Preparation of Diphenylphosphinoserine and Synthesis of Other Phosphine Containing Amino Acids Using Zinc/Copper Reagents

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Abstract: Primary and secondary iodo amino acids are converted to zinc iodides. The resulting organozinc iodides are reacted with copper, and then coupled with aryl and alkyl phosphine chlorides in good to moderate yields.

Key words: amino acids, catalysis, combinatorial chemistry, ligands, organometallic reagents, phosphine

Our research group has been using combinatorial chemistry to quickly and easily synthesize ligands for screening in asymmetric catalytic reactions.1–10 Incorporating phosphine containing amino acids 1,3 and 4 (Figure) into rigid peptide secondary structures, such as α-helices and β-turns, allows for the generation of large libraries of bis- and monophosphate ligands. Because the ligands are synthesized by solid phase peptide chemistry, a wide variety of ligands with different structures and chiral environments can be made. In any parallel approach it is critical that the starting materials be readily available. In this paper we report a new and efficient route to one of the key building blocks necessary for our approach, diphenylphosphinoserine (Pps) 1. The synthesis of a cyclohexyl and ethyl derivatives of 1 as well as routes to derivatives of phosphines 3 and 4 are also reported.

Diphenylphosphinoserine (Pps) 1 (R = Ph, R’ = Fmoc or Boc) is a useful building block for the parallel synthesis of peptide based phosphine ligands.11 The synthesis of 1 has proven to be one of the slow steps in the synthesis of libraries of phosphine ligands. The routes in the literature generally need multiple steps with chromatography required after a number of the steps.9,11,12 While the route using chiral oxazolidinones (Scheme 1) has been used successfully for a number of years a more direct route was desired.

Boc protected 3-iodo alanine methyl ester 5 is commercially available in both enantiomeric forms. This molecule is also accessible in two steps from Boc-Ser-OMe.13,14 Jackson has converted this functionalized amino acid to zinc copper species 2 and used it in the synthesis of unnatural amino acids.15 Additionally Knochel has reacted various zinc iodides with chlorodiphenylphosphine to obtain phosphines in high yields.16 A combination of these precedents provides a facile route to a number of phosphine amino acids (Scheme 2).

Scheme 1
Following Knochel’s procedure, commercially available iodo amino acid 5 attempts to couple the zinc iodide with activated zinc.\(^\text{17}\) Attempts to couple the zinc iodide directly with chlorodiphenylphosphine and in the presence of catalytic copper or palladium failed. It was ultimately found that a stoichiometric amount of the THF soluble salt CuCN·2LiCl followed by addition of chlorodiphenylphosphine provided the desired product. Presumably the reactive intermediate is the zinc/copper species 6. Coupling 6 with \(\text{Ph}_2\text{PCl}\) and protection of the phosphine as the sulfide gave enantiomERICALLY pure 7 in 75% yield. Hydrolysis of the ester provided the Boc protected acid. Conversion of the \(N\)-Boc protected amino acid to the \(N\)-Fmoc protected amino acid was effected in 80% from 7. Phosphine containing amino acids and esters such as 7 and 8 are readily incorporated into peptides by standard solid phase peptide synthesis. The sulfide protecting group can be removed with Raney nickel or by methylation followed by treatment with HMPT to yield the free phosphine.

This route has been successfully used to synthesize a number of phosphine containing amino acids (Table). In addition to chlorodiphenylphosphine, diethyl and dicyclohexylphosphine chlorides have been used as the electrophile. It has been found that the chlorodi-tert-butylphosphine does not react with the metalated amino acid. In the case of reaction of 5 to give product 7 the reaction has been run on a 10 gram scale without a decrease in the yield of the product. Substituted bis(4-fluorophenyl)phosphate chloride reacts to give the expected product. 2-Chloro-1,3,2-dioxaphospholane smoothly reacts to provide 13, however the yield is reduced upon purification. The bromo amino acid does not appear to undergo reaction with zinc at temperatures below 35 °C. Heating to 60 °C yields the product from elimination, the protected dehydroalanine.

Secondary iodides also undergo the reaction; however with loss of stereochemistry at the carbon bearing the iodide.\(^\text{18–20}\) Despite this problem, this is a viable route to such molecules. This is particularly true considering one often does not know which diastereomer will have chirality that is complementary to the chirality of the peptide.

In conclusion, the route reported above provides enantio-merically pure phosphine containing serine derivatives from commercially available starting materials in two steps for the Boc protected derivative (75% yield) and four steps for the Fmoc protected version (60% yield). The electrophile that is reacted with zinc/copper reagent 6 can be aryl, substituted aryl and primary or secondary alkyl chlorophosphines, as well as, phosphate chlorides.\(^\text{21,22}\) Secondary iodides from threonine and hydroxypoline work in moderate yields, but in low diastereoselectivity. In that a variety of different phosphine containing amino acids can be synthesized from commercially available starting materials, this route represents a significant improvement over the existing methods available for the synthesis of these versatile molecules.

All chemicals were reagent grade from Aldrich, Bachem or Strem and used as supplied, except where noted. THF was distilled from sodium benzenophenone ketyl. Reactions were monitored by TLC using Aldrich polyester silica gel 60 F254 plates (0.25 mm). Flash chromatography was performed using ICN Silitech 32-63 D, 60 Å. \(^1^H\) NMR spectra were obtained using a Varian Mercury 300 spectrometer (300 MHz) and are reported in parts per million (δ) relative to TMS. Coupling constants (J) are reported in Hertz. \(^3^1^P\) NMR spectra were obtained using a Varian Mercury 300 spectrometer (75 MHz) and are reported in δ relative to \(\text{H}_3\text{PO}_4\) (0.00 ppm) as an external reference. HPLC samples were run on a Chiralcel OD column using a 9:1 hexane–propan-2-ol mobile phase at 0.8 mL/min and 25 °C with UV detection at 204 nm. All reactions were carried out under \(\text{N}_2\) in oven-dried glassware. All reported yields are isolated and unoptimized.

### Phosphine Containing Amino Acids; Methyl (2S)-2-[(tert-Butyloxy carbonyl)amino]-3-(diphenylphosphinyl)propionate [Boc-Pps(S)-O-Me, 7]; Typical Procedure

A flask charged with zinc dust (<10 micron, 0.3 g, 1.5 mmol, 3.0 equiv) was gently heated in vacuo, allowed to cool and back filled with \(\text{N}_2\). THF (1 mL), DMF (0.24 mL, 3.0 mmol, 2 equiv) and 1,2-dibromoethane (16 μL, 0.18 mmol, 4% to \(\text{Zn}\)) were added via syringe. The flask was heated to ebullition with a heat gun, while stirred vigorously, then allowed to cool to r.t. This process was repeated four times. TMSCl (18 μL, 0.14 mmol, 3% to zinc) was added and allowed to stir for 30 min. In a separate flask, \(N\)-(tert-butoxy carbonyl)-3-iodo-D-alanine methyl ester (5; 0.5 g, 1.5 mmol,
for 2 h. After the reaction, sulfur (0.14 g, 4.5 mmol, 3 equiv) was added to the mixture as a solid and the reaction was allowed to stir for 15 h. The insoluble material was filtered and the THF was removed at reduced pressure. CH₂Cl₂ (20 mL) was added to the remaining material and swirled vigorously. The insoluble material was removed by filtration, and the silica gel (2–3 g) was added. The CH₂Cl₂ was removed at reduced pressure, and the silica gel was loaded onto a chromatography column containing silica gel and purified (35% EtOAc–hexanes, Rₖ 0.31) to give 7 as a white foam (0.475 g, 75%).

1H NMR (300 MHz, CDCl₃): δ = 7.9–7.8 (m, 4 H), 7.6–7.4 (m, 6 H), 5.48 (d, 1 H, J = 6.6 Hz), 4.70–4.65 (m, 1 H), 3.6 (s, 3 H), 3.33 (m, 1 H), 3.12 (ddd, 1 H, J = 3.9, 12.7, 13 Hz), 1.28 (s, 9 H).

13C NMR (75 MHz, CDCl₃): δ = 171.8, 171.64, 155.05, 131.81, 131.30, 131.16, 131.14, 131.0, 129.08, 128.97, 128.91, 128.81, 80.17, 52.87, 33.74, 32.97, 22.83.

13P NMR (120 MHz, CDCl₃): δ = 38.69.

EI-HRMS: m/z calc 420.1398, obsd 420.1398.

IR (film): 2990, 1770, 1730, 1500, 1430, 1360, 1170, 1100, 560 cm⁻¹.

Methyl (2S)-2-[(tert-Butoxycarbonyl)amino]-3-(diethyl-phosphinothioyl)propionate [Boc-Eps(S)-OMe, 9]

Typical procedure was followed using 5 (0.616 g, 1.87 mmol) and diethylphosphine chloride (0.35 mL, 3.0 mmol) to give 9 (0.4 g, 65%) as a clear oil after purification by flash silica gel chromatography (35% EtOAc–hexanes, Rₖ 0.22).

1H NMR (300 MHz, CDCl₃): δ = 5.72 (d, 1 H, J = 7.4 Hz), 4.61–4.48 (m, 1 H), 3.7 (s, 3 H), 2.50–2.36 (m, 2 H), 2.0–1.8 (m, 4 H), 1.39 (s, 9 H), 1.20–1.07 (m, 6 H).

13C NMR (75 MHz, CDCl₃): δ = 172.0, 171.8, 155.5, 80.5, 53.0, 50.4, 30.6, 30.0, 28.5, 25.3, 25.2, 24.6, 24.5, 6.64, 6.57, 6.51.

13P NMR (120 MHz, CDCl₃): δ = 51.66.

EI-HRMS: m/z calc 323.132, obsd 323.132.

IR (neat): 2976, 2938, 2882, 1810, 1752, 1714, 1499, 1450, 1436, 1394, 1371, 1313, 1254, 1212, 1165, 1105, 1048, 1024, 768, 567 cm⁻¹.

Methyl (2S)-2-[(tert-Butoxycarbonyl)amino]-3-(dicyclohexylphosphinothioyl)propionate [Boc-Cps(S)-OMe, 10]

Typical procedure was followed using 5 (1.0 g, 3.0 mmol) and dicyclohexylphosphine chloride (1.0 g, 4.3 mmol) to give 10 (0.51 g, 40%) as a white foam after purification by flash silica gel chromatography (20% EtOAc–hexanes, Rₖ 0.24).

1H NMR (300 MHz, CDCl₃): δ = 5.9 (d, 1 H, J = 6.9 Hz), 4.58 (m, 1 H), 3.76 (s, 3 H), 2.48 (m, 1 H), 2.38 (m, 1 H), 2.00–1.60 (m, 11 H), 1.6–1.2 (s, 9 H, 6.9 Hz), 1.20–1.07 (m, 6 H).

13C NMR (75 MHz, CDCl₃): δ = 171.92, 171.80, 155.29, 80.12, 52.83, 50.61, 38.63, 38.55, 37.99, 37.91, 28.45, 26.8–26.4 (m, 26.0–25.5 (m), 25.18.

13P NMR (120 MHz, CDCl₃): δ = 58.00.

EI-HRMS: m/z calc 432.23373, obsd 432.23350.

IR (film): 2981, 2938, 2882, 1745, 1714, 1504, 1249, 1165, 1048, 1024, 768, 567 cm⁻¹.

Methyl (2S)-2-[(tert-Butoxycarbonyl)amino]-3-[bis(4-fluorophenyl)phosphinothioyl]propionate (12)

Typical procedure was followed using 5 (0.5 g, 1.5 mmol) and bis(4-fluoropheny)phosphine chloride (0.6 mL, 3.5 mmol) to give 12 (0.5 g, 73%) as a white foam after purification by flash silica gel chromatography (35% EtOAc–hexanes, Rₖ 0.25).

### Table: Coupling of Zinc/Copper Reagents Derived from Iodo Amino Acids with Phosphine/Phosphite Chlorides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Iodide</th>
<th>Phosphine/Phosphite Chloride</th>
<th>Product</th>
<th>Yield (a) (%)</th>
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<td>R = Ph</td>
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<td>75</td>
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<tr>
<td>2</td>
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<td>R = 4-FC₆H₄</td>
<td>12</td>
<td>73</td>
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(a) Isolated yields.
(b) Yields are unoptimized.
(c) Products were enantiomerically pure as determined by chiral HPLC.
(d) Decomposed on silica gel.
(e) δ = 0% (determined by 31P NMR spectroscopy).
(f) δ = 50% (determined by 31P NMR spectroscopy).

1 equiv) was dissolved in THF (2 mL) and added dropwise via syringe to the zinc suspension. The flask and syringe were then rinsed with THF (1 mL) and that solution was added to the reaction. Upon completion of the zinc insertion determined by TLC (typically about 2 h) stirring was halted to allow the zinc to settle (about 30 min). In a separate flask charged with CuCN·2LiCl (CuCN: 0.14 g, 1.5 mmol, 1 equiv; LiCl: 0.13 g, 3.0 mmol, 2 equiv), which had been heated to 140–150°C in an oil bath under vacuum for at least 2 h, was added THF (3 mL). After the salts had dissolved, the solution was cooled to 0°C and the solution of the zinc iodide was filtered through a syringe filter dropwise into the copper solution. The reaction was stirred for 15 min and then chlorodiphenylphosphine (0.54 mL, 3.0 mmol, 2 equiv) was added dropwise via syringe. The reaction was allowed to stir at 0°C for 10 min then allowed to stir at r.t.
3.33–3.23 (m, 1 H), 3.11–3.01 (m, 1 H), 1.23 (s, 9 H).

Typical procedure was followed using Acid 1-tert-S (2102, 805, 722 cm⁻¹).

FAB-HRMS: FAB-HRMS: chlorodiphenylphosphine (0.54 mL, 3.0 mmol) to give S chromatography (50% EtOAc–hexanes, Rf 0.29).

(0.184 g, 38%) as a white solid after purification by flash silica gel chromatography (35% EtOAc–hexanes, Rf 0.21).

IR (KBr): 3059, 2975, 2880, 1745, 1698, 1480, 1435, 1396, 1365, 1259, 1208, 1169, 1124, 1027, 999, 923, 892, 750, 713, 691, 638, 586, 526, 501 cm⁻¹.

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References