Catalytic Enantioselective Friedel-Crafts Alkylations with α' -Phosphoric Enones

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Supporting Information**General Information**

All reactions were carried out under nitrogen in flame-dried glassware with magnetic stirring. Analytical thin layer chromatography (TLC) was performed on Merck precoated silica gel F₂₅₄ plates. Visualization was accomplished with UV light (254 nm), exposure to iodine vapour, or treatment with acidic anisaldehyde staining followed by heating. Purification of reaction products were carried out by flash column chromatography using Merck 60, 230-400 mesh ASTM.

¹H NMR was recorded on Bruker Fourier Transform AM 300 (300 MHz), and Bruker Fourier Transform AM 400 (400 MHz). Chemical shifts were reported in ppm using solvent as the internal standard (CDCl₃ at 7.24 ppm or C₆D₆ at 7.15 ppm). Data are reported as: b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constant, J in Hz. ¹³C NMR spectra were recorded on Bruker Fourier Transform AM 300 (75 MHz), and Bruker Fourier Transform AM 400 (100 MHz). Chemical shifts were reported in ppm from tetramethylsilane, with the solvent resonance employed as the internal standard (CDCl₃ at 77.0 ppm or C₆D₆ at 128.0 ppm)

Infrared (IR) spectra were recorded in 0.1 mm path length sodium chloride cells on a BOMEM MB-100 Fourier Transform spectrometer and frequencies were given in reciprocal centimetres (cm⁻¹).

Mass spectra were obtained on VG AUTOSPEC Ultima GC/MS system using direct insertion probe (DIP) and electron impact (EI) (70 eV) method.

Analytical high performance liquid chromatography (HPLC) was performed on Agilent 11000 Series HPLC equipped with a variable wavelength detector using a Chiralcel AD-H, OD-H, OJ-H, or AS-H column.

Materials

Et₂O and THF were distilled from sodium-benzophenone, CH₂Cl₂ was distilled from CaCl₂ under nitrogen. Cu(II) triflate was purchased from the Aldrich company, stored in an inert atmosphere dry box, and used without further purification.

Substrate Syntheses

General Procedure for the Synthesis of β -Keto Phosphonates ¹

Dimethyl 2-oxopropane phosphonate

To a stirred solution of dimethyl methane phosphonate (1.0 equiv, 80 mmol, 10.0 g) in THF (100 mL) at -78°C was added 2.5 M solution of *n*-BuLi in hexane (1.0 equiv, 80 mmol, 32.2 mL). After being stirred for 30 min, methyl acetate (2.3 equiv, 185 mmol, 13.7 g) in THF (20 mL) was introduced slowly to the reaction mixture via a cannula. The mixture was stirred at -78°C for 0.5 h and then warmed up to 0°C . The reaction was quenched at 0°C with 1 M HCl aqueous solution, volatiles were removed under vacuum and extracted with CH_2Cl_2 . The combined organic layer was washed with saturated NaHCO_3 , and brine, dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by fractional distillation to give 7.49 g (56%) of the expected product as colorless oil; bp $85\text{--}90^\circ\text{C}$ (1.5 torr). Analytical data: ^1H NMR (300 MHz, CDCl_3) δ 3.66 (d, 6H), 3.01 (d, 2H), 2.18 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 199.65 (199.57), 52.95 (52.86), 42.88, 41.19, 31.29.

General Procedures for the Synthesis of α' -Phosphoric enones

Method A ^{2a}:

R = Me; Dimethyl (*E*-2-Oxo-4-methyl-3-butenyl) phosphonate, **2a**

A solution of dimethyl methylphosphonate (2.0 equiv, 40 mmol, 5.1 g) in THF (80 mL) was cooled to -78°C . A 2.5 M solution of *n*-BuLi in hexane (2.2 equiv, 44 mmol, 17.6 mL) was added to the phosphonate solution dropwise for 40 min. The reaction mixture was allowed to stir at -78°C for 1.5 h, after which time a solution of ethyl *E*-crotonate (1.0 equiv, 20 mmol, 2.5 mL) was added to the reaction mixture dropwise. The reaction mixture was allowed to warm to room temperature over a period of 20 h. The reaction was quenched with 1 M HCl aqueous solution, extracted with CH_2Cl_2 , dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate : MeOH = 50 : 1; R_f = 0.3) to give 3.2 g (84%) yield as colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 6.93 (m, 1H), 6.21 (dd, 1H), 3.73 (d, 6H), 3.18 (d, 2H), 1.89 (dd, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 190.51 (190.43), 145.34, 131.29, 52.57 (52.49), 39.17, 37.46, 17.94; IR (film): 3468, 2959, 2855, 1691, 1665, 1628, 1444, 1404, 1376, 1252, 1032, 971, 839, 813 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_7\text{H}_{13}\text{O}_4\text{P}$ $[\text{M}]^+$: 192.0551, found 192.0551.

Method B ^{2b}:

R = Et; Dimethyl (*E*-2-Oxo-4-ethyl-3-butenyl) phosphonate, **2b**

To a stirred solution of dimethyl methylphosphonate (1.0 equiv, 50 mmol, 6.4 g) in THF (65 mL) was added 2.5 M solution of *n*-BuLi in hexane (1.1 equiv, 55 mmol, 22 mL) at -78 °C. After 0.5 h, the temperature raised to -40 °C and Cu(I)I (1.0 equiv, 50 mmol, 9.5 g) was added in one portion. When the resulting mixture became black, stirring was continued for additional 1 h at this temperature and pent-2-enoyl chloride (1.0 equiv, 50 mmol, 5.9 g) was added dropwise at -78 °C. The resulting mixture was stirred overnight. After evaporation of solvents, the residue was extracted with CH₂Cl₂, washed with 1 M HCl aqueous solution, and brine, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to give 6.7 g (65%) yield as colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 6.87 (m, 1H), 6.07 (m, 1H), 3.59 (d, 6H), 3.10 (d, 2H), 2.17 (m, 2H), 0.95 (t, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 190.92 (190.84), 151.68, 128.82, 52.78 (52.69), 39.47, 37.75, 25.35, 11.76, 10.43; IR (film): 3474, 2963, 2855, 1602, 1665, 1625, 1460, 1407, 1341, 1254, 1188, 1033, 979, 883, 848, 808, 765 cm⁻¹; HRMS (EI): Exact mass calcd for C₈H₁₅O₄P [M]⁺: 206.0708, found 206.0708.

R = *i*-Pr; Dimethyl (*E*-2-Oxo-4-*i*-propyl-3-butenyl) phosphonate, **2c**

This compound was similarly prepared using Method B and full spectral data are as follows.

Colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 6.85 (dd, 1H), 6.10 (dd, 1H), 3.72 (d, 6H), 3.19 (d, 2H), 2.44 (m, 1H), 1.01 (d, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 191.47 (191.39), 156.58, 127.23, 53.05 (52.97), 39.83, 38.11, 31.22, 25.65, 21.11; IR (film): 3423, 2962, 3857, 1717, 1694, 1665, 1631, 1458, 1381, 1245, 1188, 1037, 988, 849, 818, 747 cm⁻¹; HRMS (EI): Exact mass calcd for C₉H₁₇O₄P [M]⁺: 220.0864, found 220.0864.

Method C ^{2c}:

R = CH₂CH₂Ph; Dimethyl (*E*-2-Oxo-6-phenyl-3-hexenyl) phosphonate, **2d**

To the solution of LDA, which was prepared from DIPA (3.0 equiv, 37.8 mmol, 5.3 mL) and 2.5 M solution of *n*-BuLi in hexane (2.4 equiv, 30.2 mmol, 12.1 mL) at -78 °C in THF (40 mL) was added **1'** (1.0 equiv, 12.6 mmol, 2.1 g) in THF (5 mL) under nitrogen. The reaction mixture was warmed to 0 °C and stirred for 1 h. To the reaction mixture, *trans*-cinnamaldehyde (1.2 equiv, 15.1 mmol, 2.1 g) was added dropwise at 0 °C and stirred for 4 h. After completion of the reaction, the reaction was quenched with 1 M HCl aqueous solution, extracted with CH₂Cl₂, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to give 3.2 g (85%) yield.

To a solution of **2'** (1.0 equiv, 10.7 mmol, 3.2 g) and methanesulfonyl chloride (1.2 equiv, 12.9 mmol, 1.5 g) in CH₂Cl₂ (20 mL) was added dropwise Et₃N (3.0 equiv, 32.2 mmol, 2.2 mL) at -78 °C. After being stirred at 0 °C for 20 min, the mixture was poured into ice water. The organic layer was washed with 1 M HCl aqueous solution, dried over MgSO₄, filtered, concentrated under reduced pressure. The residue was purified by column chromatography to give 2.3 g (75%) yield as yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 7.26-7.13 (m, 5H), 6.96 (m, 1H), 6.22 (d, 6.23), 3.75 (d, 6H), 3.21 (d, 2H), 2.79 (t, 2H), 2.56 (m, 2H); ¹³C NMR (300 MHz, CDCl₃) δ 190.91, 149.32, 140.52, 130.37, 128.53, 128.33, 126.27, 53.15 (53.06), 39.91, 38.20, 34.19; IR (film): 3437, 3027, 2958, 2856, 1720, 1666, 1625, 1496, 1454, 1400, 1368, 1233, 1038, 817, 751, 702 cm⁻¹; HRMS (EI): Exact mass calcd for C₁₄H₁₉O₄P [M]⁺: 282.1021, found 282.1021.

General Procedure of the Catalytic Enantioselective Friedel-Crafts Alkylation:

As a typical example, the reaction of **2a** with **3a** is described as follows: To an oven dried flask in a dry-box was added an appropriate amount Cu(II) triflate (20 mol%, 0.022 mmol, 8.1 mg) and (S)-In-Box (22 mol%, 0.024 mmol, 8.7 mg). The flask was capped with a septum and purged with CH₂Cl₂ (1 mL). The reaction was allowed to stir at room temperature for 2 h to prepare catalyst [(S)-In-Box]Cu(OTf)₂ **1a**. A solution of enone **2a** (1.0 equiv, 0.11 mmol, 21 mg) in CH₂Cl₂ (1 mL) was added to the solution of **1a**. After 0.5 h, the reaction mixture was cooled to 0 °C, and the solution of an indole derivative (1.2 equiv, 0.13 mmol, 15.6 mg) in CH₂Cl₂ (1 mL) was added to the reaction mixture. The reaction was maintained at 0 °C until complete consumption of the α'-phosphoric enone **2a** by TLC. After completion of the reaction, the title compound **4a** was purified by flash column chromatography to give 34.9 mg (98%) yield.

4a

Colorless oil (Ethyl acetate); ¹H NMR (400 MHz, CDCl₃) δ 8.16 (b, 1H), 7.62 (d, 1H), 7.33 (d, 1H), 7.17 (t, 1H), 7.10 (t, 1H), 6.96 (s, 1H), 3.73 (dd, 6H), 3.62 (m, 1H), 3.11 (dd, 1H), 3.01 (d, 2H), 2.92 (dd, 1H), 1.38 (d, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 201.37 (201.31), 136.51, 126.17, 121.98, 120.47, 120.37, 119.21, 119.06, 111.26, 52.99 (52.93), 51.66, 42.20, 40.93, 26.73, 21.07; IR (film) 3409, 3289, 2959, 1714, 1458, 1398, 1374, 1341, 1247, 1184,

1103, 1034, 816, 765, 746, 624 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_{15}\text{H}_{20}\text{NO}_4\text{P}$ $[\text{M}]^+$: 309.1132. Found: 309.1130; Product ratio was determined by HPLC analysis (Chiralcel AS-H, 30% *i*-PrOH/hexane = 0.3 ml/min, 254 nm); *R* isomer (minor) t_r = 27.3 min and *S* isomer (major) t_r = 30.4 min; $[\alpha]_D^{25}$ = -48.7 ° (c 0.8, CH_2Cl_2).

Colorless oil (Ethyl acetate); ^1H NMR (300 MHz, CDCl_3) δ 8.45 (b, 1H), 7.62 (d, 1H), 7.33 (d, 1H), 7.24-7.05 (m, 3H), 6.93 (s, 1H), 4.14 (q, 4H), 3.66 (m, 1H), 3.12 (dd, 1H), 3.02 (s, 1H), 2.95 (s, 1H), 2.92 (dd, 1H), 1.45 (d, 3H), 1.37 (t, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 201.68, 136.59, 126.22, 121.02, 120.48, 119.14, 119.09, 111.38, 62.63 (62.54), 51.70, 43.48, 41.80, 39.66, 26.73, 21.18, 16.38, 16.30; IR (film): 3409, 3276, 2980, 2929, 1714, 1458, 1394, 1370, 1341, 1246, 1163, 1100, 1025, 973, 794, 765, 744 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_{17}\text{H}_{24}\text{NO}_4\text{P}$ $[\text{M}]^+$: 337.1426. Found: 337.1443; Product ratio was determined by HPLC analysis (Chiralcel AS-H, 20% *i*-PrOH/hexane = 0.7 ml/min, 254 nm); *R* isomer (minor) t_r = 30.2 min and *S* isomer (major) t_r = 33.2 min; $[\alpha]_D^{25}$ = +17.00 ° (c 0.8, CH_2Cl_2).

Colorless oil (Ethyl acetate); ^1H NMR (300 MHz, CDCl_3) δ 8.36 (b, 1H), 7.63 (d, 1H), 7.33 (d, 1H), 7.17 (t, 1H), 7.09 (t, 1H), 6.94 (d, 1H), 4.70 (m, 2H), 3.64 (m, 1H), 3.12 (m, 4H), 1.36 (d, 3H), 1.31 (dd, 12H); ^{13}C NMR (75 MHz, CDCl_3) δ 201.65, 136.59, 126.26, 121.91, 120.64, 120.40, 119.15, 111.33, 71.44 (71.38), 51.54, 44.85, 43.16, 26.67, 24.02, 23.85, 23.78, 21.22; IR (film): 3409, 3266, 3057, 2979, 2932, 1714, 1458, 1386, 1375, 1341, 1245, 1179, 1142, 1104, 992, 889, 765, 743 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_{19}\text{H}_{28}\text{NO}_4\text{P}$ $[\text{M}]^+$: 365.1752. Found: 365.1756; Product ratio was determined by HPLC analysis (Chiralcel AS-H, 20% *i*-PrOH/hexane = 0.2 ml/min, 254 nm); *R* isomer (minor) t_r = 38.4 min and *S* isomer (major) t_r = 41.3 min; $[\alpha]_D^{25}$ = -6.49 ° (c 2.2, CH_2Cl_2).

Colorless oil (Ethyl acetate); ^1H NMR (400 MHz, CDCl_3) δ 8.16 (b, 1H), 7.61 (d, 1H), 7.30-7.06 (m, 13H), 6.90 (s, 1H), 3.70 (m, 1H), 3.29 (s, 1H), 3.24 (s, 1H), 3.20 (dd, 1H), 3.03 (dd, 1H), 1.39 (d, 3H); ^{13}C NMR (400 MHz, CDCl_3) δ 200.21 (200.15), 149.87, 149.77, 136.47, 129.82, 129.81, 126.09, 125.54, 125.51, 121.94, 120.61, 120.60, 120.57, 120.55, 120.41, 120.20, 119.20, 118.98, 111.30, 53.39, 51.90, 42.64, 41.35, 26.73, 21.14; IR (film): 3409, 3319, 1716, 1590, 1489, 1457, 1340, 1271, 1211, 1186, 1162, 1071, 1025, 1008, 944, 903, 764, 745, 689 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_{25}\text{H}_{24}\text{NO}_4\text{P}$ $[\text{M}]^+$: 433.1454. Found: 433.1443; Product ratio was determined by HPLC analysis

(Chiralcel AS-H, 10% *i*-PrOH/hexane = 0.5 ml/min, 220 nm); *S* isomer (major) t_r = 7.13 min and *R* isomer (minor) t_r = 7.69 min; $[\alpha]_D^{25}$ = -5.29 ° (c 3.6, CH₂Cl₂).

Colorless oil (Ethyl acetate); ¹H NMR (300 MHz, CDCl₃) δ 8.95 (b, 1H), 7.75-7.02 (m, 14H), 6.83 (s, 1H), 3.57 (m, 1H), 3.51 (s, 1H), 3.46 (s, 1H), 3.07 (dd, 1H), 2.99 (dd, 1H), 1.25 (d, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 202.57 (202.50), 136.62, 132.74, 132.33, 131.37, 131.10, 130.96, 130.82, 128.93, 128.77, 126.31, 121.71, 120.79, 120.29, 119.08, 119.00, 111.57, 60.46, 52.91, 47.64, 46.89, 21.45; IR (film): 3400, 3245, 2967, 1709, 1458, 1437, 1395, 1373, 1340, 1273, 1247, 1185, 1121, 1104, 1044, 1007, 743, 695 cm⁻¹; HRMS (EI): Exact mass calcd for C₂₅H₂₄NO₂P [M]⁺: 401.1547. Found: 401.1545; Product ratio was determined by HPLC analysis (Chiralcel AD-H (IA), 30% *i*-PrOH/hexane = 0.5 ml/min, 254 nm); *S* isomer (major) t_r = 26.5 min and *R* isomer (minor) t_r = 30.6 min; $[\alpha]_D^{25}$ = -21.97 ° (c 3.2, CH₂Cl₂).

4b

Colorless oil (Ethyl acetate); ¹H NMR (400 MHz, C₆D₆) δ 7.72 (d, 1H), 7.58 (b, 1H), 7.20-7.14 (m, 4H), 6.69 (d, 1H), 3.54 (m, 1H), 3.29 (dd, 6H), 3.02 (dd, 1H), 2.90 (dd, 1H), 2.66 (m, 2H), 1.77 (m, 1H), 0.86 (t, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 201.72 (201.66), 136.52, 126.43, 121.74, 121.56, 119.15, 119.02, 117.95, 111.28, 52.91 (52.87), 49.97, 41.99, 40.72, 34.13, 28.35, 11.97; IR (film): 3409, 3276, 2958, 2926, 1715, 1458, 1398, 1339, 1248, 1184, 1034, 932, 894, 745 cm⁻¹; HRMS (EI): Exact mass calcd for C₁₆H₂₂NO₄P [M]⁺: 323.1268. Found: 323.1286; Elemental analysis calcd: C 59.44, H 6.86, N 4.33%; Found C 59.39, H 6.85, N 4.33%; Product ratio was determined by HPLC analysis (Chiralcel AD-H (IA), 20% *i*-PrOH/hexane = 0.2 ml/min, 254 nm); *S* isomer (major) t_r = 45.4 min and *R* isomer (minor) t_r = 49.0 min; $[\alpha]_D^{25}$ = +6.31 ° (c 0.4, CH₂Cl₂).

4c

Colorless oil (Ethyl acetate); ¹H NMR (400 MHz, C₆D₆) δ 7.71 (d, 1H), 7.20-7.08 (m, 4H), 6.69 (d, 1H), 3.48 (m, 1H), 3.27 (dd, 6H), 3.09 (dd, 1H), 2.99 (dd, 1H), 2.73 (m, 2H), 2.04 (m, 1H), 0.91 (dd, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 201.89 (201.83), 136.30, 127.09, 122.07, 121.81, 119.44, 119.20, 117.26, 111.15, 52.90 (52.82), 47.25,

41.88, 40.60, 39.09, 32.48, 20.51, 20.34; IR (film): 3409, 3282, 2957, 2871, 1715, 1653, 1458, 1249, 1183, 1125, 1105, 1035, 932, 886, 847, 765, 744 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_{17}\text{H}_{24}\text{NO}_4\text{P}$ $[\text{M}]^+$: 337.1442. Found: 337.1443; Elemental analysis calcd: C 60.53, H 7.17, N 4.15%; Found C 60.03, H 7.11, N 4.12%; Product ratio was determined by HPLC analysis (Chiralcel AS-H, 30% *i*-PrOH/hexane = 0.3 ml/min, 254 nm); *R* isomer (minor) t_r = 32.8 min and *S* isomer (major) t_r = 34.1 min; $[\alpha]_D^{25}$ = -8.2° (c 0.7, CH_2Cl_2).

4d

Colorless oil (Ethyl acetate); ^1H NMR (400 MHz, CDCl_3) δ 7.61 (d, 1H), 7.26 (d, 1H), 7.21 (t, 1H), 7.09 (t, 1H), 6.28 (s, 1H), 3.74 (dd, 6H), 3.64 (m, 1H), 3.10 (dd, 1H), 3.01 (s, 1H), 2.96 (s, 1H), 2.92 (dd, 1H), 1.37 (d, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.32 (201.26), 137.13, 126.53, 125.13, 121.57, 119.15, 119.06, 118.69, 109.25, 52.92 (52.90), 51.78, 42.18, 40.91, 32.52, 26.66, 21.23; IR (film): 3452, 2958, 1714, 1636, 1472, 1425, 1398, 1374, 1329, 1310, 1255, 1184, 1132, 1109, 1032, 989, 815, 744 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_4\text{P}$ $[\text{M}]^+$: 323.1284. Found: 323.1286; Product ratio was determined by HPLC analysis (Chiralcel OJ-H, 30% *i*-PrOH/hexane = 0.6 ml/min, 254 nm); *S* isomer (major) t_r = 19.0 min and *R* isomer (minor) t_r = 21.6 min; $[\alpha]_D^{25}$ = -10.0° (c 1.1, CH_2Cl_2).

4e

Colorless oil (Ethyl acetate); ^1H NMR (400 MHz, CDCl_3) δ 7.62 (d, 1H), 7.60 (d, 1H), 7.19 (t, 1H), 7.09 (t, 1H), 6.86 (s, 1H), 5.95 (m, 1H), 5.17 (dd, 2H), 4.64 (d, 2H), 3.73 (dd, 6H), 3.67 (m, 1H), 3.11 (dd, 1H), 3.01 (s, 1H), 2.95 (s, 1H), 2.91 (dd, 1H), 1.37 (d, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.31 (201.24), 136.56, 133.49, 126.77, 124.06, 121.61, 119.50, 119.24, 118.86, 117.17, 109.64, 52.96 (52.91), 51.74, 48.65, 42.21, 40.94, 26.67, 21.12; IR (film): 3419, 2957, 2917, 2850, 1715, 1646, 1613, 1467, 1373, 1261, 1187, 1031, 995, 936, 893, 743, 704 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_{18}\text{H}_{24}\text{NO}_4\text{P}$ $[\text{M}]^+$: 349.1443. Found: 349.1443; Elemental analysis calcd: C 61.88, H 6.92, N 4.01%; Found C 61.57, H 6.89, N 3.99%; Product ratio was determined by HPLC analysis (Chiralcel AS-H, 30% *i*-PrOH/hexane = 0.3 ml/min, 220 nm); *R* isomer (minor) t_r = 40.7 min and *S* isomer (major) t_r = 51.8 min; $[\alpha]_D^{25}$ = -10.5° (c 0.3, CH_2Cl_2).

4f

Colorless oil (Ethyl acetate); ^1H NMR (400 MHz, C_6D_6) δ 7.71 (d, 1H), 7.21-7.01 (m, 9H), 6.63 (d, 1H), 3.66 (m, 1H), 3.28 (dd, 6H), 2.99 (m, 2H), 2.63 (m, 4H), 2.07 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.28 (201.22), 142.17, 136.59, 128.53, 128.34, 128.22, 126.35, 125.65, 121.95, 121.72, 119.27, 117.87, 111.32, 52.92 (52.85), 50.35, 42.15, 40.88, 37.12, 33.75, 32.32; IR (film): 3411, 3277, 3025, 2953, 2925, 1714, 1495, 1456, 1398, 1340, 1248, 1183, 1034, 878, 815, 745, 702 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_{22}\text{H}_{26}\text{NO}_4\text{P}$ $[\text{M}]^+$: 399.1599. Found: 399.1599; Elemental analysis calcd: C 66.15, H 6.56, N 3.51%; Found C 66.14, H 6.56, N 3.40%; Product ratio was determined by HPLC analysis (Chiralcel AD-H (IA), 30% *i*-PrOH/hexane = 0.3 ml/min, 254 nm); *S* isomer (major) t_r = 23.3 min and *R* isomer (minor) t_r = 25.4 min; $[\alpha]_D^{25}$ = -8.7° (c 2.1, CH_2Cl_2).

4g

Colorless oil (Ethyl acetate); ^1H NMR (400 MHz, CDCl_3) δ 7.61 (d, 1H), 7.28-7.07 (m, 9H), 6.87 (s, 1H), 3.73 (s, 3H), 3.68-3.61 (dd, 6H), 3.49 (m, 1H), 3.11 (dd, 1H), 3.02 (dd, 1H), 2.92 (dd, 1H), 2.86 (dd, 1H), 2.55 (t, 2H), 2.08 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.30 (201.24), 142.24, 137.25, 128.35, 128.21, 126.82, 126.42, 125.63, 121.55, 119.37, 118.78, 116.49, 109.32, 52.93 (52.80), 50.55, 42.21, 40.94, 37.30, 33.80, 32.64, 32.29; IR (film): 3448, 2953, 2923, 2853, 1715, 1471, 1455, 1396, 1375, 1328, 1255, 1182, 1131, 1032, 815, 743, 702 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_{23}\text{H}_{28}\text{NO}_4\text{P}$ $[\text{M}]^+$: 413.1754. Found: 413.1756; Product ratio was determined by HPLC analysis (Chiralcel AS-H, 30% *i*-PrOH/hexane = 1.0 ml/min, 220 nm); *R* isomer (minor) t_r = 15.1 min and *S* isomer (major) t_r = 20.4 min; $[\alpha]_D^{25}$ = +3.9° (c 1.0, CH_2Cl_2).

4h

Colorless oil (Ethyl acetate); ^1H NMR (400 MHz, CDCl_3) δ 8.06 (b, 1H), 7.24 (t, 1H), 7.05 (d, 1H), 6.94 (d, 1H), 6.83 (dd, 1H), 3.84 (s, 3H), 3.73 (dd, 6H), 3.60 (m, 1H), 3.10 (dd, 1H), 3.02 (s, 1H), 2.96 (s, 1H), 2.90 (dd, 1H), 1.36 (d, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.45 (201.38), 153.80, 131.65, 126.56, 121.12, 120.24, 112.05, 111.91, 101.12, 55.97, 52.98 (52.92), 51.54, 42.26, 40.98, 26.62, 21.02; IR (film): 3408, 3288, 2958, 1714, 1624, 1583, 1486, 1456, 1399, 1374, 1251, 1215, 1177, 1035, 813, 723, 645 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_5\text{P}$ $[\text{M}]^+$: 339.1234. Found: 339.1236; Product ratio was determined by HPLC analysis (Chiralcel OD-H, 30% *i*-PrOH/hexane = 0.6 ml/min, 254 nm); *S* isomer (major) t_r = 16.0 min and *R* isomer (minor) t_r = 18.0 min; $[\alpha]_D^{25}$ = -20.0° (c 0.8, CH_2Cl_2).

4i

Colorless oil (Ethyl acetate); ^1H NMR (400 MHz, CDCl_3) δ 8.38 (b, 1H), 7.56 (d, 1H), 7.23 (d, 1H), 7.09 (d, 1H), 6.97 (d, 1H), 3.74 (dd, 6H), 3.58 (m, 1H), 3.09 (dd, 1H), 3.03 (s, 1H), 2.97 (s, 1H), 2.88 (dd, 1H), 1.34 (d, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.01 (200.95), 134.86, 127.26, 124.87, 122.19, 121.90, 120.20, 118.50, 112.30, 53.01 (52.98), 51.48, 42.19, 40.92, 26.45, 21.01; IR (film): 3397, 3266, 2958, 1715, 1463, 1399, 1374, 1248, 1184, 1184, 1107, 1034, 893, 864, 802, 755, 619 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_{15}\text{H}_{19}\text{ClNO}_4\text{P}$ $[\text{M}]^+$: 343.0750. Found: 343.0740; Product ratio was determined by HPLC analysis (Chiralcel OJ-H, 30% *i*-PrOH/hexane = 0.3 ml/min, 254 nm); *S* isomer (major) t_r = 37.7 min and *R* isomer (minor) t_r = 42.2 min; $[\alpha]_D^{25}$ = -14.9 $^\circ$ (c 1.0, CH_2Cl_2).

4j

Colorless oil (Ethyl acetate); ^1H NMR (400 MHz, CDCl_3) δ 8.29 (b, 1H), 7.72 (s, 1H), 7.24-7.18 (m, 2H), 6.96 (s, 1H), 3.79 (dd, 6H), 3.58 (m, 1H), 3.09 (dd, 1H), 3.04 (s, 1H), 2.97 (s, 1H), 2.89 (dd, 1H), 1.35 (d, 3H); ^{13}C NMR (400 MHz, CDCl_3) δ 200.98 (200.92), 135.12, 127.97, 124.78, 121.73, 121.61, 120.20, 112.74, 112.47, 53.05 (53.01), 51.48, 42.22, 40.95, 26.43, 21.03; IR (film): 3398, 3258, 2958, 1715, 1459, 1249, 1184, 1032, 934, 885, 839, 816, 754, 630 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_{15}\text{H}_{19}\text{BrNO}_4\text{P}$ $[\text{M}]^+$: 387.0234. Found: 387.0235; Product ratio was determined by HPLC analysis (Chiralcel OJ-H, 30% *i*-PrOH/hexane = 0.3 ml/min, 254 nm); *S* isomer (major) t_r = 40.3 min and *R* isomer (minor) t_r = 45.3 min; $[\alpha]_D^{25}$ = -11.6 $^\circ$ (c 1.0, CH_2Cl_2).

4k

Colorless oil (Ethyl acetate); ^1H NMR (400 MHz, CDCl_3) δ 8.38 (b, 1H), 7.06 (t, 1H), 6.93 (d, 1H), 6.82 (d, 1H), 6.47 (d, 1H), 3.98 (s, 3H), 3.87 (m, 1H), 3.73 (dd, 6H), 3.15 (dd, 1H), 3.06 (s, 1H), 3.00 (s, 1H), 2.80 (dd, 1H), 1.32 (d, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.95 (201.88), 154.28, 138.21, 122.65, 121.07, 119.13, 116.32, 104.57, 99.29, 54.96, 53.02 (52.89), 41.52, 40.24, 27.72, 20.95; IR (film): 3404, 3276, 2957, 2360, 2341, 1714, 1617, 1585, 1508, 1459, 1361, 1258, 1184, 1090, 1031, 972, 933, 889, 840, 739 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_5\text{P}$ $[\text{M}]^+$: 389.0187. Found: 339.1236; Product ratio was determined by HPLC analysis (Chiralcel OJ-H, 30% *i*-PrOH/hexane = 0.3 ml/min, 254 nm); *S* isomer (major) t_r = 62.4 min and *R* isomer (minor) t_r = 75.2 min; $[\alpha]_D^{25}$ = -19.8 $^\circ$ (c 0.5, CH_2Cl_2).

4l

Colorless oil (Ethyl acetate); ^1H NMR (400 MHz, C_6D_6) δ 7.27 (d, 1H), 7.15-6.95 (m, 8H), 6.63 (d, 1H), 3.65 (m, 1H), 3.60 (s, 3H), 3.27 (dd, 6H), 3.04 (dd, 1H), 2.97 (dd, 1H), 2.65-2.57 (m, 5H), 2.09 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.32, 153.86, 142.19, 131.74, 128.39, 128.25, 126.90, 125.68, 122.37, 117.79, 112.07, 111.93, 101.36, 55.98, 52.92 (52.83), 50.26, 42.24, 40.97, 37.14, 33.70, 32.10; IR (film): 3409, 3276, 3025, 2952, 1715, 1624, 1582, 1485, 1455, 1250, 1216, 1176, 1127, 1033, 803, 751, 702, 648 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_{23}\text{H}_{28}\text{NO}_3\text{P}$ $[\text{M}]^+$: 429.1722. Found: 429.1705; Product ratio was determined by HPLC analysis (Chiralcel AD-H (IA), 30% *i*-PrOH/hexane = 0.3 ml/min, 254 nm); *S* isomer (major) t_r = 22.9 min and *R* isomer (minor) t_r = 25.0 min; $[\alpha]_{\text{D}}^{25}$ = -6.51 $^\circ$ (c 0.9, CH_2Cl_2).

6a

Colorless oil (Ethyl acetate); ^1H NMR (400 MHz, C_6D_6) δ 7.23 (b, 1H), 6.36 (m, 1H), 6.31 (m, 1H), 6.11 (m, 1H), 3.39 (d, 6H), 3.36 (m, 1H), 3.08 (s, 3H), 2.90 (dd, 1H), 2.74 (m, 3H), 1.22 (d, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 199.95 (199.88), 136.71, 120.91, 106.93, 104.12, 52.09 (51.98), 51.11, 42.54, 40.87, 32.63, 26.09, 21.01; IR (film): 3997, 3415, 2960, 1715, 1649, 1492, 1460, 1400, 1375, 1299, 1256, 1184, 1033, 814, 712, 549, 466 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_{12}\text{H}_{20}\text{NO}_4\text{P}$ $[\text{M}]^+$: 273.1130. Found: 273.1133; Product ratio was determined by HPLC analysis (Chiralcel OD-H, 10% *i*-PrOH/hexane = 0.5 ml/min, 220 nm); *R* isomer (minor) t_r = 18.9 min and *S* isomer (major) t_r = 20.3 min; $[\alpha]_{\text{D}}^{25}$ = -24.54 $^\circ$ (c 1.0, CH_2Cl_2).

6b

Colorless oil (Ethyl acetate); ^1H NMR (400 MHz, C_6D_6) δ 7.23-7.07 (m, 5H), 6.37 (m, 2H), 6.12 (m, 1H), 3.38 (dd, 6H), 3.27 (m, 1H), 3.13 (s, 3H), 2.91 (dd, 1H), 2.78 (dd, 1H), 2.70 (m, 2H), 2.54 (m, 2H), 1.88 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 200.85 (200.88), 141.77, 135.19, 128.28, 128.27, 125.77, 121.02, 106.82, 104.43, 52.98 (52.92), 50.49, 42.39, 41.12, 37.47, 33.63, 33.22, 30.99; IR (film): 3429, 2954, 1714, 1658, 1494, 1454, 1398, 1297, 1250, 1183, 1127, 1032, 888, 814, 751, 703, 611 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_{19}\text{H}_{26}\text{NO}_4\text{P}$ $[\text{M}]^+$: 363.1598. Found: 363.1599; Product ratio was determined by HPLC analysis (Chiralcel OD-H, 30% *i*-PrOH/hexane = 1.0 ml/min, 220 nm); *R* isomer (minor) t_r = 9.74 min and *S* isomer (major) t_r = 16.3 min; $[\alpha]_{\text{D}}^{25}$ = -5.2 $^\circ$ (c 1.4, CH_2Cl_2).

Cleavage of Phosphonate & Determination of Absolute Configuration**Dephosphylation³**

To a suspension of sodium hydride (1.1 equiv, 0.18 mmol, 7.0 mg) in dry THF (1 mL) at room temperature was added the Friedel-Crafts adduct **4g** (1.0 equiv, 0.16 mmol, 65.7 mg) in dry THF (1 mL) slowly. After the mixture was stirred for 1 h, the resulting enolate was transferred into a stirred solution of LiAlH_4 (3.0 equiv, 0.48 mmol, 19 mg) in THF (0.5 mL) at room temperature and stirred for 0.5 h. The mixture was quenched with 10 N H_2SO_4 (0.2 mL). The solution was extracted with Et_2O . The organic phase was washed with saturated NaHCO_3 , dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to give 46.4 mg (95%) yield as colorless oil (Ethyl acetate-Hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.62 (d, 1H), 7.29-7.06 (m, 8H), 6.85 (s, 1H), 3.73 (s, 3H), 3.48 (m, 1H), 2.92 (dd, 1H), 2.83 (dd, 1H), 2.56 (t, 2H), 2.07 (m, 2H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.44, 142.29, 137.27, 128.33, 128.20, 126.86, 126.24, 125.61, 121.49, 119.33, 118.68, 116.86, 109.31, 50.37, 37.53, 33.88, 32.61, 32.52, 30.35; IR (film): 3417, 3058, 3025, 2928, 1710, 1549, 1472, 1454, 1423, 1357, 1327, 1242, 1154, 1074, 1013, 741, 701 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_{21}\text{H}_{23}\text{NO}$ $[\text{M}]^+$: 305.1770. Found: 305.1780.

HWE-Reaction⁴

To a solution of **4g** (1.0 equiv, 0.11 mmol, 45.5 mg) in EtOH (2 mL), were added K_2CO_3 (2.0 equiv, 0.22 mmol, 30.6 mg) and benzaldehyde (2.0 equiv, 0.22 mmol, 22 μL) and stirred at room temperature. After completion of the reaction, the mixture was extracted with CH_2Cl_2 , washed with H_2O , dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to give 40.3 mg (93%) yield as colorless oil (Ethyl acetate-Hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.71 (d, 1H), 7.39-7.10 (m, 14H), 6.88 (s, 1H), 6.60 (d, 1H), 3.71 (s, 3H), 3.62 (m, 1H), 3.19 (dd, 1H), 3.06 (dd, 1H), 2.62 (m, 2H), 2.17 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 199.76, 142.38, 142.34, 137.36, 134.54, 130.24, 128.78, 128.39, 128.20, 128.15, 126.95, 126.46, 126.40, 125.60, 121.49, 119.48, 118.72, 117.04, 109.38, 47.65, 37.24, 33.98, 33.14, 32.60; IR (film): 3470, 3057, 3025, 2928, 1685, 1655, 1609, 1575, 1494, 1483, 1450, 1328, 1202, 1178, 1154, 1099, 977, 741, 700 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_{28}\text{H}_{27}\text{NO}$ $[\text{M}]^+$: 393.2088. Found: 393.2093.

Determination of Absolute Configuration.⁵

α' -Phosphonate compound **4f** was transformed to the known ketone compound.^{5b} The absolute stereochemistry of products was assigned by transformation.

Yellow waxy oil (Ethyl acetate-Hexane); ¹H NMR (300 MHz, CDCl₃) δ 8.02 (b, 1H), 7.65 (d, 1H), 7.35 (d, 1H), 7.24-6.89 (m, 7H), 6.81 (s, 1H), 4.15 (m, 1H), 2.96 (m, 2H), 2.57 (t, 2H), 2.10 (m, 2H), 1.98 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 208.30, 142.13, 136.48, 128.23, 128.11, 126.31, 125.53, 121.88, 121.33, 119.16, 118.30, 111.17, 50.04, 37.23, 33.73, 32.46, 30.25; IR (film): 3415, 2925, 1702, 1494, 1455, 1421, 1357, 1243, 1158, 1098, 1011, 743, 700 cm⁻¹; HRMS (EI): Exact mass calcd for C₂₀H₂₁NO [M]⁺: 291.1627. Found: 291.1623; Product ratio was determined by HPLC analysis (Chiralcel AS-H, 10% *i*-PrOH/hexane = 0.5 ml/min, 220 nm); *R* isomer (minor) t_r = 33.0 min and *S* isomer (major) t_r = 37.3 min; $[\alpha]_D^{25}$ = +12.4 ° (c 0.8, CH₂Cl₂) 92% ee.

The corresponding *S*-stereochemistry of **7** was elucidated in previous work:^{5b} $[\alpha]_D$ = +12.6 ° (c 1.0, CH₂Cl₂) 94.6% ee

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^1H NMR (400 MHz, CDCl_3)

^{13}C NMR (100 MHz, CDCl_3)

^1H NMR (400 MHz, C_6D_6)

^{13}C NMR (100 MHz, CDCl_3)

¹H NMR (400 MHz, C₆D₆)

¹³C NMR (100 MHz, CDCl₃)

^1H NMR (400 MHz, CDCl_3)

^{13}C NMR (100 MHz, CDCl_3)

^1H NMR (400 MHz, CDCl_3)

^{13}C NMR (100 MHz, CDCl_3)

^1H NMR (400 MHz, C_6D_6)

^{13}C NMR (100 MHz, CDCl_3)

^1H NMR (400 MHz, CDCl_3)

^{13}C NMR (100 MHz, CDCl_3)

^1H NMR (400 MHz, CDCl_3)

^{13}C NMR (100 MHz, CDCl_3)

^1H NMR (400 MHz, CDCl_3)

^{13}C NMR (100 MHz, CDCl_3)

^1H NMR (400 MHz, CDCl_3)

^{13}C NMR (100 MHz, CDCl_3)

^1H NMR (400 MHz, CDCl_3)

^{13}C NMR (100 MHz, CDCl_3)

^1H NMR (400 MHz, C_6D_6)

^{13}C NMR (100 MHz, CDCl_3)

^1H NMR (400 MHz, C_6D_6)

^{13}C NMR (75 MHz, C_6D_6)

^1H NMR (400 MHz, C_6D_6)

^{13}C NMR (100 MHz, CDCl_3)

^1H NMR (300 MHz, CDCl_3)

^{13}C NMR (75 MHz, CDCl_3)

^1H NMR (400 MHz, CDCl_3)

^{13}C NMR (100 MHz, CDCl_3)

^1H NMR (400 MHz, CDCl_3)

^{13}C NMR (100 MHz, CDCl_3)