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P–C bond formation: synthesis of phosphino amino acids by palladium-catalysed cross-coupling

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Abstract

(4-Diethylphosphanyl)- and (4-diphenylphosphanyl)-derivatives of D- and L-phenylalanine have been synthesised using a palladium-catalysed cross-coupling giving the desired products in very high yields and without racemisation. © 2000 Published by Elsevier Science Ltd.

1. Introduction

There are numerous examples of industrial applications of homogeneous asymmetric catalytic processes using chiral phosphine ligands, such as the synthesis of the anti-Parkinson drug L-Dopa (Monsanto),[1] or L-phenylalanine, a component of the artificial sweetener aspartame (Enichem).[2] The use of amino acids (or peptides) as chiral supports in homogeneous catalytic systems offers a unique opportunity to develop a flexible approach to the development of chiral and catalytically active transition metal (TM) phosphine and phosphinito complexes. Phosphines and phosphinites (R-PR^1_2 and R-OPR^1_2, respectively) have proven to be extremely versatile ligands for a wide range of TM-catalysed transformations.[3–8]

2. Results and discussion

Palladium-catalysed P–C bond forming reactions were reported before by Stille,[9] using aryl halides with (trimethylstannyl)diphenylphosphine and (trimethylsilyl)diphenylphosphine. Recently examples of peptides carrying phosphino amino acid donors and their catalytic behaviour were reported.[10a,b] Racemisation of the amino acid in Pd-catalysed cross-coupling of aryl triflates was observed.[2c] Pd(0)-mediated P–C bond forming reactions involving aryl triflates and nonaflates

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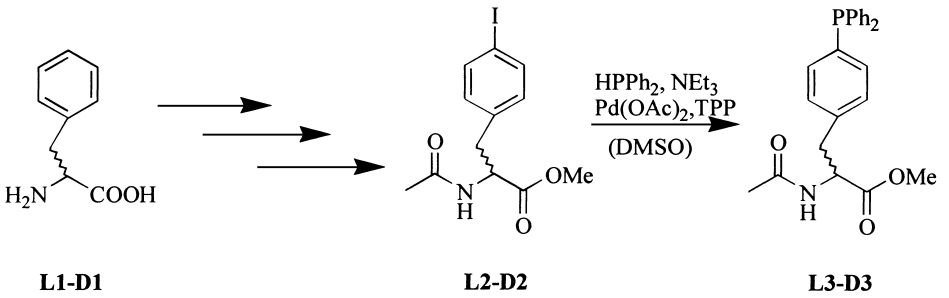
with diphenylphosphine–borane adducts were reported.[11] We decided to make use of the cross-coupling of iodophenylalanine, using triethylamine as base. In contrast to previous reports,[10c] we were able to form *N*-acetyl-(4-diphenylphosphanylphenyl)alanine methylester directly without any noticeable racemisation at the α-carbon. Furthermore, the procedure described in this paper does not require a phosphine protection–deprotection sequence. The reaction path for the Pd-catalysed reaction is shown in Scheme 1.



Scheme 1.

The fully protected *N*-acetyl-L-(4-iodophenyl)alanine methylester **L2** and *N*-acetyl-D-(4-iodophenyl)alanine methylester **D2** are readily obtained using Schwabacher's procedures[12] followed by *N*-acetyl protection using acetyl chloride and triethylamine in dichloromethane. The overall yield for these steps is 58%.

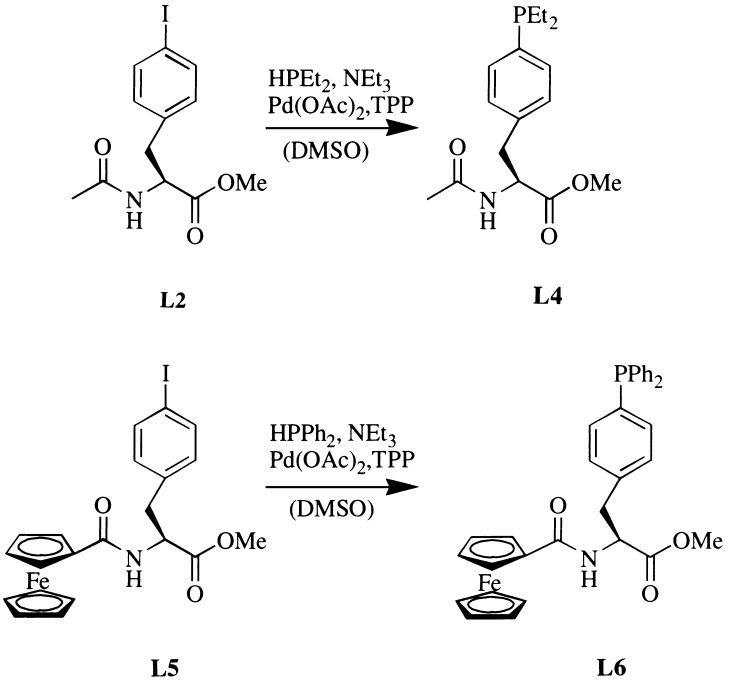
The products were identified by NMR (^{1}H, ^{13}C, ^{31}P NMR) and high resolution mass spectrometry (HRMS). The results are summarised in Table 1. Entries 3 and 4 show results of coupling reactions using different starting materials or phosphines (Scheme 2). Enantiomeric purity was determined by HPLC measurements using a Chiralpak AD column. A racemic mixture of **L3** and **D3**, obtained by mixing equivalent amounts of the reaction products, showed the expected two peaks at $t_R = 4.1$ min and 4.2 min. Pure **L3** ($t_R = 4.1$ min) and pure **D3** ($t_R = 4.2$ min) showed only one peak. These results are supported by ^{1}H NMR measurements using a chiral solvating agent, (*R*)-(–)-2,2,2-trifluoro-1-(-9-anthryl)ethanol. These measurements show a peak separation for the α-carbon, the amide N–H, and the acetyl CH_3 of the D- and L-enantiomers of 0.01 ppm in

Table 1
The results of coupling reactions of **L2**, **D2**, and **L5**

Entry	Amino Acid	Phosphine	Product	δ (^{31}P-NMR)	$[\alpha]^{25}$
1	**L2**	$HPPh_2$	**L3**	-5.7	+70
2	**D2**	$HPPh_2$	**D3**	-5.7	-70
3	**L2**	$HPEt_2$	**L4**	-16.2	*
4	**L5**	$HPPh_2$	**L6**	-5.9	-33

* specific rotation was not determined

the case of the racemic mixture. Expectedly, the pure enantiomers **L3** and **D3** exhibit only one set of signals.



Scheme 2.

3. Experimental

3.1. General methods

Manipulations of air moisture sensitive materials were conducted in an argon atmosphere using a Schlenk line. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen. Dichloromethane was distilled from calcium hydride. Triethylamine was distilled from sodium hydroxide. Methanol was distilled from magnesium. DMSO was dried using molecular sieves (4 Å). Thionyl chloride was distilled before use. All other chemicals were used as received from Aldrich. Column chromatography was carried out on 200–400 silica. ^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR spectra were recorded in $CDCl_3$, D_2O or CD_3OD on a Bruker AMX-300 spectrometer at 300.13, 75.48 and 121.49 MHz, respectively. Chemical shifts (in ppm) were measured relative to $SiMe_4$ and were referenced to the residual signal of $CHCl_3$ (δ 7.27) for ^{1}H, the $CDCl_3$ signal (δ 77.23) for $^{31}C\{^{1}H\}$, the residual signal of CD_3OH (δ 4.78) for ^{1}H, the CD_3OD signal (δ 49.3) for $^{31}C\{^{1}H\}$, the residual signal of H_2O (δ 4.65) for ^{1}H and 85% H_3PO_4 for $^{31}P\{^{1}H\}$, respectively. Mass spectra were obtained with a VG analytical 70/20 VSE chromatograph. Optical rotations were measured using a Rudolph instruments DigiPol DP781 at 589 nm (c = 1 g/100 mL, d = 100.00 mm). Determinations of enantiopurity of all compounds were carried out on a Gilson HPLC model 303 using a Chiralpak AD column.

3.2. Synthesis of N-acetyl-(L)-diphenylphosphinephenylalanine methylester **L3**

N-Acetyl-(L)-iodophenylalanine methylester **L2** (1.5 g, 4.3 mmol), diphenylphosphine (15 mL 10% solution in hexane that was removed in vacuo after adding the solution, 8.6 mmol, 2 equiv.) and triethylamine (2.4 mL, 17.2 mmol, 4 equiv.) were dissolved in 20 mL of degassed and dried DMSO. Palladium(II) acetate (0.05 g, 0.22 mmol, 5 mol%) and triphenylphosphine (0.06 g, 0.22 mmol, 5 mol%) were added and the deep red solution was stirred at 100°C for 3 h. After stirring at rt for 12 h the mixture was diluted to 200 mL with degassed ethyl acetate and washed twice with 50 mL of degassed water. After washing with 50 mL of degassed brine, drying over magnesium sulphate and filtration the solvent was removed in vacuo leaving a dark red oil. Purification by flash chromatography (R_f: 0.38, ethyl acetate) yielded a light yellow oil that solidified after drying in vacuo to give 1.69 g (4.2 mmol, 97%) of the desired compound. HRMS (FAB): calcd $C_{24}H_{24}NO_3P$: 405.1494; found: 405.1498; $[\alpha]^{25} = +70$; ^{1}H NMR ($CDCl_3$, 300 MHz) $\delta = 7.07$–7.36 (m, 14H), 6.10 (d, J = 7.8 Hz, 1H), 4.90 (apparent dd, J = 7.8 Hz, J = 5.9 Hz, 1H), 3.71 (s, 3H), 3.16 (dd, J = 5.9 Hz, J = 13.8 Hz, 1H), 3.08 (dd, J = 13.8 Hz, J = 5.9 Hz, 1H), 1.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) $\delta = 172.3$, 169.9, 128.7–137.4 (m), 53.3, 52.6, 37.9, 23.3; ^{31}P NMR ($CDCl_3$, 121.5 MHz) $\delta = -5.7$.

3.3. Synthesis of N-acetyl-(D)-diphenylphosphinephenylalanine methylester **D3**

N-Acetyl-(D)-iodophenylalanine methylester **D2** (1.5 g, 4.3 mmol), diphenylphosphine (15 mL 10% solution in hexane that was removed in vacuo after adding the solution, 8.6 mmol, 2 equiv.) and triethylamine (2.4 mL, 17.2 mmol, 4 equiv.) were dissolved in 20 mL of degassed and dried DMSO. Palladium(II) acetate (0.05 g, 0.22 mmol, 5 mol%) and triphenylphosphine (0.06 g, 0.22 mmol, 5 mol%) were added and the deep red solution was stirred at 100°C for 3 h. After stirring at rt for 12h the mixture was diluted to 200 mL with degassed ethyl acetate and washed twice with 50 mL of degassed water. After washing with 50 mL of degassed brine, drying over magnesium sulphate and filtration the solvent was removed in vacuo leaving a dark red oil. Purification by flash chromatography (R_f: 0.38, ethyl acetate) yielded a light yellow oil that solidified after drying in vacuo to give 1.71 g (4.2 mmol, 98%). HRMS (FAB): calcd. $C_{24}H_{24}NO_3P$: 405.1494; found: 405.1496; $[\alpha]^{25} = -70$; ^{1}H NMR ($CDCl_3$) $\delta = 7.06$–7.5 (m, 14H), 6.21 (d, J = 7.6 Hz, 1H), 4.87 (apparent dd, J = 6.1 Hz, J = 6.2 Hz, 1H), 3.67 (s, 3H), 3.13 (dd, J = 5.9 Hz, J = 13.8 Hz, 1H), 3.05 (dd, J = 6.0 Hz, J = 13.8 Hz, 1H), 1.95 (s, 3H); ^{13}C NMR ($CDCl_3$) $\delta = 172.3$, 169.9, 128.7–137.2 (m), 53.3, 52.5, 37.9, 23.3; ^{31}P NMR ($CDCl_3$) $\delta = -5.7$.

3.4. Synthesis of N-acetyl-(L)-diethylphosphinephenylalanine methylester **L5**

N-Acetyl-(L)-iodophenylalanine methylester **L4** (1.0 g, 2.9 mmol), diethylphosphine (7.4 mL 10% solution in hexane that was removed in vacuo after adding the solution, 5.8 mmol, 2 equiv.) and triethylamine (1.6 mL, 11.48 mmol, 4 equiv.) were dissolved in 20 mL of degassed and dried DMSO. Palladium(II) acetate (0.03 g, 0.15 mmol, 5 mol%) and triphenylphosphine (0.04 g, 0.15 mmol, 5 mol%) were added and the orange solution was stirred at 100°C for 3 h. After stirring at rt for 12 h the mixture was diluted to 200 mL with degassed ethyl acetate and washed twice with 50 mL of degassed water. After washing with 50 mL of degassed brine, drying over magnesium sulphate and filtration the solvent was removed in vacuo leaving an orange oil. Purification by filtration yielded a light yellow oil. Column chromatography of **L5** was carried out in a glovebox

using dinitrogen as inert gas. HRMS (EI): calcd $C_{16}H_{24}NO_3P$: 309.1494; found: 309.1503; ^{31}P NMR ($CDCl_3$) $\delta = -16.2$.

3.5. Synthesis of N-ferrocenoyl-(L)-diphenylphosphinephenylalanine methylester *L7*

N-Ferrocenoyl-(L)-iodophenylalanine methylester[13] **L6** (0.14 g, 0.27 mmol), diphenylphosphine (1 mL 10% solution in hexane that was removed in vacuo after adding the solution, 0.54 mmol, 2 equiv.) and triethylamine (0.14 mL, 1 mmol, 4 equiv.) were dissolved in 5 mL of degassed and dried DMSO. Palladium(II) acetate (3.2 mg, 0.014 mmol, 5 mol%) and triphenylphosphine (3.8 mg, 0.014 mmol, 5 mol%) were added and the deep red solution was stirred at 100°C for 3 h. After stirring at rt for 12 h the mixture was diluted to 50 mL with degassed ethyl acetate and washed twice with 10 mL of degassed water. After washing with 10 mL of degassed brine, drying over magnesium sulphate and filtration the solvent was removed in vacuo leaving a dark red oil. Purification by filtration gave a brown oil that solidified after drying in vacuo to give 0.15 (0.26 mmol, 97%) of the desired compound. HRMS (EI): calcd. $C_{33}H_{30}\ ^{56}FeNO_3P$: 575.1313; found: 575.1313; $[\alpha]^{25} = -33$; ^1H NMR ($CDCl_3$) $\delta = 7.17$–7.34 (m, 14H), 6.09 (d, J = 7.8 Hz, 1H), 5.03 (apparent dd, J = 5.8 Hz, J = 7.0 Hz, 1H), 4.64 (s, 1H), 4.60 (s, 1H), 4.33 (s, 2H), 4.12 (s, 5H), 3.76 (s, 3H), 3.25 (dd, J = 5.61 Hz, J = 13.9 Hz, 1H), 3.15 (dd, J = 6.7 Hz, J = 14.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) $\delta = 172.5$, 170.35, 128.7–137.1 (m), 75.5, 70.8, 70.0, 68.5, 68.3, 52.9, 52.6, 38.1, 23.3; ^{31}P NMR ($CDCl_3$) $\delta = -5.9$ (P1).

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