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Synthesis and study of amino acid based phosphinite ligands

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Abstract

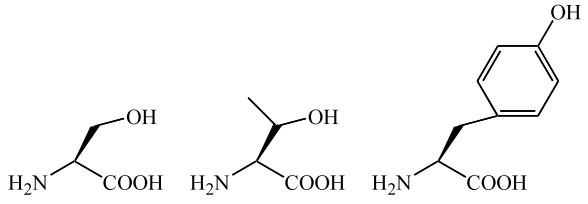
The preparation of the five new amino acid derived phosphinites Boc-Ser($OPPh_2$)-OMe (**5**), Boc-Thr($OPPh_2$)-OMe (**6**), Boc-Tyr($OPPh_2$)-OMe (**7**), Z-Ser($OPPh_2$)-OMe (**8**), and Z-β-Ala-Tyr($OPPh_2$)-OMe (**9**) is reported together with their full spectroscopic characterization. These ligands readily complex to Pd(II) and Pt(II) giving the corresponding complexes [Boc-Ser($OPPh_2$)-OMe]$_2PtCl_2$ (**10**), [Boc-Tyr($OPPh_2$)-OMe]$_2PtCl_2$ (**11**), [Boc-Thr($OPPh_2$)-OMe]$_2PtCl_2$ (**12**), [Z-β-Ala-Tyr($OPPh_2$)-OMe]$_2PtCl_2$ (**13**), [Boc-Ser($OPPh_2$)-OMe]$_2PdCl_2$ (**14**), [Boc-Tyr($OPPh_2$)-OMe]$_2PdCl_2$ (**15**), [Boc-Thr($OPPh_2$)-OMe]$_2PdCl_2$ (**16**), [Z-β-Ala-Tyr($OPPh_2$)-OMe]$_2PdCl_2$ (**17**). The X-ray structure of **10** was determined and shows the ligands being *cis* coordinated around the Pt(II) center with Pt–P distances of 2.2278(13) Å for Pt–P(1) and 2.2235(12) Å for Pt–P(2).

Keywords: Phosphinite; Amino acid; Peptide; Platinum; Palladium; X-ray; ^{31}P-NMR

1. Introduction

Phosphines and phosphites are among the most important phosphorous-based ligands in organometallic chemistry with a wide range of steric and electronic properties. These ligands have found wide-spread applications in transition metal catalyzed asymmetric transformations [1–5]. Phosphinites have been explored extensively. They provide different chemical, electronic and structural properties compared to phosphines. Thus, they open many opportunities to design new improved ligands for asymmetric catalysis. The metal–phosphorous bond are often stronger for phosphinites compared to the related phosphines due to the presence of the electron-withdrawing P–OR group. In addition, the empty σ*-orbital of the phosphinite $P(OR)R_2$ is stabilized and thus a better acceptor.

Biomolecules, such as amino acids, peptide and carbohydrates, offer a particularly convenient starting point for the synthetis of chiral ligands. They are readily available in an enantiopure form. In particular, proline-derived aminoalcohols have been popularized for the synthesis of chelating aminophosphine–phosphinite ligands [6]. Carbohydrates, have been exploited as chiral starting materials for the ligand synthesis of phosphinites, making use of the rich array of stereochemical and functional group diversity of carbohydrates [7]. Prior to this work, only proline-based phosphinito ligands were reported in the literature [8–10]. Other amino acid derived phosphinites, such as tyrosine, serine or threonine phosphinites have not been reported. Here, we report the synthesis of phosphinite ligands based on the naturally occurring L-hydroxy-amino acids, serine (**1**), tyrosine (**2**) and threonine (**3**). Whereas, there are some reports of amino acid and peptide-phosphines in the literature [18], there is a noticeable absence of peptido–phosphinites.



1 **2** **3**

Here we report the synthesis of several amino acid-based phosphinites and their palladium and platinum complexes.

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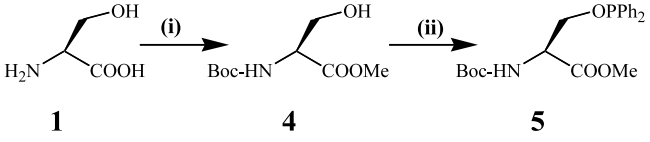
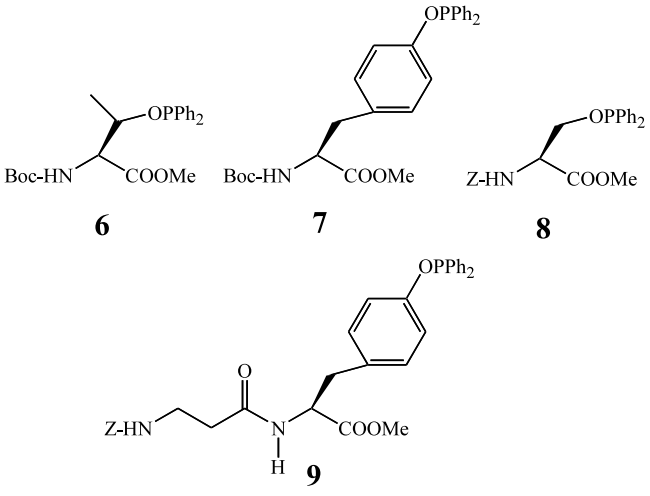
2. Results and discussion

The synthesis of phosphinites is conveniently achieved by reacting alcoholic amino acid, such as serine, threonine, and tyrosine, with one equivalent of chlorodiphenylphosphines in the presence of an organic base. Other functional groups can be conveniently protected, allowing the selective conversion of the hydroxyl group into the corresponding phosphinites. For example, the N,C-protected amino acid derivative Boc-Ser(OH)-OMe (**4**) was reacted with diphenylphosphine chloride in the presence of Et_3N and catalytic amounts of DMAP to give the corresponding phosphinite serine **5** (Scheme 1). Purification of the phosphinite ligand was readily achieved by passing the reaction solution through a pad of basic alumina. Other bases, such as pyridine, can be used in this procedure, but require evaporation in vacuo at elevated temperatures and are not completely removed by the basic alumina amounts of 4-dimethylaminopyridine (DMAP) followed by the filtration of the reaction solution through basic alumina (Scheme 1).

Other phosphinites based on threonine (**6**) and on tyrosine (**7**) were prepared under identical conditions in high yields. Other commonly used N-protecting groups, such as benzyloxycarbonyl (Z), do not interfere with phosphinite formation. Z-Ser($OPPh_2$)-OMe (**8**) was obtained under identical conditions from the corresponding N,C-protected Z-Ser-OMe.



Scheme 1. Synthesis of Boc-Ser($OPPh_2$)-OMe (**5**) from serine (**1**) via the N,C-protected serine derivative Boc-Ser(OH)-OMe (**4**): (i) Boc_2O, CH_2Cl_2; (ii) $ClPPh_2$, NEt_3, CH_2Cl_2.



This strategy is was also extended to include the dipeptide phosphinite Z-β-Ala-Tyr($OPPh_2$)-OMe (**9**), which was readily obtained from Z-β-Ala-Tyr-OMe under identical conditions.

The progress of this reaction was conveniently followed by ^{31}P-NMR spectroscopy. The signal of the starting material $ClPPh_2$ at δ 81.0 disappeared and a new singlet downfield due to the phosphinite was detected. Table 1 summarizes selected spectroscopic properties of the new phosphinite ligands. Our result agrees with chemical shifts for other phosphinites reported in the literature [7a] [8–12].

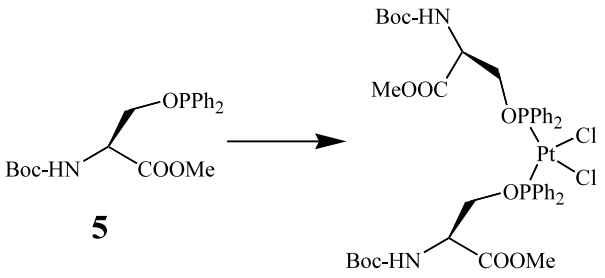
In general, for phosphinites the α-CH and β-CH_2 signals were shifted downfield upon the phosphinite formation compared to the N,C-protected amino acid derivative. The ^{13}C-NMR spectra of all phosphinito ligands prepared here showed characteristic P-C coupling constants of $^1J_{P-C}$ of 10–21 Hz and $^2J_{C-O-P}$ of 10–17 Hz consistent with the literature data. All phosphinites prepared here oxidize readily in solution upon exposure to air which has been documented in the literature for diarylphosphinites [13], but they can be stored under an inert atmosphere without decomposition.

Palladium and platinum complexes of the phosphinite ligands **5**–**9** were prepared in quantitative yields by reacting the appropriate phosphorus ligand with either Pd or Pt precursor as outlined in Scheme 2 for the synthesis of [Boc-Ser($OPPh_2$)-OMe]$_2PtCl_2$ (**10**) from (COD)$PtCl_2$ and Boc-Ser($OPPh_2$)-OMe (**5**). The same synthetic strategy was employed to obtain Pd and Pt complexes of the related phosphinites of threonine, tyrosine and of β-Ala-Tyr, which are all colorless air stable solids.

In the ^{31}P-NMR spectrum, complexes **10**–**13** exhibit singlets upfield from the position of the free ligand (Table 2). For all Pt complexes, the ^{31}P–^{195}Pt coupling constants agree with a *cis* arrangement of the phosphinite ligands around the metal center. In the solid state, the IR spectrum in CsI for two of these complexes supports the stereochemical assignment and gives two bands characteristic for a *cis* coordination of the two

Table 1
Selected ^{1}H and ^{31}P{^{1}H}-NMR chemical shift data of the diphenylphosphinito ligands Boc-Ser($OPPh_2$)-OMe (**5**), Boc-Thr($OPPh_2$)-OMe (**6**), Boc-Tyr($OPPh_2$)-OMe (**7**), Z-Ser($OPPh_2$)-OMe (**8**), and Z-β-Ala-Tyr($OPPh_2$)-OMe (**9**) in $CDCl_3$ (δ in ppm)

Compound	^{1}H			^{31}P{1H}
	NH	α-CH	β-CH_2	
5	5.31	4.61	4.10	118.3
6	5.35	4.65	4.43	113.3
7	5.06	4.58	3.06	111.1
8	5.63	4.61	4.21	118.3
9	6.02, 5.42	4.81	3.45, 3.06	111.5



Scheme 2. Synthesis of [Boc-Ser(OPPh$_2$)-OMe]$_2$PtCl$_2$ (**10**) from ligand **5** and (COD)PtCl$_2$ in CH$_2$Cl$_2$.

Table 2
^{31}P-NMR of the Pt and Pd phosphinito complexes[Boc-Ser(OPPh$_2$)-OMe]$_2$PtCl$_2$ (**10**), [Boc-Tyr(OPPh$_2$)-OMe]$_2$PtCl$_2$ (**11**), [Boc-Thr(OPPh$_2$)-OMe]$_2$PtCl$_2$ (**12**), [Z-β-Ala-Tyr(OPPh$_2$)-OMe]$_2$PtCl$_2$ (**13**), [Boc-Ser(OPPh$_2$)-OMe]$_2$PdCl$_2$ (**14**), [Boc-Tyr(OPPh$_2$)-OMe]$_2$PdCl$_2$ (**15**), [Boc-Thr(OPPh$_2$)-OMe]$_2$PdCl$_2$ (**16**), [Z-β-Ala-Tyr(OPPh$_2$)-OMe]$_2$PdCl$_2$ (**17**) in CDCl$_3$ (δ in ppm and J_{Pt-P} in Hz)

Complex	δ	J_{Pt-P} (Hz)
[Boc-Ser(OPPh$_2$)-OMe]$_2$PtCl$_2$ (**10**)	84.8	4100
[Boc-Tyr(OPPh$_2$)-OMe]$_2$PtCl$_2$ (**11**)	86.1	4220
[Boc-Thr(OPPh$_2$)-OMe]$_2$PtCl$_2$ (**12**)	76.4	4100
[Z-β-Ala-Tyr(OPPh$_2$)-OMe]$_2$PtCl$_2$ (**13**)	86.0	3760
[Boc-Ser(OPPh$_2$)-OMe]$_2$PdCl$_2$ (**14**)	112.6	
[Boc-Tyr(OPPh$_2$)-OMe]$_2$PdCl$_2$ (**15**)	111.7	
[Boc-Thr(OPPh$_2$)-OMe]$_2$PdCl$_2$ (**16**)	103.9	
[Z-β-Ala-Tyr(OPPh$_2$)-OMe]$_2$PdCl$_2$ (**17**)	111.5	

chloride ligands. The IR for **10** exhibits two absorptions at 330 and at 297 cm^{-1}. The related peptide complex **13** also exhibits two Pt–Cl vibrations at 360 and 319 cm^{-1}. These IR signals compare well with those reported for (COD)PtCl$_2$, *cis*-[(PhO)$_3$P]$_2$PtCl$_2$ and *cis*-(styrene)(PhH$_2$Si)PtCl$_2$ [14]. For the palladium reactions, strong upfield shifts were observed for serine and threonine-based complexes **14** and **16**, respectively. The tyrosine-complexes **15** and **17** showed virtually no chemical shift differences compared to the free ligand. However, the fragmentation pattern of the complexes clearly indicate coordination of the ligand to the metal centers.

Compound **10** crystallizes from chloroform/hexanes as colorless needles. Its molecular structure was determined by a single-crystal X-ray diffraction study, a view of which is presented in Fig. 1 together with selected bond lengths and angles. As expected for platinum(II), the coordination geometry around the Pt center is close to square planar having the two phosphinito amino acids ligands *cis* to each other. The structure compares well with other known Pd(II) and Pt(II) phosphinite structures [15]. The metal–phosphorus distances are similar to those found in for other M-phosphinite complexes reported in the literature.

The Pt–P bond lengths of 2.2278(13) Å for Pt–P(1) and 2.2235(12) Å for Pt–P(2) are slightly shorter that

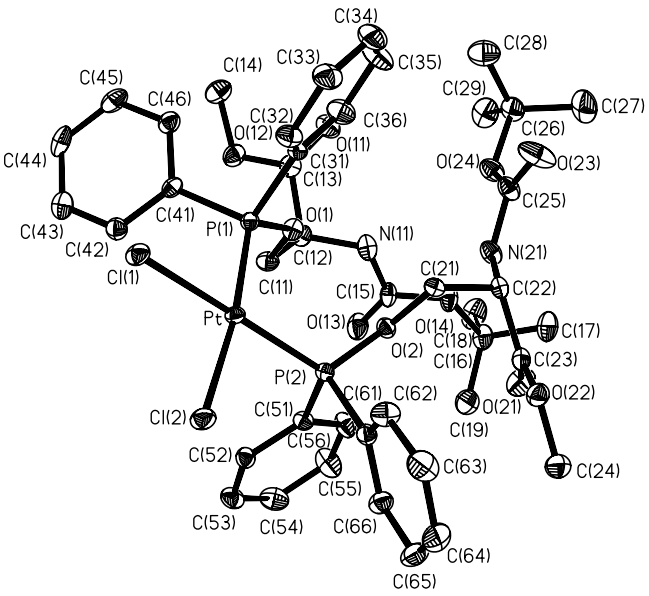


Fig. 1. ORTEP view of [Boc-Ser(OPPh$_2$)-OMe]$_2$PtCl$_2$ (**10**). Ellipsoids are drawn at the 30% probability level. All H atoms are omitted for clarity. Selected bond distances and angles: Pt–P(1) = 2.2278(13) Å, Pt–P(2) = 2.2235(12) Å, Pt–Cl(1) = 2.3663(12) Å, Pt–Cl(2) = 2.3592(13) Å, P(2)–Pt–P(1) = 95.80(5)°, P(2)–Pt–Cl(2) = 89.98(4)°, P(1)–Pt–Cl(2) = 173.13(5)°, P(2)–Pt–Cl(1) = 174.31(5)°, P(1)–Pt–Cl(1) = 88.17(4)°, Cl(2)–Pt–Cl(1) = 86.33(5)°.

those reported by Cesarotti for Pd–P, indicating stronger bonding and potentially a lower ability of the phosphinite ligand to dissociate from the metal center.

Interestingly, recrystallization of complex **16** in air from dichloromethane/petroleum ether gave yellow plates after 2 weeks. The ^{31}P-NMR of the crystals shows a singlet at δ 78.8. The ^{1}H-NMR spectrum shows the absence of any signals due to the tyrosine group, indicating the presence of the hydrolysis product. A single crystal diffraction study showed the structure to be that of di-μ-chlorobis[hydrogen bis(diphenylphosphinito)(1-)-P,P′] dipalladium, reported before by Parkins and co-workers [16]. This is an important result indicating a potential limit on the utility of tyrosine-based phosphinites and its lability towards hydrolysis.

In order to investigate the influence of the metal precursor on the stereochemistry of the complex the following experiments were carried out. Metal complexes were prepared starting from two different precursors, (COD)MCl$_2$ and (PhCN)$_2$MCl$_2$. The latter allows for the rearrangement of the complex during the reaction to the thermodynamically most favorable geometry, which presumably will have the ligands in a *trans* configuration. Our experiments show that the reaction of serine phosphinite ligand **5**, **8** and **9** with (COD)PtCl$_2$ result exclusively in the formation of the *cis* isomer. In contrast, the reaction of (PhCN)$_2$PtCl$_2$ with the tyrosin phosphinite **8** and dipeptide phosphinite **9** gives a mixture of *cis* and *trans* products. Our results compare well with earlier reports showing that product

distribution is greatly influenced by the nature of the metal precursor [17].

In summary, we have prepared a series of novel phosphinito amino acids and one phosphinito peptide and prepared the corresponding Pd and Pt complexes. The complexes exhibit the expected square planar coordination environment about the metal center. We are now investigating the reactivity of these complexes and their potential to act as catalyst in catalytic reactions and hope to compare them to related amino acid and peptide phosphine complexes [18].

3. Experimental

3.1. General

All manipulations of air moisture sensitive materials were conducted in an argon atmosphere using common Schlenk techniques. All solvents were distilled prior to use form appropriate drying agents: triethylamine was distilled from potassium hydroxide; dichloromethane was distilled from CaH_2. Diphenylphosphine chloride was redistilled before use. Unless otherwise noted, chemicals were used as received from Aldrich. Flash chromatography column was carried out on Merck Kieselgel 60 (200–400 mesh) silica. All thin layer chromatography was performed using pre-coated TLC plates with Silica Gel 60 F254. The spots were detected using iodine. ^{1}H, ^{13}C{^{1}H} and ^{31}P{^{1}H}-NMR spectra were recorded on a Bruker AMX-300 spectrometer at 300.13, 75.48 and 121.49 MHz, respectively. Chemical shifts (δ) were measured relative to $SiMe_4$ and were referenced to the residual signal of $CHCl_3$ (δ 7.27) for ^{1}H and the $CDCl_3$ signal (δ 77.23) for ^{13}C{^{1}H}. For ^{31}P{^{1}H} 85% H_3PO_4 was used as an external reference. Mass spectra were obtained with VG Analytical 70/20 VSE chromatograph. GC MS analyses were performed on Fision 8060, 8000 series optical rotations were measured using Rudolph instruments DigiPol DP781 at 589 nm ($c = 0.01$ g 1.00 ml^{-1}, $d = 100.00$ mm, in CH_2Cl_2, unless specified otherwise). The mass of compounds (15 mg–5 g) were reported with an accuracy of ± 1 mg.

3.2. Preparation of Z-β-Ala-Tyr-OMe

Z-β-Ala-OH (2.0 mmol, 0.45 g) was dissolved in 20 ml of dry CH_2Cl_2 and cooled to 0 °C. Then solid HOBt (2.2 mmol, 0.30 g) and EDC (2.2 mmol, 0.42 g) were added. H-Tyr-OMe·HCl (2.2 mmol, 0.51 g) was placed in second flask. CH_2Cl_2 (20 ml) and NEt_3 (1.5 ml) were added via syringe, until all solid starting material dissolved. This solution was added to the mixture of Z-β-Ala-OH and HOBt, EDC. Reaction was allowed to warm up to room temperature and stirred for 24 h until the TLC showed the consumption of the starting materials. The reaction mixture was washed with saturated solutions of sodium bicarbonate, followed by 10% citric acid, saturated solution of sodium bicarbonate, and finally distilled water. The organic phase was dried over $MgSO_4$, which was followed by the removal of the solvent in vacuo. The desired product was obtained as a white solid after purification by flash column chromatography ($CHCl_3$/hexanes/MeOH 85:10:5 $R_f = 0.21$). Yield 1.36 g (68%). LRMS (FAB), *m/z* (relative intensity): 401 ([M+1]$^+$ 17), 149 (16), 95 (26), 91 (55), 70 (42), 54 (100). HRMS of $C_{21}H_{25}N_2O_6$ Calc. [M+ H]$^+$ 401.1712, Found [M+1]$^+$ 401.1711. ^{1}H-NMR (δ, $CDCl_3$): 7.83 (1H, br s, OH), 7.31 (5H, s, CH_{ar} Z), 6.90 (2H, d, $J = 8.3$ Hz, CH_{ar} Tyr), 6.72 (2H, d, $J = 8.3$ Hz, CH_{ar} Tyr), 6.66 (1H, d, $J = 7.8$ Hz, NH Tyr), 5.66 (1H, m, NH Ala), 5.07 (2H, s, CH_2), 4.79 (1H, m, CH Tyr), 3.67 (3H, s, OCH_3), 3.36 (2H, m, CH_2 Ala), 3.00 (2H, m, CH_2 Tyr), 2.33 (2H, m, CH_2 Ala). ^{13}C{^{1}H}-NMR (δ, $CDCl_3$): 172.2 (C=O), 171.6 (C=O), 156.8 (C=OZ), 155.7 (C_{ar}–OH), 136.3 (C_{ar} Z), 130.2 (C_{ar} Tyr), 128.0 (C_{ar} Z), 127.9 (C_{ar} Z), 126.9 (C_{ar}), 115.6 (C_{ar} Tyr) 66.7 (CH_2 Z), 53.6 (C_{ar} Tyr), 52.3 (OCH_3), 37.2, 36.9, 35.8 (CH_2).

3.3. General procedure for phosphinito ligands

To a flask containing the N,C-protected hydroxy-amino acid and dichloromethane (20 ml), three equivalents of triethylamine and catalytic amounts of DMAP (10 mol%) were added. An amount of diphenylphosphine chloride equimolar to the amino acid amount was added dropwise using 1-ml Hamilton syringe. The mixture was stirred overnight and then the solution was filtered through basic alumina. After removal of the solvent under reduced pressure, the desired phosphinito-product was obtained.

3.4. Boc-Ser(OPPh$_2$)-OMe (5)

Boc-Ser(OH)-OMe (4.6 mmol, 1.00 g), triethylamine (13.7 mmol, 1.90 ml), DMAP (0.056 g), diphenylphosphine chloride (4.5 mmol, 0.82 ml). Product: white solid. Yield 1.09 g (60%). Anal. Calc. for $C_{21}H_{26}NO_5P$: C 62.52, H 6.50, N 3.47; Found: C 62.57, H 6.41, N 3.35%. LRMS (FAB), *m/z* (relative intensity): 404 ([M+1]$^+$ 8), 219 (40), 203 (100), 201 (28), 154 (23), 136 (21), 57 (65). HRMS of $C_{21}H_{27}NO_5P$ Calc. [M+ H]$^+$ 404.1627 found [M+ H]$^+$ 404.1625. $[\alpha]_{D25} = +25$ [10^{-1} ° cm^2 g^{-1}]. ^{31}P{^{1}H}-NMR (δ, $CDCl_3$): 118.3 (s). ^{1}H-NMR (δ, $CDCl_3$): 7.42 (5H, m, H_{ar}), 7.09 (5H, m, H_{ar}), 5.31 (1H, d, $J = 9.0$ Hz, NH), 4.51 (1H, m, CH), 4.25 (1H, m, CH_2), 4.10 (1H, m, CH_2), 3.68 (3H, s OCH_3), 1.45 (3H, s, CH_3). ^{13}C{^{1}H}-NMR (δ, $CDCl_3$): 170.9 (C=O), 155.4 (C=O), 141.4 (d, $J_{C-P} = 17.8$ Hz, C–P), 130.8 (m, C_{ar}), 130.4, 129.8, 128.7 (C_{ar}), 80.2 (C–O),

70.2 (d, $J_{C-P} = 20.0$ Hz, C_β), 55.2 (C_α), 55.1 (OCH_3), 28.5 (CH_3).

3.5. Boc-Thr($OPPh_2$)-OMe (**6**)

Boc-Thr(OH)-OMe (5.9 mmol, 1.37 g), triethylamine (18.0 mmol, 2.5 ml), DMAP (0.072 g), diphenylphosphine chloride (6.0 mmol, 1.0 ml). Product: oil. Yield 0.74 g (30%). $^{31}P\{^1H\}$-NMR (δ, $CDCl_3$): 113.3 (s). LRMS (FAB), *m/z* (relative intensity): 418 ($[M+1]^+$, 22), 219 (27), 203 (100), 160 (17), 57 (40). HRMS of $C_{22}H_{29}NO_5P$ Calc. $[M+H]^+$ 418.1783 found $[M+1]^+$ 418.1790. ^1H-NMR (δ, $CDCl_3$): 7.43–7.33 (10H, m, H_{ar}), 5.34 (1H, d, $J = 9.9$ Hz, NH), 4.65 (1H, m, CH_α), 4.43 (1H, d, $J = 9.9$ Hz, CH_β), 3.41 (3H, s, OCH_3), 1.48 (3H, s, CH_3), 1.36 (3H, d, $J = 6.0$ Hz, CH_3). $^{13}C\{^1H\}$-NMR (δ, $CDCl_3$): 171.2 (C=O), 156.3 (C=O), 142.5 (d, $J_{C-P} = 15.8$ Hz, C–P), 141.8 (d, $J_{C-P} = 17.3$ Hz, C–P), 131.0, 130.3, 129.6, 128.5 (C_{ar}), 80.2 (C–O), 77.2 (d, $J_{C-P} = 21.1$ Hz, $CH_{2\beta}$), 59.1 (C_α), 52.3 (OCH_3), 28.5 (CH_3), 19.2 (CH_3).

3.6. Boc-Tyr($OPPh_2$)-OMe (**7**)

Boc-Tyr(OH)-OMe (5.6 mmol, 1.67 g), triethylamine (16.8 mmol, 2.3 ml), DMAP (0.068 g), diphenylphosphine chloride (5.6 mmol, 1.0 ml). Product: colourless oil. Yield 1.07 g (40%). $^{31}P\{^1H\}$-NMR (δ, $CDCl_3$): 111.1 (s). LRMS (FAB), *m/z* (relative intensity): 480 ($[M+1]^+$, 20), 440 (82), 387 (61), 336 (25), 201 (87), 133 (100), 107 (27), 57 (82). HRMS of $C_{27}H_{31}NO_5P$ Calc. $[M+H]^+$ 480.1940 found $[M+1]^+$ 480.1938. ^1H-NMR (δ, $CDCl_3$): 7.63 (4H, m, H_{ar}), 7.40 (6H, m, H_{ar}), 7.07 (4H, m, H_{ar}), 5.06 (1H, d, $J = 8.0$ Hz, NH), 4.58 (1H, m, CH_α), 3.70 (3H, s, OCH_3), 3.06 (2H, m, $CH_{2\beta}$), 1.44 (3H, s, CH_3). $^{13}C\{^1H\}$-NMR (δ, $CDCl_3$): 172.2 (C=O), 156.2 (d, $J_{C-P} = 10.0$ Hz, C–O–P), 155.1 (C=O Boc), 140.7 (d, $J_{C-P} = 17.6$ Hz, C–P), 135.3 (d, $J_{C-P} = 6.9$ Hz, C_{ar}), 130.5, 130.3, 130.2 (C_{ar}), 130.1 (C_{ar}), 129.7 (C_{ar}), 118.8 (d, $J_{C-P} = 10.7$ Hz, C_{ar}), 79.6 (C–O), 54.5 (C_α), 52.0 (OCH_3), 37.3 (CH_2), 28.2 (CH_3).

3.7. Z-Ser($OPPh_2$)-OMe (**8**)

Z-Ser(OH)-OMe (3.9 mmol, 1.00 g), triethylamine (12 mmol, 1.7 ml), DMAP (0.047 g), diphenylphosphine chloride (3.9 mmol, 0.71 ml). Product: oil. Yield 0.68 g (40%). LRMS (FAB), *m/z* (relative intensity): 438 ($[M+1]^+$, (18), 387 (5), 309 (7), 203 (11), 91 (100). HRMS of $C_{24}H_{25}NO_5P$ Calc. $[M+H]^+$ 438.1471 Found $[M+1]^+$ 438.1474. $[\alpha]_{D25} = +13$ [10^{-1} ° cm^2 g^{-1}]. $^{31}P\{^1H\}$-NMR (δ, $CDCl_3$): 118.3 (s). ^1H-NMR (δ, $CDCl_3$): 7.36 (15H, m, H_{ar}), 5.63 (1H, d, $J = 8.3$ Hz, NH), 5.13 (2H, s, CH_2), 4.61 (1H, m, CH_α), 4.30 (1H, m, CH_2), 4.15 (1H, m, CH_2), 3.64 (3H, s, OCH_3). $^{13}C\{^1H\}$-NMR (δ, $CDCl_3$): 170.5 (C=O), 155.9 (C=O), 141.3 (d, $J_{C-P} =$ 17.9 Hz C–O–P), 136.3 (C_Z), 130.7, 130.4, 129.8, 128.8, 128.7, 128.5, 128.4, 128.3 (C_{ar}), 70.1 (d, $J_{C-P} = 20.2$ Hz, CH_2 Ser), 67.2 (CH_2 Z), 55.5 (C_α), 52.7 (OCH_3).

3.8. Z-β-Ala-Tyr($OPPh_2$)-OMe (**9**)

Z-β-Ala-Tyr(OH)-OMe (2.0 mmol, 0.86 g), triethylamine (4.0 mmol, 0.6 ml), DMAP (0.025 g), diphenylphosphine chloride (2.0 mmol, 0.36 ml). Product: colourless oil. Yield 0.70 g (60%). $^{31}P\{^1H\}$-NMR (δ, $CDCl_3$): 111.5 (s). LRMS (FAB), *m/z* (relative intensity): 585 ($[M+1]^+$, 17), 201 (20), 185 (20), 154 (25), 147 (60), 136 (43), 91 (46), 73 (100). HRMS of $C_{33}H_{34}N_2O_6P$ Calc. $[M+H]^+$ 585.2154, Found $[M+1]^+$ 585.2153. $[\alpha]_{D25} = +30$ [10^{-1} ° cm^2 g^{-1}]. ^1H-NMR (δ, $CDCl_3$): 7.58 (5H, m, H_{ar}), 7.40 (10H, m, H_{ar}), 7.04 (4H, m, H_{ar}), 6.02 (1H, d, $J = 7.4$ Hz, NH), 5.42 (1H, m, NH), 5.09 (2H, s, CH_2), 4.81 (1H, m, CH_α), 3.71 (3H, s, OCH_3), 3.45 (2H, m, CH_2), 3.06 (2H, m, CH_2), 2.41 (2H, m, CH_2). $^{13}C\{^1H\}$-NMR (δ, $CDCl_3$): 172.1 (C=O), 171.5 (C=O), 156.9 (C=O_Z), 140.3 (d, $J_{C-P} = 17.6$ Hz, C–O–P), 135.5 (d, $J_{C-P} = 7.2$ Hz, C–P), 130.4, 129.9, 129.8, 128.2, 119.2 (C_{ar}), 66.8 (CH_{2Z}), 53.4 (C_α), 52.6 (OCH_3), 37.2, 36.0 (CH_2).

3.9. General procedure for phosphinite–metal complexes

To the suspension of the metal precursor ($Cl_2Pt(COD)$, $Cl_2Pt(PhCN)_2$ or $Cl_2Pd(PhCN)_2$) in CH_2Cl_2 (10 ml), a solution of the phosphinito-ligand (two equivalents) in CH_2Cl_2 (10 ml) was added dropwise. The mixture was stirred for 24 h at room temperature. After evaporation of the solvent in vacuo the corresponding phosphinito–metal complexes were obtained as colorless to slightly yellow solids in nearly quantitative yields.

3.10. [Boc-Ser($OPPh_2$)-OMe]$_2PtCl_2$ (**10**)

$Cl_2Pt(COD)$ (0.06 mmol, 0.022 g), Boc-Ser($OPPh_2$)-OMe (0.12 mmol, 0.050 g). Elem. Anal. Calc for $C_{42}H_{52}Cl_2N_2O_{10}P_2Pt$: C 46.14, H 4.89, N 2.61; Found: C 46.45, H 4.99, N 2.35%. IR (CsI, disk) $\nu_{(Pt-Cl)}$ 297, 330 cm^{-1}. $^{31}P\{^1H\}$-NMR (δ, $CDCl_3$): 84.8 (s), $J_{Pt-P} = 4103$ Hz. LRMS (FAB), *m/z* (relative intensity): 1037 ($[M-Cl+1]^+$ 82), 1000 (20), 900 (40), 826 (30), 800 (100). ^1H-NMR (δ, $CDCl_3$): 7.69–7.39 (20H, br m, CH_{ar}), 5.43 (2H, d, $J = 6.0$ Hz, NH), 4.27 (2H, br m, CH_α), 4.00 (4H, br m, CH_2), 3.51 (6H, s, OCH_3), 1.46 (18H, s, CH_3). $^{13}C\{^1H\}$-NMR (δ, $CDCl_3$): 169.9 (C=O), 155.2 (C=O), 132.7, 132.3, 132.1, 128.9, 128.4 (m, C_{ar}), 80.9 (C–O), 68.2 (CH_2), 53.8 (C_α), 52.8 (OCH_3), 28.5 (CH_3).

3.11. [Boc-Tyr(OPPh$_2$)-OMe]$_2$PtCl$_2$ (**11**)

$Cl_2Pt(COD)$ (0.05 mmol, 0.019 g), Boc-Tyr($OPPh_2$)-OMe (0.1 mmol, 0.050 g). Elem. Anal. Calc for $C_{54}H_{60}Cl_2N_2O_{10}P_2Pt$: C 52.95, H 4.94, N 2.29; Found: C 53.40, H 5.21, N 1.86%. $^{31}P\{^1H\}$-NMR (δ, $CDCl_3$): 86.1 (s, $J_{P-Pt} = 4223$ Hz). LRMS (FAB), *m/z* (relative intensity): 1152 $[M-2Cl-1]^+$, 25), 1096 (48), 1053 (16), 952 (64), 892 (23), 802 (100), 599 (92) HRMS of $C_{54}H_{59}N_2O_{10}P_2Pt$ Calc. $[M-2Cl-1]^+$ 1152.3293, Found [M-2Cl-1]$^+$ 1152.3298. ^1H-NMR (δ, $CDCl_3$): 7.60 (10H, m, H_{ar}), 7.42 (7H, m, H_{ar}), 7.30 (13H, m, H_{ar}), 6.85 (4H, m, H_{ar}), 6.47 (4H, m, H_{ar}), 4.94 (2H, d, $J = 8.2$ Hz, NH), 4.52 (2H, m, CH_α), 3.69 (6H, s, OCH_3), 3.01 (4H, m, CH_2), 1.43 (18H, s, CH_3). $^{13}C\{^1H\}$-NMR (δ, $CDCl_3$): 172.2 (C=O), 155.2 (C=O), 152.1 (C–O–P), 133.0, 132.0, 130.4, 128.1, 128.0, 121,3 (C_{ar}), 80.3 (C–O), 54.5 (C_α), 52.5 (OCH_3), 37.8 (CH_2), 28.2 (CH_3).

3.12. [Boc-Thr(OPPh$_2$)-OMe]$_2$PtCl$_2$ (**12**)

$Cl_2Pt(COD)$ (0.06 mmol, 0.022 g), Boc-Thr($OPPh_2$)-OMe (0.12 mmol, 0.050 g). $^{31}P\{^1H\}$-NMR (δ, $CDCl_3$): 76.4 (s, $J_{P-Pt} = 4100$ Hz). LRMS (FAB), *m/z* (relative intensity): 1065 ($[M-Cl+1]^+$). ^1H-NMR (δ, $CDCl_3$): 7.59–7.27 (20H, m, H_{ar}), 5.58 (2H, m, NH), 5.16 (2H, m, CH_α), 4.39 (2H, d, $J = 7.9$ Hz, CH_β), 3.60 (6H, s, OCH_3), 1.53 (6H, d $J = 5.9$ Hz, CH_3), 1.47 (18H, s, CH_3). $^{13}C\{^1H\}$-NMR (δ, $CDCl_3$): 170.7 (C=O), 155.7 (C=O), 134.8, 133.8 (C–P), 132.2, 131.5, 131.3, 128.8, 128.2 (C_{ar}), 80.6 (C–O), 76.8 (C_β), 58.3 (C_α), 52.6 (OCH_3), 28.5 (CH_3), 19.0 (CH_3).

3.13. [Z-β-Ala-Tyr(OPPh$_2$)-OMe]$_2$PtCl$_2$ (**13**)

$Cl_2Pt(COD)$ (0.06 mmol, 0.022 g), Z-β-Ala-Tyr($OPPh_2$)-OMe (0.12 mmol, 0.060 g). $^{31}P\{^1H\}$-NMR (δ, $CDCl_3$): 86.0 (s, $J_{P-Pt} = 3755$ Hz). LRMS (FAB), *m/z* (relative intensity): 1435 ($[M+2]^+$, 32), 1399 (37), 1363 (100), 1017 (22), 980 (40), 778 (31), 670 (29), 598 (32). ^1H-NMR (δ, $CDCl_3$): 7.58 7.38 (38H, br m, H_{ar}), 6.47 (2H, d, $J = 5.8$ Hz, NH), 5.59 (1H, m, NH), 5.06 (2H, s, CH_2), 4.76 (1H, m, CH_α), 3.67 (3H, s, OCH_3), 3.40 (2H, m, CH_2), 3.04 (2H, m, CH_2), 2.37 (2H, m, CH_2). $^{13}C\{^1H\}$-NMR (δ, $CDCl_3$): 171.8 (C=O), 171.3 (C=O), 156.6 (C=O), 136.7 (C–O–P), 132.8 (C–P), 131.8, 130.5, 129.8, 128.7, 128.2, 121.4 (C_{ar}), 66.8 (CH_{2Z}), 53.5 (C_α), 52.6 (OCH_3), 37.2, 36.0 (CH_2).

3.14. [Boc-Ser(OPPh$_2$)-OMe]$_2$PdCl$_2$ (**14**)

$Cl_2Pd(PhCN)_2$ (0.06 mmol, 0.023 g), Boc-Ser($OPPh_2$)-OMe (0.12 mmol, 0.050 g). Elem. Anal. Calc for $C_{42}H_{52}Cl_2N_2O_{10}P_2Pd$: C 51.26, H 5.33, N 2.85; Found: C 51.72, H 5.87, N 2.39%. $^{31}P\{^1H\}$-NMR (δ, $CDCl_3$): 112.6 (s). LRMS (FAB), *m/z* (relative intensity): 949 ($[M-Cl+2]^+$, 5), 911(10), 302 (46), 154 (80), 136 (73), 73 (40), 57 (100). ^1H-NMR (δ, $CDCl_3$): 7.68–7.50 (20H, m, H_{ar}), 5.36 (2H, d, $J = 9.4$ Hz, NH), 4.22 (2H, br m, CH_α), 3.94 (4H, br m, CH_2), 3.70 (6H, s, OCH_3), 1.45 (18H, s, CH_3). $^{13}C\{^1H\}$-NMR (δ, $CDCl_3$): 169.8 (C=O), 155.2 (C=O), 133.0, 132.9, 132.5, 132.4, 129.3, 129.0, 128.6 (C_{ar}), 80.8 (C–O), 68.5 (CH_2), 54.0 (C_α), 52.8 (OCH_3), 28.5 (CH_3).

3.15. [Boc-Tyr(OPPh$_2$)-OMe]$_2$PdCl$_2$ (**15**)

$Cl_2Pd(PhCN)_2$ (0.05 mmol, 0.019 g), Boc-Tyr($OPPh_2$)-OMe (0.1 mmol, 0.050 g). $^{31}P\{^1H\}$-NMR (δ, $CDCl_3$): 111.7 (s). LRMS (FAB), *m/z* (relative intensity): 1101 ($[M-Cl+2]^+$, 7), 1065 (7), 556 (50), 514 (47), 291 (920), 147 (20), 91 (20), 57 (100). HRMS of $C_{54}H_{60}ClN_2O_{10}P_2Pd$ Calc.$[M-Cl]^+$ 1099.2447, Found $[M-Cl]^+$ 1099.2487. ^1H-NMR (δ, $CDCl_3$): 7.65 (10H, m, H_{ar}), 7.46, 7.32 (20H, m, H_{ar}), 6.84 (4H, m, H_{ar}), 6.45 (4H, m, H_{ar}), 4.93 (2H, d, $J = 7.8$ Hz, NH), 4.51 (2H, m, CH_α), 3.68 (6H, s, OCH_3), 2.99 (4H, m, CH_2), 1.42 (18H, s, CH_3). 13C{1H}-NMR, $CDCl_3$): 172.2 (C=O), 155.2 (C=O), 152.1 (C–O–P), 133.1, 133.0, 132.1, 130.5, 128.2, 121.1 (C_{ar}), 80.3 (C–O), 54.5 (C_α), 52.5 (OCH_3), 37.7 (CH_2), 28.5 (CH_3).

3.16. [Boc-Thr(OPPh$_2$)-OMe]$_2$PdCl$_2$ (**16**)

$Cl_2Pd(PhCN)_2$ (0.06 mmol, 0.023 g), Boc-Thr($OPPh_2$)-OMe (0.12 mmol, 0.050 g). $^{31}P\{^1H\}$-NMR (δ, $CDCl_3$): 103.9 (s). LRMS (FAB), *m/z* (relative intensity): 975 $[M-Cl-1]^+$, 939 $[M-2Cl-2]^+$, 877 $[M-OCH_3-2]$. ^1H-NMR (δ, $CDCl_3$): 7.65, 7.46 (20H, m, H_{ar}), 5.56 (2H, m, CH_α), 5.52 (2H, d $J = 9.7$ Hz, NH), 4.46 (2H, d $J = 9.4$ Hz, CH_β), 3.54 (6H, s, OCH_3), 1.53 (6H, d $J = 6.3$ Hz, CH_3), 1.45 (18H, s, CH_3). $^{13}C\{^1H\}$-NMR (δ, $CDCl_3$): 171.0 (C=O), 156.3 (C=O), 133.7 (C–P), 132.4, 131.3, 129.3, 128.2, 128.1, 128.0 (C_{ar}), 80.3 (C–O), 78.2 (C_β), 58.8 (C_α), 52.8 (OCH_3), 28.5 (CH_3), 19.6 (CH_3).

3.17. [Z-β-Ala-Tyr(OPPh$_2$)-OMe]$_2$PdCl$_2$ (**17**)

$Cl_2Pd(PhCN)_2$ (0.06 mmol, 0.023 g), Z-β-Ala-Tyr($OPPh_2$)-OMe (0.12 mmol, 0.060 g). $^{31}P\{^1H\}$-NMR (δ, $CDCl_3$): 111.5 (s). LRMS (FAB), *m/z* (relative intensity): 1273 ($[M-2Cl-1]^+$, 11), 891 (30), 801 (20), 689 (100), 661 (30), 594 (29), 585 (35), 550 (90), 535 (57), 522 (83), 506 (47). ^1H-NMR (δ, $CDCl_3$): 7.60 7.33 (30H, m, H_{ar}), 6.87 6.87 (8H, m, H_{ar}), 6.46 (2H, d, $J = 7.8$ Hz, NH), 5.59 (1H, m, NH), 5.06 (2H, s, CH_2), 4.77 (1H, m, CH_α), 3.67 (3H, s, OCH_3), 3.39 (2H, m, CH_2), 2.99 (2H, m, CH_2), 2.36 (2H, m, CH_2). $^{13}C\{^1H\}$-NMR (δ, $CDCl_3$): 171.8 (C=O), 171.4 (C=O), 156.6 (C=O), 136.6 (C–O–P), 134.3 (C–P), 131.8, 130.4, 129.7,

Table 3
Crystal data and structure refinement for of [Boc-Ser($OPPh_2$)-$OMe]_2PtCl_2$ (**10**)

Empirical formula	$C_{45}H_{55}Cl_{11}N_2O_{10}P_2Pt$
Formula weight	430.89
Temperature (K)	193(2)
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	
a (Å)	9.8067(12)
b (Å)	17.130(2)
c (Å)	35.040(4)
Volume (Å^3)	5886.4(12)
Z	4
Density (calculated) (g m^{-3})	1.615
Absorption coefficient (mm^{-1})	2.990
$F(0\,0\,0)$	2856
Crystal size (mm)	$0.43 \times 0.39 \times 0.09$
θ range for data collection (°)	1.32–26.45
Limiting indices	$-12 < h < 12$, $-21 < k < 21$, $-16 < l < 43$
Reflections collected	12 078
Independent reflections	11 458
Data/restraints/parameters	11 458/0/640
Goodness-of-fit on F^2	1.132
Final R indices [$I > 2\sigma(I)$]	$R = 0.0358$, $wR = 0.0812$
R indices (all data)	$R = 0.0382$, $wR = 0.0819$
Abs. structure parameter	0.006(5)
Largest diff. peak and hole (e Å^{-3})	0.85 and −1.01

129.2, 126.8, 121.7 (C_{ar}), 66.7 (CH_{2Z}), 53.5 (C_α), 52.5 (OCH_3), 37.2, 35.9 (CH_2).

3.18. X-ray crystallography

Suitable crystals of **10** were obtained by layering a CH_2Cl_2 solution of **10** with ether. Colorless needles suitable for X-ray crystallography were deposited after 2 days. Data for **10** were measured using a Siemens Smart CCD diffractometer using Mo–K_α radiation (graphite monochromated) with ω scans. The structures was solved using direct methods. All non-hydrogen atoms were refined anisotropically using full-matrix least-squares on F^2. The final R value for **10** was $R = 0.0358$ and $wR = 0.0812$ for 11458 reflection with $I > 2\sigma(I)$ (12078 total reflections). Crystallographic details have been summarized in Table 3.

4. Supplemental material

Crystallographic data excluding structure factors have been deposited at the Cambridge Crystallographic Data Centre (CCDC no. 202084). This material can be obtained upon request to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-1223-336033; email: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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