backbone chirality. Spectroscopic studies suggested that there is a dynamic mixture of chelate and monophosphine donor complexes. Chloride ion effects did not reveal any firm evidence for a single catalytically active complex. These results, though interesting by virtue of their nonconformity, do not allow us to proceed with a rational design strategy for new ligand systems. It is clear that nitrogen substitution patterns in these ligand systems are important to the observed enantioselectivity, but the mechanism of the selection is unclear at this time.

6. Experimental

Our general experimental details have been reported.[27]

6.1. (*S*)-*N*-Formyl-*N*-phenyl-2-amino-3-methylbutan-1-ol 11

Formic acid (98%, 340 μL, 8.9 mmol) was added dropwise to acetic anhydride (680 μL, 7.3 mmol) at 0°C. When the addition was complete the mixture was heated at 60°C for 2 h then allowed to cool to room temperature. Tetrahydrofuran (10 mL) was added and the solution cooled to 0°C before addition of a solution of (*S*)-*N*-phenyl-2-amino-3-methylbutan-1-ol[1b] (500 mg, 2.8 mmol) in tetrahydrofuran (10 mL). The reaction mixture was stirred at room temperature for 4 h before the volatiles were removed in vacuo. Toluene (2×10 mL) was added and removed in vacuo to yield a yellow oil which was purified by flash column chromatography on silica (30% ethyl acetate/light petroleum) affording **11** (545 mg, 94%); $[\alpha]_D^{21} = -37.0$ (*c* 1, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3418, 3063, 2965, 2967, 1661, 1594; δ_H (250 MHz, $CDCl_3$) 1.00 (6H, pseudo-t, *J* 6.5, $CH(CH_3)_2$), 2.34 (1H, dsept, *J* 10.1, 6.5, $CH(CH_3)_2$), 3.75–4.04 (3H, m, NC*H* and $CHCH_2OH$), 7.20–7.55 (5H, m, Ar*H*), 8.3 (1H, s, NC*H*O); δ_C (63 MHz, $CDCl_3$) 19.9 ($CH(CH_3)_2$), 20.7 ($CH(CH_3)_2$), 27.3 ($CH(CH_3)_2$), 61.9 (CH_2OH), 67.5 (N*C*H), 126.4 (Ar), 125.5 (Ar), 141.2 (Ar), 164.6 (N*C*HO); *m*/*z* (EI^+) 207.1263 (M^+, 15%, $C_{12}H_{17}O_2N$ requires 207.1259), 176 (M^+–31CH_2OH, 99%), 150 (M^+–43*i*-Pr, 33%), 118 (20%).

6.2. (*S*)-*N*-Formyl-*N*-phenyl-2-amino-3-methylbutyl-1-diphenylphosphine 12

To a solution of **11** (1.24 g, 6 mmol) in dichloromethane (12 mL) at 0°C was added thionyl chloride (0.44 mL, 6 mmol) dropwise. The mixture was allowed to stir at room temperature for 1 h before pouring onto pH 7 buffer (50 mL). The layers were separated and the aqueous layer extracted with dichloromethane (3×20 mL). The combined organics were washed with brine (20 mL), dried over magnesium sulfate and concentrated in vacuo to yield the crude product (1.23 g, 91%), which was used crude in the next step. A small sample was purified by flash column chromatography on silica to yield the amino chloride as a clear oil; $[\alpha]_D^{21} = -36.0$ (*c* 0.75, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3063, 2967, 2874, 1681, 1595m; δ_H (250 MHz, $CDCl_3$) [rotamers] 1.01, 1.06 and 1.18 [4.5:4.5:1] (6H, 3d, *J* 6.7 $CH(CH_3)_2$), 1.84–1.96 and 2.15 [1:8] (1H, m and dsept, *J* 10.4, 6.7, $CH(CH_3)_2$), 3.35–3.54 and 3.52–3.85 [1:8] (2H, 2m, CH_2Cl), 4.14–4.27 (1H, m, NC*H*), 7.27–7.46 (5H, m, Ar*H*), 8.31 and 8.39 [8:1] (1H, 2s, NC*H*O); δ_C (63 MHz, $CDCl_3$) [rotamers] 19.7, 20.3, 20.8 and 20.9 ($CH(CH_3)_2$), 30.1 ($CH(CH_3)_2$), 43.3 and 43.9 (CH_2Cl), 62.3 and 68.7 (N*C*H), 127.0–129.5 (Ar), 163.7 and 168.3 (N*C*HO); *m*/*z* (EI^+) 225.0919 (M^+, 30%, $C_{12}H_{16}ON^{35}Cl$ requires 225.0920), 182 (M^+–43, *i*-Pr, 90%), 176 (M^+–49CH_2Cl, 30%), 154 (M^+–71*i*-Pr and CHO, 100%), 121 (50%).

To a suspension of potassium *tert*-butoxide (1.97 g, 17.6 mmol) in tetrahydrofuran (40 mL) was added diphenylphosphine (2.0 mL, 11.7 mmol). This mixture was stirred at room temperature for 20 min. Following addition of the crude amino chloride from above (2.64 g, 11.7 mmol) the reaction was allowed to stir for 12 h (or until the red colour had completely faded to colourless). The reaction mixture was poured onto water (100 mL) and the aqueous layer was extracted with ethyl acetate (3×50 mL). The combined organic extract was washed with brine (100 mL), dried over magnesium sulfate and concentrated in vacuo to yield the crude product. Purification by flash column chromatography on silica (20% ethyl acetate/light petroleum) gave **12** (3.30 g, 74%) as a colourless oil; $[\alpha]_D^{21} = -42.0$ (*c* 1.2, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3054, 2963, 2872, 1681, 1594; δ_H (250 MHz, $CDCl_3$) [rotamers] 0.90–0.94 (3H, m, $CH(CH_3)_2$), 1.00–1.05 (3H, m, $CH(CH_3)_2$), 1.89–2.56 (3H, m, $CH(CH_3)_2$ and $CHCH_2PPh_2$), 3.05–3.18 and 3.8–3.95 [1:5] (1H, 2br-m, NC*H*), 7.24–7.46 (15H, m, Ar*H*), 8.08 and 8.39 [1:5] (1H, 2s, NC*H*O); δ_P not recorded; δ_C (63 MHz, $CDCl_3$) 20.5 ($CH(CH_3)_2$), 20.6 ($CH(CH_3)_2$), 30.1 (d, $J_{C\text{-}P}$ 13.0, CH_2PPh_2), 32.7 (d, $J_{C\text{-}P}$ 6.8, ($CH(CH_3)_2$), 61.3 (d, $J_{C\text{-}P}$ 6.2 N*C*H), 61.9 (CH_2PPh_2), 124.7–141.0 (Ar), 163.5, (N*C*HO); *m*/*z* (EI^+) 375.1740 (M^+, 5%, $C_{24}H_{26}ONP$ requires 375.1752), 332 (M^+–43*i*-Pr, 15%), 255 (M^+–120PhNCHO, 85%), 202 (100%).

6.3. (*S*)-*N*-Phenyl-*N*-methyl-2-amino-3-methylbutyl-1-diphenylphosphine-borane 13

Borane–dimethylsulfide complex (1.67 mL, 17.6 mmol) was added dropwise to a solution of **12** (3.31 g, 8.8 mmol) in tetrahydrofuran (40 mL) at 0°C and the reaction was allowed to stir at room temperature for 12 h. The reaction was quenched by slow addition of ethereal hydrogen chloride (1 M, 3 mL) and the volatiles

removed in vacuo. The residue was taken up in methanol (2×20 mL) and this was removed in vacuo. The resulting oil was partitioned between diethyl ether (20 mL) and sodium hydroxide solution (1 M, 20 mL) and the aqueous layer was extracted with diethyl ether (3×10 mL). The combined organics were washed with brine (20 mL), dried over magnesium sulfate and concentrated in vacuo. The crude product was purified by column chromatography on silica (10% ethyl acetate/light petroleum) to give **13** as a white solid (2.97 g, 89%); mp 100–102°C; (found: C, 76.87; H, 8.17; N, 3.70; $C_{24}H_{31}NPB$ requires: C, 76.81; H, 8.33; N, 3.73%); $[\alpha]_D^{21}=-110.0$ (*c* 1, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3048, 2960, 2924, 2404, 2364, 2334, 1598, 1505, 1435; δ_H (250 MHz, $CDCl_3$) 0.74 (3H, d, *J* 6.5, (CH(CH_3)$_2$), 1.05 (3H, d, *J* 6.5, (CH(CH_3)$_2$), 1.97 (1H, dsept, *J* 6.5, 9.2, C*H*(CH$_3$)$_2$), 2.31 (3H, s, NCH_3), 2.47 (1H, ddd, *J* 14.6, 10.0 (^{1}H–^{31}P), 2.7, CHC*H*α*H*βPPh$_2$), 2.68–2.85 (1H, m, CHCHα*H*β*H*PPh$_2$), 4.01 (1H, qd, *J* 10.4, 2.6, NC*H*), 6.57 (1H, t, *J* 7.3, *p*-NAr*H*), 6.66 (2H, d, *J* 8.6, *o*-NAr*H*), 7.04 (2H, dd, *J* 8.6, 7.3, *m*-NAr*H*), 7.00–7.68 (10H, m, PAr*H*); δ_P (101 MHz, $CDCl_3$) 15.5 br; δ_C (63 MHz, $CDCl_3$) 20.0 (CH(*C*H$_3$)$_2$), 20.8 (CH(*C*H$_3$)$_2$), 27.8 (d, $J_{C\text{-}P}$ 36.8, *C*H$_2$PPh$_2$), 32.2 (N*C*H$_3$), 33.7 (d, $J_{C\text{-}P}$ 10.7, ((*C*H(CH$_3$)$_2$), 59.4 (N*C*H), 112.3 (Ar), 115.8 (Ar), 128.1–132.6 (Ar), 148.9 (Ar); *m*/*z* (EI$^+$) 375.2390 (M$^+$, 10%, $C_{24}H_{31}NPB$ requires 375.2402), 361 (M$^+$–14BH$_3$, 8%), 332 (M$^+$–43*i*-Pr, 50%), 318 (M$^+$–57BH$_3$ and *i*-Pr, 60%), 185 (PPh$_2$, 100%).

6.4. (*S*)-*N*-Phenyl-*N*-methyl-2-amino-3-methylbutyl-1-diphenylphosphine 6

A solution of **13** (640 mg, 1.79 mmol) in toluene (2 mL) was warmed to 40°C in the presence of 1,4-diazabicyclo-[2.2.2]-octane (210 mg, 1.87 mmol) for 12 h. After removal of the solvent in vacuo the resulting white solid residue was washed with light petroleum (3×5 mL) and removed by filtration and concentration of the organics in vacuo gave the crude product. This was purified by flash column chromatography on silica (5% ethyl acetate/light petroleum) to afford the product **6** as a white solid (540 mg, 87%); mp 132–134°C; (found: C, 79.63; H, 7.98; N, 3.92; $C_{24}H_{28}NP$ requires: C, 79.75; H, 7.81; N, 3.87%); $[\alpha]_D^{21}=+13.5$ (*c* 2, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3054, 2957, 2808, 1597, 1504, 1433; δ_H (250 MHz, $CDCl_3$) 0.67 (3H, d, *J* 7.0, (CH(CH_3)$_2$), 0.92 (3H, d, *J* 7.0, (CH(CH_3)$_2$), 1.85 (1H, dsept, *J* 9.1, 7.0, C*H*(CH$_3$)$_2$), 2.27 (1H, ddd, *J* 14.0, 11.0 (^{1}H–^{31}P), 3.4 CHC*H*α*H*βPPh$_2$), 2.46–2.55 (1H, m, CHCHα*H*β*H*PPh$_2$), 2.49 (3H, s, NCH_3), 3.37–3.51 (1H, m, NC*H*), 6.41 (2H, d, *J* 8.2, *o*-NAr*H*), 6.53 (1H, t, *J* 7.3, *p*-NAr*H*), 7.03 (2H, dd, *J* 8.2, 7.3 *m*-NAr*H*), 7.16–7.30 (10H, m, PAr*H*); δ_P (101 MHz, $CDCl_3$) –20.8; δ_C (63 MHz, $CDCl_3$) 20.7 (CH(*C*H$_3$)$_2$), 20.9 (CH(*C*H$_3$)$_2$), 30.8 (N*C*H$_3$), 31.9 (d, $J_{C\text{-}P}$ 12.7, *C*H$_2$PPh$_2$), 33.5 (d, $J_{C\text{-}P}$ 7.0, (*C*H(CH$_3$)$_2$), 62.0 (d, $J_{C\text{-}P}$ 11.7, N*C*H), 112.6 (Ar), 115.8 (Ar), 128.1–133.7 (Ar), 138.1–140.1 (Ar), 150.8 (Ar); *m*/*z* (EI$^+$) 361.1960 (M$^+$, 15%, $C_{24}H_{28}NP$ requires 361.1959), 318 (M$^+$–43*i*-Pr, 100%), 183 (45%), 162 (M$^+$–199CH$_2$PPh$_2$, 95%).

6.5. Methyl (*S*)-*N*-*iso*-propyl-2-amino-3-methyl-butanoate 14

To a solution of (*S*)-valine methyl ester (5.88 g, 45 mmol) in methanol (75 mL) was added acetone (5.0 mL, 67 mmol) and sodium cyanoborohydride (11.30 g, 180 mmol). The reaction was allowed to stir overnight at room temperature. Volatiles were removed in vacuo and the residue partitioned between water (75 mL) and dichloromethane (50 mL). The aqueous layer was extracted with dichloromethane (3×30 mL). The combined organics were washed with brine (75 mL), dried over magnesium sulfate and the solvent was removed in vacuo. The product was purified by passing through a short column of silica gel (20% ethyl acetate/light petroleum) to yield **14** as a clear oil (7.53 g, 97%); $[\alpha]_D^{21}=-76.5$ (*c* 1, CH_2Cl_2); ν_{max} (film)/cm^{-1} 2964, 2873, 1736; δ_H (250 MHz, $CDCl_3$) 0.90 (3H, d, *J* 6.4, CCH(CH_3)$_2$), 0.93 (3H, d, *J* 6.7, CCH(CH_3)$_2$), 0.97 (3H, d, *J* 6.2, NCH(CH_3)$_2$), 1.03 (3H, d, *J* 6.4, NCH(CH_3)$_2$), 1.75–1.95 (1H, m, CC*H*(CH$_3$)$_2$), 2.63 (1H, sept, *J* 6.2, NC*H*(CH$_3$)$_2$), 3.05 (1H, d, *J* 5.8, NC*H*CO$_2$Me), 3.70 (3H, s, CO$_2$CH_3); δ_C (63 MHz, $CDCl_3$) 18.8 (CCH(*C*H$_3$)$_2$), 19.6 (CCH(*C*H$_3$)$_2$), 22.1 (NCH(*C*H$_3$)$_2$), 23.91 (NCH(*C*H$_3$)$_2$), 31.8 (C*C*H(CH$_3$)$_2$), 47.4 (N*C*H(CH$_3$)$_2$), 51.4 (CO$_2$*C*H$_3$), 64.8 (N*C*HCO$_2$Me), 176.3 (C=O); *m*/*z* (EI$^+$) 174.1798 (MH$^+$, 70%, $C_9H_{20}O_2N$ requires 174.1494), 130 (M$^+$–44*i*-PrH, 30%), 114 (M$^+$–60CO$_2$CH$_3$H, 100%), 72 (CHNH-*i*-Pr, 70%).

6.6. (*S*)-*N*-Formyl-*N*-*iso*-propyl-2-amino-3-methyl-1-butanol 15

To a suspension of lithium aluminium hydride (132 mg, 3.50 mmol) in anhydrous tetrahydrofuran (8 mL) at 0°C was added a solution of **14** (300 mg, 1.73 mmol) in tetrahydrofuran (4 mL). The reaction mixture was allowed to stir at room temperature for 1 h and quenched at 0°C by careful addition of water (0.1 mL), aqueous sodium hydroxide (15% w/v, 0.1 mL) and water (0.3 mL). The resulting white precipitate was removed by filtration and the residue was washed with tetrahydrofuran (2×10 mL). The organics were dried over magnesium sulfate and concentrated in vacuo to yield the crude amino alcohol (100 mg, 94%), as a colourless oil, which was used without further purification; $[\alpha]_D^{21}=+32.1$ (*c* 2, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3382, 2961, 2872; δ_H (250 MHz, $CDCl_3$) 0.88 (3H, d, *J* 6.8, CCH(CH_3)$_2$), 0.94 (3H, d, *J* 6.8, CCH(CH_3)$_2$), 1.01 (3H, d, *J* 6.2, NCH(CH_3)$_2$), 1.06 (3H, d, *J* 6.2, NCH(CH_3)$_2$), 1.75 (1H, pseudo-oct, *J* 6.8, CC*H*(CH$_3$)$_2$), 2.45 (1H, ddd, *J* 7.3, 6.8, 4.5, NC*H*CH$_2$OH) 3.03 (1H, sept, *J* 6.2 NC*H*(CH$_3$)$_2$), 3.20 (1H, dd, *J* 10.4, 7.3, CHC*H*αHβ), 3.53 (1H, dd, *J* 10.4, 4.5, CHCHα*H*β); δ_C (63 MHz, $CDCl_3$) 18.3 (CCH(*C*H$_3$)$_2$), 19.6 (CCH(*C*H$_3$)$_2$), 23.5 (NCH(*C*H$_3$)$_2$), 23.8 (NCH(*C*H$_3$)$_2$), 29.7 (C*C*H(CH$_3$)$_2$), 46.5 (N*C*H(CH$_3$)$_2$), 60.8 (N*C*HCH$_2$OH), 61.2 (*C*H$_2$OH); *m*/*z* (EI$^+$) 146.1545 (MH$^+$, 5%, $C_8H_{20}ON$ requires 146.1545), 114 (MH$^+$–32CH$_2$OH$_2$, 100%), 102 (MH$^+$–44*i*-PrH, 60%).

Formic acid (98%, 52 μL, 1.4 mmol) was added dropwise to acetic anhydride (130 μL, 1.4 mmol) at 0°C. When the addition was complete the mixture was heated at 60°C for 2 h and then allowed to cool to room temperature. Tetrahydrofuran (5 mL) was added and the solution was cooled to 0°C before the addition of a solution of the crude amino alcohol from above (200 mg, 1.4 mmol) in tetrahydrofuran (5 mL). The reaction was allowed to warm slowly to room temperature and stirred for 2 h before the volatiles were removed in vacuo. Toluene (2×5 mL) was added and removed in vacuo to yield the crude product, which was purified by flash column chromatography on silica (20% light petroleum/ethyl acetate) to afford **15** (118 mg, 50%) as a clear oil; $[\alpha]_D^{21}=+91.6$ (*c* 1.2, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3386, 2963, 2925, 2878, 1648; δ_H (250 MHz, $CDCl_3$) [rotamers] 0.89–1.04 (6H, m, CCH(CH_3)$_2$), 1.24–1.32 (6H, m, NCH(CH_3)$_2$), 1.70–2.66 (2H, br-m, O*H* and CC*H*(CH$_3$)$_2$), 2.89–2.98 (1H, m, NC*H*(CH$_3$)$_2$), 3.55–4.21 (3H, m, NC*H*(CH$_3$)$_2$ and CHCH_2OH), 8.10 and 8.22 [1:3] (1H, 2s, NC*H*O); δ_C (63 MHz, $CDCl_3$) [rotamers] 19.9–22.8 CCH(*C*H$_3$)$_2$ and NCH(*C*H$_3$)$_2$), 25.2 and 28.2 (C*C*H(CH$_3$)$_2$), 45.1 and 51.4 (N*C*H(CH$_3$)$_2$), 62.0 and 64.4 (*C*H$_2$OH), 65.0 (N*C*HCH$_2$OCHO), 163.8 (N*C*HO); *m*/*z* (EI$^+$) 174.1492 (MH$^+$, 100%, $C_9H_{20}O_2N$ requires 174.1494), 142 (MH$^+$–32CH$_2$OH, 30%) 100 (7%), 88 (7%), 72 (7%).

6.7. [(3*S*)-3,5-Dihydro-3-*iso*-propyl-5-oxooxazolo[2,3-*a*]*iso*-indol-9b(2*H*)-yl]phosphine oxide 16

A mixture of (*S*)-valinol (2.08 g, 20 mmol) and phthalic anhydride (2.96 g, 20 mmol) in xylene (60 mL) was heated to reflux under Dean–Stark conditions for 2 h. After cooling, removal of solvent in vacuo produced the crude product which was purified by flash column chromatography on silica (20% ethyl acetate/light petroleum) to give the phthalimide derivative (2.75 g, 60%) as a white solid; mp not recorded; $[\alpha]_D^{21}=+8.1$ (*c* 2.0, CH_2Cl_2) {lit.[13] $[\alpha]_D^{20}=+8.33$ (*c* 2.9, EtOH)}; δ_H (250 MHz, $CDCl_3$) 0.80 (3H, d, *J* 6.7, CH(CH_3)$_2$), 1.05 (3H, d, *J* 6.7, CH(CH_3)$_2$), 2.50 (1H, dsept, *J* 10.4, 6.7, C*H*(CH$_3$)$_2$), 2.98 (H, dd, *J* 9.5, 2.7, O*H*), 3.87–4.03 (2H, m, CHCH_2OH), 4.08–4.20 (1H, m, NC*H*), 7.68–7.77 (2H, m, Ar*H*), 7.80–7.90 (2H, m, Ar*H*); δ_C (63 MHz, $CDCl_3$) 19.9 (CH(*C*H$_3$)$_2$), 20.0 (CH(*C*H$_3$)$_2$), 27.0 (*C*H(CH$_3$)$_2$), 60.0 (N*C*H), 62.3 (*C*H$_2$OH), 123.4 (Ar*C*H), 131.7 (Ar*C*), 134.2 (Ar*C*H), 169.4 (C=O); *m*/*z* (EI$^+$) 234 (MH$^+$, 100%), 216 (MH$^+$–18OH$_2$, 25%).

To a stirred solution of the phthalimide derivative (1.0 g, 4.27 mmol) in dichloromethane (1 mL) and pyridine (1 mL) was added *p*-toluenesulfonyl chloride (0.90 g, 4.31 mmol). The mixture was allowed to stir for 12 h before addition of 10% hydrochloric acid (10 mL), followed by extraction with dichloromethane (3×10 mL). The combined organics were washed with saturated aqueous copper(II) sulfate solution (3×20 mL), saturated sodium bicarbonate solution (3×10 mL) and brine (20 mL) before drying over magnesium sulfate. Removal of solvent in vacuo gave the crude tosylate (1.63 g, 98%) as a white solid; mp 44–45.5°C (lit.[13] 45–47°C); $[\alpha]_D^{21}=+10.0$ (*c* 2.0, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3064, 2968, 2932, 2875, 1775, 1713 1612, 1598; δ_H (250 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.7, CH(CH_3)$_2$), 0.97 (3H, d, *J* 6.7, CH(CH_3)$_2$), 2.24–2.40 (1H, m, C*H*(CH$_3$)$_2$), 2.33 (2H, s, ArCH_3), 3.90 (1H, td, *J* 10.4, 4.0, NC*H*), 4.35 (1H, dd, *J* 10.7, 4.0, CHC*H*αHβOH), 4.68 (1H, pseudo-t, *J* 10.4, CHCHα*H*β*O*H), 7.14 (2H, d, *J* 8.4, tosyl *o*-Ar*H*), 7.66 (2H, d, *J* 8.4, tosyl *m*-Ar*H*), 7.68–7.77 (4H, m, phthalimide Ar*H*); δ_C (63 MHz, $CDCl_3$) 16.9 (CH(*C*H$_3$)$_2$), 17.7 (CH(*C*H$_3$)$_2$), 19.6 (*C*H(CH$_3$)$_2$), 25.5 (Ar*C*H$_3$), 54.5 (N*C*H), 68.9 (*C*H$_2$OTs), 121.2–132.0 (Ar*C*H), 142.7 (Ar*C*SO$_2$R), 166.0 (C=O); *m*/*z* (EI$^+$) 387.1139 (MH$^+$, 10%, $C_{20}H_{21}O_5NS$ requires 387.1140), 347 (30%), 304 (50%), 202 (100%), 148 (98%).

To a suspension of potassium hydride (86 mg, 2.16 mmol) in tetrahydrofuran (10 mL) was added diphenylphosphine (354 μL, 2.06 mmol) and the mixture was stirred at room temperature for 30 min. To the resulting red mixture was added a solution of the tosylate from above (800 mg, 2.06 mmol) in tetrahydrofuran (5 mL), and the reaction was stirred at room temperature for 36 h before being poured into water (10 mL). Extraction of the aqueous layer with diethyl ether (3×20 mL) and combination of the organic extracts was followed by washing with brine (30 mL) and drying over magnesium sulfate. Removal of the solvent in vacuo gave the crude product which was purified by flash column chromatography on silica (40% ethyl acetate/light petroleum), and after exposure to air for 3 days characterised as the oxide **16**, a white solid (362 mg, 42%); mp 209–211°C; $[\alpha]_D^{21}=+8.3$ (*c* 1.2, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3057, 2963, 2900, 2870, 1719, 1611, 1591; δ_H (250 MHz, $CDCl_3$) 0.87 (3H, d, *J* 6.7, CH(CH_3)$_2$), 1.02 (3H, d, *J* 6.7, CH(CH_3)$_2$), 2.46 (1H, dsept, *J* 10.7, 6.7, C*H*(CH$_3$)$_2$), 3.59–3.70 (1H, m, NC*H*), 4.68 (1H, t, *J* 7.9, CHC*H*αHβO), 4.98 (1H, t, *J* 7.3, CHCHα*H*β*O*H), 6.62 (1H, d, *J* 7.6, Ar*H*), 7.11–8.05 (13H, m, Ar*H*); δ_P (101 MHz, $CDCl_3$) 32.0; δ_C (63 MHz, $CDCl_3$) 19.6 (CH(*C*H$_3$)$_2$), 21.6 (CH(*C*H$_3$)$_2$), 32.6 (*C*H(CH$_3$)$_2$), 64.0 (N*C*HCH$_2$), 79.1 (CH*C*H$_2$O), 103.4 (ArN*C*PO), 123.6–143.0 (ArH), 173.7 (C=O); *m*/*z* (CI$^+$) 418.1577 (MH$^+$, 35%, $C_{25}H_{24}O_3NP$ requires 418.1572), 342 (M$^+$–77Ph, 25), 293 (MH$^+$–125P(O)Ph, 35%) 218 (MH$^+$–200P(O)Ph$_2$, 50%), 203 (100%).

6.8. (*S*)-*N*-*tert*-Butoxycarbonyl-2-*iso*-propylaziridine 18

To a suspension of potassium hydride (87 mg, 2.18 mmol) in dimethylformamide (15 mL) was added diphenylphosphine (375 μL, 2.18 mmol) and the reaction was stirred at room temperature for 20 min. The mixture was cooled to −35°C and stirred for a further 20 min before a solution of **17**[15] (778 mg, 2.18 mmol) in dimethylformamide (5 mL) was added dropwise. The reaction was allowed to stir at this temperature for 2 h before warming to room temperature prior to addition of diethyl ether (30 mL). The organics were washed with water (4×20 mL), then brine (30 mL) and dried over magnesium sulfate. Removal of the solvent in vacuo gave the crude product, which was purified by flash column chromatography on silica (2% ethyl acetate/light petroleum) to yield **18** as a white solid (250 mg, 40%); mp 193–194°C; $[\alpha]_D^{21}$ not recorded; ν_{max}

(film)/cm^{-1} 3060, 2969, 1719; δ_H (250 MHz, $CDCl_3$) 0.95 (3H, d, *J* 6.7, CCH(CH_3)$_2$), 1.05 (3H, d, *J* 6.7, CCH(CH_3)$_2$), 1.35–1.44 (10H, m, C(CH_3)$_3$ and CC*H*(CH$_3$)$_2$), 1.93 (1H, d, *J* 4.0, CHC*H*αHβN), 2.12 (1H, ddd, *J* 7.0, 6.1, 3.7, NC*H*CH$_2$), 2.22 (1H, d, *J* 6.1, CHCHα*H*βN); δ_C (63 MHz, $CDCl_3$) 18.3 (CH(*C*H$_3$)$_2$), 18.9 (CH(*C*H$_3$)$_2$), 27.1 (*C*H(CH$_3$)$_2$), 29.8 (N*C*H$_2$CH), 30.1 (NCH$_2$*C*H), 79.9 (*C*(CH$_3$)$_3$), 162.1 (N*C*O*t*-Bu); *m*/*z* (EI$^+$) 358.1670 (M$^+$, 0%, $C_{17}H_{28}O_5NS$ requires 358.1688), 319 (MH$^+$−56C(CH$_3$)$_3$, 100%), 204 (M$^+$−171OSO$_2$C$_6$H$_4$Me, 45%), 165 (35%), 147 (95%).

6.9. (*S*)-*N*-*tert*-Butoxycarbonyl-2-amino-3-methylbutyl-1-diphenylphosphine-borane 19

To a suspension of triphenylphosphine-borane (3.50 g, 12.6 mmol) in tetrahydrofuran (8.5 mL) was added finely cut strips of lithium metal freshly washed with methanol, then tetrahydrofuran. The mixture was allowed to stir for 12 h at room temperature before the addition of *tert*-butyl chloride (1.40 mL, 12.6 mmol), followed by cooling to −78°C (30 min). This was transferred slowly, via cannula, over a 30 min period, to a solution of **17**[15] (0.30 g, 8.4 mmol) in tetrahydrofuran (40 mL), also at −78°C. The mixture was stirred at this temperature for a further 2 h, then slowly warmed to room temperature and stirred for 12 h prior to pouring onto water (100 mL). The aqueous layer was extracted with diethyl ether (3×50 mL) followed by combination of the organics, washing with brine (80 mL) and drying over magnesium sulfate. Removal of the solvent in vacuo gave the crude product which was purified by flash column chromatography on silica (8% ethyl acetate/light petroleum) to yield **19** as a white solid (2.28 g, 71%); (found: C, 68.10; H, 8.50; N, 3.94; $C_{22}H_{33}O_2NPB$ requires: C, 68.58; H, 8.63; N, 3.64%); mp 114–117°C; $[\alpha]_D^{21}$ = −110.0 (*c* 1, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3444, 2967, 2932, 2370, 2343, 2248, 1706, 1438; δ_H (250 MHz, $CDCl_3$) 0.79–0.87 (6H, br-m, CH(CH_3)$_2$), 1.32 (9H, s, C(CH_3)$_3$), 1.92–2.2 (1H, br-m, C*H*(CH$_3$)$_2$), 2.35–2.55 (2H, br-m, CH_2PPh$_2$BH$_3$), 3.58–3.78 (1H, br-m, NC*H*), 4.52 (1H, br-s, N*H*), 7.37–7.50 (6H, m, Ar*H*), 7.62–7.75 (4H, m, Ar*H*); δ_P (101 MHz, $CDCl_3$) 13.8 br; δ_C (63 MHz, $CDCl_3$) 17.8 (CH(*C*H$_3$)$_2$), 18.8 (CH(*C*H$_3$)$_2$), 28.3 (C(*C*H$_3$)$_3$), 28.4 (d, $J_{P\text{-}C}$ 36, *C*H$_2$PPh$_2$BH$_3$), 32.8 (*C*H(CH$_3$)$_2$), 52.3 (N*C*H), 79.0 (O*C*(CH$_3$)$_3$), 128.8–132.3 (Ar*C*), 154.8 (N*C*O); *m*/*z* (FAB) 402.719 (NH$_4$–M$^+$, 15%, $C_{22}H_{37}N_2O_2PB$ requires 402.2722), 384 (M$^+$, 45%) 328 (M$^+$−56C(CH$_3$)$_3$, 70%), 202 (50%), 284 (M$^+$−100CO$_2$*t*-Bu, 35%), 187 (HPPh$_2$, 100%).

6.10. (*S*)-2-Amino-3-methylbutyl-1-diphenylphosphine 20

To a stirred solution of **19** (1.0 g, 2.6 mmol) in toluene (20 mL) was added 1,4-diazabicyclo-[2.2.2]-octane (0.35 g, 3.1 mmol) and the mixture was warmed to 40°C for 12 h. The solvent was removed in vacuo and the resulting residue was taken up in light petroleum, the white solid was removed by filtration and washed with light petroleum (3×5 mL). Removal of the solvent in vacuo gave the crude product which was purified by flash column chromatography on silica (8% ethyl acetate/light petroleum) to yield the free phosphine as a clear gum (0.94 g, 97%); $[\alpha]_D^{21}$ = +16.6 (*c* 1.2, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3420, 3349, 3053, 2963, 2873, 1698, 1586, 1503, 1434; δ_H (250 MHz, $CDCl_3$) 0.85 (3H, d, *J* 6.7, CH(CH_3)$_2$), 0.87 (3H, d, *J* 6.7, CH(CH_3)$_2$), 1.41 (9H, s, C(CH_3)$_3$), 1.75–1.98 (1H, br-m, C*H*(CH$_3$)$_2$), 2.05–2.35 (2H, br-m, CH_2PPh$_2$), 3.40–3.68 (1H, br-m, NC*H*), 4.41 (1H, br-d, *J* 9.2, N*H*), 7.25–7.50 (10H, m, Ar*H*); δ_P (101 MHz, $CDCl_3$) −22.3; δ_C (63 MHz, $CDCl_3$) 17.5 (CH(*C*H$_3$)$_2$), 18.9 (CH(*C*H$_3$)$_2$), 28.4 (C(*C*H$_3$)$_3$), 32.3 (d, $J_{P\text{-}C}$ 13.0, *C*H$_2$PPh$_2$), 32.7 (d, $J_{P\text{-}C}$ 8.0, *C*H(CH$_3$)$_2$), 53.6 (d, $J_{P\text{-}C}$ 14.0, N*C*H), 78.9 (O*C*(CH$_3$)$_3$), 128.4–133.2 (Ar*C*), 138.8 (d, $J_{P\text{-}C}$ 13.0, Ar*C*P), 155.3 (N*C*O); *m*/*z* (FAB) 371.2007 (M$^+$, 5%, $C_{22}H_{30}O_2NP$ requires 371.2014), 314 (M$^+$−56C(CH$_3$)$_3$, 80%), 244 (100%), 199 (CH$_2$PPh$_2$, 75%), 183 (40%).

To a solution of the free phosphine prepared above (2.50 g, 6.74 mmol) in dichloromethane (20 mL) was added trifluoroacetic acid (6.75 mL, 8.76 mmol) dropwise and the mixture was allowed to stir at room temperature for 2 h. The reaction was poured carefully onto ice cold aqueous sodium hydroxide solution (1 M, 30 mL) and washed with further sodium hydroxide (2×30 mL) before washing with brine (50 mL). The organic layer was dried over magnesium sulfate and evaporated to give the crude product. This was passed through a short column of silica to yield **20** as a clear oil (1.69 g, 93%); (found: C, 75.08; H, 8.27; N, 5.20; $C_{17}H_{22}NP$ requires: C, 75.25; H, 8.17; N, 5.16%); $[\alpha]_D^{21}$ = +73.0 (*c* 1.5, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3052, 2956, 2874, 1585, 1503, 1433; δ_H (250 MHz, $CDCl_3$) 0.88 (6H, t, *J* 6.4, CH(CH_3)$_2$), 1.70 (1H, septd, *J* 6.7, 4.6, C*H*(CH$_3$)$_2$), 1.93 (1H, ddd, *J* 13.3, 10.0 (^{1}H–^{31}P), 2.7, C*H*αHβPPh$_2$), 2.32 (1H, dt, *J* 13.3, 2.7, CHα*H*βPPh$_2$), 2.55–2.69 (1H, m, NC*H*), 7.30–7.50 (10H, m, Ar*H*); δ_P (101 MHz, $CDCl_3$) −20.9; δ_C (63 MHz, $CDCl_3$) 17.2 (CH(*C*H$_3$)$_2$), 18.9 (CH(*C*H$_3$)$_2$), 34.5 (d, $J_{P\text{-}C}$ 7.0, *C*H(CH$_3$)$_2$), 34.8 (d, $J_{P\text{-}C}$ 11.0, *C*H$_2$PPh$_2$), 54.1 (d, $J_{P\text{-}C}$ 13.0, N*C*H), 128.3–133.3 (Ar*C*); *m*/*z* (EI$^+$) 271.1488 (M$^+$, 20%, $C_{17}H_{22}NP$ requires 271.1490), 254 (M$^+$−17NH$_3$, 25%) 228 (M$^+$−43*i*-Pr, 20%) 200 (CH$_2$PPh$_2$, 100%), 185 (PPh$_2$, 60%).

6.11. (*S*)-*N*-*iso*-Propyl-2-amino-3-methylbutyl-1-diphenylphosphine 21

To a suspension of basic alumina (163 mg) in acetone (500 μL) was added a solution of **20** (100 mg, 0.37 mmol) in acetone (500 μL) and the mixture was stirred at room temperature for 12 h. The reaction mixture was filtered and the residue washed with acetone (1 mL). Removal of solvent in vacuo gave the crude imine as a colourless oil (113 mg, 99%); $[\alpha]_D^{21}$ = +33.3 (*c* 0.12, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3071, 2958, 2871, 1586, 1434; δ_H (250 MHz, $CDCl_3$) 0.80 (3H, d, *J* 6.7, CH(CH_3)$_2$), 0.90 (3H, d, *J* 6.7, CH(CH_3)$_2$), 1.57 (3H, s, NC(CH_3)$_2$), 1.75–1.85 (1H, m, C*H*(CH$_3$)$_2$), 1.86 (3H, s, NC(CH_3)$_2$), 2.29 (1H, dd, *J* 13.4, 9.3, C*H*αHβPPh$_2$), 2.45 (1H, dt, *J* 13.4, 2.9, CHα*H*βPPh$_2$), 3.11–3.25 (1H, m, NC*H*CH$_2$PPh$_2$), 7.22–7.48 (10H, m, Ar*H*); δ_P (101 MHz, $CDCl_3$) −19.3; δ_C (63 MHz, $CDCl_3$) 18.7 (CH(*C*H$_3$)$_2$), 19.5 (CH(*C*H$_3$)$_2$), 29.0 (NC(*C*H$_3$)$_2$), 29.3 (NC(*C*H$_3$)$_2$), 33.4 (d, $J_{P\text{-}C}$ 12, *C*H$_2$PPh$_2$), 34.3 (d, $J_{P\text{-}C}$ 9, *C*H(CH$_3$)$_2$), 63.3 (d, $J_{P\text{-}C}$ 13, N*C*HCH$_2$PPh$_2$), 128.1–

133.3 (Ar*C*), 165.5 (N*C*(CH_3)$_2$); *m*/*z* (EI$^+$) 312.1880 (MH^+, 15%, $C_{20}H_{27}NP$ requires 312.1881), 272 (60%), 202 (CH_2PPh_2H, 25%), 187 (PPh_2H, 100%).

To a suspension of lithium aluminium hydride (126 mg, 3.31 mmol) in anhydrous tetrahydrofuran (3 mL) at 0°C was added a solution of the crude imine from above (344 mg, 1.10 mmol) in tetrahydrofuran (2 mL). The reaction mixture was heated under reflux for 12 h and then quenched at 0°C by careful addition of water (0.1 mL), aqueous sodium hydroxide (15% w/v, 0.1 mL) and water (0.3 mL). The resulting white precipitate was removed by filtration and the residue washed with tetrahydrofuran (2×10 mL). The organics were dried over magnesium sulfate and concentrated in vacuo to yield the crude product, which was purified by flash column chromatography on silica (1% triethylamine/10% ethyl acetate/light petroleum) to give **21** as a colourless oil (100 mg, 94%); $[\alpha]_D^{21}=+60.0$ (*c* 1.0, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3053, 2957, 2663, 1603, 1586, 1434; δ_H (250 MHz, $CDCl_3$) 0.80 (3H, d, *J* 7.0, CH(CH_3)$_2$), 0.87 (3H, d, *J* 7.0, CH(CH_3)$_2$), 0.89 (3H, d, *J* 6.2, NCH(CH_3)$_2$), 0.91 (3H, d, *J* 6.2, NCH(CH_3)$_2$), 1.87–2.01 (2H, m, CC*H*(CH_3)$_2$ and C*H*α*H*βPPh_2), 2.20 (1H, ddd, *J* 13.4, 4.9 (^{1}H–^{31}P), 9.3, CHα*H*βPPh_2), 2.39–2.51 (1H, m, NC*H*CH_2PPh_2), 2.75 (1H, sept, *J* 6.2, NC*H*(CH_3)$_2$), 7.28–7.50 (10H, m, Ar*H*); δ_P (101 MHz, $CDCl_3$) −21.0; δ_C (63 MHz, $CDCl_3$) 17.3 (CH(*C*H_3)$_2$), 18.2 (CH(*C*H_3)$_2$), 23.2 (NCH(*C*H_3)$_2$), 23.8 (NCH(*C*H_3)$_2$), 30.7 (C*C*H(CH_3)$_2$), 31.0 (d, $J_{P\text{-}C}$ 13.0, *C*H_2PPh_2), 46.0 (N*C*H(CH_3)$_2$), 57.0 (d, $J_{P\text{-}C}$ 13, N*C*HCH_2PPh_2), 128.3–133.4 (Ar*C*); *m*/*z* (EI$^+$) 313.1957 (M^+, 5%, $C_{20}H_{28}NP$ requires 313.1959), 270 (M^+–43*i*Pr, 50%), 200 (CH_2PPh_2, 50%), 185 (PPh_2, 40%) 114 (M^+–199CH_2PPh_2, 100%).

6.12. (*S*)-*N*-*iso*-Propyl-*N*-methyl-2-amino-3-methylbutyl-1-diphenylphosphine 7

Formic acid (98%, 82 μL, 2.18 mmol) was added dropwise to acetic anhydride (167 μL, 1.77 mmol) at 0°C. When the addition was complete the mixture was heated at 60°C for 2 h and then allowed to cool to room temperature. Tetrahydrofuran (1 mL) was added and the solution cooled to 0°C before addition of a solution of **21** (213 mg, 0.68 mmol) in tetrahydrofuran (2 mL). The reaction was allowed to warm slowly to room temperature and stirred for 12 h before the volatiles were removed in vacuo. Toluene (2×5 mL) was added and removed in vacuo to yield the crude product, which was purified by flash column chromatography on silica (1% triethylamine/20% ethyl acetate/light petroleum) to afford the *N*-formyl derivative as a clear oil (231 mg, 99%); $[\alpha]_D^{21}=+80.0$ (*c* 1.0, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3052, 2971, 2873, 1668, 1585, 1434; δ_H (250 MHz, $CDCl_3$) [rotamers] 0.85–0.95 (6H, m, CCH(CH_3)$_2$), 1.31–1.50 (6H, m, NCH(CH_3)$_2$), 1.91 (1H, pseudo-oct, *J* 6.7, CC*H*(CH_3)$_2$), 2.19 (1H, ddd, *J* 14.6, 10.0 (^{1}H–^{31}P), 5.2, C*H*α*H*βPPh_2), 2.51 (1H, dt, *J* 14.6, 3.4, CHα*H*βPPh_2), 2.72–2.87 and 3.50 [1:1] (1H, m and overlap, NC*H*CH_2PPh_2), 3.45 and 3.58 [1:1] (1H, 2sept, *J* 7.0, 6.7, NC*H*(CH_3)$_2$), 7.20–7.50 (10H, m, Ar*H*), 7.80 and 8.39 [1:1] (1H, 2s, NC*H*O); δ_P (101 MHz, $CDCl_3$) [rotamers] −21.6 and −22.4; δ_C (63 MHz, $CDCl_3$) [rotamers] 20.0, 20.2, 20.5 and 20.6 (CCH(*C*H_3)$_2$), 24.3 and 24.7 (NCH(*C*H_3)$_2$), 30.1 and 30.5 (2d, $J_{P\text{-}C}$ 15.0 and 18.0, *C*H_2PPh_2), 32.0 and 32.2 (2d, $J_{P\text{-}C}$ 7.0 and 6.0, C*C*H(CH_3)$_2$), 47.0 (N*C*H(CH_3)$_2$), 62.8 (d, $J_{P\text{-}C}$ 13.0, N*C*HCH_2PPh_2), 128.5–133.89 (Ar*C*) 162.3 and 163.7 (N*C*HO); *m*/*z* (EI$^+$) 341.1898 (M^+, 15%, $C_{21}H_{28}ONP$ requires 341.1908), 298 (M^+–43*i*-Pr, 95%) 271 (60%), 186 ($CH_2PPh_2H^+$, 60%).

To a suspension of lithium aluminium hydride (79 mg, 2.08 mmol) in tetrahydrofuran (2 mL) at 0°C was added a solution of the *N*-formyl derivative from above (236 mg, 0.69 mmol) in tetrahydrofuran (1.5 mL). The reaction mixture was stirred at room temperature for 12 h then quenched at 0°C by careful addition of water (0.1 mL), aqueous sodium hydroxide (15% w/v, 0.1 mL) and water (0.3 mL). The resulting white precipitate was removed by filtration and the residue was washed with tetrahydrofuran (2×5 mL). The organics were dried over magnesium sulfate and concentrated in vacuo to yield the crude product, which was purified by flash column chromatography on silica (0.5% triethylamine/10% ethyl acetate/light petroleum) to give **7** as a colourless oil (184 mg, 81%); (found: C, 76.81; H, 9.09; N, 4.19; $C_{21}H_{30}NP$ requires: C, 77.03; H, 9.23; N, 4.28%); $[\alpha]_D^{21}=+15.8$ (*c* 1.9, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3070, 2960, 2782, 1664, 1586, 1433; δ_H (250 MHz, $CDCl_3$) 0.83–0.91 (12H, m, CH(CH_3)$_2$ and NCH(CH_3)$_2$), 1.91 (1H, septd, *J* 6.7, 5.2, C*H*(CH_3)$_2$), 2.12–2.18 (4H, m, NCH_3 and C*H*α*H*βPPh_2), 2.24 (1H, dd, *J* 13.7, 7.0, CHα*H*βPPh_2), 2.42–2.57 (1H, m, NC*H*CH_2PPh_2), 2.73 (1H, sept, *J* 6.4, NC*H*(CH_3)$_2$), 7.27–7.50 (10H, m, Ar*H*); δ_P (101 MHz, $CDCl_3$) −18.0; δ_C (63 MHz, $CDCl_3$) 20.3 (CH(*C*H_3)$_2$), 20.4 (CH(*C*H_3)$_2$), 20.5 (NCH(*C*H_3)$_2$), 21.0 (NCH(*C*H_3)$_2$), 28.7 (d, $J_{P\text{-}C}$ 13.0, *C*H_2PPh_2), 31.6 (*C*H(CH_3)$_2$), 32.0 (N*C*H_3), 52.9 (N*C*H(CH_3)$_2$), 62.2 (d, $J_{P\text{-}C}$ 12.0, N*C*HCH_2PPh_2), 128.2–133.43 (Ar*C*); *m*/*z* (EI$^+$) 327.2117 (M^+, 25%, $C_{21}H_{30}NP$ requires 327.2116), 284 (M^+–43*i*Pr, 100%), 185 (PPh_2, 40%) 128 (M^+–199CH_2PPh_2, 50%).

6.13. (*S*)-*N*,*N*-Diphenyl-2-amino-3-methylbutyl-1-diphenylphosphine 8

To a solution of (*S*)-*N*,*N*-diphenylvalinol[1b] (1.75 g, 6.9 mmol) in dichloromethane (70 mL) at 0°C was added triethylamine (1.9 mL, 13.7 mmol). Methanesulfonyl chloride (0.74 mL, 9.6 mmol) was added dropwise and the mixture was stirred at this temperature for 1 h. The reaction mixture was poured onto ice-cold sodium hydroxide (1 M, 80 mL) and the aqueous layer was extracted with dichloromethane (3×50 mL). The organics were washed with brine (80 mL) and dried over magnesium sulfate. The crude product was purified by flash column chromatography on silica (10% ethyl acetate/light petroleum) to give the product mesylate (1.46 g, 60%) as a white solid, mp 94–95°C (found: C, 64.66; H, 6.98; N, 4.15; $C_{18}H_{23}O_3NS$ requires: C, 64.84; H, 6.96; N, 4.20%); $[\alpha]_D^{21}=-114.0$ (*c* 1, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3039, 2968, 2875, 1590, 1496; δ_H (250 MHz, $CDCl_3$) 1.00 (3H, d, *J* 6.7, CH(CH_3)$_2$), 1.18 (3H, d, *J* 6.7, CH(CH_3)$_2$), 1.95–2.10 (1H, m, C*H*(CH_3)$_2$), 2.70

(3H, s, SO_2CH_3), 4.09 (1H, td, *J* 9.3, 4.1NC*H*), 4.31 (1H, pseudo-t, *J* 9.3, CHC*Hα*Hβ), 4.51 (1H, dd, *J* 10.5, 4.1, CHCHα*Hβ*), 6.96–7.01 (6H, m, Ar*H*), 7.23–7.29 (4H, m, Ar*H*); δ_C (63 MHz, $CDCl_3$) 20.4 ($CH(CH_3)_2$), 20.9 ($CH(CH_3)_2$), 31.0 ($CH(CH_3)_2$), 37.2 ($CH_2SO_2CH_3$), 65.0 (N*C*H), 67.8 ($CH_2SO_2CH_3$), 122.1 (Ar), 123.1 (Ar), 129.4 (Ar), 147.4 (Ar); *m*/*z* (EI^+) 333.1395 (M^+, 20%, $C_{18}H_{23}O_3NS$ requires 333.1399), 290 (M^+–43*i*-Pr, 40%), 182 (M^+–31$CH_2OSO_2CH_3$, 100%), 77 (Ph, 20%).

To a suspension of potassium *tert*-butoxide (149 mg, 1.3 mmol) in tetrahydrofuran (10 mL) was added diphenylphosphine (114 μL, 0.6 mmol) and this was stirred at room temperature for 20 min. Following the addition of the mesylate from above (222 mg, 0.7 mmol) the reaction was allowed to stir overnight (or until the red colour had completely faded to colourless). The reaction mixture was poured onto water (20 mL) and the aqueous layer was extracted with ethyl acetate (2×10 mL). The combined organics were washed with brine (20 mL), dried over magnesium sulfate and concentrated in vacuo to yield the crude product. Purification by column chromatography on basic alumina (1% ethyl acetate/light petroleum) gave **8** (178 mg, 69%) as an amorphous waxy white solid; mp 82.5–85°C; $[\alpha]_D^{21} = -22.5$ (*c* 2, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3054, 2958, 2871, 1588, 1495; δ_H (250 MHz, $CDCl_3$) 0.95 (6H, pseudo-t, *J* 6.7, ($CH(CH_3)_2$), 2.11 (1H, dsept, *J* 9.2, 6.7, C*H*(CH_3)$_2$), 2.29 (1H, ddd, *J* 14.0, 10.7 (^{1}H–^{31}P), 4.6, CHC*Hα*HβPPh$_2$), 2.52 (1H, dt, *J* 14.0, 4.6, CHCHα*Hβ*PPh$_2$), 3.70 (1H, qd, *J* 9.2, 3.4, NC*H*), 6.85–7.00 (6H, m, Ar*H*), 7.08–7.58 (14H, m, Ar*H*); δ_P (101 MHz, $CDCl_3$) –20.3; δ_C (63 MHz, $CDCl_3$) 21.1 ($CH(CH_3)_2$), 21.2 ($CH(CH_3)_2$), 27.4 (d, $J_{C\text{-}P}$ 13.9, CH_2PPh_2), 35.1 (d, $J_{C\text{-}P}$ 6.3, ($CH(CH_3)_2$), 63.2 (d, $J_{C\text{-}P}$ 12.8, N*C*H), 121.3 (Ar), 123.3 (Ar), 127.8–140.1 (Ar), 149.0 (Ar); *m*/*z* (EI^+) 423.2106 (M^+, 35%, $C_{29}H_{30}NP$ requires 423.2116), 380 (M^+–43*i*-Pr, 100%), 224 (M^+–199CH_2PPh_2, 75%), 185 (PPh_2, 45%).

6.14. Allylic substitution procedures: *trans*-(*R*)-methyl 2-carbomethoxy-3,5-diphenylpent-4-enoate 23

6.14.1. Standard procedures for temperature study. Method A: A solution of acetate **22** (200 mg, 0.8 mmol), allyl-palladium chloride dimer (7.3 mg, 0.02 mmol) and ligand (0.08 mmol) in dichloromethane (3.0 mL) was stirred at room temperature for 15 min, then cooled to the appropriate temperature (15 min). To this was added a solution of dimethyl malonate (273 μL, 2.4 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (583 μL, 2.4 mmol) dropwise, followed by potassium acetate (2 mg, 0.03 mmol). The reaction was monitored by TLC and on completion the volatiles were removed in vacuo and purification by flash column chromatography (7% ethyl acetate/light petroleum) gave **23** as a colourless oil; δ_H (250 MHz, $CDCl_3$), 3.53 (3H, s, CO_2CH_3), 3.70 (3H, s, CO_2CH_3), 3.95 (1H, d, *J* 10.9, C*H*(CO_2CH_3)$_2$), 4.27 (1H, dd, *J* 10.9, 8.2, C*H*CH(CO_2CH_3)$_2$), 6.32 (1H, dd, *J* 15.0, 8.2, PhCH=C*H*), 6.48 (41H, d, *J* 15.0, PhC*H*=CH), 7.51–7.44 (10H, m, Ar*H*).

Method B: A solution of acetate **22** (200 mg, 0.8 mmol), allyl-palladium chloride dimer (7.3 mg, 0.02 mmol) and ligand (0.08 mmol) in tetrahydrofuran (1.0 mL) was stirred at room temperature for 15 min, then cooled to the appropriate temperature (15 min). In a separate vessel, sodium hydride in mineral oil (48 mg, 1.19 mmol) was washed with hexane (3×1 mL) and dried under high vacuum. Tetrahydrofuran (1.5 mL) was added, followed by dropwise addition of dimethyl malonate (136 μL, 1.19 mmol). This solution was cooled to the appropriate temperature (15 min) before the other solution was added rapidly via cannula (0.5 mL wash). The reaction was monitored by TLC and on completion diluted with diethyl ether (15 mL) before washing with ice-cold saturated aqueous ammonium chloride (3×20 mL), brine (30 mL), dried over magnesium sulfate and concentrated in vacuo. Purification by flash column chromatography (7% ethyl acetate/light petroleum) gave **23** as a colourless oil.

6.14.2. Procedure for chloride ion effect study. Method B for the standard procedure above was employed, at –20°C. The allyl-palladium chloride dimer (0.02 mmol) was replaced with bis(benzylideneacetone)-palladium (23 mg, 0.04 mmol) and 2 equivalents of ligand (0.08 mmol) were used.

6.14.3. Procedure for 1:1 ligand:palladium stoichiometry study. Method B for the standard procedure above was employed, at –20°C. The amount of ligand used was 0.04 mmol (1 equiv.) and employed with either allyl-palladium chloride dimer (0.02 mmol) or bis(benzylideneacetone)-palladium (23 mg, 0.04 mol).

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