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The preparation of *trans*-2,5-dialkylpyrrolidinylbenzyl-diphenylphosphines: new phosphinamine ligands for asymmetric catalysis

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Abstract

The preparation of new phosphinamine ligands **3a**, **3b**, possessing an enantiopure *trans*-2,5-dialkylpyrrolidinyl unit is described. Of the three synthetic approaches investigated, two proved successful with similar overall yields of 50–60%. One approach forms the *trans*-2,5-dialkylpyrrolidine unit first and then the diphenylphosphine is introduced whilst the other reverses the order of introduction. In each approach the key step is the cyclocondensation of an amine with an enantiopure, dialkyl-substituted 1,4-diol cyclic sulfate. An X-ray crystal structure of the palladium dichloride complex **13** of ligand **3a** is presented.

1. Introduction

The broad range of catalytic asymmetric transformations to which transition metal complexes of chiral phosphinamine ligands may be applied reflects their complexity as an effective class of ligand system.[1–3] In contrast to diphosphines and diamines, the asymmetry induced by such heterobidentate systems is determined by a combination of steric and electronic interactions. In the case of phosphinamines, Akermark obtained spectroscopic evidence for the different electronic properties of the donor atoms in a study of phosphinamine palladium allyl complexes.[4] This concept of electronic disparity was subsequently used in the design of chiral phosphinamine ligands possessing different chiral elements and backbone scaffolding. Of the wide range of phosphinamine ligands prepared to date the amino alcohol derived diphenylphosphinooxazolines **1**, reported independently by the groups of Pfaltz, Williams and Helmchen,[5] have been one of the most successful, affording excellent enantioselectivities for a number of reactions. The effect of having a more basic nitrogen donor atom in a phosphinamine ligand was investigated

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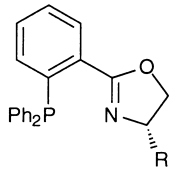
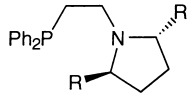
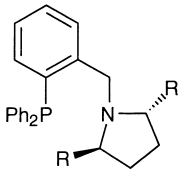
by Koga, who prepared diphenylphosphinopyrrolidines of type **2**.[6] Poor enantioselectivities of 11–20% were obtained using palladium complexes of **2** in the test reaction between sodium dimethylmalonate and 1,3-diphenylpropenyl acetate, whereas 99% ee was obtained using ligand **1** (R=Bn).[5a] We were also interested in phosphinamine ligands possessing the asymmetry inducing, chiral 2,5-disubstituted pyrrolidine unit.[7,8] Therefore, we now report the preparation of ligands of type **3**, which possess a more rigid backbone and in which, upon complexation, would increase the chelate ring size from five to six when compared to complexes of **2**.[9]



1
R = Bn, *i*-Pr, *t*-Bu, etc.



2
R = Me, Et, Bn.

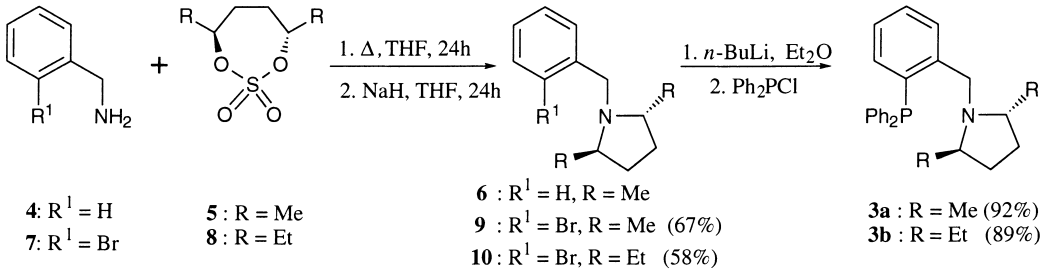


3a: R = Me.
3b: R =Et.

2. Results and discussion

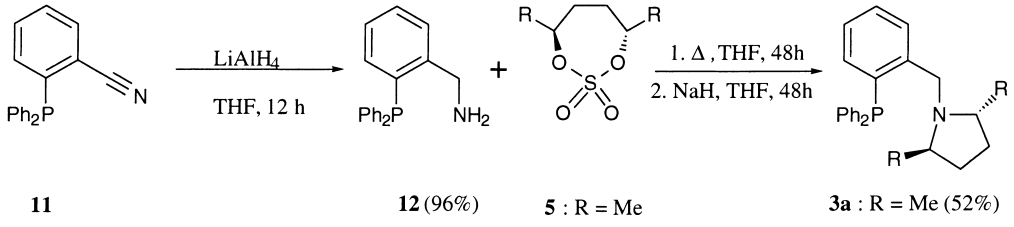
The preparation of 2,5-disubstituted pyrrolidines has recently been reviewed by Figadère, and of the approaches described,[10] the transamination of 1,4-dihydroxy derivatives appeared to be the most attractive to our needs. Enantiopure 1,4-dimesylates were used by Masamune and Chong to prepare *trans*-2,5-dimethyl- and diphenyl-pyrrolidines, respectively,[11,12] and by McGrath to prepare *trans*-2,5-dimethyl- and diphenyl-pyridinylpyrrolidines.[13] 1,4-Diacetates were used by Knochel to synthesise *trans*-2,5-diferrocenyl pyrrolidines. 1,4-Diol cyclic sulfates were exploited in heterocyclisations most notably by Burk in the preparation of his DuPhos ligands.[14] These dihydroxy derivatives were also used as pyrrolidine precursors as evidenced by the Machinaga synthesis of *trans*-2-butyl-5-pentylpyrrolidine,[15] an ant venom alkaloid, and by Gallagher in a recent intramolecular example.[16] Such literature precedent prompted our proposed synthesis of **3a**, **3b**, where the key step is the cyclocondensation of an amine with enantiopure 2,5-dimethyl- or 2,5-diethyl-1,4-diol cyclic sulfate.[17] This differs from Koga's approach to prepare **2**, as he used a preformed *trans*-2,5-disubstituted pyrrolidine which was subsequently joined to the backbone.

The first synthetic route to this class of ligand investigated was the condensation of benzylamine **4** with 2,5-hexanediol cyclic sulfate **5** which afforded the corresponding benzylpyrrolidine **6** in 60% yield (Scheme 1). The next step in this strategy relied on this benzylic tertiary amine acting as an ortho-lithiating group for the introduction of the diphenylphosphino group.[18] However, despite numerous attempts, this reaction did not proceed with chlorodiphenylphosphine or indeed a range of other electrophiles. Hence a different approach to the desired ligand system was required involving the starting amine, possessing a bromine atom in the 2-position for the proposed lithium–halogen exchange prior to reaction with chlorodiphenylphosphine. Therefore, 2-bromobenzylamine **7** was reacted with the (2*S*,5*S*)-hexanediol cyclic sulfate **5** in THF for 24 h, after which time a salt, presumed to be a zwitterion, had precipitated. Subsequent reaction with NaH in THF for a further 24 h afforded the (2*R*,5*R*)-1-[(2-bromophenyl)methyl]-2,5-dimethylpyrrolidine **9** in 67% yield. Reaction of **9** in diethyl ether at −10°C with *n*-butyllithium for 30 min and then at ambient temperature for 2 h gave a white precipitate which was then treated with chlorodiphenylphosphine to afford ligand **3a** in 92% yield. The ethyl analogue **3b** was similarly prepared in 89% yield starting from pyrrolidine **10**, which was synthesised from (3*S*,7*S*)-octanediol cyclic sulfate **8** and 2-bromobenzylamine **7** in 58% yield.



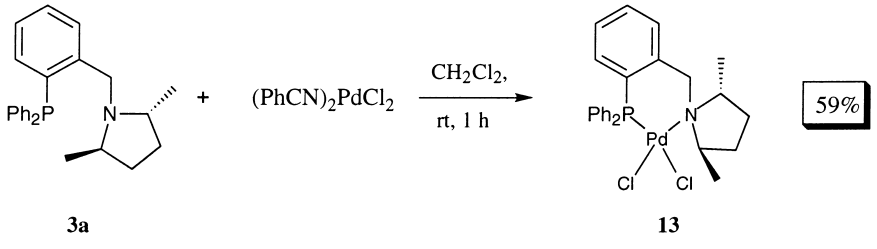
Scheme 1.

Although this second route was successful, we also investigated a third pathway in which the diphenylphosphino group was already in place prior to the cyclocondensation about the benzylic primary amine. Therefore, we prepared 2-diphenylphosphinobenzonitrile by reduction of the commercially available 2-bromobenzonitrile, an approach identical to that used by the group of Seebach.[19] The nitrile **11** was reduced with lithium aluminium hydride to 2-diphenylphosphinobenzylamine **12** in 96% yield (Scheme 2). Subsequent pyrrolidine ring formation after refluxing in THF and treatment with sodium hydride afforded ligand **3a** in a yield of 52%. Interestingly, no salt precipitation occurred during the heterocyclisation process. Since there is no significant difference in the overall yield obtained from both successful approaches, either may be used, although the latter, convergent route is to be favoured.



Scheme 2.

Once prepared, we wished to test the chelating ability of these ligands prior to testing them for their enantiodifferentiating ability in catalysis. As phosphinamines have proved successful in palladium-mediated carbon–carbon bond forming processes we first prepared a palladium dichloride complex. Using standard chemistry, one equivalent of ligand **3a** was reacted with bis-benzonitrile palladium dichloride in methylene chloride to afford the palladium dichloride complex **13** in 59% yield (Scheme 3).



Scheme 3.

Once bound, the rotation about the benzylic carbon to nitrogen bond is no longer possible and this is clearly seen by comparing the ^{1}H NMR spectra of ligand **3a** and the palladium dichloride complex **13**. In **3a**, the methyl groups at the 2,5-positions resonate at 0.90 ppm whilst in **13**, one methyl appears at 1.52 and the other at 1.75 ppm. In addition, the methine protons (H-2, H-5) in **3a** appear as a multiplet at 2.86 ppm and in **13**, resonate at 3.04 ppm for H-5 and 5.47 ppm for H-2, indicating that the latter proton is in a highly deshielded region of space, presumably in close proximity to the metal atom.

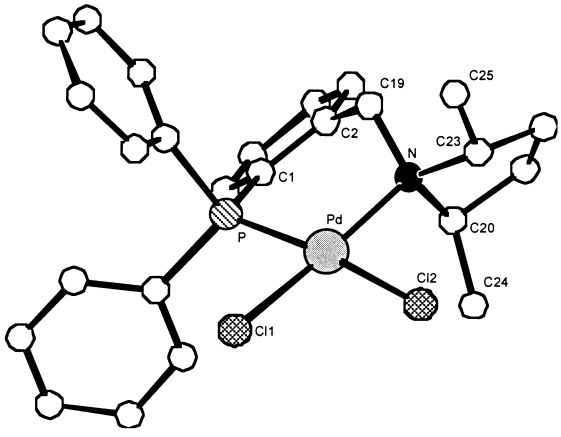


Figure 1. Crystal structure of the Pd dichloride complex **13**. Selected distances (Å) and angles (°): Pd–N 2.138(3), Pd–P 2.237(1), Pd–Cl1 2.286(1), Pd–Cl2 2.370(1), P–Pd–N 92.5(1), Cl1–Pd–Cl2 86.51(4), P–Pd–Cl1 86.21(4), N–Pd–Cl2 94.8(1)

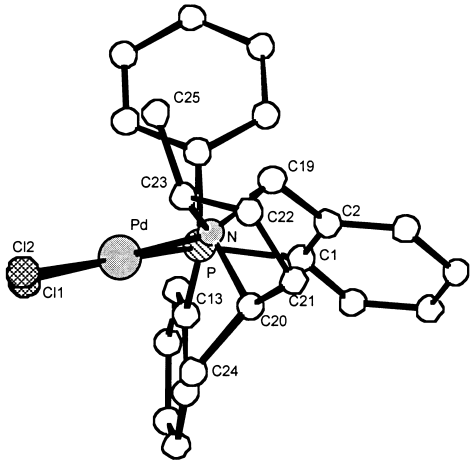


Figure 2. X-Ray crystal structure (side view) highlighting the pyrrolidine ring conformation and the positions of the C24 and C25 methyl groups

Crystals suitable for X-ray structure determination were grown by isothermal diffusion from methylene chloride/diethyl ether. The results of this analysis are summarised in Figs. 1 and 2. The coordination of the phosphinopyrrolidine ligand to the square-planar coordinated Pd atom appears to be relatively strain-free since the bite angle at the metal atom is close to 90° [92.5(1)°]. There is, however, a clear *trans*-effect and the Pd–Cl1 distance of 2.286(1) Å is significantly shorter than the Pd–Cl2 distance of 2.370(1) Å.

As a result of coordination to the metal, the phosphinopyrrolidine ligand **3a** adopts a conformation such that C2 lies approximately in the mean coordination plane of the metal atom (−0.13 Å), with C19 above (+0.74 Å) and C1 below (−0.58 Å) this plane (Fig. 2). A consequence of this geometry is that one of the methyl groups of the substituted pyrrolidine ring takes up a position in close proximity to the metal [C24…Pd 3.187(5) Å] (sum of van der Waals radii 3.1 Å).

Work is currently in progress investigating the catalytic behaviour of complexes of the ligands **3a** and **3b**. Some of the initial results (e.g. in the palladium catalysed asymmetric allylic substitution and Heck reactions) are promising. These and other applications, in addition to the preparation of analogous phosphinamine ligands, will form the subject of future publications from this group.[20]

3. Experimental

3.1. General

NMR spectra were recorded on a Jeol 270 MHz or a Varian Unity 500 MHz spectrometer. ^{1}H chemical shifts are reported in δ ppm relative to $CHCl_3$ (7.27 ppm), ^{13}C chemical shifts are reported relative to the central peak of $CDCl_3$ (77.0 ppm), and ^{31}P chemical shifts are reported relative to 85% aqueous phosphoric acid (0.0 ppm). Elemental microanalyses were carried out in house using a Carlo Erba 1106 elemental analyser. Electron impact mass spectra were determined on a VG Analytical 770 mass spectrometer with attached INCOS 2400 data system in the EI mode unless otherwise stated. IR spectra were recorded on a Perkin–Elmer Paragon 1000 FT spectrometer. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected.

Solvents were dried immediately before use by distillation from standard drying agents. 2-Bromobenzylamine hydrochloride, chlorodiphenylphosphine, lithium aluminium hydride (Aldrich Chemical Co.) and (3*S*,7*S*)-octanediol cyclic sulfate (Strem Chemical Co.) were commercially available and were used as purchased. (2*S*,5*S*)-Hexanediol cyclic sulfate and 2-(diphenylphosphino)benzonitrile were prepared by literature procedures.[14,21] $PdCl_2$ was obtained on loan from Johnson Matthey. *n*-Butyllithium was used as a 1.6 M solution in hexane. Sodium hydride was used as a 60% dispersion in mineral oil. Separations by column chromatography were performed using Merck Kieselgel 60 (Art. 7734) and Merck aluminum oxide 90 (Art. 1097) and by preparative thin layer chromatography using Merck aluminum oxide 60 (Art. 1104) Type E.

3.2. (−)-(2R,5R)-1-[(2-Bromophenyl)methyl]-2,5-dimethylpyrrolidine **9**

2-Bromo-benzylamine (0.48 g, 2.6 mmol) and (2*S*,5*S*)-hexanediol cyclic sulfate (0.47g, 2.6 mmol) were placed in a Schlenk tube under nitrogen. THF (7 ml) was added via syringe and the solution was refluxed for 48 h. After this time the mixture was cooled to 0°C and sodium hydride (0.07 g, 2.9 mmol) was added. The reaction was stirred at room temperature for 1 h and then refluxed for 24 h. The solvent was removed in vacuo and the residue dissolved in ether. The organic phase was washed successively with 10% ammonium chloride solution, water and brine, dried with sodium sulfate and the solvent removed in vacuo to afford a yellow oil. The residual yellow oil was purified by column chromatography (90 g silica gel; petroleum spirits:diethyl ether 2:1; R_f=0.54), to give (−)-(2*R*,5*R*)-1[(2-bromophenyl)methyl]-2,5-dimethylpyrrolidine as a colourless oil (0.45 g, 65%). Found: C, 58.1; H, 6.5; N, 5.0; Br, 28.9. $C_{13}H_{18}NBr$ requires C, 58.2; H, 6.8; N, 5.2; Br, 28.8%; ^{1}H NMR (270 MHz): δ ($CDCl_3$) 7.61 (d, 1H, J=7.7 Hz, H-6), 7.51 (dd, 1H, J=7.9, 1.3 Hz, H-5), 7.26 (t, 1H, J=7.4 Hz, H-4), 7.06 (dt, 1H, J=7.8, 1.9 Hz, H-3), 3.84 (d, 1H, J=15.6 Hz, benzylic-H), 3.72 (d, 1H, J=15.7 Hz, benzylic-H), 3.11–3.09 (m, 2H, H-2′, H-5′), 2.08–1.96 (m, 2H, H-3′$_a$, H-4′$_b$), 1.44–1.33 (m, 2H, H-3′$_a$, H-4′$_b$), and 0.96 (d, 6H, J=6.2 Hz, Me-2′, Me-5′); ^{13}C NMR (67.8 MHz): δ ($CDCl_3$) 140.0 (C-2), 132.4 (C-6), 130.6 (C-5), 127.8 (C-4), 127.2 (C-3), 123.5 (C-1), 55.3 (C-2′, C-5′), 50.7 (benzylic-C), 31.2 (C-3′, C-4′), and 17.5 (Me-2′, Me-5′); ν_{max} (neat)/cm^{-1} 3060 (m) (Ar–H), 2959 (s) (C–H), 1565 (m) (Ar–Br), 1456 (m) (Ar–Br), 747 (m) (Ar–H); m/z (EIMS, 70 eV) 267 (6%, M−1), 252 (100, M−CH_3), 169 (75, M−$C_6H_{12}N$), and 90 (23, M−$C_6H_{12}NBr$); $[\alpha]_D^{21}$=−65.4 (c=1.00, $CHCl_3$).

3.3. (−)-{2-[((2R,5R)-2,5-Dimethylpyrrolidinyl)methyl]phenyl}diphenylphosphine **3a**

n-Butyllithium (0.5 ml, 1.6 M, 0.8 mmol) was added dropwise at −10°C to a solution of (−)-(2*R*,5*R*)-1[(2-bromophenyl)methyl]-2,5-dimethylpyrrolidine (0.20 g, 0.7 mmol) in ether (0.5 ml). The reaction was stirred at −10°C for 0.5 h and then at room temperature for 2 h until a white precipitate was observed. The reaction mixture was cooled to −78°C and chlorodiphenylphosphine (0.13 ml, 0.7 mmol) was added over a period of 10 min. The reaction was allowed to warm to room temperature and stirred for a further 24 h. A 10% ammonium chloride solution (10 ml) was added and the reation mixture was extracted with CH_2Cl_2 (3×10 ml). Drying over anhydrous magnesium sulfate and removal of the organic sovent in vacuo yielded a brown oil which was purified by column chromatography (40 g alumina, petroleum spirits:diethyl ether 50:1, R_f=0.42) affording (−)-{2-[((2*R*,5*R*)-2,5-dimethylpyrrolidinyl)methyl]phenyl}diphenylphosphine as a white solid (0.26 g, 92%), m.p. 68–69°C. Found: C, 80.1; H, 7.6; N, 3.7; P, 8.5. $C_{25}H_{28}NP$ requires C, 80.4; H, 7.6; N, 3.7; P, 8.3%; ^{1}H NMR (500 MHz): δ ($CDCl_3$) 7.59 (dd, 1H, J=7.8, 1.8 Hz, H-6), 7.22–7.19 (m, 11H, H-5, PPh_2), 7.14 (t, 1H, J=7.9 Hz, H-4), 6.89 (dd, 1H, J=7.4, 1.8 Hz, H-3), 3.96 (d, 1H, J=14.0 Hz, benzylic-H), 3.82 (dd, 1H, J=14.0, J_{P-H}=2.8 Hz, benzylic-H), 2.88–2.84 (m, 2H, H-2′, H-5′), 1.62–1.57 (m, 2H, H-3′$_a$, H-4′$_b$), 1.15–1.08 (m, 2H, H-3′$_b$, H-4′$_a$), 0.90 (d, 6H, J=6.7 Hz, Me-2′, Me-5′); ^{13}C NMR (67.8 MHz): δ ($CDCl_3$) 145.5 (d, J_{P-C}=22.5 Hz, C-1′′), 138.5 (d, J_{P-C}=11.8 Hz, C-1′′′), 137.4 (d, J_{P-C}=18.6 Hz, C-2), 136 (d, J_{P-C}=15.0 Hz, C-1), 134.1–133.5 (C-2′′, C-2′′′, C-6), 129.0 (C-4′), 128.9 (C-6′′, C-6′′′), 128.5 (C-3′′, C-3′′′), 128.4 (C-5′′, C-5′′′), 128.3 (C-4′′, C-4′′′), 128.2 (C-5), 126.7 (C-3), 54.9 (C-2′, C-5′), 50.4 (d, J_{P-C}=19.3 Hz, benzylic-C), 30.7 (C-3′, C-4′), and 17.1 (Me-2′, Me-5′); ^{31}P NMR (109.3Hz): δ ($CDCl_3$) −16.3; ν_{max} (KBr)/cm^{-1} 3052 (m) (Ar–H), 2962 (s) (C–H), 1434 (s) (P–Ph), 1118 (s) (P–Ph), and 678 (s) (Ar–H); m/z (EIMS, 70 eV) 373 (11%, M^+), 288 (40), 276 (90), 183 (32), 98 (100), and 77 (22); $[\alpha]_D^{21}$=−70.6 (c=0.5, $CHCl_3$).

3.4. (−)-(2R,5R)-1[(2-Bromophenyl)methyl]-2,5-diethylpyrrolidine **10**

2-Bromobenzylamine (0.45 g, 2.42 mmol) and (3*S*,6*S*)-octanediol cyclic sulfate (0.5 g, 2.42 mmol) were placed in a Schlenk tube under nitrogen. THF (5.0 ml) was added via syringe and the solution was refluxed for 60 h. After cooling to 0°C, sodium hydride (0.106 g, 2.55 mmol) was added. The reaction was stirred at room temperature for 1 h and then refluxed for 24 h. The solvent was removed in vacuo and the residue dissolved in ether. The organic phase was washed successively with 10% ammonium chloride solution, water and brine, dried with sodium sulfate and the solvent removed in vacuo to afford a yellow oil. The residual yellow oil was purified by column chromatography (90 g of silica gel; petroleum spirits:diethyl ether 9:2; R_f=0.52), to give (−)-(2*R*,5*R*)-1[(2-bromophenyl)methyl]-2,5-diethylpyrrolidine as a colourless oil (0.410 g, 57%). Found: C, 60.8; H, 7.4; N, 4.9; Br, 25.6. $C_{15}H_{22}NBr$ requires C, 60.8; H, 7.5; N, 4.7; Br, 26.9%; ^{1}H NMR (270 MHz): δ ($CDCl_3$) 7.60 (s, 1H, H-6), 7.49 (dd, 1H, J=7.9, 1.1 Hz, H-5), 7.30–7.24 (m, 1H, H-4), 7.09–7.03 (m, 1H, H-3), 3.97 (d, 1H, J=16.1 Hz, benzylic-H), 3.72 (d, 1H, J=16.1 Hz, benzylic-H), 2.89 (s, 2H, H-2′, H-5′), 1.93–1.97 (m, 2H, H-3′$_a$, H-4′$_b$), 1.60–1.43 (m, 2H, H-3′a, H-4′$_b$, H-8), 1.22–1.08 (m, 2H, H-6′), and 0.78 (t, 6H, J=7.5 Hz, Me-7′, Me-9′); ^{13}C NMR (67.8 MHz): δ ($CDCl_3$) 139.2 (C-2), 132.4 (C-6), 130.5 (C-5), 127.8 (C-4), 127.2 (C-3), 123.4 (C-1), 62.6 (benzylic-C), 50.6 (C-2′, C-5′), 28.1 (C-3′, C-4′), 23.8 (C-6′, C-8′), and 10.7 (C-7′, C-9′); ν_{max} (neat)/cm^{-1} 2961 (s) (C–H), 2874 (m) (C–H), 1564 (m) (Ar–Br), 1460 (m) (Ar–Br); m/z (EIMS, 70 eV) 296 (3%, M^+), 266 (67, M−CH_2CH_3), 169 (87, M−$C_8H_{16}N$), and 90 (42, M−$C_8H_{16}NBr$); $[\alpha]_D^{21}$=−51.6 (c=1, $CHCl_3$).

3.5. (−)-{2-[((2R,5R)-2,5-Diethylpyrrolidinyl)methyl]phenyl}diphenylphosphine **3b**

n-Butyllithium (0.47 ml, 0.75 mmol) was added dropwise at 10°C to a solution of (−)-(2*R*,5*R*)-1[(2-bromophenyl)methyl]-2,5-diethylpyrrolidine (0.210 g, 0.7 mmol) in ether (1.0 ml). The reaction was stirred at −10°C for 0.5 h and then at room temperature for 5 h until a white precipitate was observed. The reaction mixture was cooled to −78°C and chlorodiphenylphosphine (0.12 ml, 0.7 mmol) was added over a period of 10 min. The reaction was allowed warm to room temperature and stirred for 24 h. A 10% ammonium chloride solution (10 ml) was added and the reaction mixture was extracted with CH_2Cl_2 (3×5 ml). Drying over anhydrous magnesium sulfate and removal of the organic sovent in vacuo yielded a brown oil which was purified by preparative thin layer chromatography (alumina, petroleum spirits:diethyl ether 50:1, R_f=0.42) to afford (−)-{2-[((2*R*,5*R*)-2,5-diethylpyrrolidinyl)methyl]phenyl}diphenylphosphine as a colourless oil (0.200 g, 75%). Found: C, 80.4; H, 8.2; N,3.4; P,7.4. $C_{27}H_{32}NP$ requires C, 80.7; H, 8.0; N, 3.5; P, 7.7%; ^{1}H NMR (270 MHz): δ ($CDCl_3$) 7.55 (s, 1H, H-6), 7.26–7.12 (m, 11H, H-5 and PPh_2), 7.04 (t, 1H, J=7.4 Hz, H-4), 6.80–6.75 (m, 1H, H-3), 3.94 (dd, 1H, J=14.7 Hz, J_{P-H}=3.3 Hz, benzylic-H), 3.82 (d, 1H, J=14.8 Hz, benzylic-H), 2.57 (s, 2H, H-2′, H-5′), 1.55–1.33 (m, 4H, H-3′$_a$, H-4′$_b$, H-8), 1.05–0.91 (m, 2H, H-3′$_b$, H-4′$_a$), 0.83–0,76 (m, 2H, H-6′), and 0.63 (t, 6H, J=7.5 Hz, H-7′, H-9′); ^{13}C NMR (67.8 MHz): δ ($CDCl_3$) 10.81 (Me-7′, Me-9′), 23.38 (C-6′, C-8′), 27.57 (C-3′, C-4′), 49.56 (d, J_{P-C}=21.4 Hz, benzylic-C), 61.91 (C-2′, C-5′), 126.53 (C-3), 128.43 (d, J_{P-C}=6.4 Hz, C-5), 128.70 (d, J_{P-C}=6.5 Hz, C-3′′), 133.57 (C-4′′), 133.67 (C-4), 133.99 (d, J_{P-C}=18.3 Hz, C-2), 135.29 (d, J_{P-C}=13.9 Hz, C-6), 137.10 (d, J_{P-C}=8.6 Hz, C-1), 139.09 (d, J_{P-C}=12.9 Hz, C-1′′), and 146.62 (d, J_{P-C}=22.4 Hz, C-2′′); ^{31}P NMR (109.3 MHz): δ ($CDCl_3$) −16.2; ν_{max}(neat)/cm^{-1} 3052 (m) (Ar–H), 2958 (s) (C–H), 2872 (m) (C–H), and 1433 (s) (P–Ph); m/z (EIMS, 70 eV) 401 (9%, M^+), 372 (12), 288 (21), 275 (37), and 126 (100); $[\alpha]_D^{21}$=−54.9 (c=0.5, $CHCl_3$).

3.6. [2-(Diphenylphosphino)phenyl]methylamine **12**

Lithium aluminium hydride (0.45 g, 11.86 mmol) was placed in a two-necked round-bottom flask in an atmosphere of argon. THF (40 ml) was added and the solution was stirred for 10 min. 2-(Diphenylphosphino)benzonitrile (3.09 g, 10.78 mmol) in THF (25 ml) was added to the reaction at room temperature over a period of 15 min. The reaction was refluxed for 4 h and cooled to 0°C. Ice (20 g) was slowly added until all of the excess lithium aluminium hydride had been quenched. A 1 M solution of sodium hydroxide (100 ml) was added and the resulting suspension was transferred to a separatory funnel. The aqueous layer was removed and the organic layer was washed again with sodium hydroxide (50 ml) and water (50 ml). Removal of the solvent in vacuo afforded a yellow solid which when recrystallised from hexane yielded [2-(diphenylphosphino)phenyl]methylamine (3.20 g, 94%) as fine yellow crystals, m.p. 95–96°C; (ethyl acetate:methanol 5:1; R_f=0.59). Found: C, 78.40; H, 6.24; N, 4.76; P, 10.59. $C_{19}H_{18}NP$ requires C, 78.35; H, 6.19; N, 4.81; P, 10.65; ^{1}H NMR (270 MHz): δ ($CDCl_3$) 1.60–1.78 (br. s, 2H, NH_2), 4.03 (d, 2H, J=1.4 Hz, benzylic-H), 6.81–6.93 (m, 1H, H-6), 7.07–7.19 (m, 1H, H-3), 7.71–7.77 (m, 12H, P-Ph_2, H-4, H-5); ^{31}P NMR (109.3 MHz): δ ($CDCl_3$): −15.3; ν_{max} (KBr) 3377 and 3318 (N–H), 1432 (C=C aryl) cm^{-1}; m/z 291 (M^+, 22%), 274 (100), 196 (47) and 104 (17).

3.7. (−)-{2-[((2R,5R)-2,5-Dimethylpyrrolidinyl)methyl]phenyl}diphenylphosphine **3a**

[2-(Diphenylphosphino)phenyl]methylamine (0.67 g, 2.30 mmol) and (2*S*,5*S*)-hexanediol cyclic sulphate (0.41 g, 2.30 mmol) were placed in a Schlenk tube under argon. THF (10 ml) was added and the solution was refluxed for 48 h. The reaction was cooled to room temperature, sodium hydride (61 mg,

2.53 mmol) was added and the reaction was refluxed for a further 48 h. Upon transferral of the reaction to a separatory funnel, dichloromethane (20 ml) was added and the organic layer was washed with a 10% ammonium chloride solution (2×20 ml). Two further washings with water (20 ml) and brine (20 ml), followed by drying over anhydrous magnesium sulphate and removal of the solvent in vacuo yielded a brown oil. The oil was purified by column chromatography (hexane:ether 5:1; R_f=0.50), to afford (−)-{2-[((2*R*,5*R*)-2,5-dimethylpyrrolidinyl)methyl]phenyl}diphenylphosphine (0.252 g, 30%) as a pale yellow solid, m.p. 68–69°C, identical in all respects to a previously prepared sample.

*3.8. {2-[((2*R*,5*R*)-2,5-Dimethylpyrrolidinyl)methyl]phenyldiphenylphosphine}palladium(II) dichloride **13***

Dichlorobis(benzonitrile)palladium (II) (21.80 mg, 56.84 mmol) and (−)-{2-[((2*R*,5*R*)-2,5-dimethyl pyrrolidinyl)methyl]phenyl}diphenylphosphine (23.47 mg, 62.83 mmol) were dissolved in 1.0 ml of argon-saturated CH_2Cl_2 and placed under argon in an ampoule equipped with a Young valve. The reaction mixture was kept at room temperature for 0.5 h. To the yellow solution was added slowly, 2.5 ml of argon-saturated ether. There was immediate precipitation of a yellow solid and storage at ambient temperature for 3 days afforded {2-[((2*R*,5*R*)-2,5-dimethylpyrrolidinyl)methyl]phenyldiphenylphosphine}-palladium(II) dichloride as bright yellow crystals (18.59 mg, 59%), m.p. 175–176°C (dec.). Found: C, 54.4; H, 5.2; N, 2.7; Cl, 12.9; P, 5.6. $C_{25}H_{28}NCl_2PPd$ requires C, 54.5; H, 5.2; N, 2.7; Cl, 12.9; P, 5.6%; ^{1}H NMR (500 MHz): δ ($CDCl_3$) 1.52 (d, 3H, J=7.0 Hz, Me-5′), 1.65–1.73 (m, 1H, H-4_b′), 1.75 (d, 3H, J=7.0 Hz, Me-2′), 1.77–1.82 (m, 1H, H-3_b′), 1.88–1.95 (m, 1H, H-3_a′), 1.96–2.02 (m, 1H, H-4_a′), 3.01–3.07 (m, 1H, H-5′), 3.40 (dd, 1H, J=12.7 Hz, 8.9, benzylic-H_b), 3.99 (dd, 1H, J=12.7 Hz, 0.9, benzylic-H_a), 5.43–5.51 (m, 1H, H-2′), 6.95 (t, 1H, J=2.1 Hz, H-3), 7.40–7.59 (m, 11H, PPh_2, H-5), 7.95 (dd, 2H, J=6.9, 0.8 Hz, H-6, H-4); ^{13}C NMR (67.8 MHz): δ ($CDCl_3$) 15.82 (Me-5′), 24.86 (Me-2′), 28.92 (C-4′), 30.17 (C-3), 57.62 (benzylic-C), 64.32 (C-5′), 65.38 (C-2′), 126.11, 126.32, 126.73, 128.57, 130.18, 131.32, 131.37, 132.23, 132.38, 132.44 (arom. C–H), 129.25, 133.74, 135.18, 139.20 (arom. C); ^{31}P NMR (109.3 MHz): δ ($CDCl_3$) −16.3; ν_{max} (KBr) 3055 (Ar–H), 2957 (aliph C–H), 1435 (P–Ph), 1094 cm^{-1} (Pd–Cl); $[\alpha]_D^{21}$=−164.8 (c=0.5, $CHCl_3$).

*3.9. X-Ray analysis of **13***

Crystals were obtained from CH_2Cl_2/Et_2O, $C_{25}H_{28}Cl_2NPPd$: M_r=550.75 g mol^{-1}, yellow, crystal size 0.14×0.63×0.63 mm, *a*=7.646(1), *b*=7.810(1), *c*=39.788(4) Å, *U*=2375.6(4) $Å^3$, *T*=293 K, orthorhombic, $P2_12_12_1$, [No. 19] *Z*=4, d_{cal}=1.54 g cm^{-3}, μ=1.09 mm^{-1}, Enraf–Nonius CAD4 diffractometer, λ=0.71069 Å, ω−2θ scan, 10 594 reflections, 5197 independent, 5156 observed, [$I>2\sigma(I)$] $[(\sin\theta)/\lambda]_{max}$=0.65 $Å^{-1}$, analytical absorption correction (T_{max} 0.8628, T_{min} 0.5478), direct methods (SHELXS-97, Sheldrick, G. M. *Acta Cryst*. **1990**, *A46*, 467–473), least-squares refinement (on F_o^2, SHELXL-97, Sheldrick, G. M., University of Göttingen, 1997), H riding, 273 refined parameters, *R*=0.035 (obs. data), R_w=0.089 (Chebyshev weights), final shift/error 0.001, residual electron density +0.750 e $Å^{-3}$. Full structural details have been deposited with the Cambridge Crystallographic Data Centre.

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