

Synthesis of Rovafovir Etalafenamide (Part III): Evolution of the Synthetic Process to the Phosphonamidate Fragment

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SUPPORTING INFORMATION

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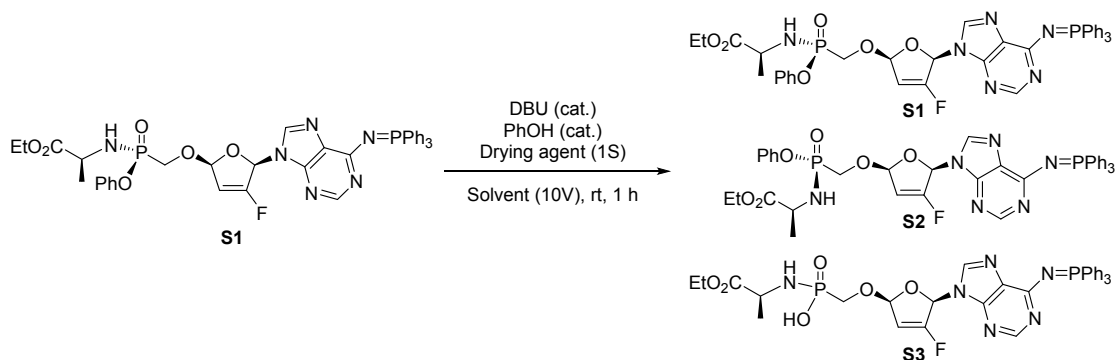
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S1. Epimerization at Phosphorus

Optimization of P-Epimerization Reaction Conditions

Screening of conditions identified DBU as a suitable reagent to carry out the epimerization at phosphorus of compound **S1**. A catalytic amount of DBU (≥ 20 mol%) yielded **S1** and its phosphorus epimer **S2** in a nearly 2:1 ratio within an hour, whereas lower amounts of DBU (5-10 mol%) resulted in little to no epimerization. Addition of a catalytic amount of phenol greatly accelerated the reaction, providing a nearly 1:1 mixture of **S1** and **S2** within one hour. Reagents other than DBU (phenol, phenoxide, triethylamine) gave little to no epimerization. The epimerization reaction also generated **S3** as the main impurity, presumably by hydrolysis of **S1** occurring under non-anhydrous, basic conditions. To limit the amount of hydrolysis, the reaction was run in the presence of drying agents. The addition of 4Å powdered molecular sieves (1S) limited the hydrolysis of **S1** to 3-8% AN.

Table S1. Optimization of Epimerization Reaction Conditions on Substrate S1



Entry	Conditions				Results (% AN) ^a		
	Base (mol%)	PhOH (mol%)	Solvent	Drying agent	S1	S2	S3
1	PhONa (20)	—	DCM	—	80.0	1.1	1.0
2	PhONa (100)	—	DCM	—	6.2	4.5	56.2
3	—	20	DCM	—	78.5	—	—
4	Et ₃ N (20)	20	DCM	—	72.1	2.4	3.0
5	DBU (5)	—	DCM	—	80.0	—	—
6	DBU (10)	—	DCM	—	75.0	1.1	5.0
7	DBU (20)	—	DCM	—	36.4	18.0	24.7
8	DBU (5)	5	DCM	—	69.2	—	1.2
9	DBU (10)	10	DCM	—	65.1	2.2	4.5
10	DBU (20)	20	DCM	—	29.9	26.5	19.2
11	DBU (20)	10	DCM	—	53.2	15.6	12.4
12	DBU (20)	10	DCM	4Å MS powder	36.7	39.6	4.6
13	DBU (20)	10	THF	—	53.7	13.7	14.0
14	DBU (20)	10	THF	4Å MS powder	37.7	36.2	7.7
15	DBU (20)	10	MeCN	—	44.5	21.3	14.6
16	DBU (20)	10	MeCN	4Å MS powder	48.9	29.2	3.1

a. Determined by UPLC-MS.

General Procedure A: Epimerization Experiments (Tables 1, 2, 5, 7, S1)

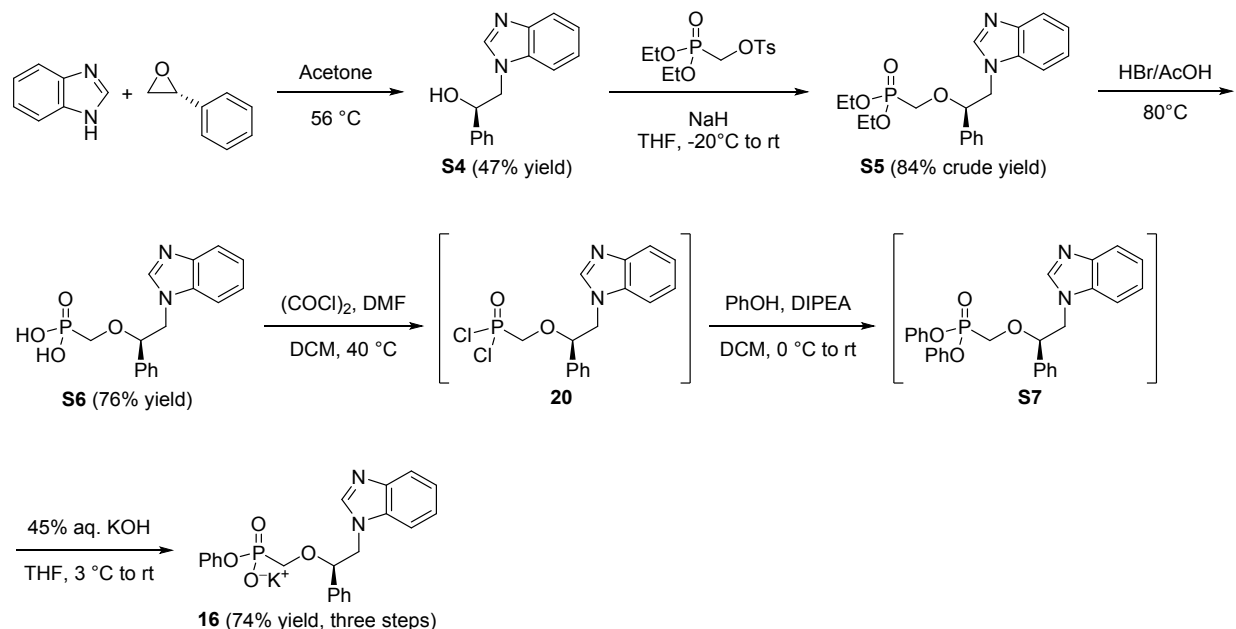
The substrate **13**, **15**, **27a**, **28a**, **27c**, or **S1** (1.0 equiv) was added to a reaction vial, followed by the solvent (5-10V), the drying agent (0-1S), phenol (0-20 mol%), the base (0-100 mol%), and a stir bar. The vial was sealed and flushed with nitrogen. The mixture was stirred at room temperature for 1 hour to 4 days. A sample was withdrawn and analyzed by UPLC, UPLC-MS, or ³¹P NMR.

Procedure for the Epimerization of **13** (Scheme 4)

13 (50.1 g of 58 wt% solution in EtOH, corresponding to 29.1 g of **13**, 77.2 mmol, 1.0 equiv) was charged to a round-bottom flask and dissolved in DCM (100 mL, 2V). Water (100 mL, 2V) was added, the mixture agitated for 15 minutes, then transferred into a separatory funnel. The bottom organic layer was discharged and washed with water (100 mL, 2V) two more times. The DCM solution was transferred into a 250-mL reactor. 4Å, powdered, activated molecular sieves (25.0 g, 0.5S) were charged and the mixture agitated under nitrogen atmosphere at 20 °C for 1 hour (water not detected by KF analysis). DBU (2.38 g, 15.4 mmol, 0.2 equiv) was charged. The mixture was agitated at 20 °C for 20 hours. The mixture was sampled for conversion to **12/13** by UPLC (69.8% AN, 47:53 dr). The mixture was discharged, filtered, and the reactor and filter cake washed with DCM (40 mL, 0.8V). The filtrate was poured into a round-bottom flask containing 1 M aq. phosphate buffer (100 mL, 2V, pH = 6) pre-cooled to 0 °C. The mixture was agitated while warming to room temperature, then transferred into a separatory funnel. The bottom organic layer was discharged and washed with additional 1 M aq. phosphate buffer (50 mL, 1V). The organic layer was treated with silica gel (10 g, 0.2S) for 1 hour at room temperature. The mixture was filtered and concentrated to ca. 2V. 96.5 g of a **12/13** mixture was obtained as an orange, 29.0 wt% solution in DCM (68.8% AN purity by UPLC, 95.8% assay yield, 47:53 (*S_P*)/(*R_P*)).

S2. Stereoselective Synthesis

Synthesis of Compound 16



(R)-2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-ol (S4). A 2-L, jacketed glass-lined reactor was charged with benzimidazole (200 g, 1.70 mol, 1.0 equiv), (*R*)-(+)-phenyloxirane (225 g, 1.87 mol, 1.1 equiv) and acetone (1.3 L, 6.5V). The reactor contents were heated to reflux (internal temperature = 56 °C) until the conversion was deemed satisfactory (as judged by ¹H NMR). After 93 hours, the reaction mixture was cooled to -5 °C and seeded with seed crystals (0.11 g). The resulting slurry was aged for 1 hour prior to isolation by vacuum filtration. **S4** was obtained as a white crystalline solid (190 g, 47% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.79 (s, 1H), 7.56 (br d, 1H), 7.42 – 7.32 (m, 6H), 7.22 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.16 (dt, *J* = 8.4, 1.2 Hz, 1H), 5.12 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.37 (dd, *J* = 14.4, 4.0 Hz, 1H), 4.29 (dd, *J* = 14.4, 8.0 Hz, 1H), 3.97 (br s, 1H) ppm.

Diethyl (R)-[(2-(1H-benzo[d]imidazol-1-yl)-1-phenylethoxy)methyl]phosphonate (S5). A 4-L, jacketed glass-lined reactor was charged with **S4** (100 g, 0.42 mol, 1.0 equiv), (diethoxyphosphoryl)methyl 4-methylbenzenesulfonate (150 g, 0.47 mol, 1.1 equiv) and THF (1.1 L, 11V). The reactor contents were cooled to -20 °C, then sodium hydride (60% dispersion in mineral oil, 12 g, 0.50 mol, 1.2 equiv) was slowly charged portion-wise. Agitation was continued at -20 °C for 20 minutes prior to ramp heating to 22 °C over 2 hours. The reaction mixture was diluted with EtOAc (2.0 L, 20V) and carefully quenched with water (0.5 L, 5V). The ethyl acetate layer was concentrated to ca. 1V, diluted with a mixture of MeCN (0.5 L, 5V), heptanes (0.5 L, 5V) and water (80 mL, 0.8V), and agitated for 30 minutes prior to layer separation. The top layer (heptane) containing mineral oil was discarded. The bottom layer (MeCN/water) was concentrated to ca. 1V, diluted with EtOAc (0.5 L, 5V), and washed twice with 5% aq. NaCl solution (0.5 L, 5V). The organic layer was concentrated to dryness to yield compound **S5** as dark brown oil (140 g, 84% yield, 94.2% AN purity by ³¹P NMR). ³¹P NMR (162 MHz, CDCl₃) δ 20.4 ppm.

(R)-[(2-(1H-benzo[d]imidazol-1-yl)-1-phenylethoxy)methyl]phosphonic acid (S6). A 4-L, jacketed glass-lined reactor was charged with a solution of crude **S5** (340 g, 0.88 mol, 1.0 equiv) in EtOAc (1.4 L, 4V). The reactor contents were concentrated to ca. 1.5 V. Glacial acetic acid (30 mL) was charged to the reactor, followed by 33% HBr in acetic acid (0.6 L). The reactor outlet was connected to a caustic scrubber prior to heating the reactor contents to reflux (jacket temperature set to 80 °C) for 2 hours. The reactor contents were then cooled to 22 °C, diluted with water (2.0 L, 6V), and washed with EtOAc (1.0 L, 3V). The aqueous layer was cooled to 6 °C and the pH was adjusted to 2.7 using 50% aq. NaOH solution. The resulting slurry was aged at 6 °C for 1 hour, then filtered. The crude solid was suspended in EtOAc (1.5 L, 4.5V) and agitated for 30 minutes prior to isolation by vacuum filtration. After drying, compound **S6** was isolated as an off-white solid (219 g, 76% yield, 100% AN purity by ³¹P NMR). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.23 (s, 1H), 7.66-7.51 (m, 2H), 7.36 – 7.26 (m, 5H), 7.24 – 7.16 (m, 2H), 4.91 (dt, *J* = 6.3, 5.2 Hz, 1H), 4.56 (dd, *J* = 14.6, 6.6 Hz, 1H), 4.51 (dd, *J* = 14.6, 5.0 Hz, 1H), 3.40 (d, *J* = 9.6 Hz, 2H) ppm. ³¹P NMR (162 MHz, DMSO-*d*₆) δ 16.0 ppm.

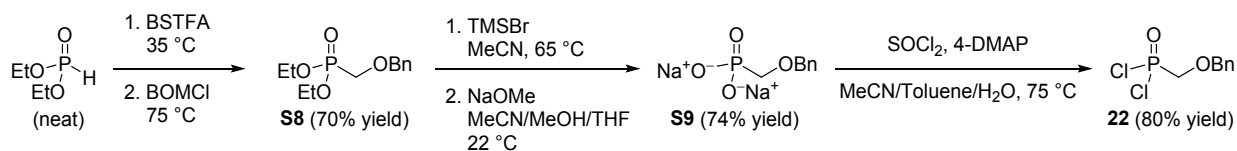
Potassium phenyl [((R)-2-(1H-benzo[d]imidazol-1-yl)-1-phenylethoxy)methyl]phosphonate (16). A 4-L, jacketed glass-lined reactor was charged with **S6** (98.1 g, 0.29 mol, 1.0 equiv), DCM (0.98 L, 10V) and DMF (0.51 g, 7.0 mmol, 0.02 equiv). The reactor contents were adjusted to 40 °C, then a solution of oxalyl chloride (180.8 g, 1.42 mol, 4.8 equiv) in DCM (0.30 L, 3V) was added slowly over 45 minutes. The reaction mixture was aged at 40 °C for 1 hour. In-process analysis indicated complete conversion to **20**. ³¹P NMR (162 MHz, CDCl₃) δ 39.5 ppm (100% AN). The reactor contents were distilled under vacuum with a maximum jacket temperature of 45 °C to a final volume of ca. 1V. DCM (0.26 L, 2.7V) was added to the concentrate and distillation to 1V was repeated twice prior to dissolving the concentrate in DCM (0.98 L, 10V). The reactor contents were cooled to 0 °C, then phenol (73.9 g, 0.78 mol, 2.7 equiv) was added in one portion. To the reaction mixture at 0 °C, DIPEA (121.8 g, 0.94 mol, 3.2 equiv) was added slowly over 15 minutes while maintaining the internal temperature below 25 °C. The reactor contents were adjusted to 22 °C and aged for 20 hours. In-process analysis indicated complete conversion to **S7**. ³¹P NMR (162 MHz, CDCl₃) δ 13.3 ppm (100% AN). The reactor contents were distilled under vacuum with a maximum jacket temperature of 40 °C to a final volume of ca. 1V. The concentrate was dissolved in THF (1.0 L, 10V) and the reactor contents were cooled to 3 °C. 45% aq. KOH solution (228 g, 1.83 mol, 6.2 equiv) was charged slowly while maintaining the temperature below 25 °C, then the reactor contents were aged at 22 °C for 1.5 hours. At the end of the reaction, the mixture was filtered, and the filtrate distilled to a final volume of ca. 1V. The concentrate was dissolved in MTBE (0.51 L, 5.2V) and extracted with water (0.20 L, 2V). The aqueous layer was washed with MTBE (0.51 L, 5.2V), adjusted to pH = 6 using conc. aq. HCl (41.4 g), and washed with MTBE three times (0.51 L, 5.2V). DCM (0.38 L, 3.9V) and NaCl (30.8 g) were then added to the aqueous layer and agitation continued for 15 minutes prior to layer separation. The organic layer was dried over magnesium sulfate (200.2 g), filtered, and concentrated to dryness to yield crude solids. The crude product was suspended in MTBE (0.27 L, 2.8V) and agitated at 40 °C for 30 minutes prior to isolation by vacuum filtration. After drying, compound **16** was isolated as pale brown solid (96.9 g, 74% yield over three steps). ¹H NMR (400 MHz, CD₃OD) δ 8.38 (s, 1H), 7.72 – 7.59 (m, 1H), 7.55 – 7.42 (m, 1H), 7.37 – 6.87 (m, 12H), 4.81 (dt, *J* = 5.7, 5.1 Hz, 1H), 4.56 (dd, *J* = 14.5, 6.4 Hz, 1H), 4.52 (dd, *J* = 14.5, 4.3 Hz, 1H), 3.60 (dd, *J* = 13.2 Hz, *J* = 9.3 Hz, 1H), 3.39 (dd, *J* = 13.1 Hz, *J* = 9.5 Hz, 1H) ppm. ³¹P NMR (162 MHz, CD₃OD) δ 11.4 ppm.

Synthesis of Compounds 18 and 19 (Schemes 6 and 7)

Ethyl (R)-[((R)-2-(1H-benzo[d]imidazol-1-yl)-1-phenylethoxy)methyl](phenoxy)phosphoryl-L-alaninate (19). A 250-mL round-bottom flask was charged with **20** as a DCM stock solution (1.06 g in 7.98 mL, 2.9 mmol, 1.0 equiv) and cooled to -5 °C. A solution of **11** (0.44 g, 2.9 mmol, 1.0 equiv) and *N*-methylimidazole (0.86 g, 10.4 mmol, 3.6 equiv) in DCM (2.3 mL, 2V) was added to the reaction mixture over 5 minutes. After agitation at -5 °C for 1 hour, a solution of phenol (0.27 g, 2.9 mmol, 1.0 equiv) and *N*-methylimidazole (0.24 g, 2.9 mmol, 1.0 equiv) in DCM (2.3 mL, 2V) was added to the reaction mixture over 15 minutes. The reaction mixture was agitated at 22 °C for 19 hours. At the end of the reaction, in-process analysis by ³¹P NMR indicated conversion to a mixture of diastereomers **19/18** in 66:34 ratio. The mixture was diluted with DCM (6.6 mL, 6.6V) and washed with water (5.3 mL, 5.3V). The organic layer was concentrated to dryness and purified by chromatography using a gradient of 3% MeOH/DCM. A mixture of compounds **19** and **18** in 65:35 ratio was obtained as an amber oil in 34% yield (0.50 g). ³¹P NMR (162 MHz, CDCl₃) δ 22.1 (**19**), 20.4 (**18**) ppm. LRMS [M+H]⁺ Calcd for C₂₇H₃₁N₃O₅P: 508.2, found 508.5

Ethyl (S)-[((R)-2-(1H-benzo[d]imidazol-1-yl)-1-phenylethoxy)methyl](phenoxy)phosphoryl-L-alaninate (18). A 500-mL round bottom flask was charged with **20** as a DCM stock solution (8.14 g in 100 mL, 20.1 mmol, 1.0 equiv) and cooled to -5 °C. A solution of **11** (3.08 g, 20.1 mmol, 1.0 equiv) and *N*-methylimidazole (5.93 g, 72.2 mmol, 3.6 equiv) in DCM (40 mL, 5V) was added to the reaction mixture over 5 minutes. After agitation at -5 °C for 30 minutes, **11** (0.16 g, 1.0 mmol, 0.05 equiv) in DCM (5 mL) was added and agitation continued at -5 °C for 30 minutes. A solution of 3-nitrophenol (2.77 g, 19.9 mmol, 1.0 equiv) and *N*-methylimidazole (1.67 g, 20.3 mmol, 1.0 equiv) in DCM (40 mL, 5V) was then added to the reaction mixture over 5 minutes. The reaction mixture was agitated at 22 °C for 16 hours. At the end of the reaction, in-process analysis by ³¹P NMR indicated conversion to a mixture of P-diastereomers in 67:33 ratio in favor of **21**. The reaction mixture was concentrated to dryness, diluted with *i*PrOAc, and washed with 12.5% aq. NH₄Cl solution (50 mL, 10V), followed by 7.5% aq. NaHCO₃ solution (50 mL, 10V). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to dryness to afford 7.60 g of crude **21** as a 65:35 mixture of P-diastereomers (99.3% AN purity by ³¹P NMR). ³¹P NMR (162 MHz, CDCl₃) δ 23.9 (**21**), 21.9 ppm. Crude material **21** (7.15 g, 12.6 mmol) was dissolved in DCM (107 mL, 15V) in a 1-L jacketed reactor and the reactor contents were cooled to -10 °C. Sodium phenoxide (1.46 g, 12.6 mmol, 1.0 equiv) was charged to the reaction in one portion and agitation continued at -10 °C for 25 minutes prior to quenching with water (72 mL, 10V). Layers were separated and the organic layer washed with water (89 mL, 12V) and brine (71 mL, 10V). The aqueous layer was back-extracted with DCM (47 mL, 7V). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to dryness to yield 6.36 g of a crude mixture of **18** and **19** in 79:21 ratio as an amber oil (62% crude yield, 96.8% AN purity by ³¹P NMR). ³¹P NMR (162 MHz, CDCl₃) δ 22.3 (**19**), 20.6 (**18**) ppm.

Synthesis of Starting Materials **22** and **23**

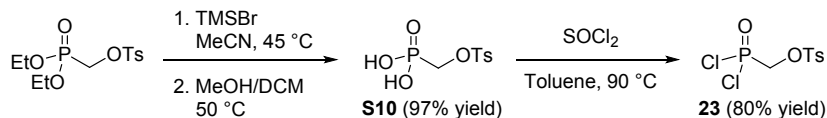


Diethyl (benzyloxymethyl)phosphonate (S8). A 3-L, jacketed glass-lined reactor equipped with potassium hydroxide scrubber was charged with diphenyl phosphite (250 g, 1.80 mol, 1.0 equiv) and warmed to an internal temperature of 35-40 °C. *N,O*-bis(trimethylsilyl)trifluoroacetamide (525 g, 2.04 mol, 1.1 equiv) was added over 45 minutes while maintaining the temperature of the batch at 35-50 °C. The mixture was aged for 3.5 hours, then sampled for conversion to diethyl trimethylsilyl phosphite. ³¹P NMR (162 MHz, CDCl₃) δ 127.4 ppm (96.8 %AN). The mixture was warmed to an internal temperature of 75-80 °C and benzyl chloromethyl ether (300 g, 1.92 mol, 1.1 equiv) was charged over 50 minutes while maintaining the temperature of the batch at 75-85 °C. The mixture was aged for an additional 16 hours at an internal temperature of 75 °C, then sampled for conversion to **S8**. ³¹P NMR (162 MHz, CDCl₃) δ 21.1 ppm (74.6% AN). The batch was cooled to 3 °C and adjusted to pH 6-8 with 5.3% aq. K₂CO₃ solution (1.15 L, 4.6V) while maintaining the internal temperature below 30 °C. The internal temperature was adjusted to 22 °C and the mixture agitated for 30 minutes. Toluene (950 mL, 3.8V) was added and the mixture agitated for 30 minutes. The phases were separated, the aqueous layer was returned to the reactor and extracted with toluene (860 mL, 3.4V) at 22 °C for 60 minutes. The combined organic layers were concentrated under vacuum with a maximum jacket temperature of 50 °C to a final volume of ca. 500 mL (2.0V), providing 328 g of crude **S8** as a pale yellow oil (70% yield, > 99% AN purity by ³¹P NMR). ¹H NMR (400 MHz, CDCl₃) δ 7.36 – 7.14 (m, 5H), 4.62 (s, 2H), 4.15 (q, *J* = 7.2 Hz, 4H), 3.76 (d, *J* = 9.2 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 6H) ppm. ³¹P NMR (162 MHz, CDCl₃) δ 21.5 ppm.

Sodium (benzyloxymethyl)phosphonate (S9). A 3-L, jacketed glass-lined reactor equipped with potassium hydroxide scrubber was charged with crude **S8** (300 g, 1.62 mol, 1.0 equiv) and acetonitrile (2.25 L, 7.5V). The contents were adjusted to an internal temperature of 22 °C. A distillation adapter was attached and bromotrimethylsilane (600 g, 3.92 mol, 3.4 equiv) was charged slowly over 20 minutes, maintaining the internal temperature at 22-30 °C. The internal temperature was adjusted to 65-70 °C, the mixture agitated for 30 minutes, then sampled for conversion to the intermediate bis(trimethylsilyl) ester. ³¹P NMR (162 MHz, CDCl₃) δ 4.8 ppm (97.3% AN). The reaction mixture was concentrated under vacuum with a maximum jacket temperature of 50 °C to a final volume of ca. 560 mL (1.9V). The distillate, containing bromotrimethylsilane and ethyl bromide, was quenched by charging carefully to excess aqueous sodium hydroxide solution and agitating for at least 30 minutes. The concentrated reaction mixture was diluted with acetonitrile (447 mL, 1.5V), methanol (2050 mL, 6.8V) and water (30 mL, 0.1V), providing a clear pale yellow solution. The internal temperature was adjusted to 22 °C and 25 wt% sodium methoxide in methanol (690 g, 730 mL, 3.19 mol, 2.8 equiv) was charged over 40 minutes while maintaining internal temperature at 22-30 °C, forming a thick, mobile white slurry. THF (1020 mL, 3.4V) was charged and the mixture was agitated at 22 °C for 1 hour. The slurry was filtered, deliquored, and the solids were smoothed and then rinsed with acetonitrile (192 mL, 0.64V). The solids were dried at 40 °C under vacuum, providing 294 g of **S9** as a white solid with trace inorganic impurities (74% yield, 96.2% AN purity by ³¹P NMR). ¹H NMR (400 MHz, D₂O)

δ 7.53 – 7.36 (m, 5H), 5.09 (s, 2H), 4.62 (d, J = 8.3 Hz, 2H) ppm. ^{31}P NMR (162 MHz, D_2O) δ 13.4 ppm.

(Benzyloxymethyl)phosphonic dichloride (22). A 3-L, jacketed glass-lined reactor equipped with potassium hydroxide scrubber was charged with **S9** (100 g, 406 mmol, 1.0 equiv), 4-dimethylaminopyridine (2.00 g, 16.3 mmol, 0.04 equiv), acetonitrile (64 mL, 0.64V), toluene (690 mL, 6.9V), and water (7.00 g, 406 mmol, 1.0 equiv). The mixture was agitated and the internal temperature was adjusted to 22 °C, forming a white slurry. Thionyl chloride (236 g, 1.98 mol, 4.9 equiv) was added over 30 minutes maintaining the internal temperature below 70 °C and limiting off-gassing to avoid pressurization. A thin white slurry formed during addition and the internal temperature was then adjusted to 75-80 °C. The mixture was agitated for 4 hours and then sampled for estimation of yield of **22** by ^{31}P NMR with triphenyl phosphate as standard. ^{31}P NMR (162 MHz, CDCl_3) δ 42.1 ppm (96.9% AN, excluding standard resonance at -12.2 ppm; estimate 90-95% yield based on input amount). The mixture was adjusted to an internal temperature of 45-50 °C, then concentrated under vacuum with a maximum jacket temperature of 45 °C to a final volume of ca. 500 mL (5.0V). The thick yellow slurry was diluted with toluene (460 mL, 4.6V) and further concentrated under vacuum with a maximum jacket temperature of 45 °C to a final volume of ca. 500 mL (5.0V). The slurry was drained to a nitrogen-flushed Nalgene bottle and the reactor was rinsed forward to a separate Nalgene bottle with toluene (115 mL, 1.2V). The slurry was filtered carefully under a nitrogen atmosphere using glass fiber filter papers (cellulose papers were found to quench the dichloride) previously dried in a vacuum oven at 50 °C for at least 12 hours. The reactor rinse was applied to the filter cake, the clear yellow filtrates were combined and the volume measured (445 mL total). The solution concentration was quantified by ^{31}P NMR with triphenyl phosphate as standard. ^1H NMR (400 MHz, CDCl_3) δ 7.50 – 7.30 (m, 5H, obscured by toluene solvent peaks), 4.60 (s, 2H), 3.96 (d, J = 2.0 Hz, 2H) ppm. ^{31}P NMR (162 MHz, CDCl_3) δ 42.1 ppm (95.9% AN, excluding standard resonance at -12.2 ppm; 0.75 M **22**, 80-85% yield, not corrected for input purity). The solution could be stored in a freezer (-15 to -25 °C) with little to no loss in purity by ^{31}P NMR. To prepare solutions in different solvents for subsequent reactions, a solution of **22** was concentrated under vacuum at a maximum jacket or bath temperature of 40 °C, diluted with the appropriate solvent, and the solution concentration determined as above. Care must be taken to avoid exposure to adventitious water, such as rinsing glassware with dry solvents and flushing with nitrogen prior to use.



(Tosyloxymethyl)phosphonic acid (S10). A 2-L, jacketed glass-lined reactor equipped with potassium hydroxide scrubber was charged with (diethoxyphosphoryl)methyl 4-methylbenzenesulfonate (100 g, 310 mmol, 1.0 equiv) and acetonitrile (1.00 L, 10.0V). The contents were adjusted to an internal temperature of 22 °C. Bromotrimethylsilane (143 g, 931 mmol, 3.0 equiv) was charged slowly, maintaining the internal temperature at 20-30 °C. The internal temperature was adjusted to 45-50 °C, the contents agitated for 2.5 hours, then sampled for conversion to the intermediate bis(trimethylsilyl) ester. ^{31}P NMR (162 MHz, CDCl_3) δ 16.6 ppm (98.6 %AN). The reaction mixture was concentrated under vacuum with a maximum jacket temperature of 25 °C to a final volume of ca. 100-200 mL (1-2V). Dichloromethane (151 mL,

1.5V) was charged and the mixture was concentrated under vacuum with a maximum jacket temperature of 50 °C to a final volume of ca. 100-200 mL (1-2V). Methanol (253 mL, 2.5V) was charged and the mixture was concentrated in vacuo with a maximum jacket temperature of 50 °C to a final volume of ca. 100-200 mL (1-2V). The distillate, containing bromotrimethylsilane and ethyl bromide, was quenched by charging carefully to a mixture of methanol and excess aqueous sodium hydroxide solution and agitating for at least 30 minutes prior to disposal. Dichloromethane (189 mL, 1.9V) was charged and the mixture was adjusted to an internal temperature of 22 °C. The clear colorless solution was transferred to a 1-L round-bottom flask and methanol (111 mL, 1.1V) was charged. The solution was concentrated on a rotary evaporator with a maximum bath temperature of 40 °C until distillation stopped, yielding a thick yellow liquid. The solvent charge and distillation to thick yellow liquid was repeated first with methanol (95 mL, 0.95V), and then dichloromethane (133 mL, 1.3V). The yellow liquid was dried under vacuum at ambient temperature to provide 80.22 g of **S10** (97% yield, 97.8% AN purity by ³¹P NMR) as a pink-tinted solid that could be ground with a mortar and pestle and stored. ¹H NMR (400 MHz, CDCl₃) δ 8.59 (s, 2H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.14 (d, *J* = 10.4 Hz, 2H), 2.43 (s, 3H) ppm. ³¹P NMR (162 MHz, CDCl₃) δ 15.8 ppm.

(Dichlorophosphoryl)methyl 4-methylbenzenesulfonate (23). A 1-L, jacketed glass-lined reactor equipped with potassium hydroxide scrubber was charged with **S10** (50 g, 188 mmol, 1.0 equiv) and toluene (570 mL, 11.4V). The mixture was agitated and the internal temperature was adjusted to 22 °C, forming a white slurry. Thionyl chloride (112 g, 939 mmol, 5.0 equiv) was added over 15 minutes maintaining the temperature below 30 °C. The internal temperature was then adjusted to 80-90 °C over 1 hour by gradually increasing the jacket temperature with a linear ramp. The mixture was agitated for 5 hours, then cooled to 22 °C by decreasing the jacket temperature to 22 °C over 1 hour, and held at 22 °C overnight. The mixture was sampled for conversion to **23**. ³¹P NMR (162 MHz, CDCl₃) δ 34.5 ppm (72.5% AN). The mixture was adjusted to an internal temperature of 65 °C, then concentrated under vacuum with a maximum jacket temperature of 90 °C until distillation ceased (1-2V). The clear amber liquid was diluted with toluene (574 mL, 11.5V), concentrated under vacuum with a maximum jacket temperature of 90 °C until distillation ceased (1-2V), then diluted with additional toluene (574 mL, 11.5V) and concentrated under vacuum with a maximum jacket temperature of 80 °C to a final volume of ca. 100 mL (2V). The solution was diluted with dichloromethane (377 mL, 7.5V), then concentrated under vacuum with a maximum jacket temperature of 45 °C until an off-white solid began to form (ca. 100 mL). Dilution with dichloromethane (377 mL, 7.5V) and concentration under vacuum to a final volume of ca. 200 mL (4V) were repeated, then the solution was discharged from the reactor to a nitrogen-flushed Nalgene bottle. The solution was further diluted with dichloromethane (40 mL, 0.8V) to provide 210 mL of final solution of **23**. The solution concentration was quantified by ³¹P NMR with triphenyl phosphate as standard. ¹H NMR (400 MHz, CDCl₃) δ 7.80 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 4.64 (d, *J* = 10.4 Hz, 2H), 2.44 (s, 3H) ppm. ³¹P NMR (162 MHz, CDCl₃) δ 34.5 ppm (90.9% AN, excluding standard resonance at -12.2 ppm; 0.72 M **23**, 80-85% yield, not corrected for input purity).

General Procedure B: Synthesis of *O*- and/or *N*-Substituted Derivatives **12, 13, 15, 25, 26, S11-S17**

A vial or round bottom flask was charged with a stir bar and the appropriate dichloride solution (**22** or **23**) in the given solvent (DCM, MeCN, or a mixture of MeCN/DCM). The mixture was cooled to -5 to 0 °C under a nitrogen atmosphere. A solution of the appropriate alanine derivative (**11** or **24**, or corresponding free base) and base (*N*-methylimidazole, triethylamine, 4-dimethylaminopyridine) was then charged dropwise. The solution was aged for 1-22 hours at 0-22 °C and then sampled for conversion to the monochloridate intermediate by ³¹P NMR. If the mixture had been warmed, it was then cooled back to -5 to 0 °C. A solution in DCM or MeCN of the appropriate phenol (phenol, 4-nitrophenol, or 3-nitrophenol), with or without added *N*-methylimidazole, was charged dropwise. The mixture was agitated for 0.5-2 hours at -5 °C to 0 °C, then warmed gradually to 22 °C. The % AN of product and diastereomeric ratio were determined by UPLC or ³¹P NMR. The mixture could be further purified by aqueous workup with added dichloromethane (if not already present) and one to three neutral water washes, followed by purification by column chromatography to remove residual base impurities.

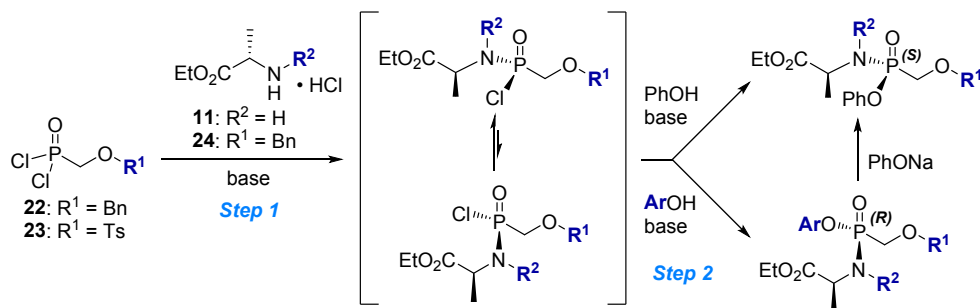
Summary of *O*- and/or *N*-Substituted Derivatives **12, 13, 15, 25, 26, S11-S17**

Derivatives **12, 13, 15, 25, 26, S11-S17** were synthesized according to General Procedure B using the conditions indicated in Table S2. Phosphorus configuration was assigned as follows:

- **12** and **13** were assigned by ³¹P NMR and UPLC retention time of authentic substances, with stereochemistry originally assigned in the first-generation route after SMB separation and conversion to **1** and **30**.
- **15** and **S11** were assigned after hydrogenolysis of a 78:22 mixture to a 75:25 mixture of **1** and **30**.
- **S12** and **S13** were assigned by correlation of chemical shifts: with *N*-Bn derivatives, the diastereomer with higher chemical shift is (*S*_P) (see **15/S11, 26/S16**); with *N*-H derivatives, the diastereomer with higher chemical shift is (*R*_P) (see **12/13, 27a/28a, 27b/28b, 27d/28d**).
- **S14** and **S15** were assigned by tosylation of **1** and **30**, respectively.
- **26** and **S16** were assigned by synthesis: a mixture of **15** and **S8** (75:25) was subjected to hydrogenolysis conditions that cleaved the *O*-benzyl group only, and the resulting hydroxymethyl phosphoramidate was then tosylated.
- **S17** and **25** were assigned by correlation of chemical shifts to **15/S11** and **26/S16**.

Table S2.

Conditions for the Synthesis of Derivatives 12, 13, 15, 25, 26, S8-S14



Entry	Phosphonic dichloride	Alanine derivative (equiv)	Step 1 conditions	Monochloridate ³¹ P NMR ^b (ppm)	Phenol (equiv)	Step 2 conditions	Product total % AN	(S _p):(R _p) dr	(S _p) isomer	(S _p)-isomer ³¹ P NMR ^b (ppm)	(R _p) isomer	(R _p)-isomer ³¹ P NMR ^b (ppm)
1	22	11 (1.1)	NMI (2.2 equiv) MeCN, -5 to 22 °C	36.9, 36.5	PhOH (1.1)	NMI (1.1 equiv) MeCN, -5 to 22 °C	74.9 ^c	40:60		21.9		22.8
2	22	24 ^a (1.1)	TEA (3.0 equiv) NMI (1.0 equiv) DCM, -5 °C	42.0, 41.3	PhOH (1.05)	NMI (1.1 equiv) DCM, -5 to 22 °C	70.3 ^d	74:26		24.8		24.3
3	22	24 ^a (1.1)	DMAP (3.0 equiv) NMI (1.0 equiv) DCM, 0 to 22 °C	N/A	PhOH (1.05)	NMI (1.1 equiv), DCM, 0 to 22 °C	11.5 ^c	20:80	15	24.8	S11	24.3
4	22	24 ^a (1.1)	DMAP (3.0 equiv) NMI (1.0 equiv) DCM, 0 to 22 °C	N/A	4-(NO ₂)- C ₆ H ₄ OH (1.05)	NMI (1.15 equiv), DCM, 0 to 22 °C	61.2 ^d	41:59		25.8		25.3
5	23	11 (1.0)	NMI (3.5 equiv) DCM/MeCN, 0 °C	N/A	PhOH (1.0)	NMI (1.0 equiv) DCM, 0 to 22 °C	79.0 ^d	59:41		16.6		15.7
6	23	24 (1.0)	NMI (3.5 equiv) DCM/MeCN, 0 °C	34.9, 32.5	PhOH (1.0)	DCM, 0 to 22 °C	56.9 ^d	4:96		18.6		18.1
7	23	24 (1.0)	NMI (3.5 equiv) DCM/MeCN, 0 °C	N/A	3-(NO ₂)- C ₆ H ₄ OH (1.0)	DCM, 0 to 22 °C	44.1 ^d	4:96		20.1		19.6

a. The free base of the alanine derivative was used.

b. ³¹P NMR acquired in CDCl₃.

c. Determined by UPLC with UV detection at 260 nm; residual phenol was excluded from % AN calculation.

d. Determined by ³¹P NMR in CDCl₃.

Synthesis of Compound 26 via 25 (Scheme 8)

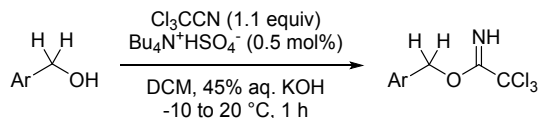
Ethyl *N*-benzyl-*N*-[(*R*)-(benzyloxymethyl)(3-nitrophenoxy)phosphoryl]-*L*-alaninate (25). A 0.62 M DCM solution of **23** (5.30 mL, 3.30 mmol, 1.0 equiv) was added to a 10-mL glass vial containing a stir bar and cooled to 0 °C in an ice bath under nitrogen. A solution of **24** (0.804 g, 3.30 mmol, 1.0 equiv) and *N*-methylimidazole (0.945 g, 11.5 mmol, 3.5 equiv) in acetonitrile (3.9 mL) was charged dropwise over ca. 10 minutes. After 1 hour at 0 °C, a solution of 3-nitrophenol (0.473 g, 3.40 mmol, 1.0 equiv) in DCM (8.5 mL) was charged dropwise over ca. 10 minutes. After warming to room temperature, the mixture was sampled for conversion to **25**. ³¹P NMR (162 MHz, CDCl₃) δ 20.1 (1.8% AN, **S17**), 19.6 (42.3% AN, **25**) ppm. The mixture was transferred to a separatory funnel and extracted with water (30 mL). The organic layer was separated and further extracted with 25% aq. NaCl solution (15 mL). The organic layer was dried over sodium sulfate (10 g), filtered, and concentrated under vacuum to provide crude **25** as an amber oil. Purification by column chromatography afforded 0.65 g of **25** as a pale yellow oil (34% yield, 96:4 dr). ¹H NMR (400 MHz, CDCl₃) δ 8.00 (d, 1H), 7.80 (s, 1H), 7.77 (d, 2H), 7.54 (d, 1H), 7.45 (t, 1H), 7.30 (d, 2H), 7.20-7.30 (m, 5H), 4.40-4.60 (m, 4H), 4.25 (dd, 1H), 3.97-4.10 (m, 2H), 2.43 (s, 3H), 1.40 (d, 3H), 1.19 (t, 3H) ppm. ³¹P NMR (162 MHz, CDCl₃) δ 19.6 ppm.

Ethyl *N*-benzyl-*N*-[(*S*)-phenoxy(tosyloxymethyl)phosphoryl]-*L*-alaninate (26). A solution of **25** (125 mg, 0.217 mmol, 1.0 equiv) in DCM (2.8 mL) was charged to an 8-mL glass vial containing a stir bar and cooled to 0 °C in an ice bath under nitrogen. Sodium phenoxide (26.3 mg, 0.227 mmol, 1.05 equiv) was charged, the mixture was warmed to 22 °C, and agitated for 18 hours. The mixture was sampled for conversion to **26**. ³¹P NMR (162 MHz, CDCl₃) δ 19.6 (33.3% AN, **25**), 18.6 (55.0% AN, **26**), 18.1 ppm (9.0% AN, **S16**). Additional DCM (2 mL) and sodium phenoxide (15.2 mg, 0.131 mmol, 0.60 equiv) were charged and the mixture agitated at 22 °C for additional 18 hours, at which point the reaction was sampled for conversion to **26**. ³¹P NMR (162 MHz, CDCl₃) δ 19.6 (1.9% AN, **25**), 18.6 (83.4% AN, **26**), 18.1 ppm (14.7% AN, **S16**).

S3. Selective Crystallization

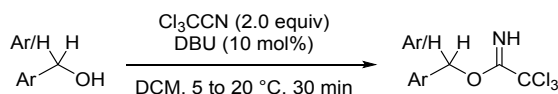
General Procedures C: Synthesis of Trichloroacetimidates (TCAs)

General Procedure C1: Basic PTC Conditions



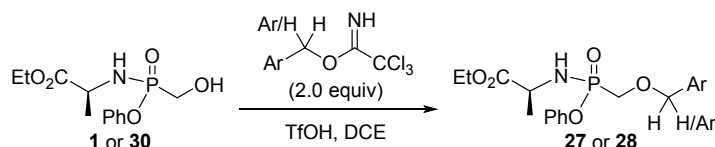
A reactor was charged with the primary benzylic alcohol (1.0 equiv), DCM (6V), 45% aq. KOH (6V) and tetrabutylammonium hydrogen sulfate (0.5 mol%). The reactor contents were cooled to an internal temperature of -10 °C. While agitating the mixture, trichloroacetonitrile (1.1 equiv) was added at a rate such to maintain the internal temperature below 0 °C. The mixture was agitated for 30 minutes at -15 °C, then warmed to 20 °C and agitated for 30 minutes. Layers were separated and the bottom aqueous layer was extracted with DCM (2 × 5V). The combined organic layers were washed with 5M aq. ammonium chloride (2 × 5V), dried with Na₂SO₄ (1S), and filtered through a pad of celite. The filtrate was concentrated to approximately 2V, then hexanes (2-4V) were added to induce the precipitation of the desired trichloroacetimidate as a white solid. The product was collected by filtration and dried (80%-quantitative yield).

General Procedure C2: DBU Conditions



A reactor was charged with the primary or secondary benzylic alcohol (1.0 equiv), DCM (10V) and trichloroacetonitrile (2.0 equiv). The reactor contents were cooled to an internal temperature of 5 °C. While agitating the mixture, DBU (10 mol%) was added at a rate such to maintain the internal temperature below 15 °C. At the end of the addition, the mixture was warmed to 20 °C and agitated for 30 minutes. The reactor contents were concentrated to approximately 2V, then filtered through a pad of silica gel (2S) previously treated with DCM. The pad of silica gel was further washed with DCM (10V). The filtrate was concentrated to dryness and treated with a small amount of hexanes to afford the desired trichloroacetimidate as a white or yellow solid in quantitative yield after drying.

General Procedure D: Synthesis of Analogs 27 and 28



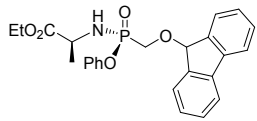
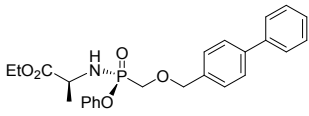
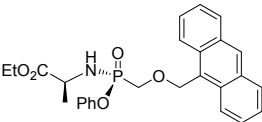
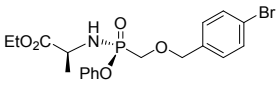
1 or **30** (1.0 equiv), the trichloroacetimidate (2.0 equiv), and DCE (7V) were added to a round-bottom flask containing a stir bar. The mixture was stirred at rt until all solids dissolved. Trifluoromethanesulfonic acid (5-50 mol%) was added. The reaction was heated to the temperature indicated in Table S3. When conversion to **27** or **28** was deemed satisfactory (as judged by ³¹P

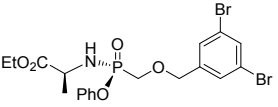
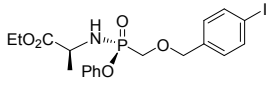
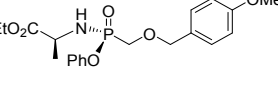
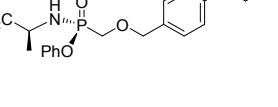
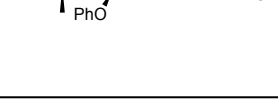
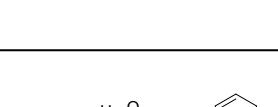

NMR), the mixture was cooled to rt and filtered through pad of silica gel (3S) previously treated with DCM. The pad of silica gel was further washed with a 1:1 DCM/EtOAc mixture (7V). The filtrate was concentrated to dryness and the residue purified by silica gel column chromatography (eluting with DCM/EtOAc mixtures) to afford **27** or **28**.

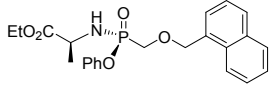
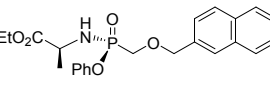
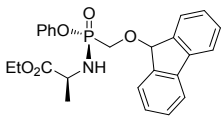
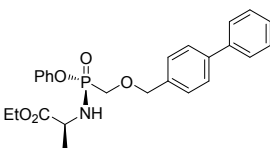
Summary of Analogs 27 and 28

Analogs **27a-c**, **27e-n**, **28a-b** were synthesized according to General Procedure D using the conditions indicated in Table S3. The synthesis of compounds **27d** and **28d** is reported in the Experimental Section.

Table S3. Conditions for the Synthesis of Analogs 27/28 and Characterization Data

Compound	TCA Procedure	TfOH (mol%)	T (°C)	Time (h)	Yield (%)	Characterization
 27a	C2	5	50	0.25	74	Crystalline solid, mp = 118 °C. ¹ H NMR (400 MHz, CDCl ₃) δ 7.66 (d, <i>J</i> = 7.6 Hz, 1H), 7.65 (d, <i>J</i> = 7.6 Hz, 1H), 7.57 (d, <i>J</i> = 7.4 Hz, 1H), 7.43 – 7.38 (m, 3H), 7.34 – 7.29 (m, 3H), 7.27 – 7.21 (m, 3H), 7.17 – 7.13 (m, 1H), 5.73 (s, 1H), 4.25 – 4.09 (m, 3H), 3.60 (t, <i>J</i> = 10.4 Hz, 1H), 3.44 (dd, <i>J</i> = 13.0, 10.9 Hz, 1H), 3.37 (dd, <i>J</i> = 13.0, 9.1 Hz, 1H), 1.34 (d, <i>J</i> = 7.1 Hz, 3H), 1.24 (t, <i>J</i> = 7.1 Hz, 3H). ³¹ P NMR (162 MHz, CDCl ₃) δ 22.6 ppm.
 27b	C1	5	50	0.5	74	Crystalline solid, mp = 79-81 °C. ¹ H NMR (400 MHz, CDCl ₃) δ 7.63 – 7.55 (m, 4H), 7.48 – 7.43 (m, 2H), 7.39 – 7.36 (m, 3H), 7.34 – 7.29 (m, 2H), 7.25 – 7.22 (m, 2H), 7.20 – 7.11 (m, 1H), 4.64 (d, <i>J</i> = 11.9 Hz, 1H), 4.61 (d, <i>J</i> = 12.0 Hz, 1H), 4.24 – 4.01 (m, 3H), 3.90 (dd, <i>J</i> = 13.3, 9.7 Hz, 1H), 3.84 (dd, <i>J</i> = 13.3, 7.9 Hz, 1H), 3.56 (t, <i>J</i> = 10.4 Hz, 1H), 1.33 (d, <i>J</i> = 7.1 Hz, 3H), 1.20 (t, <i>J</i> = 7.1 Hz, 3H) ppm. ³¹ P NMR (162 MHz, CDCl ₃) δ 21.5 ppm.
 27c	C2	5	0	18	23	Crystalline solid, mp = 140-144 °C. ¹ H NMR (400 MHz, CDCl ₃) δ 8.50 (s, 1H), 8.38 (d, <i>J</i> = 8.8 Hz, 2H), 8.04 (d, <i>J</i> = 8.4 Hz, 2H), 7.56 (t, <i>J</i> = 6.8 Hz, 2H), 7.49 (t, <i>J</i> = 7.9 Hz, 2H), 7.26 – 7.21 (m, 2H), 7.13 – 7.09 (m, 3H), 5.64 (d, <i>J</i> = 11.9 Hz, 1H), 5.59 (d, <i>J</i> = 11.9 Hz, 1H), 4.10 – 3.83 (m, 5H), 3.46 (t, <i>J</i> = 10.4 Hz, 1H), 1.12 (d, <i>J</i> = 7.1 Hz, 3H), 1.07 (t, <i>J</i> = 7.1 Hz, 3H). ³¹ P NMR (162 MHz, CDCl ₃) δ 21.8 ppm.
 27e	C1	10	50	1	59	Waxy solid. ¹ H NMR (400 MHz, CDCl ₃) δ 7.47 (d, <i>J</i> = 8.3 Hz, 2H), 7.35 – 7.29 (m, 2H), 7.24 – 7.19 (m, 2H), 7.18 – 7.14 (m, 3H), 4.55 (d, <i>J</i> = 12.1 Hz, 1H), 4.50 (d, <i>J</i> = 12.1 Hz, 1H), 4.17 – 4.01 (m, 3H), 3.86 (dd, <i>J</i> = 13.3, 9.6 Hz, 1H), 3.80 (dd, <i>J</i> = 13.3, 8.0 Hz, 1H), 3.55 (t, <i>J</i> = 10.4 Hz, 1H), 1.31 (d, <i>J</i> = 7.1 Hz, 3H), 1.20 (t, <i>J</i> = 7.1 Hz, 3H) ppm. ³¹ P NMR (162 MHz, CDCl ₃) δ 21.3 ppm.

Compound	TCA Procedure	TfOH (mol%)	T (°C)	Time (h)	Yield (%)	Characterization
 27f	C1	35	70	2	11	Waxy solid. ¹ H NMR (400 MHz, CDCl ₃) δ 7.61 (t, <i>J</i> = 1.8 Hz, 1H), 7.38 (d, <i>J</i> = 1.8 Hz, 2H), 7.36 – 7.30 (m, 2H), 7.25 – 7.22 (m, 2H), 7.20 – 7.14 (m, 1H), 4.55 (d, <i>J</i> = 12.5 Hz, 1H), 4.50 (d, <i>J</i> = 12.5 Hz, 1H), 4.21 – 4.01 (m, 3H), 3.88 (dd, <i>J</i> = 13.3, 9.3 Hz, 1H), 3.83 (dd, <i>J</i> = 13.3, 8.1 Hz, 1H), 3.56 (t, <i>J</i> = 10.3 Hz, 1H), 1.34 (d, <i>J</i> = 7.1 Hz, 3H), 1.22 (t, <i>J</i> = 7.1 Hz, 3H) ppm. ³¹ P NMR (162 MHz, CDCl ₃) δ 20.5 ppm.
 27g	C2	10	50	0.5	57	Crystalline solid, mp = 55-58 °C. ¹ H NMR (400 MHz, CDCl ₃) δ 7.68 (d, <i>J</i> = 8.3 Hz, 2H), 7.34 – 7.28 (m, 2H), 7.24 – 7.20 (m, 2H), 7.16 (t, <i>J</i> = 7.3 Hz, 1H), 7.04 (d, <i>J</i> = 8.5 Hz, 2H), 4.54 (d, <i>J</i> = 12.1 Hz, 1H), 4.50 (d, <i>J</i> = 12.1 Hz, 1H), 4.21 – 3.98 (m, 3H), 3.86 (dd, <i>J</i> = 13.3, 9.6 Hz, 1H), 3.80 (dd, <i>J</i> = 13.3, 8.0 Hz, 1H), 3.54 (t, <i>J</i> = 10.3 Hz, 1H), 1.32 (d, <i>J</i> = 7.1 Hz, 3H), 1.20 (t, <i>J</i> = 7.1 Hz, 3H) ppm. ³¹ P NMR (162 MHz, CDCl ₃) δ 21.1 ppm.
 27h	C2	20	50	2	28	Oil. ¹ H NMR (400 MHz, CDCl ₃) δ 7.33 – 7.28 (m, 2H), 7.24 – 7.19 (m, 4H), 7.17 – 7.12 (m, 1H), 6.89 – 6.85 (m, 2H), 4.52 (d, <i>J</i> = 11.7 Hz, 1H), 4.50 (d, <i>J</i> = 11.6 Hz, 1H), 4.18 – 4.02 (m, 3H), 3.82 (dd, <i>J</i> = 13.4, 9.7 Hz, 1H), 3.81 (s, 3H), 3.75 (dd, <i>J</i> = 13.4, 7.8 Hz, 1H), 3.55 (t, <i>J</i> = 10.3 Hz, 1H), 1.31 (d, <i>J</i> = 7.1 Hz, 3H), 1.21 (t, <i>J</i> = 7.1 Hz, 3H). ³¹ P NMR (162 MHz, CDCl ₃) δ 21.9 ppm.
 27i	C1	10	50	1	68	Crystalline solid, mp = 58-60 °C; ¹ H NMR (400 MHz, CDCl ₃) δ 7.47 – 7.27 (m, 7H), 7.25 – 7.19 (m, 4H), 7.17 – 7.10 (m, 1H), 6.95 (d, <i>J</i> = 8.6 Hz, 2H), 5.07 (s, 2H), 4.52 (d, <i>J</i> = 14.1 Hz, 1H), 4.49 (d, <i>J</i> = 14.1 Hz, 1H), 4.20 – 3.99 (m, 3H), 3.82 (dd, <i>J</i> = 13.3, 9.7 Hz, 1H), 3.76 (dd, <i>J</i> = 13.3, 7.9 Hz, 1H), 3.56 (t, <i>J</i> = 10.1 Hz, 1H), 1.31 (d, <i>J</i> = 7.1 Hz, 3H), 1.20 (t, <i>J</i> = 7.1 Hz, 3H) ppm. ³¹ P NMR (162 MHz, CDCl ₃) δ 21.8 ppm.
 27j	C2	20	50	1	11	Oil. ¹ H NMR (400 MHz, CDCl ₃) δ 7.33 – 7.27 (m, 2H), 7.24 – 7.19 (m, 2H), 7.17 – 7.11 (m, 1H), 6.80 – 6.71 (m, 3H), 5.95 (s, 2H), 4.48 (d, <i>J</i> = 11.6 Hz, 1H), 4.44 (d, <i>J</i> = 11.6 Hz, 1H), 4.19 – 4.04 (m, 3H), 3.81 (dd, <i>J</i> = 13.3, 9.7 Hz, 1H), 3.75 (dd, <i>J</i> = 13.3, 7.9 Hz, 1H), 3.58 (t, <i>J</i> = 10.4 Hz, 1H), 1.31 (d, <i>J</i> = 7.1 Hz, 3H), 1.21 (t, <i>J</i> = 7.2 Hz, 3H). ³¹ P NMR (162 MHz, CDCl ₃) δ 21.7 ppm.
 27k	C2	10	50	1	20	Oil. ¹ H NMR (400 MHz, CDCl ₃) δ 7.39 – 7.11 (m, 10H), 6.59 (d, <i>J</i> = 16.0 Hz, 1H), 6.20 (dt, <i>J</i> = 15.9, 6.2 Hz, 1H), 4.21 (d, <i>J</i> = 6.2 Hz, 2H), 4.19 – 4.06 (m, 3H), 3.90 (dd, <i>J</i> = 13.3, 9.7 Hz, 1H), 3.84 (dd, <i>J</i> = 13.3, 7.8 Hz, 1H), 3.55 (t, <i>J</i> = 10.3 Hz, 1H), 1.34 (d, <i>J</i> = 7.1 Hz, 3H), 1.21 (t, <i>J</i> = 7.1 Hz, 3H). ³¹ P NMR (162 MHz, CDCl ₃) δ 21.7 ppm.
 27l	C2	5	10	0.25	93	Oil. ¹ H NMR (400 MHz, CDCl ₃) δ 7.31 – 7.17 (m, 14H), 7.13 – 7.08 (m, 1H), 5.34 (s, 1H), 4.16 (ddt, <i>J</i> = 15.4, 10.0, 7.1 Hz, 1H), 4.03 (dq, <i>J</i> = 10.7, 7.1 Hz, 1H), 3.87 (dq, <i>J</i> = 10.8, 7.2 Hz, 1H), 3.79 (dd, <i>J</i> = 13.0, 9.8 Hz, 1H), 3.73 (dd, <i>J</i> = 13.1, 8.2 Hz, 1H), 3.53 (t, <i>J</i> = 10.3 Hz, 1H), 1.28 (d, <i>J</i> = 7.1 Hz, 3H), 1.10 (t, <i>J</i> = 7.1 Hz, 3H). ³¹ P NMR (162 MHz, CDCl ₃) δ 21.6 ppm.

Compound	TCA Procedure	TfOH (mol%)	T (°C)	Time (h)	Yield (%)	Characterization
 27m	C1	10	50	2	69	Crystalline solid, mp = 48-51 °C. ¹ H NMR (400 MHz, CDCl ₃) δ 8.17 – 8.10 (m, 1H), 7.92 – 7.81 (m, 2H), 7.58 – 7.49 (m, 2H), 7.46 – 7.40 (m, 2H), 7.28 – 7.21 (m, 2H), 7.18 – 7.09 (m, 3H), 5.06 (d, <i>J</i> = 12.0 Hz, 1H), 5.02 (d, <i>J</i> = 12.0 Hz, 1H), 4.19 – 3.95 (m, 3H), 3.90 (dd, <i>J</i> = 13.3, 9.7 Hz, 1H), 3.83 (dd, <i>J</i> = 13.3, 7.9 Hz, 1H), 3.51 (t, <i>J</i> = 10.5 Hz, 1H), 1.21 (d, <i>J</i> = 7.1 Hz, 3H), 1.15 (t, <i>J</i> = 7.2 Hz, 3H). ³¹ P NMR (162 MHz, CDCl ₃) δ 21.6 ppm.
 27n	C2	50	15	3	37	Oil. ¹ H NMR (400 MHz, CDCl ₃) δ 7.84 – 7.81 (m, 3H), 7.74 (s, 1H), 7.51 – 7.47 (m, 2H), 7.42 (d, <i>J</i> = 8.4 Hz, 1H), 7.31 – 7.22 (m, 4H), 7.14 (t, <i>J</i> = 7.2 Hz, 1H), 4.77 (d, <i>J</i> = 12.0 Hz, 1H), 4.72 (d, <i>J</i> = 12.0 Hz, 1H), 4.23 – 3.98 (m, 3H), 3.93 – 3.32 (m, 2H), 3.57 (t, <i>J</i> = 10.2 Hz, 1H), 1.32 (d, <i>J</i> = 7.1 Hz, 3H), 1.16 (t, <i>J</i> = 7.1 Hz, 3H). ³¹ P NMR (162 MHz, CDCl ₃) δ 21.6 ppm.
 28a	C2	5	50	0.25	65	Crystalline solid, mp = 88-91 °C. ¹ H NMR (400 MHz, CDCl ₃) δ 7.66 (d, <i>J</i> = 7.5 Hz, 1H), 7.65 (d, <i>J</i> = 7.5 Hz, 1H), 7.61 (d, <i>J</i> = 7.4 Hz, 1H), 7.49 – 7.36 (m, 3H), 7.33 – 7.20 (m, 6H), 7.17 – 7.13 (m, 1H), 5.77 (s, 1H), 4.16 (q, <i>J</i> = 7.1 Hz, 2H), 4.20 – 4.10 (m, 1H), 3.63 (t, <i>J</i> = 10.2 Hz, 1H), 3.45 (dd, <i>J</i> = 12.9, 10.7 Hz, 1H), 3.38 (dd, <i>J</i> = 12.9, 9.4 Hz, 1H), 1.33 (d, <i>J</i> = 7.0 Hz, 3H), 1.24 (t, <i>J</i> = 7.1 Hz, 3H). ³¹ P NMR (162 MHz, CDCl ₃) δ 23.2 ppm.
 28b	C1	5	50	0.5	39	Crystalline solid, mp = 51-54 °C. ¹ H NMR (400 MHz, CDCl ₃) δ 7.61 – 7.51 (m, 4H), 7.45 – 7.15 (m, 9H), 7.11 (t, <i>J</i> = 7.0 Hz, 1H), 4.67 (d, <i>J</i> = 11.9 Hz, 1H), 4.62 (d, <i>J</i> = 11.9 Hz, 1H), 4.19 – 4.03 (m, 3H), 3.87 (dd, <i>J</i> = 13.2, 9.2 Hz, 1H), 3.82 (dd, <i>J</i> = 13.2, 8.2 Hz, 1H), 3.53 (t, <i>J</i> = 10.2 Hz, 1H), 1.29 (d, <i>J</i> = 7.1 Hz, 3H), 1.19 (t, <i>J</i> = 7.1 Hz, 3H). ³¹ P NMR (162 MHz, CDCl ₃) δ 22.5 ppm.

General Procedure E: Selective Crystallization Experiments (Tables 6, 8, 10, 11)

A mixture of substrates **27a/28a**, **27c/28c**, **27d/28d**, or **1/30** (1.0 equiv) was added to a reaction vial, followed by the solvent (2-20V) and a stir bar. The mixture was gently heated until all solids dissolved (if applicable), then cooled to the indicated temperature. A sample was withdrawn and centrifuged. Solids and mother liquor were analyzed by UPLC or ³¹P NMR.

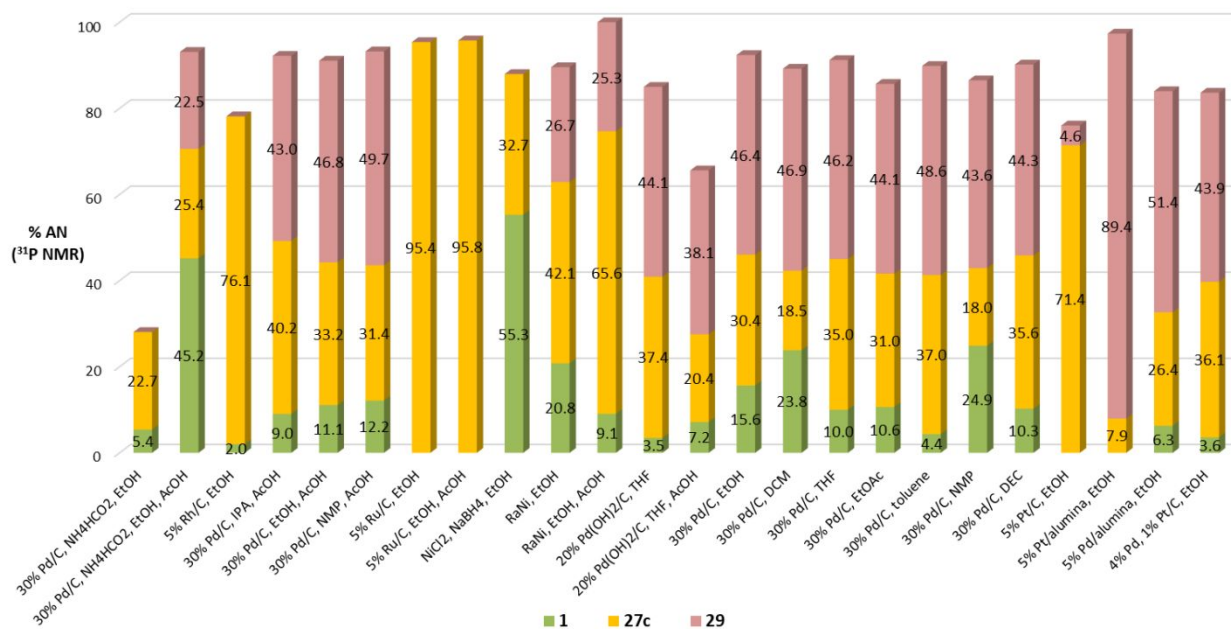
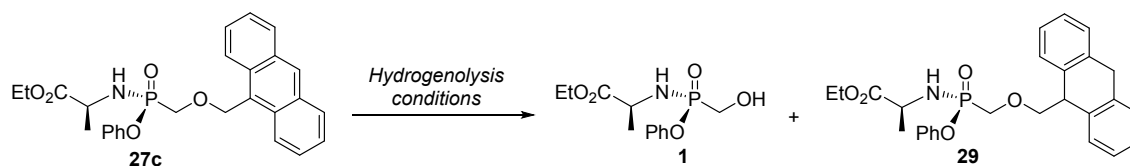
General Procedure F: CIAT Experiments (Table 9)

27c was subjected to epimerization following General Procedure A, in the presence of DBU (20 mol%), PhOH (10 mol%), 4Å, powdered, activated molecular sieves (1S), and DCM (10V). The mixture was filtered to afford a solution of **27c/28c** (51:49 dr). The solution was split among 40-mL reaction vials and the vial contents concentrated to dryness. A stir bar and the solvent(s) were added. The resulting suspension was allowed to equilibrate for 1-4 days at the indicated temperature. The mixture was filtered and the filter cake washed with the reaction solvent(s) (3V). The solids were dried at 40 °C and weighed to determine % recovery. Solids and mother liquor were analyzed by ³¹P NMR to determine dr.

Hydrogenolysis of **27c**

Conditions for the hydrogenolysis of **27c** were screened using the following procedure: reaction vials containing stir bars were charged with **27c** (50 mg), solvent (10V), and catalyst (0.25-0.50S). Ammonium formate (5 equiv), sodium borohydride (0.2 equiv), or acetic acid (1 equiv) was also charged, where applicable. The vials were inerted in a Parr stainless steel pressure vessel and held under 3-5 bar of H₂ for 24 hours at 22 °C. The resulting solutions were analyzed by ³¹P NMR.

The competing hydrogenation at the 9- and 10-positions of the anthracene ring (**29**, ³¹P NMR δ 21.6 ppm) occurred under most of the conditions screened. Formation of **29** could be suppressed using nickel boride (made in situ from NiCl₂ and NaBH₄, 0.2 equiv each), however with a modest 55% conversion to **1**.



S4. Second-Generation Synthesis

Process Mass Intensity

PMI was calculated using the Process Mass Intensity Calculation Tool available from the ACS Green Chemistry Institute® (<https://www.acs.org/content/acs/en/greenchemistry/research-innovation/tools-for-green-chemistry.html>).

Table S4. PMI for First-Generation Route

Step	PMI	
1	Total	30
	<i>Reactants/Reagents</i>	8
	<i>Solvents</i>	10
	<i>Water</i>	12
2	Total	40
	<i>Reactants/Reagents</i>	4
	<i>Solvents</i>	29
	<i>Water</i>	7
3	Total	19
	<i>Reactants/Reagents</i>	2
	<i>Solvents</i>	17
	<i>Water</i>	0
4	Total	38
	<i>Reactants/Reagents</i>	2
	<i>Solvents</i>	27
	<i>Water</i>	9
Cumulative	Total	328
	<i>Reactants/Reagents</i>	45
	<i>Solvents</i>	198
	<i>Water</i>	85

Table S5.

PMI for Second-Generation Route

Step	PMI	
1	Total	49
	<i>Reactants/Reagents</i>	5
	<i>Solvents</i>	36
	<i>Water</i>	8
2	Total	53
	<i>Reactants/Reagents</i>	3
	<i>Solvents</i>	31
	<i>Water</i>	19
3	Total	58
	<i>Reactants/Reagents</i>	3
	<i>Solvents</i>	55
	<i>Water</i>	0
Cumulative	Total	275
	<i>Reactants/Reagents</i>	16
	<i>Solvents</i>	201
	<i>Water</i>	58

NMR Spectra of Compounds 35, 27d, 28d, 1, 30

