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Synthesis and application to asymmetric allylic amination of substituted monodonor diazaphospholidine ligands

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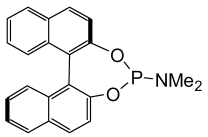
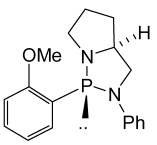
Abstract—The synthesis of a series of substituted monodonor diazaphospholidine ligands is described. A regioselective lithiation process is a key step in one of these syntheses. The compounds are designed to be incorporated into soluble polymer and other solid phase supports. Enantiomeric excesses of up to 88% were observed when these compounds were employed in palladium-catalysed asymmetric amination reactions.

1. Introduction

The use of enantiomerically pure phosphorus-donor ligands in asymmetric catalysis is now well established.[1] Although the majority of international research work has focussed on the use of phosphines, some dramatic recent breakthroughs have been achieved with homochiral phosphites and ligands which contain P–N and P–O bonds.[2] Of the many ligands reported, bidentate ligands have traditionally been regarded as the most effective and efficient, primarily due to the stability of their complexes and the well-defined stereochemical environment which they create around metal centres. However the discovery of the remarkable catalytic properties of ligands such as MONOPHOS **1**,[3] and related compounds,[4] has reignited interest in monodonor reagents.

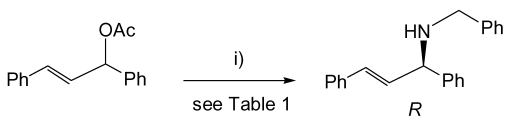


MONOPHOS **1**



SEMI-ESPHOS **2**

In previous studies in this group, we have reported the synthesis and applications of a series of ligands containing the diazaphospholidine ring structure.[5] As well as being stereochemically well-defined P-donor reagents, diazaphospholidines are extremely easy to prepare in large quantities through the simple reaction of a dichloro- or bis(dimethyamino)phosphine with a suitable diamine.[2] Our studies of monodonor diazaphospholidine ligands culminated in the synthesis of SEMI-ESPHOS **2**, a robust and readily-preparable ligand which is capable of generating high levels of asymmetric induction in reactions such as allylic amination (Scheme 1, Table 1).[5] In this ligand, the presence of the methoxy group is essential in order for products of high e.e. to be generated, whilst the *C*1-symmetric structure of the compound generates products of higher e.e. than corresponding ligands generated from *C*2-symmetric amines. Although there is a chiral centre at the P atom, the synthesis of the ligands, carried out at elevated temperature, results in formation of a single diastereoisomer of product.



Scheme 1. *Reagents and conditions*: (i) 10 mol% ligand, 5 mol% $[Pd_2(dba)_3]$, 2 equiv. $PhCH_2NH_2$, DCM, rt, 2d.

Table 1.

Ligand	Yield%	e.e. (%)
2	80	86 (*R*)
5	70	76 (*R*)
6	82	82 (*R*)
7	81	75 (*R*)
8	90	88 (*R*)

Keywords: asymmetric; catalyst; ligand; allylic; substitution; amination.
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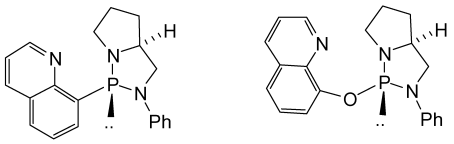
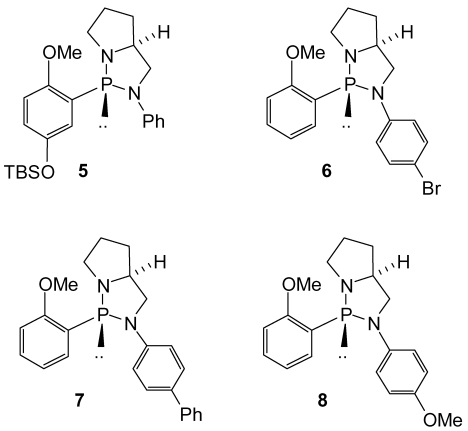
Similar ligands have been reported by other researchers, most notably Buono, including **3**[6] and, more recently, **4**.[7] Ligand **3** also gives excellent enantioselectivities in allylic amination reactions, although both **3** and **4** behave as bidentate ligands, rather than monodentate, as is the case with **1** and **2**. Buono has also reported the synthesis of **2** as an intermediate towards some P═O containing ligands for use in diethylzinc additions to aldehydes.[6c,8]



3 **4**



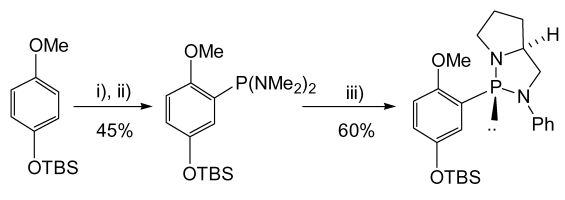
5 **6** **7** **8**

It is clear, therefore, that monodonor diazaphospholidine ligands are valuable tools for asymmetric catalysis. However, significant further research is still required in order to define the full scope and limitations of these materials. In this paper we report the synthesis and applications to asymmetric allylic amination of a series of substituted diazaphospholidine ligands which are designed to act as models for solid-supported derivatives.

2. Results and discussion

Our objective was to prepare the SEMI-ESPHOS derivatives **5**–**8**, and to evaluate these materials in allylic amination reactions. The selection of these materials was made on the basis that the modifications would allow us to gauge the effect of substitutions at particular positions on the ability of the ligand to function. Each of the derivatives has been selected on the basis that the position of functionalisation is some distance from the phosphorus atom, and should not therefore interfere with its mode of action. This prerequisite is essential if the ligands are to be attached to a solid support through the positions indicated.

Compound **5** was attractive because the 5-oxygen substituted provides a remote position for attachment of a supporting group. The target compound was prepared through the route illustrated in Scheme 2, pivotal to which was a regioselective *ortho*-lithiation of **9** (prepared by TBS protection of *para*-methoxyphenol) to give **10**.



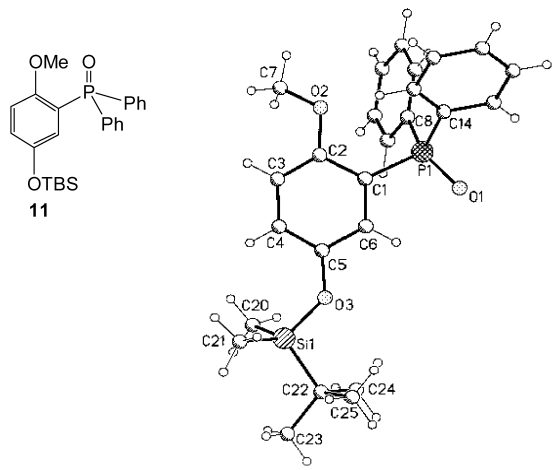
9 **10** **5**

Scheme 2. *Reagents and conditions*: (i) *n*BuLi, THF, −78°C. (ii) $ClP(NMe_2)_2$, THF, −78°C. (iii) *S*-(2-phenylaminomethyl)pyrolidine (1 equiv.), toluene, reflux, 2 days.

In this process the lithiation is selective for the less-hindered position adjacent to the smaller methoxy group. This selectivity was confirmed by the isolation of **11**, formed by trapping with $Ph_2P(O)Cl$. The X-ray crystallographic structure of this compound is shown in Figure 1.

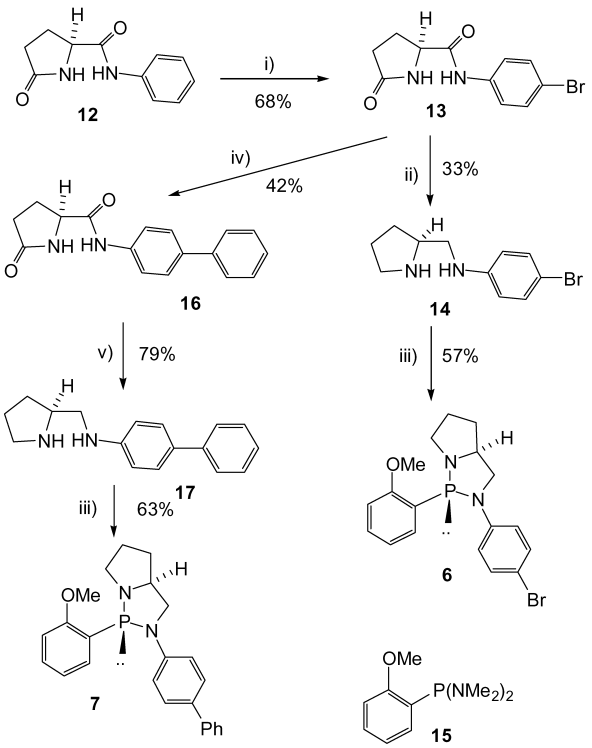
The synthesis of **5** was completed by condensation with *S*-(2-phenylaminomethyl)pyrolidine (2 steps from L-glutamic acid) under reflux in toluene. In this process the reaction is complete when the volatile dimethylamine side-product has been fully expelled from the reaction mixture, a process which can be conveniently followed by monitoring of the pH of the gases emerging from the reaction.

Compound **6** was prepared from the cyclic proanilide **12**, which was available in quantity from L-glutamic acid (Scheme 3). The reaction of **12** with bromine resulted in *para*-bromination of the N-aryl ring to give **13** in 68% yield. The reduction of **13** to diamine **14** was achieved in low yield through reduction with lithium aluminium hydride at room temperature overnight. This reaction can be accelerated by heating the reaction mixture at reflux, but under these conditions significant debromination is observed. The condensation of **14** with the bis(dimethylamino)phosphine intermediate **15**[9] resulted in formation of the target **6** in 57% yield.



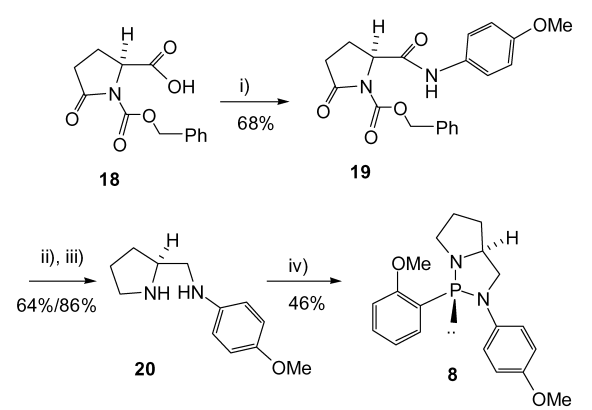
11

Figure 1. X-Ray crystallographic structure of **11**.



Scheme 3. *Reagents and conditions*: (i) 2 equiv. Br_2, AcOH, 2 days. (ii) $LiAlH_4$, THF, rt, o/n. (iii) 1 equiv. **15**, toluene, reflux, 3 days. (iv) 5 mol% $Pd(OAc)_2$, 2.5 equiv. phenylboronic acid, 2.5 equiv. K_2CO_3, H_2O, 100°C, 90 min. (v) $LiAlH_4$, THF, reflux, 3 h.

Compound **7** was also formed through a similar sequence (Scheme 3). For this compound, it was necessary to introduce the second aromatic ring through a Suzuki coupling reaction.[10] Conditions had to be optimised for this reaction, which delivered **16** in 42% yield. The conversion in the Suzuki reaction could be improved with the addition of a quantity of tetrabutylammonium bromide, however, the ammonium salt proved difficult to separate from the product. The success of the Suzuki reaction effectively permits the introduction of a range of aryl groups to the ligand. Reduction of **16** provided the diamine **17** in 79% yield, and this was converted to **7** upon condensation with **15** in 63% yield.



Scheme 4. *Reagents and conditions*: (i) 1.2 equiv. *para*-methoxyaniline, EtOAc, 1.2 equiv. EtOCOCl, −15°C, 1 h; 0°C, 1 h; rt, 48 h. (ii) 20 atm H_2, Pd/C, EtOH. (iii) 2.5 equiv. $LiAlH_4$, THF, reflux, 3 h. (iv) 1 equiv. **15**, toluene, reflux, 3 days.

To prepare ligand **8**, the sequence of reactions illustrated in Scheme 4 was employed. *N*-Benzylcarboxylate protected L-proline **18** was condensed with *para*-methoxyaniline to give **19**, which was then converted to diamine **20** in a two-step process of deprotection followed by reduction with lithium aluminium hydride. A two-step process was required here because direct reduction of the *N*-protecting group would have resulted in N-methylation. It should also be noted that we chose not to start from L-glutamic acid in this instance because of the difficulty of removal of the unreacted substituted aniline from the reaction; unlike aniline itself, the *para*-methoxy derivative cannot be distilled off. The synthesis of **8** was completed by the condensation of **20** with **15**.

In X-ray crystal structures of all previous examples of diazaphosphidine ligands such as **2** and its derivatives, the condensation reaction with the precursor diamine derivative is always diastereospecific, and results in formation of the isomer in which the lone pair on P is *cis* to the three-carbon bridge in the pyrolidine ring component.[5c,6,7] We therefore assign the relative configuration of compounds **5**–**8** as depicted in the schemes on this basis. In order to provide further evidence, however, the X-ray crystallographic structure of **8** was also obtained as a representative example (Fig. 2). As can clearly be seen, the relative configuration at the P atom matches that observed for other ligands of this type.

With ligands **5**–**8** in hand, we were able to assess the effect of each substitution on the enantioselectivity of the allylic amination reaction (Scheme 1), which can be conveniently followed by chiral HPLC. As can be seen in Table 1, the modifications do not have a substantially deleterious effect on the selectivity of the reaction. In all cases, under conditions modified relative to our earlier publication[5c] similar levels of yield and enantioinduction were achieved relative to those originally obtained with SEMI-ESPHOS **2**.

In conclusion, we have been able to demonstrate that the structure of SEMI-ESPHOS can be modified at several positions to generate derivatives which are equally effective at directing allylic amination reactions. We are currently investigating the use of this chemistry for the attachment of monodonor diazaphospholidine ligands to solid and polymer supports, and the results of these studies will be reported in due course.

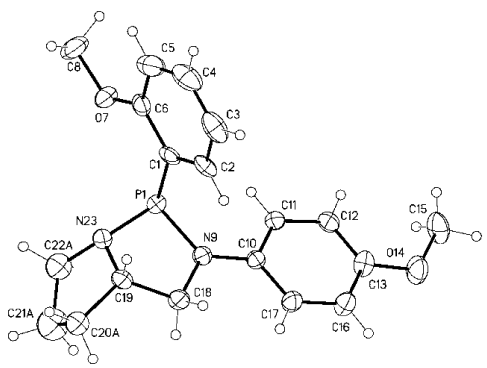


Figure 2. X-Ray crystallographic structure of **8**.

3. Experimental

3.1. General

General experimental conditions have been described in a previous publication.[11] Compounds **9**,[14] **18**[16,17] and **15**[9] were prepared following literature procedures. The method for the allylic amination reaction has been described in a previous publication.[9]

3.1.1. Synthesis of 5-oxo-prolin-anilide. L-Glutamic acid (40.0 g, 0.27 mol) was dissolved in aniline (300 mL, 3.29 mol) and the reaction mixture heated to 200°C for 45–50 min. The deep orange/red coloured solution was allowed to cool before being placed under vacuum. Excess aniline was removed from the reaction mixture using vacuum distillation. The reaction mixture was allowed to cool before adding acetone (100 mL) to the remaining red/brown oil. The resulting cloudy solution was filtered using a sinter funnel to give a white/brown solid, which was washed with further acetone whilst on the sinter. The filtrate was concentrated in vacuo and acetone was again added to give further crude product. The combined crude product was crushed using a pestle mortar and allowed to dry further. The crude product was recrystallised from hot methanol (~250 mL) to give the pure product as a white crystalline solid (16.79 g, 30% yield), mp 183–185°C, lit. mp 189–191°C;[12] δ_H (250 MHz, *d*-DMSO) 10.05 (1H, bs, NH), 7.91 (1H, bs, NH), 7.65 (2H, dd, J=1.2, 8.7 Hz, CH), 7.35 (2H, t, J=7.8 Hz, CH), 7.15 (1H, t, J=7.4 Hz, CH), 4.37 (1H, dd, J=4.4, 4.9 Hz, CH), 2.63–2.14 (4H, m, CH_2); δ_C (300 MHz, *d*-DMSO) 177.8 (C=O), 171.6 (C=O), 139.2 (C), 129.1 (CH), 123.8 (CH), 119.7 (CH), 56.7 (CH), 29.6 (CH_2), 25.7 (CH_2); *m/z* (EI) 204 (M^+), 149 ($M^+-C_3H_3O$), 84 ($M^+-C_7H_6NO$), 71 (C_3H_5NO), 57 (C_2H_3NO), 41 (C_2HO); $[\alpha]_D^{22}$=+19.6 (c=1, methanol), lit. $[\alpha]_D^{22}$=+18.5 (c=1, methanol) corresponding to (*S*)-isomer.[12]

3.1.2. (*S*)-2-(Phenylaminomethyl) pyrrolidine. THF (150 mL) was added to lithium aluminium hydride (7.49 g, 197 mmol) and the resulting suspension was allowed to stir whilst being cooled to 0°C. 5-Oxo-prolin-anilide (16.08 g, 78.82 mmol) was added carefully as a solid to the suspension of lithium aluminium hydride and then heated to reflux for 2 h. The reaction mixture was allowed to cool before the addition of sodium sulphate decahydrate (30.0 g), which was then allowed to stir for 1 h. The grey coloured reaction mixture was filtered through a plug of celite and the filtrate concentrated in vacuo to give the crude product as a pale green oil. The crude product was purified by vacuum distillation (122°C, 0.5 Torr), (lit. bp 117–120°C/0.4 Torr)[12] to give the product as a clear oil (11.80 g, 85% yield). Following experimental data was in accordance with published data;[12,13] δ_H (250 MHz, $CDCl_3$) 7.19 (2H, dd, J=7.4, 8.5 Hz, CH), 6.71–6.61 (3H, m, CH), 4.11 (1H, bs, NH), 3.42–3.32 (1H, m, CH), 3.17 (1H, dd, J=4.6, 12.0 Hz, NH), 2.98–2.90 (3H, m, $2CH_2$), 1.97–1.64 (4H, m, $2CH_2$), 1.51–1.39 (1H, m, CH_2); δ_C (300 MHz, $CDCl_3$) 148.6 (C), 129.2 (CH), 117.3 (CH), 113.0 (CH), 57.7 (CH^4, 48.5 (CH_2), 47.2 (CH_2), 30.3 (CH_2), 25.8 (CH_2); *m/z* (EI) 176 (M^+), 107 ($M^+-C_4H_9N$), 93 (C_6H_7N), 70 (C_4H_8N); $[\alpha]_D^{22}$=+22.2 (c=1, ethanol), lit. $[\alpha]_D^{22}$=+19.1 (c=1, ethanol) corresponding to (*S*)-isomer.[12]

3.1.3. Phosphine oxide 11. 4-Methoxyphenyl dimethyl-*t*-butylsilyl ether, **9**, (1.0 g, 4.20 mmol) was dissolved in THF (20 mL) and cooled to −78°C. *n*-Butyllithium (2.5 M, 1.76 mL, 4.41 mmol) was added to the cooled reaction mixture which was then allowed to warm to room temperature over 3–4 h. Diphenylphosphinic chloride (0.99 g, 4.20 mmol) was then added to the precooled reaction mixture and stirred overnight. The reaction mixture was diluted using DCM (50 mL) and washed using saturated $NaHCO_3$ solution (200 mL), dried using magnesium sulphate and concentrated in vacuo to give the crude product as a white solid. Recrystallisation from toluene gave the product **11** as a white crystalline solid (0.62 g, 34% yield), mp 134–135°C; δ_H (250 MHz, $CDCl_3$) 7.70 (4H, dd, J=1.5, 6.7 Hz, Ar), 7.54–7.39 (6H, m, Ar), 7.10 (1H, dd, J=2.9, 14.2 Hz, Ar), 6.99 (1H, dd, J=3.0, 8.9 Hz, Ar), 6.80 (1H, dd, J=6.1, 8.9 Hz, Ar), 3.49 (3H, s, CH_3), 0.93 (9H, s, CH_3), 0.09 (6H, s, CH_3); δ_C (300 MHz, $CDCl_3$) 155.4 (d, J_{CP}=3.1 Hz, *ipso* C), 149.3 (d, J_{CP}=14.6 Hz, *ipso* C), 133.6 (*ipso* C), 132.5 (*ipso* C), 131.7 (d, J_{CP}=10.0 Hz, Ar), 131.4 (d, J_{CP}=2.3 Hz, Ar), 128.0 (d, J_{CP}=13.0 Hz, Ar), 125.7 (d, J_{CP}=7.7 Hz, Ar), 125.1 (d, J_{CP}=3.1 Hz, Ar), 121.2 (*ipso* C), 112.7 (d, J_{CP}=8.4 Hz, Ar), 55.7 (CH_3), 26.0 (CH_3), 18.5 (C), −4.2 (CH_3); δ_P (300 MHz, $CDCl_3$) 27.97; ν_{max} (nujol)/cm^{-1} 1287, 1216, 1179, 1155, 1118, 1016, 960; *m/z* (EI) 438 (M^+), 420 (M^+-H_2O), 381 ($M^+-C(CH_3)_3$), 365 ($M^+-C(CH_3)_3O$), 347 ($M^+-C_6H_5OH_2$), 201, 183, 135, 91, 77, 73, 57, 41; HRMS found $[M]^+$ 438.1777, requires 438.1780.

Crystal data. Crystal character: colourless prism. Crystal dimensions 0.46×0.25×0.20 mm^3, $C_{25}H_{31}O_3PSi$, M=438.56, monoclinic, a=10.989(2), b=16.162(3), c=13.431(3) Å, α=90°, β=92.114(5)°, γ=90°, U=2383.8(8) $Å^3$, T=180(2) K, space group $P2_1/n$, Z=4, μ(Mo Kα)=0.222 mm^{-1}, least squares refinement on 5599 reflection positions, λ=0.71073 Å, D(cal)=1.222 mg/m^3, F(000)=936, $R1$=0.0402, $wR2$=0.1150.

3.1.4. Formation of 3-[(bis(dimethylamino)-phosphino]-4-methoxyphenyldimethyl-*t*-butylsilyl ether 10. 4-Methoxyphenyl dimethyl-*t*-butylsilyl ether, **9**, (12.0 g, 50.40 mmol) was dissolved in THF (60 mL) and cooled to −78°C. *n*-BuLi (21.18 mL, 52.94 mmol) was added to the cooled reaction mixture and allowed to warm to room temperature. In a separate flask hexamethylphosphorus triamide (5.42 g, 6.04 mL, 33.28 mmol) was added to phosphorus trichloride (2.28 g, 1.45 mL, 16.64 mmol) and the mixture was heated at 80°C for 30 min. The contents of the second flask were diluted using THF (2×15 mL), transferred via cannula to the *ortho*-lithiated substrate and the reaction mixture allowed to stir overnight. The reaction mixture was diluted using DCM (80 mL) and washed with saturated $NaHCO_3$ solution (4×100 mL). The $NaHCO_3$ layer was extracted using DCM (200 mL) and the combined organic layers were dried using magnesium sulphate. The solvent was removed in vacuo to give the crude product as a red oil which was purified by vacuum distillation (0.02 Torr, 136°C) to give the product **10** as a clear oil (8.13 g, 45% yield); δ_H (250 MHz, $CDCl_3$) 7.37 (1H, t, J=3.7 Hz, Ar), 6.94–6.89 (1H, m, Ar), 6.56 (1H, dd, J=4.7, 8.7 Hz, Ar), 3.77 (3H, s, CH_3), 2.80 (12H, d, J_{PH}=9.5 Hz, CH_3), 0.98 (9H, s, CH_3), 0.17 (6H, s, CH_3); δ_C (300 MHz, $CDCl_3$)

155.1 (d, J_{CP}=14.9 Hz, *ipso* C), 149.2 (*ipso* C), 130.1 (d, J_{CP}=13.2 Hz, *ipso* C), 123.8 (J_{CP}=5.8 Hz, Ar), 120.0 (Ar), 111.0 (Ar), 56.2 (CH_3^1), 41.7 (d, J_{CP}=18.4 Hz, CH_3), 25.7 (CH_3), 18.2 (C), −4.4 (CH_3); δ_P (300 MHz, $CDCl_3$) 96.35; ν_{max} (nujol)/cm^{-1} 1270, 1213, 1034, 979, 957; *m/z* (CI) 357 (MH^+), 325 (MH^+-MeO), 312 (MH^+-NMe_2), 267 ($MH^+-(NMe_2)_2$), 238 ($MH^+-P(NMe_2)_2$), 224 ($MH^+-C_6H_{15}OSi$); HRMS found $[M]^+$ 356.2052, requires 356.2049.

3.1.5. Diazaphospholidine 5. (*S*)-2-(Phenylaminomethyl)-pyrrolidine, (3.15 g, 0.02 mol) was dissolved in toluene (50 mL) and added to the 3-[(bis(dimethylamino)-phosphino]-4-methoxyphenyl dimethyl-*t*-butylsilyl ether, **10** (6.35 g, 0.02 mol). The reaction mixture was then heated at reflux for 3 days, the release of dimethylamine was monitored using damp litmus paper. The pale yellow coloured reaction mixture was concentrated in vacuo to give the crude product as a yellow solid. This was transferred to a sinter funnel and washed with diethyl ether to give the product **5** as a pale yellow solid (4.75 g, 60% yield), mp 108–109°C; δ_H (250 MHz, C_6D_6) 7.25–7.20 (1H, m, Ar), 7.09–7.00 (3H, m, Ar), 6.89–6.79 (3H, m, Ar), 6.48 (1H, dd, *J*=4.1, 8.7 Hz, Ar), 3.91–3.81 (1H, m, CH), 3.37 (3H, s, CH_3), 3.32–3.15 (3H, m, CH_2), 2.85–2.77 (1H, m, CH_2), 1.69–1.60 (1H, m, CH_2), 1.58–1.43 (2H, m, CH_2), 1.33–1.25 (1H, m, CH_2), 1.00 (9H, s, CH_3), 0.10 (6H, s, CH_3); δ_C (300 MHz, C_6D_6) 156.5 (d, J_{CP}=14.9 Hz, *ipso* C), 149.6 (*ipso* C), 147.5 (d, J_{CP}=14.4 Hz, *ipso* C), 131.1 (d, J_{CP}=28.7 Hz, *ipso* C), 129.3 (d, J_{CP}=1.2 Hz, Ar), 122.1 (d, J_{CP}=3.4 Hz, Ar), 121.5 (Ar), 117.9 (d, J_{CP}=3.4 Hz, Ar), 115.8 (d, J_{CP}=12.6 Hz, Ar), 112.1 (d, J_{CP}=1.2 Hz, Ar), 64.4 (d, J_{CP}=8.0 Hz, CH), 55.6 (CH_3), 53.4 (d, J_{CP}=5.2 Hz, CH_2), 52.5 (d, J_{CP}=29.9 Hz, CH_2), 31.2 (CH_2), 26.0 (d, J_{CP}=5.8 Hz, CH_2), 25.1 (CH_3), 18.4 (C), −4.4 (CH_3); δ_P (300 MHz, C_6D_6) 108.08; ν_{max} (nujol)/cm^{-1} 1597 (NH), 1572 (NH), 1323, 1272, 1218, 1172, 1025, 944, 837; *m/z* (EI) 442 (M^+), 373 ($M^+-C_4NH_7$), 337 ($M^+-C_7H_7N$), 311 ($M^+-OSi(CH_3)_2C(CH_3)_3$), 296, 268 ($M^+-C_{11}H_{14}N_2$), 211, 205 ($C_{11}H_{14}$ PN_2), 181 ($CH_3OC_6H_4OSi(CH_3)_2$), 149 ($C_6H_4OSi(CH_3)_2$), 119 (C_6H_4OSi); HRMS found $[M]^+$ 442.2215, requires 442.2205; $[\alpha]_D^{22}$=−366.5 (*c*=1, benzene).

3.1.6. Synthesis of 5-oxo-prolin-(4-bromo-anilide) 13. Bromine (29.40 g, 9.48 mL, 183.75 mmol) was added to a solution containing 5-oxo-prolin-anilide, (19.75 g, 96.84 mmol) dissolved in acetic acid (120 mL) and the reaction mixture allowed to stir for 2 days. Sodium metathiosulphate solution (200 mL) was added to the deep red coloured reaction mixture and allowed to stir for 30 min. The resulting thick white coloured suspension was filtered using a sinter funnel, and whilst on the sinter, washed with sodium metathiosulphate solution (100 mL), water (100 mL) and methanol (200 mL) to give the pure product **13** as a white solid (18.50 g, 68% yield), mp 225–227°C; δ_H (250 MHz, *d*-DMSO) 10.20 (1H, bs, NH), 7.90 (1H, bs, NH), 7.60 (2H, d, *J*=9.0 Hz, Ar), 7.50 (2H, *J*=9.0 Hz, Ar), 4.18 (1H, dd, *J*=4.4, 8.4 Hz, CH), 2.41–1.94 (4H, m, CH_2); δ_C (300 MHz, *d*-DMSO) 177.8 (C=O), 171.8 (C=O), 138.5 (C), 131.9 (CH), 121.6 (CH), 115.5 (C), 56.8 (CH), 29.6 (CH_2), 25.6 (CH_2); ν_{max} (solid state)/cm^{-1} 3305 (NH asymmetric stretch), 3275 (NH asymmetric stretch), 1687 (C=O, amide band 1), 1660 (C=O, amide band 1), 1607, 1546 (NH bend, amide band 2); *m/z* (CI) 285 (Br^{81}, M^++1, 25%), 283 (Br^{79}, M^++1, 25%), 205, 84; HRMS found $[M]^+$ 282.0003, requires 282.0004; $[\alpha]_D^{22}$=+30.5 (*c*=1, acetic acid).

3.1.7. (*S*)-(4′-Bromophenylaminomethyl)pyrrolidine 14. Lithium aluminium hydride (3.06 g, 80.53 mmol) was added to THF (70 mL) and the resulting suspension cooled in an ice bath. 5-Oxo-prolin-(4-bromo-anilide), **13**, (9.12 g, 32.21 mmol) was added carefully as a solid to the cooled suspension and the reaction mixture allowed to stir at room temperature overnight. Sodium sulphate decahydrate (26.0 g) was added as a solid to the reaction mixture and allowed to stir for 1 h. The grey coloured reaction mixture was filtered through a plug of celite and washed with DCM (60 mL). The filtrate was concentrated in vacuo to give the crude product as an oil which was purified by Kugelrohr distillation (0.5 Torr, ~225°C) to give, on standing, the product **14** as a pale yellow solid (2.63 g, 33% yield), mp 110–111°C; δ_H (250 MHz, $CDCl_3$) 7.24 (2H, d, *J*=8.9 Hz, Ar), 6.47 (2H, d, *J*=8.9 Hz, Ar), 3.38–3.31 (1H, m, CH), 3.12 (1H, dd, *J*=4.6, 12.0 Hz, NH), 2.94–2.85 (3H, m, CH_2, NH), 1.96–1.69 (4H, m, CH_2), 1.46 (2H, m, CH_2); δ_C (300 MHz, *CDCl*$_3$) 147.6 (*ipso* C), 131.8 (CH), 114.5 (CH), 108.7 (*ipso* C), 57.4 (CH), 48.5 (CH_2), 46.5 (CH_2), 29.5 (CH_2), 25.8 (CH_2); ν_{max} (nujol)/cm^{-1} 3281 (NH stretch), 1596 (NH bend), 1550 (NH bend), 1404, 1319, 1257, 815; *m/z* (EI) 257 (Br^{81}, 25%, M^+), 255 (Br^{79}, 25%, M^+), 187 ($M^+Br^{81}-C_4H_8N$, 65%), 185 ($M^+Br^{79}-C_4H_8N$, 65%), 70; HRMS found $[M]^+$ 254.0419, requires 254.0419; $[\alpha]_D^{22}$=+29.7 (*c*=0.5, chloroform).

3.1.8. Synthesis of 5-oxo-prolin-(4-phenyl-anilide) 16. Phenylboronic acid (4.50 g, 36.88 mmol) was added to a suspension of 5-oxo-prolin-(4-bromo-anilide), **13**, (4.20 g, 14.84 mmol) in water (60 mL). A solution of palladium diacetate (0.17 g, 0.74 mmol) and potassium carbonate (5.12 g, 37.10 mmol) in water (60 mL) was added to the reaction mixture and heated at reflux for 1 h.[15] The reaction mixture was allowed to cool before being extracted with EtOAc (300 mL), dried using magnesium sulphate, filtered and concentrated in vacuo to give the crude product as an off-white solid. Recrystallisation from methanol gave the pure product **16** as a white solid (1.80 g, 42% yield), mp 227–229°C; δ_H (250 MHz, *d*-DMSO) 10.17 (1H, s, NH), 7.94 (1H, s, NH), 7.73 (2H, d, *J*=8.8 Hz, Ar), 7.64 (4H, d, *J*=7.9 Hz, Ar), 7.44 (2H, t, *J*=7.5 Hz, Ar), 7.35–7.29 (1H, m, Ar), 4.22 (1H, dd, *J*=4.0, 8.2 Hz, CH), 2.44–1.95 (4H, m, CH_2); δ_C (300 MHz, *d*-DMSO) 177.5 (C=O), 171.4 (C=O), 139.6 (*ipso* C), 138.3 (*ipso* C), 135.1 (*ipso* C), 128.9 (Ar), 127.0 (Ar), 126.9 (Ar), 126.2 (Ar), 119.7 (Ar), 56.4 (CH), 29.2 (CH_2), 25.4 (CH_2); ν_{max} (solid state)/cm^{-1} 3203 (NH stretch), 1660 (C=O, amide band 1), 1594 (NH bend, amide band 2), 1519, 1486, 1402, 1105; *m/z* (FAB^+) 281 (MH^+), 154 ($C_{12}H_{10}$), 111 ($C_5H_6NO_2$), 83 (C_4H_5NO); HRMS found $[M+H]^+$ 281.1294, requires 281.1290; $[\alpha]_D^{22}$=+29 (*c*=1, chloroform).

3.1.9. Synthesis of (*S*)-2-(Biphenylaminomethyl)pyrrolidine 17. 5-Oxo-prolin-(4-phenyl-anilide), **16**, (1.70 g, 6.44 mmol) was added as a solid to a cooled suspension of lithium aluminium hydride (0.62 g, 16.31 mmol) in THF

(40 mL) and the reaction mixture heated at reflux for 2 h. The reaction mixture was cooled before solid sodium sulphate decahydrate (6.20 g) was added to the reaction mixture and allowed to stir for 1 h. The reaction mixture was filtered through a plug of celite and concentrated in vacuo to give the crude product as a green oil. This was dissolved in hot cyclohexane, filtered to remove any impurities and concentrated in vacuo to give the product **17** as a pale yellow solid (1.21 g, 79% yield), mp 72–73°C; δ_H (250 MHz, $CDCl_3$) 7.55–7.51 (2H, m, Ar), 7.46–7.35 (3H, m, Ar), 7.27–7.21 (2H, m, Ar), 6.69 (2H, d, J=8.5 Hz, Ar), 4.26 (1H, br s, NH), 3.46–3.36 (1H, m, CH), 3.25–3.18 (1H, dd, J=4.3, 11.6 Hz, NH), 3.03–2.91 (2H, m, CH_2), 2.00–1.69 (4H, m, CH_2), 1.67–1.43 (2H, m, CH_2); δ_C (300 MHz, $CDCl_3$) 147.9 (*ipso* C), 141.2 (*ipso* C), 130.0 (*ipso* C), 128.5 (Ar), 127.8 (Ar), 126.2 (Ar), 125.9 (Ar), 113.1 (Ar), 57.6 (CH^4), 48.5 (CH_2), 46.3 (CH_2), 29.5 (CH_2), 1595 (NH bend), 1531, 1310, 1273, 1210, 1092; *m/z* (CI) 253 (MH^+), 183 ($C_{13}H_{13}N$), 170 ($C_{12}H_{12}N$), 154 ($C_{12}H_{10}$), 84 ($C_5H_{10}N$), 70 (C_4H_8N); HRMS found $[M]^+$ 252.1619, requires 252.1626; $[\alpha]_D^{22}$=+27.2 (c=0.5, chloroform).

3.1.10. Synthesis of *N*-(benzyloxycarbonyl)prolin[(4′-methoxy)-anilide] 19.[16,17] *N*-Benzyloxycarbonyl proline, **18**, (10.0 g, 40.16 mmol) was dissolved in EtOAc (100 mL) and cooled to −15°C. *N*-Methylmorpholine (4.87 g, 5.30 mL, 48.19 mmol) and ethyl chloroformate (5.23 g, 4.61 mL, 48.19 mmol) were added to the precooled reaction mixture which was stirred for 20 min. Methoxyaniline (5.93 g, 48.19 mmol) was then added to the reaction mixture which was kept at −15°C for 1 h, at −0°C for a further 1 h before being allowed to stir at room temperature for 48 h. The brown coloured reaction mixture was diluted with EtOAc (200 mL) and washed with water (200 mL), saturated $NaHCO_3$ solution (200 mL), NaCl solution (200 mL), 3% HCl (200 mL), NaCl solution (200 mL), dried with magnesium sulphate and concentrated in vacuo to give the crude product as a pale pink coloured solid. The crude product was transferred to a sinter funnel and washed with diethyl ether (200 mL) and recrystallised from toluene to give the pure product **19** as a white solid (9.69 g, 68% yield), mp 124–125°C; δ_H (250 MHz, $CDCl_3$) 9.02 (1H, br, NH), 7.40–7.20 (7H, br, Ar), 6.80 (2H, d, J=9.0 Hz, CH), 5.20 (2H, br, CH_2), 4.48 (1H, br, CH), 3.77 (3H, s, CH_3), 3.50 (2H, br, CH_2), 2.28 (4H, br, CH_2); δ_C (300 MHz, $CDCl_3$) 169.1 (C═O), 163.7 (C═O), 156.7 (*ipso* C), 156.1 (*ipso* C), 136.2 (*ipso* C), 128.5 (Ar), 128.2 (Ar), 127.9 (Ar), 121.3 (Ar), 113.9 (Ar), 67.5 (CH_2), 60.9 (CH), 55.4 (CH_3), 47.1 (CH_2), 27.5 (CH_2), 24.6 (CH_2); ν_{max} (nujol)/cm^{-1} 3279 (NH stretch), 3137 (NH stretch), 1698 (C═O, amide band 1), 1670 (C═O, amide band 1), 1606 (NH bend, amide band 2), 1552 (NH bend, amide band 2), 1317, 1245, 1167, 1119, 1035; *m/z* (EI) 354 (M^+), 204 ($C_{12}H_{14}NO_2$), 149 ($C_8H_7NO_2$), 122 (C_7H_8NO), 91 (C_7H_7), 70 (C_4H_8N); HRMS found $[M]^+$ 354.1581, requires 354.1580; $[\alpha]_D^{22}$=−29.9 (c=1, chloroform).

3.1.11. Synthesis of (*S*)-prolin-[(4′-methoxy)-anilide. N-(Benzyloxycarbonyl)-prolin[(4′-methoxy)-anilide], **19**, (9.69 g, 9.89 mmol) was dissolved in methanol (80 mL) within a hydrogenation vessel and 5% Pd/charcoal (0.90 g) added. The reaction mixture was placed on a hydrogenation machine and hydrogenated for 3–4 days (until pressure gauge remained constant). The reaction mixture was filtered through a plug of celite, washed with diethyl ether and concentrated in vacuo to give the crude product as an oil. This oil was dissolved in hot cyclohexane and allowed to cool. The cyclohexane was filtered using a sinter funnel and the solid on the sinter was washed with cold cyclohexane to give the product as a white solid (3.88 g, 64% yield), mp 80–81°C; δ_H (250 MHz, $CDCl_3$) 9.62 (1H, s, NH), 7.51 (2H, d, J=9.0 Hz, CH), 6.86 (2H, d, J=8.9 Hz, CH), 3.84 (1H, dd, J=5.3, 9.2 Hz, CH), 3.78 (3H, s, CH_3), 3.14–2.95 (2H, m, CH_2), 2.63 (1H, s, NH), 2.27–2.00 (2H, m, CH_2), 1.82–1.70 (2H, m, CH_2); δ_C (300 MHz, $CDCl_3$) 173.0 (C═O), 155.9 (*ipso* C), 131.1 (*ipso* C), 120.7 (CH), 114.0 (CH), 60.8 (CH), 55.4 (CH_3), 47.2 (CH_2), 30.6 (CH_2), 26.8 (CH_2); ν_{max} (nujol)/cm^{-1} 3340 (NH stretch), 3238 (NH stretch), 1660 (C═O, amide band 1), 1590 (NH bend, amide band 2), 1519 (NH bend), 1298, 1263, 1178, 1099, 1032; *m/z* (EI) 220 (M^+), 149 ($C_8H_7NO_2$), 123 (C_7H_8NO), 108 (C_7H_8O), 70 (C_4H_8N); HRMS found $[M+H]^+$ 221.1291, requires 221.1290; $[\alpha]_D^{22}$=−27.7 (c=1, chloroform).

3.1.12. Synthesis of (*S*)-2-[*N*-(4′-methoxyphenyl)-aminomethyl]pyrrolidine 20. THF (50 mL) was added to lithium aluminium hydride (1.66 g, 43.76 mmol) and the resulting suspension cooled to 0°C for 30 min. (*S*)-Prolin-[(4′-methoxy)-anilide], (3.85 g, 17.50 mmol) was added carefully as a solid to the cooled suspension of lithium aluminium hydride and the reaction mixture then heated to reflux for 3 h. The reaction mixture was allowed to cool before the addition of sodium sulphate decahydrate (8.0 g) as a solid and allowed to stir for 1 h. The resulting grey coloured reaction mixture was then filtered through a plug of celite and washed with diethyl ether. The combined organic layer was concentrated in vacuo to give the crude product as a pale yellow liquid and purified using Kugelrohr distillation (0.5 mm, 220°C) to give the product **20** as a pale green liquid (3.10 g, 86% yield); δ_H (250 MHz, $CDCl_3$) 6.77 (2H, d, J=9.0 Hz, CH), 6.60 (2H, d, J=9.0 Hz, CH), 3.74 (3H, s, CH_3), 3.40–3.31 (1H, m, CH), 3.10 (1H, dd, J=4.7, 11.9 Hz, NH), 2.94–2.86 (3H, m, CH_2, NH), 1.96–1.63 (4H, m, $2CH_2$), 1.50–1.40 (2H, m, CH_2); δ_C (300 MHz, $CDCl_3$) 151.9 (*ipso* C), 142.8 (*ipso* C), 114.8 (CH), 114.2 (CH), 57.6 (CH), 55.7 (CH_3), 49.7 (CH_2), 46.4 (CH_2), 29.5 (CH_2), 25.8 (CH_2); ν_{max} (liquid film)/cm^{-1} 3346 (NH stretch), 2952 (CH stretch), 2870 (CH stretch), 1618 (NH bend), 1514 (CH), 1464 (CH), 1408, 1306, 1235, 1180, 1127, 1102, 1038; *m/z* (EI) 206 (M^+), 137 ($M^+-C_4H_7N$), 122 (C_7H_8NO), 83 ($C_5H_{10}N$), 70 (C_4H_8N); HRMS found $[M]^+$ 206.1419, requires 206.1419; $[\alpha]_D^{22}$=+27.7 (c=1, chloroform).

3.1.13. Diazaphospholidine ligand 6. (*S*)-(4′-Bromophenylaminomethyl)pyrrolidine, **14** (2.51 g, 9.86 mmol) was dissolved in toluene (40 mL) and added to *ortho*-[bis(dimethylamino)]-phosphino-anisole, **15**, (2.24 g, 9.86 mmol). The reagents were allowed to dissolve fully before heating the reaction mixture at reflux for 3 days. The reaction mixture was allowed to cool before the reaction mixture was concentrated in vacuo to give the crude product as a pale brown oil. Diethyl ether and hexane were added to the crude product and the solid formed was isolated by filtration. This solid was dissolved in hot cyclohexane and undissolved solid was filtered off. The cyclohexane layer

was concentrated in vacuo to give the product **6** as a yellow solid (2.18 g, 57% yield), mp 80–81°C; δ_H (250 MHz, C_6D_6) 7.36 (1H, ddd, J=1.7, 4.0, 7.3 Hz, Ar), 7.27 (2H, dd, J=2.2, 6.9 Hz, Ar), 7.12–7.02 (1H, m, Ar), 6.83 (1H, t, J=7.3 Hz, Ar), 6.69 (2H, dd, J=2.2, 6.8 Hz, Ar), 6.44 (1H, dd, J=2.3, 6.8 Hz, Ar), 3.73–3.69 (1H, m, CH), 3.20 (3H, s, CH_3), 3.33–3.01 (2H, m, CH_2), 2.91 (1H, dd, J=7.5, 9.0 Hz, CH_2), 2.57–2.51 (1H, m, CH_2), 1.58–1.37 (3H, m, CH_2), 1.21–1.13 (1H, m, CH_2); δ_C (300 MHz, C_6D_6) 161.8 (J_{CP}=15.5 Hz, *ipso* C), 146.6 (J_{CP}=15.5 Hz, *ipso* C), 131.8 (Ar), 130.9 (J_{CP}=2.9 Hz, Ar), 130.8 (Ar), 129.8 (*ipso* C), 120.5 (Ar), 117.6 (J_{CP}=12.7 Hz, Ar), 110.7 (Ar), 109.9 (*ipso* C), 64.6 (J_{CP}=8.6 Hz, CH_3), 54.8 (CH), 53.2 (J_{CP}=5.2 Hz, CH_2), 52.5 (J_{CP}=29.8 Hz, CH_2), 31.4 (CH_2), 26.1 (J_{CP}=6.3 Hz, CH_2); δ_P (300 MHz, C_6D_6) 109.11; ν_{max} (solid state)/cm^{-1} 2918 (CH), 2837 (CH), 1586 (NH), 1488, 1470, 1314, 1270, 1235, 1180; *m/z* (EI) 392 (M^+ Br^{81}), 390 (M^+ Br^{79}), 285 ($C_{11}H_{13}Br^{81}N_2P$), 283 ($C_{11}H_{13}Br^{79}N_2P$), 207 ($C_{11}H_{14}NOP$), 185 ($C_7H_6Br^{81}N$), 183 ($C_7H_6Br^{79}N$), 84 ($C_5H_{10}N$), 70 (C_4H_8N); HRMS found $[M]^+$ 390.0497, requires 390.0497; $[\alpha]_D^{22}=-381$ (c=1, benzene).

3.1.14. Diazaphospholidine ligand 7. (*S*)-2-(Biphenylaminomethyl)pyrrolidine, **17**, (1.14 g, 4.52 mmol) was dissolved in toluene (30 mL) and added to *ortho*-[bis(dimethylamino)]-phosphino-anisole, 15, (1.03 g, 4.52 mmol). The reagents were allowed to dissolve fully before heating the reaction mixture at reflux for 3 days. The reaction mixture was allowed to cool before removing the solvent in vacuo to give the crude product as a white solid. The crude product was dissolved in hot toluene (18 mL) and the precipitate that formed was filtered off and washed with cold toluene to give the product **7** as a white solid (1.13 g, 63% yield), mp 212–214°C; δ_H (250 MHz, $CDCl_3$) 7.57–7.21 (9H, m, Ar), 6.95–6.84 (4H, m, Ar), 4.09–4.01 (1H, m, CH), 3.82 (3H, s, CH_3), 3.62–3.57 (1H, m, CH_2), 3.47–3.41 (1H, m, CH_2), 3.32–3.14 (2H, m, CH_2), 2.15–2.05 (1H, m, CH_2), 1.95–1.75 (3H, m, CH_2); δ_C (300 MHz, $CDCl_3$) 161.3 (J_{CP}=16.1 Hz, *ipso* C), 146.5 (J_{CP}=15.5 Hz, *ipso* C), 141.2 (*ipso* C), 130.7 (Ar), 130.4 (*ipso* C), 130.3 (J_{CP}=2.9 Hz, Ar), 129.0 (*ipso* C), 128.7 (Ar), 127.6 (Ar), 126.4 (Ar), 126.1 (Ar), 120.4 (Ar), 115.6 (J_{CP}=13.2 Hz, Ar), 110.8 (Ar), 64.3 (J_{CP}=8.6 Hz, CH_3), 55.7 (CH_3), 53.5 (J_{CP}=4.6 Hz, CH_2), 52.5 (J_{CP}=29.9 Hz, CH_2), 31.0 (CH_2), 25.7 (J_{CP}=10.3 Hz, CH_2); δ_P (300 MHz, $CDCl_3$) 96.51; ν_{max} (nujol)/cm^{-1} 3362 (NH), 1602 (NH), 1571 (NH), 1519, 1327, 1270, 1234, 1021; *m/z* (EI) 388 (M^+), 281 ($M^+-C_7H_7O$), 207 ($C_{11}H_{13}NOP$), 181 ($C_8H_{10}N_2OP$), 149 ($C_7H_5N_2P$), 83 (C_5H_9N), 70 (C_4H_8N); HRMS found $[M+H]^+$ 388.1702, requires 388.1704; $[\alpha]_D^{22}=-488$ (c=1, benzene).

3.1.15. Diazaphospholidine ligand 8. (*S*)-2-[*N*-(4′-Methoxyphenyl)aminomethyl]pyrrolidine, **20**, (2.70 g, 13.1 mmol) was dissolved in toluene (60 mL) and added to *ortho*-[bis(dimethylamino)]-phosphino-anisole **15**, (2.96 g, 13.11 mmol). The reagents were allowed to dissolve fully before being heated at reflux for 3 days. The reaction mixture was allowed to cool before removing the solvent in vacuo to give the crude product as a green solid. The crude product was transferred to a sinter funnel and washed with diethyl ether to give the crude product as a white crystalline solid. The crude product was recrystallised from toluene (5 mL) and the solid product filtered off and washed with cold toluene to give the product **8** as a crystalline solid (2.07 g, 46% yield), mp 159–160°C; δ_H (250 MHz, C_6D_6) 7.48 (1H, ddd, J=1.9, 3.8, 7.2 Hz, Ar), 7.13–7.10 (1H, m, Ar), 6.95 (2H, dd, J=1.9, 9.0 Hz, Ar), 6.87–6.82 (3H, m, Ar), 6.48 (1H, dd, J=3.8, 8.1 Hz, Ar), 3.84–3.76 (1H, m, CH), 3.41–3.13 (3H, m, CH_2), 3.38 (3H, s, CH_3), 3.27 (3H, s, CH_3), 2.83–2.77 (1H, m, CH_2), 1.66–1.43 (3H, m CH_2), 1.31–1.22 (1H, m, CH_2); δ_C (300 MHz, C_6D_6) 161.9 (J_{CP}=14.9 Hz, *ipso* C), 152.8 (*ipso* C), 141.8 (J_{CP}=14.9 Hz, *ipso* C), 131.1 (J_{CP}=2.9 Hz, Ar), 130.5 (Ar), 130.5 (J_{CP}=28.2 Hz, *ipso* C), 120.5 (Ar), 116.7 (J_{CP}=12.1 Hz, Ar), 114.9 (Ar), 110.7 (Ar), 64.7 (J_{CP}=8.0 Hz, CH_3), 55.3 (CH_3), 54.9 (CH_3), 53.7 (J_{CP}=5.7 Hz, CH_2), 52.7 (J_{CP}=29.9 Hz, CH_2), 31.4 (CH_2), 26.2 (J_{CP}=6.3 Hz, CH_2); δ_P (300 MHz, C_6D_6) 109.61; ν_{max} (nujol)/cm^{-1} 1613 (NH), 1583 (NH), 1509, 1310, 1270, 1236, 1024; *m/z* (EI) 342 (M^+), 235 ($M^+-C_7H_7O$), 207 ($C_{11}H_{14}NOP$), 152 (C_7H_7NOP), 108 (C_7H_8O), 70 (C_4H_8N); HRMS found $[M+H]^+$ 342.1504, requires 342.1497; $[\alpha]_D^{22}=-466$ (c=1, benzene).

Crystal data. Crystal character: colourless prism. Crystal dimensions 0.40×0.40×0.10 mm^3, $C_{19}H_{23}N_2O_2P$, M=342.36, orthorhombic, a=7.1825(6), b=7.9276(6), c=31.138(2) Å, α=90°, β=90°, γ=90°, U=784.38(8) $Å^3$, T=180(2) K, space group $P2(1)2(1)2(1)$, Z=4, μ(Mo Kα)=0.222 mm^{-1}, least squares refinement on 3124 reflection positions, λ=0.71073 Å, D(cal)=1.283 mg/m^3, F(000)=728, $R1$=0.0788 wR^2=0.1986.

Crystallographic data (excluding structure factors) for the structures in this paper have been depostited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 209695 (compound **11**) and CCDC 209696 (compound **8**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44-1223-336033 or email: deposit@ccdc.cam.ac.uk].

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