First asymmetric synthesis of α-methylphosphophenylalanine derivatives using sulfinimine derived chiral enantiopure aziridine-2-phosphonates

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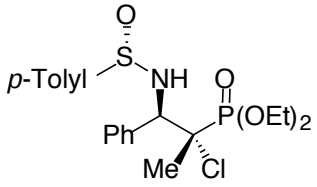
SUPPLEMENTARY MATERIAL

General Procedure. Column chromatography was performed on silica gel, Merck grade 60 (230-400 mesh). Analytical and preparative thin layer chromatography was performed on precoated silica gel plates (250 and 1000 μm) purchased from Analtech Inc. TLC plates were visualized by quenching of UV fluorescence (λ_{max} 254 nm), staining with iodine or staining with 10% w/v ammonium molybdate in 2 N sulfuric acid. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 341 polarimeter. IR spectra were recorded using NaCl plates or as KBr discs, on a Mattson 4020 FTIR spectrometer. ^{1}H, ^{13}C and ^{31}P NMR were recorded on a General Electric Omega 500, operating at 500, 125 and 202 MHz repectively. The ^{1}H and ^{13}C spectra are referenced to solvent residues as an internal standard and ^{31}P spectra referenced externally to 85% H_3PO_4. HRMS were performed in the Department of Chemistry, Drexel University, Philadelphia, PA using a Fissions ZAB HF double focusing mass spectrometer. Elemental analyses were performed in the Department of Chemistry, University of Pennsylvania, Philadelphia, PA.

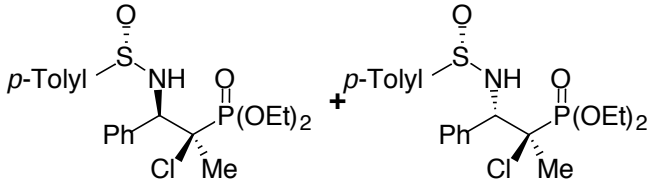
THF and Et_2O were freshly distilled under an inert atmosphere from a purple solution of sodium/benzophenone ketyl. Anhydrous CH_2Cl_2, DMSO and LP were obtained by refluxing over calcium hydride followed by distillation under an inert atmosphere. LP refers to the fractions of petroleum ether which boil within the range 35-60 °C. All other reagents were used as obtained from commercial sources or purified by methods described in D. P. Perrin and W. L. F. Armarego, 'Purification of Laboratory Chemicals,' Third Edition, Pergamon Press, 1988. All reactions were performed under an inert atmosphere of argon unless otherwise stated and all glassware was vacuum or oven dried before use.

Diethyl (*S*$_S$, *1R 2R*)-(+)-1-chloro-1-methyl-2-phenyl-2-(*p*-toluenesufinamide)ethylphosphonate (3) and a (69:31) mixture of diethyl (*S*$_S$,*1S 2R*)-1-chloro-1-methyl-2-phenyl-2-(*p*-toluenesufinamide)ethylphosphonate (4) and diethyl (*S*$_S$,*1S, 2S*)-1-chloro-1-methyl-2-phenyl-2-(*p*-toluenesufinamide)ethylphosphonate (5). In a 250 mL round-bottom flask equipped with a magnetic stirrer bar, rubber septum and argon balloon was placed (*S*)-(+)-*N*-(benzylidene)-*p*-toluenesulfinamide (**1**)[1] (1.14 g, 4.69 mmol) and diethyl chloroethylphosphonate[2] (2.06 g, 10.3 mmol) dissolved in THF (120 mL). The stirred solution was cooled to -78 °C and

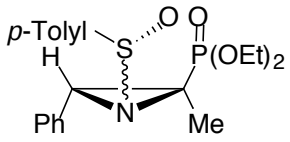
$LiN(SiMe_3)_2$ (10.3 mL, 1M in THF, 10.3 mmol) was added dropwise *via* syringe. After stirring at -78 °C for 20 min, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl (5 mL) and warmed to rt. After dilution with H_2O (20 mL) the mixture was extracted with Et_2O (3 × 100mL) and CH_2Cl_2 (100 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated to give a yellow oil. Flash chromatography (SiO_2, CH_2Cl_2-EtOAc, 15:1; 2:1; gradient elution) afforded recovered diethyl chloroethylphosphonate (657 mg), (+)-**3** (1.16 g, 56%) as a white solid and an inseparable 69:31 mixture of **4** and **5** (478 mg, 23%) as a colourless oil; Crystals of (+)-**3** suitable for X-ray analysis were obtained by slow recrystallisation from ether-LP (1:1).



(+)-**3**: R_f 0.25 (CH_2Cl_2-EtOAc, 5:1); mp 102 °C; $[\alpha]_D^{20}$ +24.3 (c 1.01, $CHCl_3$); IR (NaCl) 3212, 1243, 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (3H, t, ^3J 7), 1.25 (3H, t, ^3J 7), 1.79 (3H, d, $^3J_{PH}$ 14) 2.29 (3H, s), 3.94-4.05, 4.14-4.18 (4H, m), 4.66 (1H, dd, $^2J_{PH}$ 15, ^3J 7.5), 5.94 (1H, d, ^3J 7.5, exchanges with D_2O), 7.00- 7.12 (2H, m), 7.09-7.17 (5H, m), 7.36-7.38 (2H, m); ^{13}C NMR ($CDCl_3$) δ 15.9 (d, $^3J_{PC}$ 4), 16.3 (d, $^3J_{PC}$ 6), 21.1, 25.2, 61.9 (d, $^2J_{PC}$ 4), 63.2 (d, $^2J_{PC}$ 6), 64.6 (d, $^2J_{PC}$ 6), 67.4 (d, $^1J_{PC}$ 157), 125.6, 127.2, 127.5, 128.8, 129.1, 138.2, 140.6, 140.8; ^{31}P NMR ($CDCl_3$) δ 19.42; MS (FAB^+) *m/z* 444 [100%, $MH(^{35}Cl)^+$], 426 [43], 390 [44], 304 [98]; Anal. calcd for $C_{20}H_{27}ClNO_4PS$: C, 54.11; H, 6.13; N, 3.16. Found C, 54.08; H, 6.37; N, 3.09%.

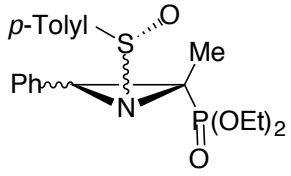


69:31 mixture of **4** and **5** (when distinguishable, data for major stereoisomer **4** is given first): R_f 0.3 (CH_2Cl_2-EtOAc, 5:1); $[\alpha]_D^{20}$ +59.8 (c 0.895, $CHCl_3$); IR (NaCl) 3217, 1242, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33, 1.40, (6H, t, ^3J 7), 1.49, 1.72 (3H, d, $^3J_{PH}$ 14, 15) 2.26, 2.41 (3H, s), 4.12-4.34 (4H, m), 4.87-4.92 (1H, m), 5.91, 5.99 (1H, d, ^3J 4.5, 3, exchanges with D_2O), 7.07- 7.60 (9H, m); ^{13}C NMR ($CDCl_3$) δ 16.2 (br), 21.1 (br), 25.1 (br), 58.9, 61.4, 62.9, 64.1 (br), 64.8 (br), 65.9 (d, $^1J_{PC}$ 159), 67.7 (d, $^1J_{PC}$ 159), 125.1, 125.7, 127.3, 127.6, 127.7, 128.7, 128.8, 129.6, 129.7, 130.6, 136.7 (d, $^3J_{PC}$ 10), 135.7 (d, $^3J_{PC}$ 10), 140.6, 140.8, 141.5, 142.3; ^{31}P NMR ($CDCl_3$) δ 20.42, 20.88; Anal. calcd for $C_{20}H_{27}ClNO_4PS$: C, 54.11; H, 6.13; N, 3.16. Found C, 54.14; H, 6.24; N, 3.06%.

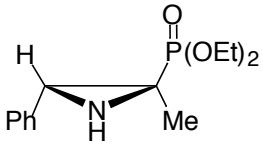


Diethyl (*S*$_S$,*2R*,*3R*)-(+)-2-methyl-3-phenyl-1-(*p*-toluenesulfinyl)-aziridine-2-phosphonate (6). Typical procedure for aziridinyl phosphonate formation: In a 50 mL round-bottom flask equipped with a magnetic stirrer bar, rubber septum and argon inlet was placed sodium hydride (32.4 mg, 60% dispersion in oil, 811 μmol) which was washed with anhydrous LP (3 × 3 mL) [Washing performed by adding LP *via* syringe, stirring vigorously, allowing to settle, and removing liquid *via* syringe.] Residual solvent was removed under aspirator pressure and THF (8 mL) was added. To this stirred suspension was added phosphonate (+)-**3**

(180 mg, 405 μmol) dissolved in THF (2 mL) *via* syringe. After 20 min, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl (2 mL). The mixture was diluted with H_2O (10 mL) and extracted with Et_2O (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated to give a colourless oil. Flash chromatography (SiO_2, CH_2Cl_2-EtOAc, 5:1) afforded (+)-**6** in a 10:1 mixture of invertomers as a colourless oil (114 mg, 69%); R_f 0.35 (CH_2Cl_2-EtOAc, 5:1); $[\alpha]_D^{20}$ +5.2 (c 1.4, $CHCl_3$); IR (NaCl) 1254, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (3H, d, $^3J_{PH}$11, major), 1.38 (3H, t, ^3J 7), 1.43 (3H, t, ^3J 7), 1.94 (3H, d, $^3J_{PH}$12.5, minor), 2.43 (3H, s, major), 2.44 (3H, s, minor), 4.18-4.33 (4H, m), 4.41 (1H, d, $^3J_{PH}$10, major), 6.89-6.92 (2H, m, minor), 7.07-7.09 (2H, m, major), 7.22-7.24 (3H, m), 7.31-7.34 (2H, m), 7.67-7.69 (2H, m, minor), 7.74-7.75 (2H, m, major); ^{13}C NMR ($CDCl_3$) (major invertomer only) δ 12.8, 16.4-16.5 (m), 21.5, 43.2, 45.4 (d, $^1J_{PC}$ 181), 62.7 (d, $^2J_{PC}$ 6), 63.0 (d, $^2J_{PC}$ 6), 125.2, 127.8, 127.9, 128.1, 129.5, 133.5 141.8, 144.2; ^{31}P NMR ($CDCl_3$) δ 24.32; MS (FAB$^+$) *m/z* 408 [93%, MH$^+$], 268 [100, M$^+$-MeC_6H_4SO]; HRMS ($C_{20}H_{27}NO_4PS^+$) found 408.1398; calcd 408.1401; Anal. calcd for $C_{20}H_{26}NO_4PS$: C, 58.95; H, 6.43; N, 3.44. Found C, 58.85; H, 6.43; N, 3.22%.

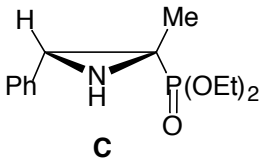


Diethyl (*S*$_S$,*2S*,*3R*)-2-methyl-3-phenyl-1-(*p*-toluenesulfinyl)-aziridine-2-phosphonate (A) and diethyl (*S*$_S$,*2S*,*3S*)-2-methyl-3-phenyl-1-(*p*-toluenesulfinyl)-aziridine-2-phosphonate (B). The same procedure as for the preparation of (+)-**6** was applied, using a 69:31 mixture of **4** and **5** to afford a 69:31 mixture of **A** and **B** (81%, 1.32 mmol scale). Flash chromatography (SiO_2, CH_2Cl_2-EtOAc, 5:1) did not give further purification and afforded a 62:38 mixture of **A** and **B** as a colourless oil (45%) (when distinguishable, data for major stereoisomer **A** is given first); R_f 0.2 (CH_2Cl_2-EtOAc, 5:1); $[\alpha]_D^{20}$ +8 (c 0.8, $CHCl_3$); IR (NaCl) 1252, 1022 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09-1.19 (6H, m), 1.40-1.49 (3H, m), 1.94 (3H, d, $^3J_{PH}$ 12), 2.45, 2.35 (3H, s), 3.66-4.43 (5H, m), 7.02-7.34 (7H, m), 7.67-7.80 (2H, m); ^{13}C NMR ($CDCl_3$) δ 15.6-16.4 (m), 21.3, 40.8, 44.5-45.8 (m), 46.8, 61.8 (d, $^2J_{PC}$ 6), 62.5 (d, $^2J_{PC}$ 6), 62.3 (d, $^2J_{PC}$ 6), 63.2 (d, $^2J_{PC}$ 6), 124.7, 124.9, 127.2, 127.3, 127.7, 127.8, 128.0, 129.6, 132.8, 133.8 141.9, 142.3, 142.5, 142.6; ^{31}P NMR ($CDCl_3$) δ 19.04, 23.66; Anal. calcd for $C_{20}H_{26}NO_4PS$: C, 58.95; H, 6.43; N, 3.44. Found C, 58.51; H, 6.56; N, 3.36%.

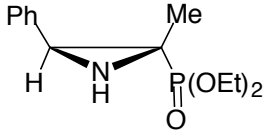


Diethyl (*2R*,*3R*)-(+)-2-methyl-3-phenyl-aziridine-2-phosphonate (7). In a 50 mL round-bottom flask, equipped with a magnetic stirrer bar, rubber septum and argon balloon was placed sulfinyl aziridine (+)-**6** (240 mg, 589 μmol) dissolved in acetone-H_2O (1:1, 14 mL). The vigorously stirred solution was cooled to 0 °C and TFA (226 μL, 2.94 mmol) added *via* syringe. After stirring for 10 min, the reaction mixture was diluted with H_2O (10 mL) and aqueous NH_4OH added until pH 9 was attained. The mixture was extracted with Et_2O (2 × 20 mL) and CH_2Cl_2 (2 × 20 mL), the combined organic phases dried ($MgSO_4$), filtered and concentrated to give a colourless oil. Flash chromatography (SiO_2, CH_2Cl_2-

EtOAc, 2:1) afforded (+)-**7** as a colourless oil (121 mg, 76%); R_f 0.5 (CH_2Cl_2-EtOAc, 2:1); $[\alpha]_D^{20}$ +26 (c 0.56, $CHCl_3$); IR (NaCl) 3246, 1251, 1024 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (3H, d, $^3J_{PH}$ 12), 1.39 (3H, t, ^3J 7), 1.41 (3H, t, ^3J 7), 1.69 (1H, br.s), 3.68 (1H, d, $^3J_{PH}$ 10), 4.16-4.25 (4H, m), 7.28-7.36 (5H, m); ^{13}C NMR ($CDCl_3$) δ 13.0 (d, $^2J_{PC}$ 8), 16.5 (d, $^3J_{PC}$ 6), 34.5 (d, $^1J_{PC}$ 183), 40.5, 62.5 (d, $^2J_{PC}$ 6), 127.4, 127.9, 128.1, 135.5; ^{31}P NMR ($CDCl_3$) δ 28.50; MS (FAB$^+$) *m/z* 292 [48%, MNa^+], 270 [100, MH^+]; HRMS ($C_{13}H_{21}NO_3P^+$) found 270.1251; calcd 270.1259; Anal. calcd for $C_{13}H_{20}NO_3P$: C, 57.98; H, 7.49; N, 5.20. Found C, 57.63; H, 7.50; N, 5.06%.



C

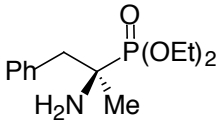


D

Diethyl (*2 S,3R*)-(-)-2-methyl-3-phenyl-aziridine-2-phosphonate (C) and diethyl (*2S,3S*)-(-)-2-methyl-3-phenyl-aziridine-2-phosphonate (D). In a 100 mL round-bottom flask equipped with a magnetic stirrer bar, rubber septum and argon balloon was placed a 62:38 mixture of sulfinyl aziridines **A** and **B** (138 mg, 339 μmol) dissolved in acetone-H_2O (1:1, 8 mL). The vigorously stirred solution was cooled to 0 °C and TFA (131 μL, 1.70 mmol) added *via* syringe. After stirring for 25 min, the reaction mixture was diluted with H_2O (10 mL) and aqueous NH_4OH added until pH 9 was attained. The mixture was extracted with Et_2O (2 × 20 mL) and CH_2Cl_2 (3 × 20 mL), the combined organic phases dried ($MgSO_4$), filtered and concentrated to give a colourless oil. Flash chromatography (SiO_2, EtOAc) afforded (-)-**D** (34.8 mg, 38%) and (-)-**C** (49.8 mg, 55%) as colourless oils:

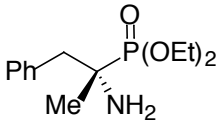
(-)-**C**; R_f 0.25 (EtOAc); $[\alpha]_D^{20}$ -6.9 (c 0.88, $CHCl_3$); IR (NaCl) 3241, 1238, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10-1.16 (6H, m), 1.59 (3H, d, $^3J_{PH}$ 11), 3.19 (1H, d, $^3J_{PH}$ 6.5), 3.56-3.60 (1H, m), 3.79-3.84 (3H, m), 7.23-7.33 (3H, m), 7.40-7.42 (2H, m); ^{13}C NMR ($CDCl_3$) δ 16.1 (br), 21.7 (br), 45.7 (br), 61.6 (d, $^2J_{PC}$ 6), 61.9 (d, $^2J_{PC}$ 6), 127.2, 127.6, 127.9, 135.8; ^{31}P NMR ($CDCl_3$) δ 24.38; MS (FAB$^+$) *m/z* 539 [5%, M_2H^+], 270 [100, MH^+]; HRMS ($C_{13}H_{21}NO_3P^+$) found 270.1253; calcd 270.1259.

(-)-**D**; $[\alpha]_D^{20}$ -26 (c 0.56, $CHCl_3$); MS (FAB$^+$) *m/z* 270 [100%, MH^+]; HRMS ($C_{13}H_{21}NO_3P^+$) found 270.1253; calcd 270.1259; spectroscopic data as for (+)-**7**.

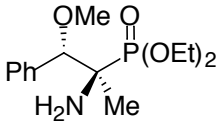


Diethyl (*R*)-(+)-1-amino-1-methyl-2-phenylethylphosphonate (8). General procedure for hydrogenation of aziridines: In a 10 mL round-bottom flask equipped with a magnetic stirrer bar, rubber septum and argon balloon was placed aziridine (+)-**7** (64 mg, 238 μmol) and Pd/C (140 mg, 10% Pd), suspended in MeOH (2 mL). To the stirred solution was added HCO_2NH_4 (98.0 mg, 1.55 mmol) in one portion. After stirring for 15 h, the reaction mixture was filtered through celite® and the residue washed with MeOH (2 × 10 mL) and Et_2O (2 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated to give a colourless oil. Flash chromatography (SiO_2, EtOAc) afforded (+)-**8** as a colourless oil (59.3 mg, 92%); R_f 0.15 (EtOAc); $[\alpha]_D^{20}$ +1.5 (c 0.75, $CHCl_3$); IR (NaCl) 3372, 3292, 1233, 1026 cm^{-1}; ^1H NMR

($CDCl_3$) δ 1.21 (3H, d, $^3J_{PH}$ 16), 1.34 (6H, app.q, ^3J 7), 1.60 (2H, br), 2.92 (1H, dd, ^2J 13.5, $^3J_{PH}$ 9), 2.98 (1H, dd, ^2J 13.5, $^3J_{PH}$ 9), 4.14-4.21 (4H, m), 7.23-7.33 (5H, m); ^{13}C NMR ($CDCl_3$) δ 16.5, 22.2, 42.7, 52.4 (d, $^1J_{PC}$ 153), 62.4 (d, $^2J_{PC}$ 6), 126.6, 127.9, 131.0, 135.5 (d, $^3J_{PC}$ 12); ^{31}P NMR ($CDCl_3$) δ 30.94; MS (FAB$^+$) *m/z* 543 [5%, M_2H^+], 272 [69, MH^+], 180 [67, M^+-Bn], 154 [100]; Anal. calcd for $C_{13}H_{22}NO_3P$: C, 57.55; H, 8.17; N, 5.16. Found C, 57.30; H, 7.93; N, 4.79%.



Diethyl (*S*)-(-)-1-amino-1-methyl-2-phenylethylphosphonate (9). The same procedure as for the preparation of (+)-**8** was applied, using either (-)-**C** or (-)-**D**. Flash chromatography (SiO_2, EtOAc, EtOAc-MeOH, 19:1) afforded (-)-**9** as a colourless oil (57%, 144 μmol scale from (-)-**C** and 61%, 111 μmol scale from (-)-**D**), which exhibited spectroscopic data as for (+)-**8**; $[\alpha]_D^{20}$ -1.4 (c 0.77, $CHCl_3$); HRMS ($C_{13}H_{22}NNaO_3P^+$) found 294.1229; calcd 294.1235.



Diethyl (*1R,2S*)-(+)-1-amino-1-methyl-2-methoxy-2-phenylethylphosphonate (10). The same procedure as for the preparation of (+)-**11** was applied except that the reaction was conducted at rt for 4d and then 55 °C for 2 d. Flash chromatography (SiO_2, EtOAc-MeOH, 49:1) afforded (+)-**30** as a colourless oil (72%, 75 μmol scale). R_f 0.25 (EtOAc-MeOH, 49:1); $[\alpha]_D^{20}$ +63 (c 0.76, $CHCl_3$); IR (NaCl) 3380, 3292, 1235, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, d, $^3J_{PH}$16) 1.26 (3H, t, ^3J 7), 1.34 (3H, t, ^3J 7), 1.54 (2H, br.s), 3.26 (3H, s), 4.02-4.22 (4H, m), 4.45 (1H, d, $^3J_{PH}$7.5), 7.31-7.38 (5H, m); ^{13}C NMR ($CDCl_3$) δ 16.3 (d, $^3J_{PC}$ 6), 16.5 (d, $^3J_{PC}$ 4), 57.0 (d, $^1J_{PC}$ 153), 57.1, 61.6 (d, $^2J_{PC}$ 8), 62.6 (d, $^2J_{PC}$ 6), 85.7, 127.8, 128.0, 128.8, 136.5 (d, $^3J_{PC}$ 8); ^{31}P NMR ($CDCl_3$) δ 29.66; MS (FAB$^+$) *m/z* 302 [94%, MH^+], 270 [31, M^+-MeO]; 180 [100]; HRMS ($C_{14}H_{25}NO_4P^+$) found 302.1510; calcd 302.1521.

References

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3. F. A. Davis and W. McCoull, *Tetrahedron Lett.*, **1999**, *40*, 249-252.