Enantioselective Synthesis of gem-Disubstituted N-Boc Diazaheterocycles via Decarboxylative Asymmetric Allylic Alkylation

Alexander W. Sun, ‡ Stephan N. Hess, ‡ and Brian M. Stoltz*

The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California, 91125, United States

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Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. tert-Butyl 3-oxopiperazine-1-carboxylate 1 was obtained from Combi-Blocks. Commercially obtained reagents were used as received. Chemicals were purchased from Sigma Aldrich/Strem/Alfa Aesar/Combi-Blocks and used as received.

Reaction temperatures were controlled by an IKAmag temperature modulator. Glove box manipulations were performed under a nitrogen atmosphere. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, iodine on silica, ninhydrin, or KMnO$_4$ staining. SiliaFlash P60 Academic Silica gel (particle size 0.040 – 0.063 mm) was used for flash chromatography.

Analytical SFC was performed with a Mettler SFC supercritical CO$_2$ analytical chromatography system utilizing a Chiralpak IC column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 254 nm. Reverse Phase Preparatory HPLC was performed with a Teledyne ISCO ACCQPrep HP125 preparative liquid chromatography system equipped with a RediSep Prep C18 5 µm column (20 x 250 mm).

$^1$H NMR spectra were recorded on a Varian Inova 600 MHz or 500 MHz spectrometer or a Bruker Avance HD 400 MHz spectrometer and are reported relative to residual CHCl$_3$ (δ 7.26 ppm) or CH$_3$OH (δ 3.31 ppm). $^{13}$C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer or a Bruker Avance HD 400 MHz spectrometer and are reported relative to residual CDCl$_3$ (δ 77.16 ppm) or CD$_3$OD (δ 49.00 ppm). Data for $^1$H NMR are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet. Data for $^{13}$C NMR are reported in terms of chemical shifts (δ ppm). Some reported spectra include minor solvent impurities of water (δ 1.56 or 4.87 ppm), ethyl acetate (δ 4.12, 2.05, 1.26 ppm), methylene chloride (δ 5.30 ppm), acetone (δ 2.17 ppm), grease (δ 1.26, 0.86 ppm), and/or silicon grease (δ 0.07 ppm), which do not impact product assignments.

IR spectra were obtained using a Perkin Elmer Paragon 1000 spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm$^{-1}$). High resolution mass spectra (HRMS) were obtained from an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI+APCI+). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm pathlength cell and are reported as: [α]$_D$$^θ$ (concentration in g/100 mL, solvent). Stereochemistry is assigned by analogy to previous results.$^1$

Preparation of Known Compounds: Allyl cyanofomate was prepared according to the method of Weber. Phosphinooxazoline (PHOX) ligands (S)-L1, (S)-L2, and achiral GlyPhox were prepared by methods described in our previous work. Di-benzyolated allylic alkylation substrate 3g was prepared according to the method of Korch. Tris(4,4’-methoxydibenzylideneacetone)dipalladium(0) [Pd2(pmdba)3] was prepared according to the method of Ibers or Fairlamb. AgOPiv was prepared using Grubbs’ procedure. tert-Butyl ((phenylsulfonyl)methyl)carbamate and benzyl ((phenylsulfonyl)methyl)carbamate were prepared according to the method of Zwierzak or Dikshit. Benzyl 3-oxopiperazine-1-carboxylate was prepared according to the method of Batey. 2-chloroallyl chloroformate was prepared according to the method of Stoltz.

Experimental Procedures for the Synthesis of Piperazinone Allylic Alkylation Substrates

tert-butyl 4-benzoyl-3-oxopiperazine-1-carboxylate (SI-1). To a solution of tert-butyl 3-oxopiperazine-1-carboxylate 1 (5.0 g, 24.9 mmol, 1 equiv) in THF (250 mL) at −78 °C was added dropwise nBuLi (11.4 mL, 2.4M solution in hexane, 27.5 mmol, 1.1 equiv) over 20 minutes. The resulting yellow solution was stirred for 10 min at −78 °C. Benzoyl chloride (3.48 mL, 30.0 mmol, 1.2 equiv) was then added dropwise at −78 °C, giving an orange solution. The reaction was stirred for 2.5 h at −78 °C, quenched by addition of saturated aqueous NH₄Cl (100 mL), and diluted with ethyl acetate (100 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over anhydrous Na₂SO₄, decanted, and concentrated under reduced pressure onto silica gel. The silica-loaded crude reaction mixture was purified by silica gel flash column chromatography (10% → 15% → 20% EtOAc/hexanes) to give protected ketopiperazine SI-1 as a white solid (3.2 g, 42.1% yield). Product identity was confirmed by comparison to previously reported characterization data.

tert-butyl 4-(4-methoxybenzoyl)-3-oxopiperazine-1-carboxylate (SI-2). To a solution of tert-Butyl 3-oxopiperazine-1-carboxylate (5.0 g, 24.9 mmol, 1 equiv) in THF (250 mL) at −78 °C was added dropwise nBuLi (11.4 mL, 2.4M solution in hexane, 27.5 mmol, 1.1 equiv) over 20 minutes. The resulting yellow solution was stirred for 10 min at −78 °C. Anisoyl chloride (4.1 mL, 30.0 mmol, 1.2 equiv) was then added dropwise at −78 °C, giving a bright orange solution. The reaction was stirred for 2 h at −78 °C, quenched by addition of saturated aqueous NH₄Cl (100 mL), and diluted with ethyl acetate (100 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over anhydrous Na₂SO₄, decanted, and
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Supporting Information

concentrated under reduced pressure onto silica gel. The silica-loaded crude reaction mixture was filtered through a plug of silica (1% → 2% MeOH/CH₂Cl₂) to give crude anisoyl protected ketopiperazine SI-2 as a white foam, which was directly used without further purification in subsequent acylation reactions with allyl cyanoformate.

benzyl 4-benzyloxy-3-oxopiperazine-1-carboxylate (SI-3). To a solution of benzyl 3-oxopiperazine-1-carboxylate⁹ (1.0 g, 4.3 mmol, 1.0 equiv) in THF (42 mL) at −78 °C was added dropwise nBuLi (1.96 mL, 2.4M solution in hexane, 4.7 mmol, 1.1 equiv) over 20 minutes. The solution was stirred for 10 min at −78 °C. Benzoyl chloride (0.595 mL, 5.1 mmol, 1.2 equiv) was then added dropwise at −78 °C, giving a light yellow solution. The reaction was stirred for 1 h at −78 °C, quenched by addition of saturated aqueous NH₄Cl (50 mL), and diluted with ethyl acetate (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄, decanted, and concentrated under reduced pressure onto silica gel. The silica-loaded crude reaction mixture was purified by silica gel flash column chromatography (33% EtOAc/hexanes) to give Bz-Cbz-protected ketopiperazine SI-3 as a white solid (1.0 g, 70.0% yield); ¹H NMR (500 MHz, CDCl₃) δ 7.61 – 7.56 (m, 2H), 7.54 – 7.49 (m, 1H), 7.44 – 7.31 (m, 7H), 5.21 (s, 2H), 4.30 (s, 2H), 3.95 (dd, J = 6.8, 4.4 Hz, 2H), 3.83 (dd, J = 6.9, 4.3 Hz, 2H); ¹³C NMR (126 MHz, CDCl₃) δ (a mixture of two rotamers) 172.8, 168.0, 167.6, 154.5, 136.0, 135.0, 132.3, 128.7, 128.5, 128.4, 128.3, 128.3, 68.0, 48.5, 43.3, 41.7, 41.4; IR (Neat Film, NaCl) 3386, 3063, 2954, 1706, 1600, 1584, 1498, 1449, 1422, 1394, 1367, 1302, 1231, 1177, 1162, 1123, 1060, 1028, 1010, 944, 857, 796, 765, 731, 699, 639, 612 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc’d for C₁₉H₁₉N₂O₄ [M+H]⁺: 339.1339, found 339.1338.

2-allyl 1-(tert-butyl) 4-benzyloxy-3-oxopiperazine-1,2-dicarboxylate (2). To a solution of Bz-protected oxopiperazine SI-1 (1.5 g, 4.9 mmol, 1.0 equiv) in THF (40 mL) at −78 °C was added LiHMDS (907 mg, 5.42 mmol, 1.10 equiv.) in THF (10mL) dropwise. The resulting orange reaction mixture was stirred for 15 min at −78 °C. Then, allyl cyanoformate (590 µL, 5.2 mmol, 1.05 equiv) was added dropwise at −78 °C, giving a yellow solution. After stirring for 1.5 h at −78 °C, the reaction was quenched with saturated aqueous NH₄Cl (20 mL) and diluted with ethyl acetate (50 mL). The aqueous phase was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried over anhydrous Na₂SO₄, decanted, and concentrated under reduced pressure onto silica. The silica-loaded crude mixture was purified by silica gel flash chromatography (10% → 20% EtOAc/hexanes) to give the allyl ester 2 as a white solid (1.3 g, 68% yield); ¹H NMR (500 MHz, CDCl₃) δ (a mixture of two rotamers) 7.59 (d, J = 7.7 Hz, 2H), 7.52 (t, J = 7.6 Hz, 1H), 7.40 (t, J = 7.6 Hz, 2H), 5.92 (m, 1H), 5.44 – 5.07 (m, 3H), 4.84 – 4.57 (m, 2H), 4.28
2-allyl 1-(tert-butyl) 4-(4-methoxybenzoyl)-3-oxopiperazine-1,2-dicarboxylate (3b). Following the procedure described for the preparation of 2, anisoyl protected oxopiperazine SI-2 (1.0 g, 3.0 mmol, 1.0 equiv) was treated with LiHMDS (550 mg, 3.3 mmol, 1.1 equiv) and acylated with allyl cyanoformate (336 µL, 3.1 mmol, 1.05 equiv) to give, after purification by silica gel flash chromatography (Dry load SiO2, 18% EtOAc/hexanes), allyl ester 3b as a white solid (566 mg, 45% yield): $^1$H NMR (400 MHz, CDCl₃) δ (a mixture of two rotamers) 7.61 (d, $J = 8.6$ Hz, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 5.91 (ddt, $J = 16.4$, 10.8, 5.8 Hz, 1H), 5.46–5.12 (m, 3H), 4.70 (s, 2H), 4.13–3.65 (m, 4H), 3.81 (s, 3H), 1.46 (m, 9H); $^{13}$C NMR (101 MHz, CDCl₃) δ (a mixture of two rotamers) 171.9, 171.8, 167.0, 164.4, 164.2, 163.4, 154.0, 153.4, 131.4, 131.0, 126.3, 119.6, 119.2, 113.6, 82.0, 81.8, 66.9, 62.5, 61.6, 55.5, 43.3, 42.8, 41.5, 40.1, 28.2; IR (Neat Film, NaCl) 3384, 3060, 2978, 2843, 2568, 2049, 1732, 1605, 1580, 1513, 1456, 1372, 1258, 1088, 1059, 959, 844, 769, 736, 706, 634 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc’d for C₂₁H₂₇N₂O₇ [M+H]⁺: 419.1813, found 419.1815.

2-allyl 1-benzyl 4-benzoyl-3-oxopiperazine-1,2-dicarboxylate (3c). Following the procedure described for the preparation of 2, Cbz protected oxopiperazine SI-3 (1.0 g, 3.0 mmol, 1.0 equiv) was treated with LiHMDS (544 mg, 3.3 mmol, 1.1 equiv) and acylated with allyl cyanoformate (331 µL, 3.1 mmol, 1.05 equiv) to give, after purification by silica gel flash chromatography (dry load SiO2, 20 → 25% EtOAc/hexanes), allyl ester 3a as a white solid (720 mg, 58% yield): $^1$H NMR (500 MHz, CDCl₃) δ (a mixture of two rotamers) 7.65 – 7.56 (m, 2H), 7.56 – 7.46 (m, 1H), 7.46 – 7.28 (m, 7H), 5.87 (ddt, $J = 47.5$, 10.7, 5.4 Hz, 1H), 5.55 – 5.04 (m, 5H), 4.84 – 4.48 (m, 2H), 4.24 – 3.99 (m, 2H), 3.99 – 3.66 (m, 2H); $^{13}$C NMR (126 MHz, CDCl₃) δ (a mixture of two rotamers) 172.4, 172.3, 166.5, 164.0, 163.8, 154.8, 154.2, 135.7, 135.6, 134.4, 132.5, 130.9, 130.8, 128.7, 128.6, 128.5, 128.4, 128.5, 128.3, 128.2, 128.1, 119.6, 119.5, 68.3, 68.2, 67.2, 67.1, 62.1, 61.9, 42.8, 42.3, 41.3, 40.8; IR (Neat Film, NaCl) 3386, 3064, 3033, 2955, 2897, 1746, 1713, 1694, 1651, 1600, 1584, 1498, 1450, 1417, 1368, 1304, 1278, 1229, 1195, 1178,
1160, 1124, 1088, 1061, 1014, 985, 951, 860, 794, 768, 729, 696, 675, 623 cm\(^{-1}\); HRMS (MM: ESI-APCI) \(m/z\) calc’d for C\(_{23}\)H\(_{32}\)N\(_2\)O\(_6\) [M+H\(^+\)]: 423.1551, found 423.1547.

**1-(tert-butyl) 2-(2-chloroallyl) 4-benzoyl-3-oxopiperazine-1,2-dicarboxylate (3d).** Following the procedure described for the preparation of 2, benzoyl protected oxopiperazine SI-1 (440 mg, 1.5 mmol, 1.0 equiv) was treated with LiHMDS (267 mg, 1.6 mmol, 1.1 equiv) and acylated with 2-chloroallyl chloroformate\(^{10}\) (235 mg, 1.5 mmol, 1.05 equiv) to give, after purification by silica gel flash chromatography (Dry load SiO\(_2\), 15% EtOAc/hexanes), 2-chloroallyl ester 3d as an off-white solid (431 mg, 70% yield): \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) (a mixture of two rotamers) 7.59–7.54 (m, 2H), 7.50–7.44 (m, 1H), 7.43–7.37 (m, 2H), 6.67 (m, 1H), 5.42–5.33 (m, 2H), 4.54 (m, 2H), 3.95–3.89 (m, 2H), 3.72 (t, \(J = 5.2\) Hz, 2H), 1.51 (s, 9H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) (a mixture of two rotamers) 167.5, 167.3, 152.4, 152.2, 151.1, 151.0, 134.9, 134.3, 131.3, 131.2, 128.5, 128.4, 128.0, 127.9, 115.9, 115.7, 107.9, 107.6, 82.3, 82.2, 69.9, 69.8, 44.2, 43.1, 42.3, 41.7, 28.3; IR (Neat Film, NaCl) 3386, 3129, 3062, 2979, 2936, 2253, 1770, 1691, 1372, 1242, 1050, 987, 950, 922, 859, 839, 764, 731, 707, 647 cm\(^{-1}\); HRMS (MM: ESI-APCI) \(m/z\) calculated for C\(_{20}\)H\(_{30}\)Cl\(_2\)N\(_2\)O\(_6\) [M+H\(^+\)]: 423.1317, found 423.1316.

**2-allyl 1-(tert-butyl) 4-(4-methoxybenzoyl)-2-methyl-3-oxopiperazine-1,2-dicarboxylate (3e).** Sodium hydride (60% in mineral oil, 25 mg, 0.62 mmol, 1.2 equiv) was added to a solution of allyl ester 2 (200 mg, 0.52 mmol, 1.0 equiv) in THF (5 mL) at 0 °C. After stirring for 30 min at 0 °C, MeI (160 \(\mu\)L, 2.57 mmol, 5.0 equiv) was added. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The reaction was quenched with aqueous NH\(_4\)Cl (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic phases were dried over anhydrous Na\(_2\)SO\(_4\), decanted, and concentrated under reduced pressure onto silica gel. The silica-loaded residue was purified by silica gel flash chromatography (20% EtOAc/hexanes) to give methylated allyl ester 3e as a colorless oil (180 mg, 85% yield): \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.59 – 7.46 (m, 3H), 7.46 – 7.32 (m, 2H), 5.92 (ddt, \(J = 17.2, 10.4, 5.8\) Hz, 1H), 5.41 – 5.19 (m, 2H), 4.66 (d, \(J = 5.8\) Hz, 2H), 4.24 – 4.09 (m, 1H), 3.93 – 3.90 (m, 2H), 3.81 – 3.64 (m, 1H), 1.84 (s, 3H), 1.46 (s, 9H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) (a mixture of two rotamers) 172.5, 169.2, 168.0, 153.2, 134.8, 132.4, 131.5, 128.4, 128.0, 119.1, 82.7, 68.7, 66.9, 43.7, 40.9, 28.3, 21.5; IR (Neat Film, NaCl) 3384, 3064, 2980, 2939, 2876, 1762, 1766, 1694, 1600, 1584, 1451, 1394, 1368, 1306, 1270, 1232, 1206, 1164, 1096, 1060, 1032, 1016, 993, 968, 936, 854, 795, 770, 727, 696, 675, 633, 618 cm\(^{-1}\); HRMS (MM: ESI-APCI) \(m/z\) calculated for C\(_{16}\)H\(_{19}\)N\(_2\)O\(_4\) [(M-Boc)+H\(^+\)]: 303.1341, found 303.1339.
2-allyl 1-(tert-butyl) 4-(4-methoxybenzoyl)-2-methyl-3-oxopiperazine-1,2-dicarboxylate (3f). Following the procedure described for the preparation of 3e, anisoyl protected oxopiperazine 3b (120 mg, 0.29 mmol, 1.0 equiv) was treated with NaH (60% in mineral oil, 13 mg, 0.32 mmol, 1.1 equiv) and methylated with Mel (90 µL, 1.43 mmol, 5.0 equiv) to give, after purification by silica gel flash chromatography (dry load SiO₂, 15% → 20% → 25% → 30% EtOAc/hexanes), methylated allyl ester 3f as a colorless oil (110 mg, 89% yield): ¹H NMR (400 MHz, CDCl₃) δ 7.56 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.9 Hz, 2H), 5.92 (ddt, J = 17.2, 10.4, 5.8 Hz, 1H), 5.40 – 5.17 (m, 2H), 4.66 (d, J = 5.8 Hz, 2H), 4.15 – 4.02 (m, 1H), 4.02 – 3.87 (m, 2H), 3.83 (s, 3H), 3.80 – 3.67 (m, 1H), 1.84 (s, 3H), 1.46 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 171.8, 169.0, 168.1, 163.4, 153.2, 131.5, 131.0, 126.6, 119.0, 113.7, 82.6, 68.5, 66.8, 55.5, 43.8, 41.0, 28.3, 21.6; IR (Neat Film, NaCl) 3081, 2978, 2938, 2842, 1766, 1702, 1604, 1579, 1512, 1460, 1394, 1368, 1308, 1287, 1259, 1235, 1208, 1169, 1114, 1095, 1060, 1021, 1004, 969, 933, 845, 789, 770, 733, 706, 648, 634 cm⁻¹; HRMS (MM: ESI-APCI) m/z calculated for C₁₈H₂₈N₂O₇ [(M-tBu)+H]⁺: 377.1343, found 377.1339.

2-allyl 1-(tert-butyl) 2-benzyl-4-(4-methoxybenzoyl)-3-oxopiperazine-1,2-dicarboxylate (3h). Following the procedure described for the preparation of 3e, anisoyl-protected allyl ester 3b (200 mg, 0.48 mmol, 1.0 equiv) was treated with potassium hydride (23 mg, 0.57 mmol, 1.2 equiv) and alkylated with benzyl bromide (170 µL, 1.43 mmol, 3.0 equiv) to give, after purification by silica gel flash chromatography (Dry load SiO₂, 20% → 25% EtOAc/hexanes), the benzyl ester 3h as a colorless oil (100 mg, 41% yield) (Note: attempts using sodium hydride as a base failed to give conversion of starting material. Instead, potassium hydride resulted in conversion to the desired product.): ¹H NMR (400 MHz, CDCl₃) δ (a mixture of two rotamers) 7.52 (m, 2H), 7.42 – 7.23 (m, 3H), 7.11 (m, 2H), 6.92 – 6.75 (m, 2H), 5.97 (ddt, J = 17.2, 10.4, 5.8 Hz, 1H), 5.50 – 5.17 (m, 2H), 4.87 – 4.57 (m, 2H), 3.86 (s, 3H), 3.79 – 3.56 (m, 4H), 2.95 (ddd, J = 13.3, 7.4, 3.0 Hz, 1H), 2.86 (br s, 1H), 1.55 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ (a mixture of two rotamers) 172.1, 168.0, 167.4, 166.9, 163.4, 153.6, 153.4, 136.0, 135.3, 131.8, 131.3, 130.7, 128.8, 128.7, 128.4, 128.2, 127.8, 127.7, 127.5, 126.6, 119.4, 118.9, 113.7, 82.9, 81.8, 72.7, 67.0, 66.5, 55.6, 44.5, 43.0, 42.2, 41.4, 40.8, 40.0, 38.8, 28.5; IR (Neat Film, NaCl) 2978, 1764, 1698, 1604, 1512, 1496, 1455, 1394, 1366, 1307, 1282, 1256, 1196, 1155, 1078, 1020, 1000, 921, 844, 768 733, 704 cm⁻¹; HRMS (MM: ESI-APCI) m/z calculated for C₂₈H₃₅N₂O₇ [M+H]⁺: 509.2282, found 509.2285.
2-allyl 1-(tert-butyl) 4-benzoyl-2-((benzzyloxy)methyl)-3-oxopiperazine-1,2-dicarboxylate (3i). Following the procedure described for the preparation of 3e, allyl ester 2 (150 mg, 0.39 mmol, 1.0 equiv) was treated with sodium hydride (17 mg, 0.42 mmol, 1.1 equiv) and alkylated with benzyl chloromethyl ether (107 µL, 0.77 mmol, 2.0 equiv) to give, after purification by silica gel flash chromatography (Dry load SiO₂, 10% → 15% EtOAc/hexanes), benzzyloxy methyl ether 3i as a colorless oil (50 mg, 55% yield BRSM):

\[ ^1H \text{ NMR (500 MHz, CDCl}_3 \] \( \delta \) (a mixture of two rotamers) 7.64 – 7.55 (m, 2H), 7.51 – 7.44 (m, 1H), 7.41 – 7.27 (m, 7H), 5.88 (ddt, \( J = 17.3, 10.4, 5.8 \) Hz, 1H), 5.40 – 5.17 (m, 2H), 4.74 – 4.47 (m, 4H), 4.38 (m, 1H), 4.17 (m, 1H), 4.08 – 3.84 (m, 4H), 1.42 (m, 9H);

\[ ^13C \text{ NMR (126 MHz, CDCl}_3 \] \( \delta \) (a mixture of two rotamers) 173.0, 167.4, 167.2, 166.5, 153.6, 153.1, 141.0, 137.9, 137.5, 134.8, 132.4, 131.6, 131.1, 128.7, 128.7, 128.6, 128.4, 128.3, 128.0, 127.7, 127.6, 127.1, 119.5, 118.9, 82.7, 81.9, 73.9, 73.3, 72.6, 71.2, 71.1, 66.8, 65.4, 43.6, 43.4, 42.5, 41.7, 28.4, 28.3; IR (Neat Film, NaCl) 3528, 3064, 3031, 2978, 2934, 1762, 1694, 1496, 1453, 1394, 1366, 1314, 1270, 1231, 1205, 1161, 1094, 1055, 1014, 972, 941, 854, 795, 770, 730, 696, 674, 624 cm⁻¹; HRMS (MM: ESI-APCI) m/z calculated for C_{24}H_{24}N_{2}O_{9} [(M-tBu)+H]^+: 453.1656, found 453.1649.

2-allyl 1-(tert-butyl) 2-(2-cyanoethyl)-4-(4-methoxybenzoyl)-3-oxopiperazine-1,2-dicarboxylate (3j). DBU (7.1 µL, 0.048 mmol, 0.10 equiv) was added to a solution of allyl ester 3f (200 mg, 0.478 mmol, 1.0 equiv) and acrylonitrile (94 µL, 1.43 mmol, 3.0 equiv) in DMF (2.4 mL) at room temperature. After stirring for 2 h at 70 °C and 24 h at 55 °C, additional DBU (14 µL, 0.1 mmol, 0.2 equiv) was added and the mixture was stirred at 70 °C for 3 h. After allowing the reaction mixture to cool to room temperature, the reaction was quenched with saturated aqueous NH₄Cl (2 mL) and diluted with EtOAc (6 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄, decanted, and concentrated under reduced pressure onto silica gel. The silica-loaded residue was purified by flash chromatography (20% EtOAc/hexanes) to give the α-cyanoethylated allyl ester 3j as a pale yellow oil (77.6 mg, 34% yield): \( ^1H \text{ NMR (400 MHz, CDCl}_3 \] \( \delta \) 7.54 (s, 2H), 6.85 (d, \( J = 8.9 \) Hz, 2H), 5.92 (ddt, \( J = 17.2, 10.4, 5.9 \) Hz, 1H), 5.36 (dd, \( J = 17.2, 1.4 \) Hz, 1H), 5.29 (d, \( J = 10.5 \) Hz, 1H), 4.69 (d, \( J = 5.8 \) Hz, 2H), 4.25 (s, 1H), 4.06 (ddd, \( J = 13.1, 5.7, 3.1 \) Hz, 1H), 3.96 (ddd, \( J = 13.1, 8.6, 3.4 \) Hz, 1H), 3.83 (s, 3H), 3.64 – 3.49 (m,
1H), 2.77 (s, 2H), 2.49 (m, 1H), 2.44 – 2.31 (m, 1H), 1.47 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.7, 167.24, 166.3, 163.5, 153.4, 131.1, 126.2, 119.6, 119.1, 113.8, 82.9, 70.5, 67.3, 55.5, 43.9, 42.3, 29.8, 28.2, 12.8; IR (Neat Film, NaCl) 2978, 2249, 1760, 1694, 1604, 1579, 1512, 1462, 1394, 1368, 1311, 1258, 1160, 1018, 933, 846, 769, 737, 704 cm$^{-1}$; HRMS (MM: ESI-APCI): m/z calc’d for C$_{24}$H$_{30}$N$_3$O$_7$ [M+H]$^+$: 472.2078, found 472.2078.

2-allyl 1-(tert-butyl) 4-(4-methoxybenzoyl)-3-oxo-2-(3-oxobutyl)piperazine-1,2-dicarboxylate (3k). To a solution of allyl ester 3b (200 mg, 0.5 mmol, 1.0 equiv) and methyl vinyl ketone (80 µL, 0.96 mmol, 2.0 equiv) in acetone (2 mL) at room temperature was added DBU (7.1 µL, 0.05 mmol, 0.1 equiv). After stirring for 24 h at 55 °C, additional DBU (7.1 µL, 0.05 mmol, 0.1 equiv) was added and the orange solution was maintained at 55 °C for an additional 24 h. The reaction mixture was allowed to cool to ambient temperature and concentrated under reduced pressure onto silica gel. The silica-loaded crude reaction mixture was purified by silica gel flash column chromatography (33% EtOAc/hexanes) to afford the ketone 3k as a pale yellow oil (90 mg, 39% yield): $^1$H NMR (400 MHz, CDCl$_3$) δ 7.56 (d, $J = 8.8$ Hz, 2H), 6.84 (d, $J = 8.9$ Hz, 2H), 5.92 (ddt, $J = 17.2, 10.4, 5.8$ Hz, 1H), 5.35 (dd, $J = 17.2, 1.5$ Hz, 1H), 5.26 (d, $J = 10.4$ Hz, 1H), 4.71 – 4.60 (m, 2H), 4.11 – 3.93 (m, 3H), 3.82 (s, 3H), 3.71 – 3.59 (m, 1H), 2.72 (q, $J = 9.3, 8.1$ Hz, 1H), 2.60 (dt, $J = 9.6, 6.2$ Hz, 3H), 2.10 (s, 3H), 1.45 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 207.8, 172.0, 167.9, 167.4, 163.4, 153.5, 131.5, 131.1, 126.6, 119.2, 113.7, 82.4, 70.6, 66.9, 55.5, 43.5, 42.1, 38.8, 29.8, 28.7, 28.3; IR (Neat Film, NaCl): 2977, 2934, 1761, 1704, 1512, 1456, 1394, 1367, 1312, 1257, 1199, 1168, 1090, 1018, 845, 768 cm$^{-1}$; HRMS (MM: ESI-APCI): m/z calc’d for C$_{25}$H$_{33}$N$_2$O$_8$ [M+H]$^+$: 489.2231, found: 489.2228.

2-allyl 1-(tert-butyl) 2-(((benzyloxy)carbonyl)amino)methyl)-4-(4-methoxybenzoyl)-3-oxopiperazine-1,2-dicarboxylate (3l). Following the procedure described for the preparation of 3m, anisoyl-protected allyl ester 3b (400 mg, 0.96 mmol, 1.0 equiv) was treated with Cs$_2$CO$_3$ (779 mg, 2.39 mmol, 2.5 equiv) and alkylated with benzyl ((phenylsulfonyl)methyl)carbamate$^5$ (350 mg, 1.15 mmol, 2.5 equiv) to give, after purification by silica gel flash chromatography (Dry load SiO$_2$, 10% → 15% → 20% EtOAc/hexanes), the aminomethyl allyl ester 3l as a white foam (300 mg, 54% yield): $^1$H NMR (400 MHz, CDCl$_3$) δ (a mixture of two rotamers) 7.69 – 7.50 (m, 2H), 7.41 – 7.25
(m, 5H), 6.95 – 6.72 (m, 2H), 5.92 (ddt, $J = 17.3, 10.4, 5.9$ Hz, 1H), 5.49 – 4.96 (m, 5H),
4.85 – 4.53 (m, 2H), 4.27 – 3.87 (m, 5H), 3.83 (d, $J = 14.6$ Hz, 3H), 3.60 (d, $J = 22.7$ Hz,
1H), 1.47 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ (a mixture of two rotamers) 171.7, 167.3,
166.5, 163.4, 156.8, 153.7, 152.7, 136.4, 134.21, 132.5, 131.5, 131.2, 129.4, 129.3, 128.9,
128.6, 128.3, 126.5, 119.8, 119.3, 113.7, 83.1, 82.1, 71.4, 70.6, 68.3, 67.8, 67.0, 55.5,
45.0, 44.2, 43.7, 42.9, 41.9, 28.3; IR (Neat Film, NaCl) 3366, 2977, 1704, 1604, 1513, 1456,
1394, 1367, 1313, 1257, 1091, 1018, 1002, 845, 767, 698 cm$^{-1}$; HRMS (MM: ESI-APCI):
m/z calc’d for C$_{30}$H$_{36}$N$_3$O$_9$ [M+H]$^+$: 582.2446, found 582.2438.

2-allyl 1-(tert-butyl) 4-benzoyl-2-(((tert-butoxycarbonyl)amino)methyl)-3-
oxopiperazine-1,2-dicarboxylate (3m). To a suspension of allyl ester 2 (200 mg, 0.5
mmol, 1.0 equiv) and tert-butyl ((phenylsulfonyl)methyl)carbamate (168 mg, 0.6 mmol,
1.2 equiv), in dichloromethane (2.5 mL) at room temperature was added Cs$_2$CO$_3$ (419 mg,
1.3 mmol, 2.5 equiv). After stirring for 3 h, saturated aqueous NH$_4$Cl (1 mL) was added
and the biphasic mixture was vigorously stirred for 20 min. The aqueous phase was
extracted with dichloromethane (3 x 3 mL). The combined organic phases were dried over
anhydrous Na$_2$SO$_4$, decanted, and concentrated under reduced pressure onto silica gel. The
silica-loaded crude reaction mixture was purified by silica gel flash column chromatography
(15% EtOAc/hexanes) to give methylcarbamate allyl ester 3m as a white foam (202 mg, 76% yield): $^1$H NMR (400 MHz, CDCl$_3$) δ (a mixture of two rotamers)
7.55 (d, $J = 7.5$ Hz, 2H), 7.49 (t, $J = 7.5$ Hz, 1H), 7.36 (t, $J = 7.7$ Hz, 2H), 5.91 (ddt,
$J = 16.5, 10.4, 5.8$ Hz, 1H), 5.34 – 5.27 (m, 2H), 4.96 (m, 1H), 4.66 (br s, 2H), 4.19 – 3.85 (m,
5H), 3.79 – 3.64 (m, 1H), 1.48 (s, 9H), 1.40 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ (a
mixture of two rotamers) 172.4, 167.3, 166.8, 156.1, 153.6, 152.9, 134.9, 132.4, 131.7,
131.1, 128.3, 128.3, 119.6, 119.0, 83.1, 82.1, 79.9, 71.4, 70.6, 67.0, 44.3, 43.8, 43.2, 42.2,
41.6, 28.4, 28.3; IR (Neat Film, NaCl) 3386, 2978, 1760, 1698, 1601, 1505, 1451, 1394,
1367, 1314, 1232, 1203, 1164, 1092, 1067, 1012, 915, 854, 766, 730, 696 cm$^{-1}$; HRMS
(MM: ESI-APCI): m/z calc’d for C$_{26}$H$_{36}$N$_3$O$_8$ [M+H]$^+$: 518.2497, found 518.2496.

Experimental Procedures for the Synthesis of Tetrahydropyrimidinone Allylic
Alkylation Substrates

tert-Butyl 4-oxotetrahydropyrimidine-1(2H)-carboxylate (SI-4). A solution of 3-
aminopropanamide hydrochloride (5 g, 40.1 mmol, 1.0 equiv), potassium hydroxide (3.38
g, 60.2 mmol, 1.5 equiv), and formaldehyde (37% in water, 5.97 mL, 80.3 mmol, 2.0 equiv) in ethanol (13 mL) was stirred at reflux for 4 h. The suspension was then maintained at 55 °C while triethylamine (5.5 mL, 40.1 mmol, 1 equiv) and di-tert-butyldicarbonate (9.2 g, 42.1 mmol, 1.05 equiv) were added successively. The reaction was stirred for 2 h at 55 °C and then allowed to cool to ambient temperature. The precipitate was filtered off, the filtrate was concentrated under reduced pressure, and was then purified by silica gel flash chromatography (1 → 3% MeOH/CHCl₃) to afford Boc-protected tetrahydropyrimidinone SI-4 as a white solid (4.09 g, 51% yield over two steps): ¹H NMR (500 MHz, CDCl₃) δ 8.14 – 7.60 (m, 1H), 4.77 – 4.61 (m, 2H), 3.58 (t, J = 6.5 Hz, 2H), 2.41 (t, J = 6.5 Hz, 2H), 1.41 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ (a mixture of two rotamers) 171.5, 153.8, 153.4, 81.1, 54.8, 54.0, 40.4, 39.4, 31.4, 28.3; IR (Neat Film, NaCl) 3193, 2970, 1710, 1643, 1488 cm⁻¹; HRMS (MM: ESI-APCI): m/z calc’d for C₉H₁₇N₂O₃ [M+H]⁺: 201.1234, found 201.1231.

**tert-Butyl 3-benzyloxytetrahydroxypyrindine-1(2H)-carboxylate (SI-5).** To a solution of tetrahydropyrimidinone SI-4 (2.07 g, 10.4 mmol, 1.0 equiv) in THF (100 mL) at −78 °C was added n-butyllithium (2.2 M in hexanes, 4.94 mL, 10.9 mmol, 1.05 equiv) dropwise over 10 min. After stirring the solution at −78 °C for 20 min, benzoyl chloride (1.43 mL, 12.4 mmol, 1.2 equiv) was added dropwise at −78 °C. The reaction solution was stirred at −78 °C for 40 min, allowed to warm up to room temperature, and was then quenched with saturated aqueous NH₄Cl (50 mL). The mixture was diluted with EtOAc (100 mL) and the aqueous phase was extracted with EtOAc (3 x 80 mL). The combined organic phases were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure onto silica gel. The silica-loaded residue was purified by silica gel flash chromatography (30% EtOAc/hexanes) to give Bz-protected tetrahydropyrimidinone SI-5 as a white solid (2.72 g, 86% yield): ¹H NMR (400 MHz, Chloroform-d) δ 7.55 (dt, J = 8.3, 1.4 Hz, 2H), 7.50 (t, J = 7.4 Hz, 1H), 7.39 (t, J = 7.6 Hz, 2H), 5.28 (s, 2H), 3.74 (t, J = 6.6 Hz, 2H), 2.68 (t, J = 6.6 Hz, 2H), 1.49 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 172.3, 170.7, 153.8, 135.0, 132.2, 128.4, 128.2, 128.1, 81.7, 57.0, 40.4, 33.4, 28.3; IR (Neat Film, NaCl) 2978, 1698, 1480, 1450, 1408, 1367, 1304, 1266, 1239, 1141, 1015, 936, 863, 797, 700, 618 cm⁻¹; HRMS (MM: ESI-APCI): m/z calc’d for C₁₆H₂₁N₂O₄ [M+H]⁺: 305.1496, found 305.1500.

5-Allyl 1-(tert-butyl) 3-benzyloxytetrahydroxypyrindine-1,5(2H)-dicarboxylate
To a solution of diisopropylamine (224 µL, 1.59 mmol, 1.2 equiv) in THF (3 mL) at −78 °C was added n-butyllithium (2.2 M in hexanes, 664 µL, 1.46 mmol, 1.1 equiv). The solution was maintained at −78 °C for 15 min and then cannulated over 10 min into a solution of Bz-protected tetrahydropyrimidine SI-5 (404 mg, 1.33 mmol, 1.0 equiv) in THF (10 mL) at −78 °C. After stirring the solution at −78 °C for 25 min, allyl cyanoformate (156 µL, 1.46 mmol, 1.1 equiv) was added dropwise at −78 °C. The reaction mixture was maintained at −78 °C for 50 min and was then quenched with saturated aqueous NH₄Cl (10 mL). The reaction mixture was diluted with EtOAc (10 mL) and allowed to warm to room temperature. The aqueous phase was extracted with EtOAc (3 x 15 mL) and the combined organic phases were dried over anhydrous Na₂SO₄, decanted, and concentrated under reduced pressure onto silica gel. The silica-loaded residue was purified by silica gel flash chromatography (18 → 20 → 30% EtOAc/hexanes) to give re-isolated starting material SI-5 (154 mg, 38% yield) and allyl ester SI-6 as a white crystalline solid (310 mg, 60% yield, 97% yield based on recovered starting material): ¹H NMR (400 MHz, CDCl₃) δ 7.70 (d, J = 7.2 Hz, 2H), 7.51 (t, J = 7.4 Hz, 1H), 7.40 (t, J = 7.6 Hz, 2H), 5.95 (ddt, J = 17.2, 10.4, 5.9 Hz, 1H), 5.37 (dq, J = 17.2, 1.5 Hz, 1H), 5.36 (m, 1H), 5.30 (dd, J = 10.4, 13 Hz, 1H), 5.17 (d, J = 12.6 Hz, 1H), 4.69 (d, J = 6.0 Hz, 2H), 4.27 (dd, J = 13.7, 5.4, 1.2 Hz, 1H), 3.85 (dd, J = 13.7, 6.2 Hz, 1H), 3.63 (t, J = 5.7 Hz, 1H), 1.49 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 172.9, 167.8, 167.0, 153.4, 134.6, 132.5, 131.3, 128.7, 128.3, 119.7, 82.3, 67.0, 58.5, 50.1, 43.9, 28.3; IR (Neat Film, NaCl) 3406, 3064, 2978, 2935, 1714, 1601, 1480, 1450, 1416, 1369, 1287, 1148, 1072, 1017, 934, 859, 796, 768, 736, 703, 626 cm⁻¹; HRMS (MM: ESI-APCI): m/z calc’d for C₂₀H₂₅N₂O₆ [M+H]⁺: 389.1707, found 389.1708.
5-allyl 1-(tert-butyl) 3-benzoyl-5-ethyl-4-oxotetrahydropyrimidine-1,5(2H)-dicarboxylate (5b). Following the procedure described for the preparation of 5a, allyl ester SI-6 (200 mg, 0.52 mmol, 1.0 equiv) was treated with cesium carbonate (336 mg, 1.03 mmol, 2.0 equiv) and alkylated with ethyl iodide (124 µL, 1.54 mmol, 3.0 equiv) to give, after purification by silica gel flash chromatography (dry load SiO$_2$, 15% EtOAc/hexanes), ethylated allyl ester 5b as a colorless oil (182 mg, 85% yield): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (a mixture of two rotamers) 7.70 (d, $J = 8.0$ Hz, 2H), 7.50 (t, $J = 7.4$ Hz, 1H), 7.38 (t, $J = 7.7$ Hz, 1H), 5.95 (ddt, $J = 16.6$, 10.4, 6.0 Hz, 1H), 5.38 (dd, $J = 17.2$, 1.5 Hz, 1H), 5.31 (d, $J = 10.3$ Hz, 2H), 5.20 (d, $J = 12.5$ Hz, 1H), 4.70 (t, $J = 6.0$ Hz, 2H), 4.47 – 4.26 (m, 1H), 3.49 (d, $J = 13.5$ Hz, 1H), 1.96 (q, $J = 7.5$ Hz, 2H), 1.49 (s, 9H), 0.96 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ (a mixture of two rotamers) 172.9, 170.4, 170.1, 169.8, 153.2, 135.0, 132.3, 131.2, 128.4, 128.2, 119.8, 81.9, 66.9, 57.9, 57.4, 56.7, 47.8, 47.4, 28.3, 26.4, 9.1; IR (Neat Film, NaCl) 2976, 1703, 1450, 1422, 1367, 1288, 1247, 1156, 1134, 1015, 942, 894, 802, 766, 718, 696 cm$^{-1}$; HRMS (MM: ESI-APCI): $m/z$ calc’d for C$_{21}$H$_{27}$N$_2$O$_6$ [M+H]$^+$: 403.1864, found 403.1868.

5-allyl 1-(tert-butyl) 3-benzoyl-5-(3-methoxy-3-oxopropyl)-4-oxotetrahydropyrimidine-1,5(2H)-dicarboxylate (5c). To a suspension of allyl ester SI-6 (100 mg, 0.26 mmol, 1.0 equiv) and potassium carbonate (178 mg, 1.29 mmol, 5.0 equiv) in acetone (1.0 mL) at room temperature was added methyl acrylate (47 µL, 0.52 mmol, 2.0 equiv). The reaction mixture was stirred for 3.5 h at 55 °C, allowed to cool to room temperature, and filtered through a cotton plug. The filter cake was washed with acetone (3 x 1 mL) and the combined organic phases were concentrated by under reduced pressure onto silica gel. The silica-loaded residue was purified by silica gel flash chromatography (19% EtOAc/hexanes) to give pyrimidinone 5c as a colorless oil (101 mg, 83% yield): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (a mixture of two rotamers) 7.70 (br s, 2H), 7.50 (t, $J = 7.4$ Hz, 1H), 7.38 (t, $J = 7.7$ Hz, 2H), 5.95 (ddt, $J = 16.6$, 10.3, 6.0 Hz, 1H), 5.38 (dd, $J = 17.1$, 1.6 Hz, 1H), 5.32 (d, $J = 10.4$ Hz, 1H), 5.25 (m, 2H), 4.70 (d, $J = 6.0$ Hz, 2H), 4.41 (m, 1H), 3.62 (s, 3H), 3.47 (m, 1H), 2.58 (ddd, $J = 16.0$, 9.5, 6.4 Hz, 1H), 2.46 – 2.33 (m, 1H), 1.39 (m, 1H), 0.96 (t, $J = 7.4$ Hz, 3H), 0.86 (d, $J = 6.0$ Hz, 3H), 0.63 (s, 9H), 0.33 (s, 3H), 0.25 (d, $J = 6.0$ Hz, 3H).
2.21 (ddd, J = 10.0, 6.3, 3.2 Hz, 2H), 1.48 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ (a mixture of two rotamers) 173.0, 172.9, 169.7, 153.1, 134.9, 132.4, 131.1, 128.4, 128.3, 120.1, 82.2, 67.2, 58.3, 57.6, 55.6, 51.9, 48.7, 48.2, 29.7, 28.3; IR (Neat Film, NaCl) 2978, 1704, 1423, 1368, 1248, 1153, 987, 803, 722, 696 cm$^{-1}$; HRMS (MM: ESI-APCI): m/z calc’d for C$_{24}$H$_{31}$N$_2$O$_8$ [M+H]$^+$: 475.2075, found 475.2074.

5-allyl 1-(tert-butyl) 3-benzoyl-5-(2-chloroallyl)-4-oxotetrahydropyrimidine-1,5(2H)-dicarboxylate (5d). To a suspension of allyl ester SI-6 (200 mg, 0.51 mmol, 1.0 equiv) and tetrabutylammonium iodide (17 mg, 0.05 mmol, 0.1 equiv), in THF (5.1 mL) at 0 °C was added NaH (60% in mineral oil, 25 mg, 0.62 mmol, 1.2 equiv). After stirring for 30 min at 0 °C, 2,3-dichloro-1-propene (95 µL, 1.02 mmol, 2 equiv) was added and the reaction mixture heated at 40 °C for 16 h. The reaction was quenched with aqueous NH$_4$Cl (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic phases were dried over anhydrous Na$_2$SO$_4$, decanted, and concentrated under reduced pressure onto silica gel. The silica-loaded residue was purified by silica gel flash chromatography (10% → 15% EtOAc/hexanes) to give 2-chloro-allyl allyl ester 5d as a colorless oil (140 mg, 59% yield): $^1$H NMR (400 MHz, CDCl$_3$) δ 7.75 (d, J = 8.6 Hz, 2H), 7.51 (s, 1H), 7.39 (t, J = 7.5 Hz, 2H), 6.07 – 5.90 (m, 1H), 5.71 – 5.48 (m, 1H), 5.33 (m, 4H), 5.03 (d, J = 12.5 Hz, 1H), 4.85 – 4.43 (m, 3H), 3.58 (mz, 1H), 3.32 (d, J = 15.1 Hz, 1H), 3.03 (d, J = 15.1 Hz, 1H), 1.48 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ (a mixture of two rotamers) 173.3, 169.9, 168.7, 153.4, 136.3, 134.9, 132.4, 131.2, 128.7, 128.2, 120.1, 118.8, 82.1, 67.7, 58.5, 57.8, 55.1, 47.7, 47.2, 41.0, 28.3; IR (Neat Film, NaCl) 2978, 1703, 1632, 1478, 1450, 1423, 1368, 1289, 1137, 902, 803, 721, 695, 633 cm$^{-1}$; HRMS (MM: ESI-APCI): m/z calc’d for C$_{23}$H$_{28}$ClN$_2$O$_6$ [M+H]$^+$: 463.1630, found 463.1641.

5-allyl 1-(tert-butyl) 3-benzoyl-5-benzyl-4-oxotetrahydropyrimidine-1,5(2H)-dicarboxylate (5e). To a solution of allyl ester SI-6 (100 mg, 0.26 mmol, 1.0 equiv) in THF (2.6 mL) at room temperature was added sodium hydride (11 mg, 0.28 mmol, 1.1 equiv). After stirring for 15 min, benzyl bromide (37 µL, 0.31 mmol, 1.2 equiv) was added. The reaction mixture was maintained at room temperature for 22 h and at 55 °C for 24 h. The reaction was quenched with aqueous NH$_4$Cl (2 mL) and diluted with EtOAc (2mL). The aqueous phase was extracted with EtOAc (3 x 3mL) and the combined organic phases were dried over anhydrous Na$_2$SO$_4$, decanted, and concentrated under reduced pressure onto silica gel. The silica-loaded residue was purified by silica gel flash chromatography (15% EtOAc/hexanes) to give benzyalted allyl ester 5e as a colorless oil (94 mg, 76%
yield): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.71 (d, $J = 7.6$ Hz, 2H), 7.52 (t, $J = 7.5$ Hz, 1H), 7.39 (t, $J = 7.5$ Hz, 2H), 7.29 – 7.19 (m, 3H), 7.14 (dd, $J = 7.4$, 2.2 Hz, 2H), 5.95 (ddt, $J = 16.6$, 10.4, 6.0 Hz, 1H), 5.44 – 5.19 (m, 3H), 4.73 (m, 3H), 4.56 – 4.37 (m, 1H), 3.50 (d, $J = 14.0$ Hz, 1H), 3.33 (d, $J = 13.9$ Hz, 1H), 3.14 (d, $J = 14.0$ Hz, 1H), 1.45 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ (a mixture of two rotamers) 173.1, 170.4, 169.3, 153.2, 135.0, 134.9, 132.4, 131.3, 130.9, 128.7, 128.7, 128.2, 127.5, 119.9, 81.9, 67.3, 58.0, 57.5, 57.3, 47.8, 47.2, 38.1, 28.3; IR (Neat Film, NaCl) 3063, 2978, 2935, 1704, 1602, 1479, 1451, 1418, 1368, 1287, 1251, 1152, 1093, 1002, 927, 902, 857, 764, 727, 697, 635 cm$^{-1}$; HRMS (MM: ESI-APCI): $m/z$ calc’d for C$_{27}$H$_{31}$N$_2$O$_6$ [M+H]$^+$: 479.2177, found 479.2180.

5-allyl 1-(tert-butyl) 3-benzoyl-5-(2-cyanoethyl)-4-oxotetrahydropyrimidine-1,5(2H)-dicarboxylate (5f). To a solution of allyl ester SI-6 (100 mg, 0.26 mmol, 1.0 equiv) and acrylonitrile (34 µL, 0.52 mmol, 2.0 equiv) in acetonitrile (1.3 mL) at room temperature was added DBU (1.9 µL, 0.013 mmol, 0.05 equiv). After 22 h at room temperature, the reaction mixture was heated to 70°C for 32 h, allowed to cool to room temperature, and treated with additional DBU (1.9 µL, 0.013 mmol, 0.05 equiv). After 2 h at 70°C, the reaction mixture was allowed to cool to room temperature, directly concentrated onto silica gel, and purified by silica gel flash chromatography (22% EtOAc/hexanes) to give cyanoethylated pyrimidinone 5f as a colorless oil (71.5 mg, 63% yield): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.72 (d, $J = 7.7$ Hz, 2H), 7.53 (t, $J = 7.4$ Hz, 1H), 7.41 (t, $J = 7.6$ Hz, 2H), 5.97 (ddt, $J = 16.7$, 10.3, 6.1 Hz, 1H), 5.41 (dd, $J = 17.4$, 1.5 Hz, 1H), 5.36 (d, $J = 10.5$ Hz, 1H), 5.28 (m, 2H), 4.74 (m, 2H), 4.41 (d, $J = 13.8$ Hz, 1H), 3.49 (d, $J = 13.8$ Hz, 1H), 2.72 (dt, $J = 16.2$, 7.9 Hz, 1H), 2.50 (dt, $J = 16.6$, 7.8 Hz, 1H), 2.20 (t, $J = 7.9$ Hz, 2H), 1.49 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ (a mixture of two rotamers) 173.0, 169.4, 169.0, 153.1, 134.6, 132.7, 130.8, 128.4, 128.4, 120.6, 118.9, 82.6, 67.6, 67.6, 58.8, 57.9, 55.1, 49.0, 48.4, 29.2, 28.4, 13.6; IR (Neat Film, NaCl) 2979, 2250, 1698, 1450, 1423, 1369, 1286, 1250, 1155, 1030, 939, 857, 803, 718, 697, 635 cm$^{-1}$; HRMS (MM: ESI-APCI): $m/z$ calc’d for C$_{23}$H$_{31}$N$_4$O$_6$ [M+NH$_4$]$^+$: 459.2238, found 459.2243.

5-allyl 1-(tert-butyl) 3-benzoyl-5-((benzyloxy)methyl)-4-oxotetrahydropyrimidine-1,5(2H)-dicarboxylate (5g). Following the procedure described for the preparation of 5a, allyl ester SI-6 (200 mg, 0.52 mmol, 1.0 equiv) was treated with sodium hydride (29 mg, 0.72 mmol, 1.4 equiv) and alkylated with benzyl chloromethyl ether (127 µL, 0.93 mmol,
1.8 equiv) to give, after two rounds of purification by silica gel flash chromatography (dry load SiO$_2$, 16 → 25% EtOAc/hexanes), BOM-alkylated allyl ester 5g as a colorless oil (57 mg, 22% yield): $^1$H NMR (400 MHz, CDCl$_3$) δ 7.73 (t, $J = 8.3$ Hz, 2H), 7.50 (t, $J = 7.9$ Hz, 1H), 7.41 – 7.24 (m, 7H), 5.94 (ddt, $J = 16.5$, 10.3, 6.0 Hz, 1H), 5.63 (d, $J = 12.2$ Hz, 1H), 5.43 – 5.25 (m, 2H), 4.95 (d, $J = 12.4$ Hz, 1H), 4.74 (dd, $J = 13.0$, 5.9 Hz, 1H), 4.70 – 4.36 (m, 4H), 4.07 (d, $J = 9.2$ Hz, 1H), 3.96 – 3.80 (m, 1H), 1.48 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ (a mixture of two rotamers) 173.2, 169.0, 168.7, 168.3, 153.6, 153.3, 137.5, 134.9, 132.2, 131.3, 131.0, 128.6, 128.1, 128.0, 127.7, 119.9, 119.7, 81.9, 73.9, 70.0, 67.1, 58.7, 57.9, 57.0, 47.0, 46.7, 28.3; IR (Neat Film, NaCl) 2978, 2360, 1704, 1453, 1418, 1368, 1290, 1248, 1153, 1128, 1072, 1003, 904, 857, 803, 735, 697, 633 cm$^{-1}$; HRMS (MM: ESI-APCI): m/z calc’d for C$_{28}$H$_{33}$N$_2$O$_7$ [M+H]$^+$: 509.2282, found 509.2279.

5-allyl 1-(tert-butyl) 3-benzoyl-5-fluoro-4-oxotetrahydropyrimidine-1,5(2H)-dicarboxylate (5h). To a solution of allyl ester SI-6 (100 mg, 0.257 mmol, 1.0 equiv) in THF (2.6 mL) at room temperature was added sodium hydride (11 mg, 0.28 mmol, 1.1 equiv). After stirring for 15 min, Selectfluor (109 mg, 0.31 mmol, 1.2 equiv) was added and the reaction mixture was stirred for 1.5 h at room temperature. The reaction was quenched with aqueous NH$_4$Cl (2 mL) and diluted with EtOAc (2 mL). The aqueous phase was extracted with EtOAc (3 x 3 mL) and the combined organic phases were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated by reduced pressure onto silica gel. The residue was purified by silica gel flash chromatography (4:1 hexanes/EtOAc) to give fluorinated allyl ester 5h as a colorless oil (92 mg, 0.226 mmol, 88%); $^1$H NMR (400 MHz, CDCl$_3$) δ (a mixture of two rotamers) 7.67 (s, 2H), 7.52 (t, $J = 7.5$ Hz, 1H), 7.39 (t, $J = 7.6$ Hz, 2H), 5.95 (ddt, $J = 16.6$, 10.3, 6.0 Hz, 1H), 5.63 – 5.07 (m, 4H), 4.88 – 4.77 (m, 1H), 4.75 (s, 1H), 4.43 (m, 1H), 3.99 (m, 1H), 1.49 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ (a mixture of two rotamers) 172.4, 165.3, 164.4, 153.1, 133.8, 132.9, 130.5, 128.6, 128.5, 120.4, 89.3 (d, $J_{CF} = 192.9$ Hz, appears as four peaks due to the presence of two rotamers and coupling with fluorine), 82.8, 67.8, 59.0, 58.4, 49.2, (d, $J_{CF} = 28.3$ Hz), 48.4 (d, $J_{CF} = 27.3$ Hz), 28.2; IR (Neat Film, NaCl) 2979, 2360, 1770, 1715, 1601, 1478, 1450, 1418, 1369, 1287, 1252, 1157, 1134, 1072, 1018, 907, 857, 829, 803, 764, 730, 695, 658, 633 cm$^{-1}$; HRMS (MM: ESI-APCI): m/z calc’d for C$_{20}$H$_{27}$FN$_5$O$_6$ [M+NH$_4$]$^+$: 424.1878, found 424.1877.
5-allyl 1-(tert-butyl) 3-benzoyl-4-oxo-5-(prop-2-yn-1-yl)tetrahydropyrimidine-1,5(2H)-dicarboxylate 5i. To a solution of allyl ester SI-6 (200 mg, 0.51 mmol, 1.0 equiv) in THF (5 mL) at 0 °C was quickly added sodium hydride (23 mg, 0.57 mmol, 1.1 equiv). After stirring at 0 °C for 30 minutes, propargyl bromide (111 µL, 1.03 mmol, 2 equiv) was added and the reaction mixture was heated to 50 °C. After three hours, more propargyl bromide (111 µL, 1.03 mmol, 2 equiv) was added and the reaction was allowed to continue for 16 h at 50 °C. The reaction was quenched with aqueous NH₄Cl (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic phases were dried over anhydrous Na₂SO₄, decanted, and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (50% CH₂Cl₂/hexanes → 70% CH₂Cl₂/hexanes → 20% EtOAc/hexanes) to afford the propargylated allyl ester 5i as a colorless oil (160 mg, 73% yield): ¹H NMR (400 MHz, CDCl₃) δ 7.74 (s, 2H), 7.50 (d, J = 7.4 Hz, 1H), 7.38 (t, J = 7.5 Hz, 2H), 5.96 (dd, J = 17.0, 10.6 Hz, 1H), 5.64 (dd, J = 12.4, 2.1 Hz, 1H), 5.39 (d, J = 17.2 Hz, 1H), 5.33 (d, J = 10.4 Hz, 1H), 5.16 – 4.88 (m, 1H), 4.82 – 4.32 (m, 3H), 4.01 – 3.63 (m, 1H), 3.03 (d, J = 18.2 Hz, 1H), 2.71 (dd, J = 17.0, 2.7 Hz, 1H), 2.09 (t, J = 2.6 Hz, 1H), 1.49 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ (a mixture of two rotamers) 173.3, 169.6, 168.6, 153.5, 134.9, 132.4, 131.2, 130.9, 128.6, 128.2, 120.0, 82.2, 78.8, 72.6, 67.5, 58.9, 58.2, 55.2, 48.2, 28.3, 23.0; IR (Neat Film, NaCl) 3280, 2978, 1704, 1600, 1479, 1450, 1422, 1368, 1287, 1245, 1155, 1140, 1073, 1016, 929, 904, 856, 803, 765, 733 695, 656 cm⁻¹; HRMS (MM: ESI-APCI): m/z calc’d for C₂₃H₂₇N₂O₆ [M+H]⁺: 427.1864, found 427.1859.
**General Procedure for Allylic Alkylation Optimization Screen**

**Table 1. Optimization of Reaction Parameters**

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[a] Screens performed on a 0.04 mmol scale. All reported yields are for isolated products. The ee values were determined by chiral SFC analysis. Bz = benzoyl, Boc = tert-butoxycarbonyl, pmdba = bis(4-methoxybenzylidene)acetone

In a nitrogen-filled glovebox, an oven-dried 1 dram vial was charged with Pd$_2$(pmdba)$_3$ (1.7 mg, 0.0015 mmol, 4 mol %), ligand (10 mol %), solvent (1 mL), and a magnetic stir bar. The vial was stirred at ambient glovebox temperature (27 °C) for 30 min and then substrate 3m (20 mg, 0.04 mmol, 1.0 equiv) was added as a solution in solvent (1.8 mL, total concentration 0.014 M). The vial was sealed with a teflon cap and heated to 40 °C. When complete consumption of the starting material was observed by thin layer chromatography, the reaction mixture was removed from the glovebox and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography to afford the oxopiperazine 4m.
General Procedure for Pd-Catalyzed Decarboxylative Allylic Alkylation Reactions

Please note The absolute configuration for all other products has been inferred by analogy.\(^1\) For respective SFC conditions, please refer to the section Determination of Enantiomeric Excess (S).

In a nitrogen-filled glovebox, an oven-dried 1 dram vial or 20 mL scintillation vial was charged with Pd\(_2\)(pmdba)\(_3\) or Pd\(_2\)(dba)\(_3\) (4 mol %), (S)-(CF\(_3\))\(_3\)-tBu-PHOX (10 mol %), hexane/toluene (2:1) and a magnetic stir bar. The vial was stirred at ambient glovebox temperature (27 °C) for 30 min and then the substrate (1.0 equiv) was added as a solution in hexane/toluene (2:1, total concentration 0.014 M or 0.033 M). The vial was sealed with a teflon cap and heated to 40 °C. When complete consumption of the starting material was observed by thin layer chromatography, the reaction mixture was removed from the glovebox and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography to afford the desired oxo piperazine.

Experimental Procedures and Spectroscopic data for the Pd-Catalyzed Decarboxylative Asymmetric Allylic Alkylation of Piperazinone Substrates

\textit{tert}-butyl (S)-2-allyl-4-benzoyl-3-oxopiperazine-1-carboxylate (4a). Following the general procedure, allyl ester 3a (25 mg, 0.064 mmol, 1.0 equiv) in toluene (1.45 mL) was added to a solution of Pd\(_2\)(dba)\(_3\) (2.3 mg, 0.0026 mmol, 4 mol %) and (S)-(CF\(_3\))\(_3\)-tBu-PHOX (3.8 mg, 0.0064 mmol, 10 mol %) in toluene (0.5 mL). Purification by flash chromatography (20% EtOAc/hexanes) gave monosubstituted oxo piperazine 4a as a yellow oil (21 mg, 90% yield, 92% ee). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) (a mixture of two rotamers) 7.64 – 7.46 (m, 3H), 7.41 (m, 2H), 5.83 (ddt, \(J = 17.2, 10.0, 7.3\) Hz, 1H), 5.22 – 5.07 (m, 2H), 4.70 (m, 1H), 4.45 – 3.99 (m, 1H), 3.99 – 3.70 (m, 2H), 3.42 (m, 1H), 2.90 – 2.52 (m, 2H), 1.50 (s, 9H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) (a mixture of two rotamers) 173.6, 170.6, 153.8, 135.3, 133.2, 132.2, 128.3, 128.3, 119.0, 81.3, 58.4, 44.5, 38.1, 37.2, 28.5. IR (Neat Film, NaCl) 2977, 2930, 1692, 1600, 1450, 1413, 1392, 1366, 1300, 1231, 1159, 1130, 1008, 973, 920, 856, 795, 762, 656 cm\(^{-1}\); HRMS (MM: ESI-APCI): \(m/z\) calc’d for C\(_{19}\)H\(_{25}\)N\(_2\)O\(_4\) [M+H]: 345.1809, found 345.1810; [\(\alpha\)]\(_D\)\(^{23.0}\) +49.5 (c 1.00, CHCl\(_3\)); SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD–H column, \(\lambda = 210\) nm, \(t_R\) (min): major = 3.741, minor = 2.682.

\textit{tert}-butyl (S)-2-allyl-4-(4-methoxybenzoyl)-3-oxopiperazine-1-carboxylate (4b).
Following the general procedure, anisoyl-protected allyl ester 3b (15 mg, 0.036 mmol, 1.0 equiv) in toluene (0.6 mL) was added to a solution of Pd₂(dba)₃ (1.7 mg, 0.0014 mmol, 4 mol %) and (S)-(CF₃)₃-tBu-PHOX (2.8 mg, 0.0036 mmol, 10 mol %) in toluene (0.5 mL). Purification by flash chromatography (20% EtOAc/hexanes) gave monosubstituted oxopiperazine 4b as a light yellow oil (12 mg, 92% yield, 96% ee): ¹H NMR (400 MHz, CDCl₃) δ (a mixture of two rotamers) 7.60 (d, J = 8.9 Hz, 2H), 6.89 (d, J = 8.9 Hz, 2H), 5.85 (ddt, J = 17.1, 10.0, 7.3 Hz, 1H), 5.24 – 5.04 (m, 2H), 4.69 (m, 1H), 4.19 (m, 1H), 3.85 (m, 5H), 3.42 (m, 1H), 2.89 – 2.56 (m, 2H), 1.49 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 173.0, 170.6, 163.3, 153.9, 133.4, 131.2, 127.1, 118.9, 113.7, 81.3, 58.4, 55.6, 44.6, 38.3, 37.4, 28.5; IR (Neat Film, NaCl) 3065, 2951, 1702, 1600, 1449, 1427, 1395, 1362, 1302, 1228, 1163, 1127, 1015, 975, 922, 796, 761, 730, 697, 656 cm⁻¹; HRMS (MM: ESI-APCI): m/z calc’d for C₂₀H₂₇N₂O₅ [M+H]⁺: 375.1914, found 375.1914; [α]₀⁺₂₃.₀ +41.7 (c 1.00, CHCl₃);

**SFC conditions**: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, tᵣ (min): major = 4.708, minor = 3.998.

**benzyl (S)-2-allyl-4-benzyloxy-3-oxopiperazine-1-carboxylate (4c)**. Following the general procedure, Cbz-protected allyl ester 3c (20 mg, 0.047 mmol, 1.0 equiv) in toluene (0.9 mL) was added to a solution of Pd₂(dba)₃ (2.2 mg, 0.0019 mmol, 4 mol %) and (S)-(CF₃)₃-tBu-PHOX (3.5 mg, 0.0047 mmol, 10 mol %) in toluene (0.5 mL). Purification by flash chromatography (20% EtOAc/hexanes) gave monosubstituted oxopiperazine 4c as a colorless oil (15 mg, 83% yield, 99% ee): ¹H NMR (500 MHz, CDCl₃) δ (a mixture of two rotamers) 7.62 – 7.46 (m, 3H), 7.44 – 7.29 (m, 7H), 5.79 (m, 1H), 5.16 (m, 4H), 4.83 (m, 1H), 4.26 (m, 1H), 3.97 (m, 1H), 3.87 (m, 1H), 3.49 (m, 1H), 2.89 – 2.53 (m, 2H); ¹³C NMR (126 MHz, CDCl₃) δ (a mixture of two rotamers) 173.5, 170.2, 154.7, 136.0, 135.2, 132.9, 132.3, 128.9, 128.8, 128.6, 128.4, 128.3, 119.3, 68.0, 58.4, 44.3, 39.6, 38.9, 37.2, 36.9; IR (Neat Film, NaCl) 3065, 2951, 1702, 1600, 1449, 1427, 1395, 1362, 1302, 1228, 1163, 1127, 1015, 975, 922, 796, 761, 730, 697, 656 cm⁻¹; HRMS (MM: ESI-APCI): m/z calc’d for C₂₂H₂₃N₂O₄ [M+H]⁺: 379.1652, found 379.1659; [α]₀⁺₂₃.₀ +66.0 (c 1.00, CHCl₃);

**SFC conditions**: 30% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, tᵣ (min): major = 4.873, minor = 6.748.

**tert-butyl (S)-4-benzoxy-2-(2-chloroallyl)-3-oxopiperazine-1-carboxylate (4d)**. Following the general procedure, 2-chloroallyl ester 3d (20 mg, 0.047 mmol, 1.0 equiv.) in hexanes/toluene (2:1, 1.9 mL) was added to a solution of Pd₂(pmdba)₃ (2.1 mg, 0.0019 mmol, 4 mol %) and (S)-(CF₃)₃-tBu-PHOX (2.8 mg, 0.0047 mmol, 10 mol %) in
tert-butyl (S)-2-allyl-4-benzoyl-2-methyl-3-oxopiperazine-1-carboxylate (4e).

Following the general procedure, methylated allyl ester 3e (23 mg, 0.057 mmol, 1.0 equiv) in toluene (1.2 mL) was added to a solution of Pd$_2$(pmdba)$_3$ (2.7 mg, 0.0023 mmol, 4 mol %) and (S)-(CF$_3$)$_2$-Bu-PHOX (3.7 mg, 0.0057 mmol, 10 mol %) in toluene (0.5 mL). Purification by flash chromatography (15% EtOAc/hexanes) gave di-substituted oxopiperezine 4e as a light yellow oil (17 mg, 85% yield, 96% ee). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.57 – 7.46 (m, 3H), 7.40 (t, J = 7.6 Hz, 2H), 5.81 – 5.67 (m, 1H), 5.17 – 5.13 (m, 1H), 5.12 (d, J = 1.1 Hz, 1H), 4.16 – 4.02 (m, 1H), 4.03 – 3.91 (m, 1H), 3.79 (ddd, J = 12.9, 9.0, 3.0 Hz, 1H), 3.53 (ddd, J = 14.1, 9.0, 2.8 Hz, 1H), 3.11 (m, 1H), 2.84 – 2.70 (m, 1H), 1.77 (s, 3H), 1.53 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 174.3, 172.8, 135.8, 133.1, 131.8, 128.3, 127.6, 119.5, 81.2, 67.3, 44.2, 42.7, 41.0, 28.6, 25.5; IR (Neat Film, NaCl) 3076, 2977, 2934, 1692, 1641, 1601, 102, 1450, 1392, 1366, 1301, 1230, 1166, 1047, 1016, 955, 922, 852, 790, 757, 727, 695 cm$^{-1}$; HRMS (MM: ESI-APCI): m/z calc’d for C$_{30}$H$_{27}$N$_2$O$_4$ [M+H]$^+$: 539.1965, found 539.1966; [$\alpha$]$_D^{22.8} +6.5$ (c 2.0, CHCl$_3$); SFC conditions: 7% IPA, 2.5 mL/min, Chiralpak AD-H column, $\lambda$ = 210 nm, $t_R$ (min): major = 7.208, minor = 4.714.

tert-butyl (S)-2-allyl-4-(4-methoxybenzoyl)-2-methyl-3-oxopiperazine-1-carboxylate (4f).

Following the general procedure, anisoyl-protected allyl ester 3f (25 mg, 0.058 mmol, 1.0 equiv) in toluene (1.3 mL) was added to a solution of Pd$_2$(pmdba)$_3$ (2.5 mg, 0.0023 mmol, 4 mol %) and (S)-(CF$_3$)$_2$-Bu-PHOX (3.4 mg, 0.0058 mmol, 10 mol %) in toluene (0.5 mL). Purification by flash chromatography (20% EtOAc/hexanes) gave di-substituted oxopiperezine 4f as a light pink oil (19 mg, 86% yield, 96% ee). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.70 – 7.53 (m, 2H), 6.99 – 6.82 (m, 2H), 5.86 – 5.67 (m, 1H), 5.23 – 5.04 (m,
Supporting Information

2H), 4.01 (dd, J = 33.5, 13.9, 5.8, 2.8 Hz, 2H), 3.85 (s, 3H), 3.74 (ddd, J = 12.7, 9.0, 2.8 Hz, 1H), 3.52 (ddd, J = 13.9, 9.0, 2.7 Hz, 1H), 3.20 (s, 1H), 2.80 (ddt, J = 14.0, 7.1, 1.2 Hz, 1H), 1.77 (s, 3H), 1.52 (s, 9H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 174.1, 172.4, 163.0, 153.9, 133.2, 130.6, 127.5, 119.4, 113.6, 81.2, 67.1, 55.5, 44.2, 42.8, 41.1, 28.6, 25.6; IR (Neat Film, NaCl) 3076, 2977, 2934, 1692, 1641, 1600, 1512, 1450, 1392, 1366, 1301, 1282, 1258, 1167, 1104, 1077, 1021, 993, 925, 839, 768, 740, 704 cm\textsuperscript{-1}; HRMS (MM: ESI-APCI): m/z calc’d for C\textsubscript{22}H\textsubscript{34}N\textsubscript{2}O\textsubscript{3} [M+H\textsuperscript{+}]: 389.2071, found 389.2083; [α]D\textsuperscript{22,0} +75.6 (c 2.9, CHCl\textsubscript{3}); SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t\textsubscript{R} (min): major = 5.370, minor = 4.278.

** tert-butyl (S)-2-allyl-4-(4-methoxybenzoyl)-2-methyl-3-oxopiperazine-1-carboxylate (4g).** Following the general procedure, di-Bz-protected allyl ester 3g (10 mg, 0.025 mmol, 1.0 equiv) in toluene (1.3 mL) was added to a solution of Pd\textsubscript{2}(dba)\textsubscript{3} (0.9 mg, 0.00098 mmol, 4 mol%) and (S)-(CF\textsubscript{3})\textsubscript{3}-tBu-PHOX (1.5 mg, 0.0025 mmol, 10 mol%) in toluene (0.5 mL). Purification by flash chromatography (20% EtOAc/hexanes) gave di-substituted oxopiperazine 4f as a colorless oil (8 mg, 89% yield, 70% ee). Product identity matched previously reported characterization data.\textsuperscript{4} SFC conditions: 10% MeOH, 2.5 mL/min, Chiralpak OJ-H column, λ = 254 nm, t\textsubscript{R} (min): major = 5.574, minor = 6.659.

** tert-butyl (R)-2-allyl-2-benzyl-4-(4-methoxybenzoyl)-3-oxopiperazine-1-carboxylate (4h).** Following the general procedure, benzylated allyl ester 3h (10 mg, 0.02 mmol, 1.0 equiv) in hexanes/toluene (2:1, 0.9 mL) was added to a solution of Pd\textsubscript{2}(pmdba)\textsubscript{3} (0.86 mg, 0.00078 mmol, 4 mol%) and (S)-(CF\textsubscript{3})\textsubscript{3}-tBu-PHOX (1.2 mg, 0.002 mmol, 10 mol%) in hexanes/toluene (2:1, 0.5 mL). Purification by flash chromatography (5% → 10% → 15% EtOAc/hexanes) gave di-substituted oxopiperazine 4h as a colorless oil (7 mg, 77% yield, 96% ee); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ (A mixture of two rotamers) 7.57 (t, J = 8.5 Hz, 2H), 7.29 (d, J = 5.7 Hz, 3H), 7.22 – 7.07 (m, 2H), 6.91 (d, J = 8.3 Hz, 2H), 5.82 (ddt, J = 17.0, 9.6, 7.1 Hz, 1H), 5.29 – 5.13 (m, 2H), 3.88 (m, 4H), 3.74 – 3.45 (m, 2H), 3.31 (m, 1H), 3.16 (d, J = 12.0 Hz, 2H), 2.98 – 2.57 (m, 2H), 1.57 (s, 9H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ (A mixture of two rotamers) 172.7, 172.3, 172.0, 163.2, 154.7, 153.4, 137.1, 136.4, 133.1, 132.6, 131.3, 130.4, 128.7, 128.5, 127.5, 127.2, 119.9, 119.7, 113.5, 82.2, 80.6, 71.7, 55.6, 43.6, 43.3, 42.9, 42.6, 41.8, 29.8, 28.9, 28.6; IR (Neat Film, NaCl) 2975, 1691, 1604, 1512, 1454, 1365, 1309, 1282, 1258, 1167, 1104, 1077, 1021, 993, 925, 839, 768, 740, 704 cm\textsuperscript{-1}; HRMS (MM: ESI-APCI): m/z calc’d for C\textsubscript{22}H\textsubscript{33}N\textsubscript{2}O\textsubscript{5} [M+H\textsuperscript{+}]: 465.2384, found 465.2390; [α]D\textsuperscript{23,4} +31.0 (c 0.47, CHCl\textsubscript{3}); SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 254 nm, t\textsubscript{R} (min): major = 7.471, minor = 5.802.
**Supporting Information**

**tert-butyl (R)-2-allyl-4-benzoyl-2-((benzylloxy)methyl)-3-oxopiperazine-1-carboxylate (4i).** (Following the general procedure, benzylloxy methyl ether allyl ester 3i (25 mg, 0.049 mmol, 1.0 equiv) in hexanes/toluene (2:1, 3.0 mL) was added to a solution of Pd$_2$(dba)$_3$ (2.2 mg, 0.0020 mmol, 4 mol%) and (S)-(CF$_3$)$_2$-tBu-PHOX (2.9 mg, 0.0049 mmol, 10 mol%) in hexanes/toluene (2:1, 0.5 mL). Purification by flash chromatography (15% EtOAc/hexanes) gave di-substituted oxopiperazine 4i as a colorless oil (20 mg, 87% yield, 92% ee). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ (A mixture of two rotamers) 7.61 (dd, $J = 8.2, 1.4$ Hz, 2H), 7.51 – 7.43 (m, 1H), 7.38 – 7.26 (m, 7H), 5.72 (ddt, $J = 17.6, 10.3, 7.4$ Hz, 1H), 5.21 – 5.09 (m, 2H), 4.57 (t, $J = 13.3$ Hz, 3H), 4.32 – 3.63 (m, 5H), 3.25 – 2.93 (m, 1H), 2.60 (br s, 1H), 1.50 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 173.3, 172.5, 153.4, 135.6, 132.1, 131.9, 128.6, 128.3, 128.2, 127.9, 127.5, 120.0, 75.1, 74.2, 73.7, 70.6, 43.5, 38.5, 37.0, 28.6; IR (Neat Film, NaCl) 3064, 2976, 2931, 1692, 1601, 1474, 1452, 1392, 1365, 1317, 1286, 1251, 1232, 1164, 1102, 1062, 1016, 969, 924, 857, 730, 696, 671 cm$^{-1}$; HRMS (MM: ESI-APCI): m/z calc’d for C$_{27}$H$_{33}$N$_2$O$_5$ [M+H]$: 465.2384$, found 465.2388; $[\text{a}]_{D}^{23.8}$ – 13.9 (c 0.33, CHCl$_3$); SFC conditions: 7% IPA, 2.5 mL/min, Chiralpak OD-H column, $\lambda = 254$ nm, $t_R$ (min): major = 3.737, minor = 4.398.

**tert-butyl (S)-2-allyl-2-(2-cyanoethyl)-4-(4-methoxybenzoyl)-3-oxopiperazine-1-carboxylate (4j).** Following the general procedure, $\alpha$-cyanooethylated allyl ester 3j (25 mg, 0.053 mmol, 1.0 equiv) in hexanes/toluene (2:1, 2.8 mL) was added to a solution of Pd$_2$(dba)$_3$ (1.9 mg, 0.0021 mmol, 4 mol%) and (S)-(CF$_3$)$_2$-tBu-PHOX (3.1 mg, 0.0053 mmol, 10 mol%) in hexanes/toluene (2:1, 1.0 mL). Purification by silica gel flash chromatography (dry load SiO$_2$, 3:1 hexanes/EtOAc) gave oxopiperazine 4j as a colorless oil (20 mg, 88% yield, 97% ee). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.63 (d, $J = 8.8$ Hz, 2H), 6.92 (d, $J = 8.9$ Hz, 2H), 5.79 (ddt, $J = 16.6, 10.4, 7.5$ Hz, 1H), 5.24 (d, $J = 1.7$ Hz, 1H), 5.20 (dd, $J = 9.9, 1.9$ Hz, 1H), 3.98 – 3.87 (m, 2H), 3.86 (s, 3H), 3.84 – 3.71 (m, 2H), 3.27 (m, 1H), 2.82 (m, 1H), 2.69 (dd, $J = 13.8, 7.4$ Hz, 1H), 2.47 (dt, $J = 14.1, 7.4$ Hz, 1H), 2.32 (t, $J = 7.2$ Hz, 2H), 1.53 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 172.4, 171.5, 163.4, 153.6, 132.0, 131.2, 127.0, 120.6, 119.1, 113.7, 82.0, 69.0, 55.6, 43.8, 43.2, 42.0, 32.3, 28.5, 13.1; IR (Neat Film, NaCl) 2976, 2933, 2359, 2247, 1694, 1605, 1579, 1512, 1456, 1366, 1281, 1258 1168, 1113, 1020, 974, 928, 843, 768, 614 cm$^{-1}$; HRMS (MM: ESI-APCI): m/z calc’d for C$_{27}$H$_{30}$N$_2$O$_5$ [M+H]$: 428.2182$, found 428.2182; $[\text{a}]_{D}^{23.2}$ – 4.3 (c 1.0, CHCl$_3$); SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak OD-H column, $\lambda = 210$ nm, $t_R$ (min): major = 6.049, minor = 5.143.
tert-butyl (S)-2-allyl-4-(4-methoxybenzoyl)-3-oxo-2-(3-oxobutyl)piperazine-1-carboxylate (4k). Following the general procedure, ketone 3k (25 mg, 0.051 mmol, 1.0 equiv) in hexanes/toluene (2:1, 2.2 mL) was added to a solution of Pd₂(dba)₃ (1.9 mg, 0.002 mmol, 4 mol %) and (S)-(CF₃)₂-tBu-PHOX (3.0 mg, 0.0051 mmol, 10 mol %) in hexanes/toluene (2:1, 1.5 mL). Purification by silica gel flash chromatography (dry load SiO₂, 30% EtOAc/hexanes) gave ketone 4k as a pale yellow oil (17 mg, 73% yield, 97% ee); ¹H NMR (400 MHz, CDCl₃) δ 7.59 (d, J = 8.9 Hz, 2H), 6.89 (d, J = 8.9 Hz, 2H), 5.79 (ddt, J = 13.8, 1.9 Hz, 2H), 3.92 – 3.81 (m, 6H), 3.80 – 3.66 (m, 1H), 3.22 (s, 1H), 2.74 (dd, J = 13.8, 7.3 Hz, 1H), 2.73, (m, 1H), 2.50 – 2.27 (m, 3H), 2.13 (s, 3H), 1.51 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 207.5, 172.6, 172.4, 163.2, 132.8, 131.0, 127.3, 120.0, 113.6, 81.6, 69.5, 55.6, 43.9, 43.2, 39.1, 32.3, 30.0, 28.6, 24.8; IR (Neat Film, NaCl) 2975, 1694, 1605, 1512, 1456, 1282, 1168, 1113, 1062, 1019, 974, 923, 841, 768 cm⁻¹; HRMS (MM: ESI-APCI): m/z calc’d for C₂₄H₂₃N₂O₆ [M+H⁺]: 445.2333, found 445.2335; [α]D²⁹.² +25.1 (c 0.97, CHCl₃); SFC conditions: 7% IPA, 2.5 mL/min, Chiralpak OD-H column, λ = 235 nm, tᵣ (min): major = 9.712, minor = 10.434.

tert-butyl (R)-2-allyl-2-(((benziloxy)carbonyl)amino)methyl)-4-(4-methoxybenzoyl)-3-oxopiperazine-1-carboxylate (4l). Following the general procedure, aminomethyl allyl ester 3l (100 mg, 0.17 mmol, 1.0 equiv) in hexanes/toluene (2:1, 10 mL) was added to a solution of Pd₂(dba)₃ (6.3 mg, 0.0069 mmol, 4 mol %) and (S)-(CF₃)₂-tBu-PHOX (10 mg, 0.017 mmol, 10 mol %) in hexanes/toluene (2:1, 2 mL). Purification by silica gel flash chromatography (15% → 20% → 30% EtOAc/hexanes) gave di-substituted oxopiperazine 4l as a yellow oil (60 mg, 65% yield, 92% ee); ¹H NMR (400 MHz, CDCl₃) δ (a mixture of two rotamers) 7.64 (t, J = 8.9 Hz, 2H), 7.44 – 7.23 (m, 5H), 6.89 (d, J = 8.5 Hz, 2H), 5.79 (dq, J = 16.8, 7.8 Hz, 1H), 5.32 – 4.93 (m, 5H), 4.31 – 3.97 (m, 1H), 3.95 – 3.64 (m, 7H), 3.64 – 3.45 (m, 1H), 3.45 – 2.87 (m, 1H), 2.64 (dd, J = 14.0, 7.3 Hz, 1H), 1.48 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 172.6, 172.3, 163.1, 156.4, 153.7, 136.6, 132.2, 131.1, 128.6, 128.4, 128.3, 127.3, 120.1, 113.6, 70.2, 67.0, 55.6, 46.9, 43.8, 43.2, 39.6, 28.6; IR (Neat Film, NaCl) 3357, 2975, 2361, 1694, 1605, 1512, 1456, 1366, 1317, 1283, 1255, 1169, 1094, 1061, 1020, 923, 841, 768, 699 cm⁻¹; HRMS (MM: ESI-APCI): m/z calc’d for C₂₉H₃₆N₂O₇ [M+H⁺]: 538.2548, found 538.2543; [α]D²⁹.⁸ +3.74 (c 2.0, CHCl₃); SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak OD-H column, λ = 280 nm, tᵣ (min): major = 8.425, minor = 7.817.
Experimental Procedures and Spectroscopic Data for the Pd-Catalyzed Decarboxylative Asymmetric Allylic Alkylation of Tetrahydropyrimidinone Substrates

**tert-Butyl**  
(R)-2-allyl-4-benzoyl-2-(((tert-butoxycarbonyl)amino)methyl)-3-oxopiperazine-1-carboxylate (4m). Following the general procedure, allyl ester 3m (100 mg, 0.19 mmol, 1.0 equiv) in hexanes/toluene (2:1, 8.0 mL) was added to a solution of Pd2(pmdba)3 (8.5 mg, 0.0077 mmol, 4 mol %) and (S)-(CF3)3-tBu-PHOX (11.4 mg, 0.019 mmol, 10 mol %) in hexanes/toluene (2:1, 4.0 mL). Purification by flash chromatography (15% EtOAc/hexanes) gave di-substituted oxopiperazine 4m as a pale yellow foam (85 mg, 93% yield, 93% ee): 1H NMR (400 MHz, CDCl3) δ (a mixture of two rotamers) 7.61 (d, J = 7.6 Hz, 2H), 7.51 (tt, J = 7.5, 2.1 Hz, 1H), 7.41 (t, J = 7.5 Hz, 2H), 5.91 – 5.66 (m, 1H), 5.19 (d, J = 15.6 Hz, 2H), 4.73 (s, 1H), 4.09 – 3.72 (m, 5H), 3.67 (dd, J = 14.0, 7.0 Hz, 1H), 3.43 – 2.97 (m, 1H), 2.72 – 2.51 (m, 1H), 1.54 (s, 9H), 1.43 (s, 9H); 13C NMR (101 MHz, CDCl3) 172.9, 172.8, 155.7, 153.6, 135.8, 132.5, 132.1, 131.9, 128.2, 128.0, 81.2, 79.7, 70.5, 46.5, 43.7, 43.2, 39.4, 28.6, 28.5; IR (Neat Film, NaCl): 1376, 1286, 1231, 1165, 1060, 1014, 921, 855, 756, 729, 696 cm⁻¹; HRMS (MM: ESI+): m/z calc’d for C25H36N3O6 [M+H]+: 474.2599, found: 474.2602; [α]D²³ +2.7 (c 1.00, CHCl3); SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak OD-H column, λ = 254 nm, tR (min): major = 4.429, minor = 3.910.

**tert-butyl**  
(R)-5-allyl-3-benzoyl-5-methyl-4-oxotetrahydropyrimidine-1(2H)-carboxylate (6a). Following the general procedure, methylated pyrimidinone 5a (15 mg, 0.037 mmol, 1.0 equiv) in hexanes/toluene (2:1, 1.0 mL) was added to a solution of Pd2(pmdba)3 (1.6 mg, 0.0015 mmol, 4 mol %) and (S)-(CF3)3-tBu-PHOX (2.2 mg, 0.0037 mmol, 10 mol %) in hexanes/toluene (2:1, 1.7 mL). Purification by silica gel flash chromatography (13% EtOAc/hexanes) gave α-methyl pyrimidinone 6a as a colorless oil (11 mg, 83% yield, 93% ee): 1H NMR (500 MHz, CDCl3) δ 7.57 – 7.46 (m, 3H), 7.40 (t, J = 7.6 Hz, 2H), 5.78 (dq, J = 16.9, 8.0 Hz, 1H), 5.31 (d, J = 8.4 Hz, 1H), 5.25 – 5.09 (m, 3H), 3.69 (d, J = 13.8 Hz, 1H), 3.55 (m, 1H), 2.52 (m, 1H), 2.31 (dd, J = 13.9, 8.0 Hz, 1H), 1.51 (s, 9H), 1.26 (s, 3H); 13C NMR (101 MHz, CDCl3) δ (a mixture of two rotamers) 176.8, 176.5, 173.9, 153.7, 135.6, 132.5, 132.1, 128.3, 127.9, 120.0, 81.8, 59.4, 59.0, 50.6, 49.7, 45.2, 41.0, 28.4, 22.4; IR (Neat Film, NaCl) 2976, 2932, 2832, 1698, 1426, 1367, 1286, 1246, 1136, 1027, 924, 858, 802, 750, 719, 695, 635 cm⁻¹; HRMS (MM: ESI+): m/z calc’d for C20H27N2O4 [M+H]+: 359.1965, found 359.1963; [α]D²³ +23.2 –25.7 (c 1.0, CHCl3);
SFC conditions: 7% IPA, 2.5 mL/min, Chiralpak OJ-H column, $\lambda = 254$ nm, $t_R$ (min): major = 3.209, minor = 2.569.

**tert-butyl** (R)-5-allyl-3-benzoyl-5-ethyl-4-oxotetrahydropyrimidine-1(2H)-carboxylate (6b). Following the general procedure, ethylated allyl ester 5b (15 mg, 0.036 mmol, 1.0 equiv) in hexanes/toluene (2:1, 1.0 mL) was added to a solution of Pd$_2$(pmdba)$_3$. (1.6 mg, 0.0014 mmol, 4 mol%) and (S)-(CF$_3$)$_3$-tBu-PHOX (2.1 mg, 0.0036 mmol, 10 mol%) in hexanes/toluene (2:1, 1.6 mL). Purification by silica gel flash chromatography (13% EtOAc/hexanes) gave $\alpha$-ethyl tetrahydropyrimdinone 6b as a colorless oil (13 mg, 98% yield, 94% ee); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.57 – 7.45 (m, 3H), 7.39 (t, $J = 7.5$ Hz, 2H), 5.87 – 5.62 (m, 1H), 5.48 – 5.24 (m, 1H), 5.20 – 5.03 (m, 3H), 3.75 (dd, $J = 14.0$, 1.4 Hz, 1H), 3.65 – 3.52 (m, 1H), 2.50 (dd, $J = 14.2$, 6.7 Hz, 1H), 2.27 (d, $J = 16.1$ Hz, 1H), 1.79 (dq, $J = 14.9$, 7.5 Hz, 1H), 1.68 (dq, $J = 14.6$, 7.4 Hz, 1H), 1.51 (s, 9H), 0.95 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ (a mixture of two rotamers) 175.8, 174.1, 153.7, 135.8, 132.9, 132.0, 128.3, 128.0, 119.7, 81.7, 59.2, 58.8, 48.6, 48.0, 47.6, 39.1, 38.6, 28.7, 28.4, 8.4; IR (Neat Film, NaCl) 2976, 2927, 1698, 1426, 1367, 1286, 1247, 1147, 925, 856, 802, 764, 696 cm$^{-1}$; HRMS (MM: ESI-APCI): $m/z$ calc’d for C$_2$H$_9$N$_2$O$_4$ [M+H]$^+$: 373.2122, found: 373.2122; [\alpha]$_D^{22.2}$ –21.0 (c 1.0, CHCl$_3$); SFC conditions: 7% IPA, 2.5 mL/min, Chiralpak OJ-H column, $\lambda = 254$ nm, $t_R$ (min): major = 3.956, minor = 2.585.

**tert-butyl** (R)-5-allyl-3-benzoyl-5-(3-methoxy-3-oxopropyl)-4-oxotetrahydropyrimidine-1(2H)-carboxylate (6c). Following the general procedure, methyl ester pyrimidinone 5c (15 mg, 0.032 mmol, 1.0 equiv) in hexanes/toluene (2:1, 1.0 mL) was added to a solution of Pd$_2$(pmdba)$_3$. (1.2 mg, 0.0013 mmol, 4 mol%) and (S)-(CF$_3$)$_3$-tBu-PHOX (1.9 mg, 0.0032 mmol, 10 mol%) in hexanes/toluene (2:1, 1.3 mL). Purification by silica gel flash chromatography (15% EtOAc/hexanes) gave methyl ester 6c as a colorless oil (9.1 mg, 67% yield, 95% ee); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.50 (dd, $J = 13.1$, 7.2 Hz, 3H), 7.38 (t, $J = 7.5$ Hz, 2H), 5.73 (dq, $J = 16.6$, 7.4 Hz, 1H), 5.47 – 5.22 (m, 1H), 5.22 – 5.04 (m, 3H), 3.66 (m, 5H), 2.49 (dt, $J = 12.9$, 6.4 Hz, 1H), 2.37 (m, 2H), 2.31 – 2.19 (m, 1H), 2.14 – 1.91 (m, 2H), 1.51 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ (a mixture of two rotamers) 175.2, 174.9, 173.9, 173.3, 153.5, 135.6, 132.1, 132.0, 128.4, 127.9, 120.3, 82.0, 59.2, 58.8, 51.1, 48.7, 47.7, 39.1, 38.8, 30.3, 28.9, 28.3; IR (Neat Film, NaCl) 2978, 1738, 1698, 1428, 1368, 1286, 1247, 1147, 925, 856, 802, 764, 696 cm$^{-1}$;
HRMS (MM: ESI-APCI): m/z calc’d for C_{23}H_{31}N_{2}O_{6} [M+H]^+: 431.2177, found 431.2173; [α]_D^{23.1} +5.5 (c 0.9, CHCl_3); SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): major = 5.591, minor = 6.372.

**tert-butyl (S)-5-allyl-3-benzoyl-5-(2-chloroallyl)-4-oxotetrahydropyrimidine-1(2H)-carboxylate (6d).** Following the general procedure, 2-chloropropenyl allyl ester 5d (20 mg, 0.049 mmol, 1.0 equiv) in hexanes/toluene (2:1, 3.0 mL) was added to a solution of Pd_2(pmdba)_3 (2.1 mg, 0.0020 mmol, 4 mol %) and (S)-(CF_3)_3-tBu-PHOX (2.9 mg, 0.0049 mmol, 10 mol %) in hexanes/toluene (2:1, 0.5 mL). Purification by flash chromatography (EtOAc/hexanes 15%) gave di-substituted oxopiperazine 6d as a yellow oil (17 mg, 94% yield, 94% ee); ^1^H NMR (400 MHz, CDCl_3) δ (a mixture of two rotamers) 7.65 – 7.45 (m, 3H), 7.40 (t, J = 7.6 Hz, 2H), 5.95 – 5.76 (m, 1H), 5.76 – 5.47 (m, 1H), 5.31 (d, J = 1.3 Hz, 1H), 5.30 – 5.16 (m, 2H), 4.92 (s, 1H), 4.05 (s, 1H), 3.61 (d, J = 14.0 Hz, 1H), 3.06 (d, J = 14.8 Hz, 1H), 2.69 – 2.55 (m, 1H), 2.45 (d, J = 14.5 Hz, 2H), 1.52 (s, 9H); ^13^C NMR (101 MHz, CDCl_3) δ (a mixture of two rotamers) 174.4, 173.9, 153.6, 137.5, 135.6, 132.1, 132.0, 128.3, 128.1, 120.8, 118.1, 82.0, 59.1, 48.2, 47.6, 46.6, 42.8, 42.3, 41.7, 28.4; IR (Neat Film, NaCl) 2977, 2930, 2360, 1698, 1424, 1368, 1288, 1245, 1142, 902, 802, 765, 724, 695, 636 cm\(^{-1}\); HRMS (MM: ESI-APCI): m/z calc’d for C_{23}H_{29}ClN_{2}O_{4} [M+H]^+: 419.1732, found 419.1732; [α]_D^{22.6} +22.2 (c 1.0, CHCl_3); SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 4.679, minor = 3.777.

**tert-butyl (S)-5-allyl-3-benzoyl-5-benzyl-4-oxotetrahydropyrimidine-1(2H)-carboxylate (6e).** Following the general procedure, benzylated allyl ester 5e (15 mg, 0.031 mmol, 1.0 equiv) in hexanes/toluene (2:1, 1.0 mL) was added to a solution of Pd_2(pmdba)_3 (1.4 mg, 0.0013 mmol, 4 mol %) and (S)-(CF_3)_3-tBu-PHOX (1.9 mg, 0.0031 mmol, 10 mol %) in hexanes/toluene (2:1, 1.2 mL). Purification by silica gel flash chromatography (13% EtOAc/hexanes) gave benzyl tetrahydropyrimidinone 6e as a colorless oil (11.5 mg, 84% yield, 95% ee); ^1^H NMR (500 MHz, CDCl_3) δ 7.58 – 7.49 (m, 3H), 7.42 (t, J = 7.7 Hz, 2H), 7.31 – 7.24 (m, 3H), 7.20 (t, J = 7.2 Hz, 2H), 5.86 (ddd, J = 16.8, 10.2, 7.9, 6.6 Hz, 1H), 5.48 – 5.25 (m, 1H), 5.22 (d, J = 10.0 Hz, 1H), 5.21 – 5.14 (m, 1H), 4.87 (d, J = 11.9 Hz, 1H), 3.89 – 3.72 (m, 1H), 3.55 (d, J = 13.7 Hz, 1H), 3.37 – 3.21 (m, 1H), 2.80 – 2.68 (m, 1H), 2.65 (dd, J = 14.0, 6.6 Hz, 1H), 2.32 – 2.19 (m, 1H), 1.52 (s, 9H); ^13^C NMR (101 MHz, CDCl_3) δ (a mixture of two rotamers) 175.4, 173.9, 153.6, 136.1, 135.6, 132.6, 132.1, 131.0, 128.5, 128.3, 128.1, 127.1, 120.2, 81.9, 58.8, 49.5, 47.2, 46.5, 41.1, 40.6, 28.4; IR (Neat Film, NaCl) 2978, 2930, 2360, 1698, 1424, 1368, 1288, 1245, 1142, 1029,
tert-butyl (R)-5-allyl-3-benzoyl-5-(2-cyanoethyl)-4-oxotetrahydropyrimidine-1(2H)-carboxylate (6f). Following the general procedure, cyanoethylated tetrahydropyrimidinone 5f (15 mg, 0.034 mmol, 1.0 equiv) in hexanes/toluene (2:1, 1.0 mL) was added to a solution of Pd2(pmdba)3 (1.2 mg, 0.0014 mmol, 4 mol %) and (S)-(CF3)3-tBu-PHOX (2.0 mg, 0.0034 mmol, 10 mol %) in hexanes/toluene (2:1, 1.4 mL). Purification by silica gel flash chromatography (20% EtOAc/hexanes) gave cyanoethylated tetrahydropyrimidinone 6f as a yellow oil (9.0 mg, 67% yield, 74% ee): 1H NMR (500 MHz, CDCl3) δ 7.56 – 7.49 (m, 3H), 7.43 (t, J = 7.6 Hz, 2H), 5.75 (ddd, J = 16.8, 10.2, 7.9, 6.6 Hz, 1H), 5.35 – 5.13 (m, 4H), 3.86 – 3.55 (m, 2H), 2.57 – 2.51 (m, 1H), 2.44 (dd, J = 10.0, 5.9 Hz, 2H), 2.32 (dd, J = 14.1, 8.0 Hz, 1H), 2.09 (dt, J = 14.6, 8.5 Hz, 1H), 1.96 (ddd, J = 14.3, 9.8, 6.2 Hz, 1H), 1.53 (s, 9H); 13C NMR (101 MHz, CDCl3) δ 174.6, 173.7, 153.4, 135.4, 132.4, 131.2, 128.5, 127.8, 121.2, 119.2, 82.5, 59.4, 48.3, 47.7, 39.1, 31.0, 28.4, 12.6; IR (Neat Film, NaCl) 2977, 2931, 2248, 1694, 1601, 1478, 1427, 1368, 1285, 1263, 1246, 1141, 1027, 926, 901, 857, 802, 763, 721, 696, 636, cm−1; HRMS (MM: ESI-APCI): m/z calc’d for C22H28N3O4 [M+H]+: 398.2074, found 398.2071; [α]D23,2 +10.0 (c 1.0, CHCl3); SFC conditions: 30% IPA, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, tR (min): major = 3.148, minor = 4.927.

tert-butyl (R)-5-allyl-3-benzoyl-5-((benzyloxy)methyl)-4-oxotetrahydropyrimidine-1(2H)-carboxylate (6g). Following the general procedure, allyl ester 5g (15 mg, 0.029 mmol, 1.0 equiv) in hexanes/toluene (2:1, 1.6 mL) was added to a solution of Pd2(pmdba)3 (1.3 mg, 0.0012 mmol, 4 mol %) and (S)-(CF3)3-tBu-PHOX (1.7 mg, 0.0029 mmol, 10 mol %) in hexanes/toluene (2:1, 0.5 mL). Purification by flash chromatography (10 → 15% EtOAc/hexanes) gave di-substituted oxopiperazine 6g as a yellow oil (13 mg, 87% yield, 87% ee): 1H NMR (400 MHz, CDCl3) δ 7.69 – 7.51 (m, 2H), 7.51 – 7.42 (m, 1H), 7.42 – 7.22 (m, 7H), 5.77 (ddt, J = 15.0, 10.3, 7.4 Hz, 1H), 5.54 – 5.49 (m, 1H), 5.28 – 5.10 (m, 2H), 5.06 (d, J = 12.1 Hz, 1H), 4.63 – 4.40 (m, 2H), 3.94 (m, 1H), 3.82 (d, J = 13.9 Hz, 1H), 3.75 (d, J = 8.9 Hz, 1H), 3.40 (d, J = 9.0 Hz, 1H), 2.42 (m, 2H), 1.50 (s, 9H); 13C NMR (101 MHz, CDCl3) δ 174.7, 173.5, 153.6, 137.8, 135.5, 132.0, 128.6, 128.3, 128.2,
tert-butyl (S)-5-allyl-3-benzoyl-5-fluoro-4-oxotetrahydropyrimidine-1(2H)-carboxylate (6h). Following the general procedure, fluorinated tetrahydropyrimidinone 5h (300 mg, 0.74 mmol, 1.0 equiv) in hexanes/toluene (2:1, 39 mL) was added to a solution of Pd2(pmdba)2 (24 mg, 0.022 mmol, 3 mol %) and (S)-(CF3)3-tBu-PHOX (35 mg, 0.059 mmol, 10 mol %) in hexanes/toluene (2:1, 15 mL). Purification by silica gel flash chromatography (15% EtOAc/hexanes) gave fluorinated tetrahydropyrimidinone 6h as a pale yellow oil (250 mg, 93% yield, 92% ee); 1H NMR (400 MHz, CDCl3) δ 7.59 (dd, J = 8.3, 1.3 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.8 Hz, 2H), 5.82 (ddt, J = 14.9, 9.6, 7.2 Hz, 1H), 5.66 – 5.34 (m, 1H), 5.29 (s, 1H), 5.25 (d, J = 5.3 Hz, 1H), 5.24 – 5.13 (m, 1H), 4.13 – 3.72 (m, 2H), 2.81 (td, J = 14.3, 6.9 Hz, 1H), 2.67 (ddd, J = 22.4, 14.5, 7.6 Hz, 1H), 1.51 (s, 9H); 13C NMR (101 MHz, CDCl3) δ (a mixture of two rotamers) 172.5, 168.23 (d, JCF = 23.6 Hz), 153.4, 134.3, 132.7, 129.7, 129.6, 128.5, 128.5, 128.3, 128.0, 121.4, 92.2 (d, JCF = 197.0 Hz, appears as four peaks due to the presence of two rotamers and coupling with fluorine), 82.4, 57.7, 49.4 (appears as four poorly resolved peaks due to the presence of two rotamers and coupling with fluorine), 38.2 (d, JCF = 22.8 Hz), 28.3; IR (Neat Film, NaCl) 2978, 1710, 1416, 1368, 1286, 1245, 1158, 1137, 906, 858, 801, 749, 723, 694, 662 cm⁻¹; HRMS (MM: ESI-APCI): m/z calc’d for C27H32N2O5 [M+H]+: 465.2384, found 465.2378; [α]D23.4 +11.9 (c 0.67, CHCl3); SFC conditions: 20% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, tR (min): major = 5.131, minor = 4.419.

tert-butyl (S)-5-allyl-3-benzoyl-4-oxo-5-(prop-2-yn-1-yl)tetrahydropyrimidine-1(2H)-carboxylate (6i). Following the general procedure, propargylated allyl ester 5i (20 mg, 0.047 mmol, 1.0 equiv) in hexanes/toluene (2:1, 2.8 mL) was added to a solution of Pd2(pmdba)2 (2.1 mg, 0.0019 mmol, 4 mol %) and (S)-(CF3)3-tBu-PHOX (2.8 mg, 0.0047 mmol, 10 mol %) in hexanes/toluene (2:1, 0.5 mL). Purification by flash chromatography (EtOAc/hexanes 5% → 10% → 15%) gave propargyl tetrahydropyrimidinone 6i as a yellow oil (15 mg, 83% yield, 90% ee); 1H NMR (400 MHz, CDCl3) δ 7.58 (s, 1H), 7.50 (t, J = 7.4 Hz, 2H), 7.39 (t, J = 7.5 Hz, 2H), 5.89 – 5.68 (m, 1H), 5.42 (s, 1H), 5.31 – 4.98 (m, 3H), 4.15 – 3.57 (m, 2H), 2.61 (dd, J = 16.9, 2.7 Hz, 2H), 2.42 (dd, J = 16.9, 2.7 Hz,
2H), 2.11 (t, J = 2.6 Hz, 1H), 1.54 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ (a mixture of two rotamers) 174.3, 173.7, 153.6, 153.4, 132.2, 131.8, 128.3, 128.2, 120.6, 82.0, 79.6, 72.4, 59.3, 58.9, 48.2, 47.8, 40.1, 39.6, 28.4, 25.1; IR (Neat Film, NaCl) 3271, 2978, 2930, 1698, 1478, 1450, 1425, 1368, 1284, 1247, 1139, 1028, 927, 854, 802, 764, 720, 695, 635 cm$^{-1}$; HRMS (MM: ESI-APCI): m/z calc’d for C$_{22}$H$_{27}$N$_2$O$_4$ [M+H]$^+$: 383.1965, found 383.1973; [α]$_D^{23}$ $^{3}$ +22.1 (c 0.47, CHCl$_3$); SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t$_R$ (min): major = 4.769, minor = 4.399.

**Experimental Procedure for the Gram Scale Decarboxylative Asymmetric Allylic Alkylation of Benzyl Tetrahydropyrimidinone 5e**

![Image](https://via.placeholder.com/150)

**tert-butyl** (S)-5-allyl-3-benzoyl-5-benzyl-4-oxotetrahydropyrimidine-1(2H)-carboxylate (6e). In a nitrogen-filled glovebox, a 250 mL schlenk flask was charged with Pd$_2$(pmdba)$_3$ (69 mg, 0.063 mmol, 4 mol %), (S)-(CF$_3$)$_3$-tBu-PHOX (99 mg, 0.17 mmol, 8 mol %), hexane/toluene (2:1, 50 mL), and a magnetic stir bar. The flask was stirred at ambient glovebox temperature (27 °C) for 30 min and then 5e (1g, 2.1 mmol, 1.0 equiv) was added as a solution in hexane/toluene (2:1, 100 mL, total concentration 0.014M). The flask was sealed with a Kontes valve, removed from the glovebox, and heated to 40 °C for 16 h. The solution was concentrated under reduced pressure and purified by silica gel flash chromatography (15% EtOAc/hexanes) to give benzyl tetrahydropyrimidinone 6e as a yellow oil (780 mg, 87% yield, 95% ee); spectroscopic data vide supra.

**Experimental Procedures for the Transformations of Decarboxylative Allylic Alkylation Products**

![Image](https://via.placeholder.com/150)

**tert-butyl** (R)-(2-allyl-4-benzoyl-3-oxopiperazin-2-yl)methylcarbamate (8). Trifluoroacetic acid (114 µL, 1.5 mmol, 20 equiv) was added dropwise to a solution of methylcarbamate oxopiperazine 4m (35 mg, 0.07 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (0.74 mL) at 0 °C. The reaction mixture was allowed to warm up to room temperature, stirred for 3 h and concentrated under reduced pressure. The residue was repeatedly taken up in CH$_2$Cl$_2$ (1.0 mL) and concentrated, four times. The crude residue was then purified by silica gel flash chromatography (10% MeOH/CH$_2$Cl$_2$) to yield deprotected oxopiperazine 8 as a pale yellow foam (27 mg, 73% yield); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.48 (t, J = 8.0 Hz, 3H), 7.37 (t, J = 7.4 Hz, 2H), 5.66 (dd, J = 16.0, 8.8 Hz, 1H), 5.30 (d, J = 9.8 Hz, 1H), 5.25 (d, J = 16.8 Hz, 1H), 3.99 – 3.79 (m, 1H), 3.73 –
3.55 (m, 1H), 3.44 – 3.16 (m, 2H), 3.05 (d, J = 13.2 Hz, 1H), 2.89 (d, J = 11.6 Hz, 1H), 2.76 (dd, J = 14.0, 7.0 Hz, 1H), 2.45 (dd, J = 14.2, 7.1 Hz, 1H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 173.7, 172.4, 135.5, 132.2, 129.7, 128.4, 128.0, 122.5, 62.0, 47.0, 43.5, 39.7, 38.1; IR (Neat Film, NaCl) 2976, 1682, 1470, 1282, 1203, 1135, 926, 836, 799, 722, 696 cm\(^{-1}\); HRMS (MM: ESI-APCI): m/z calc’d for C\(_{15}\)H\(_{20}\)N\(_3\)O\(_4\) [M+H]\(^+\): 274.1550, found 274.1555; \([\alpha]\)\(_D\)\(^{22,3}\) +15.1 (c 1.0, CHCl\(_3\)).

tert-butyl \((R)-2\text{-allyl}-2-(((\text{tert-butoxycarbonyl})amino)methyl)-3\text{-oxopiperazine-1-carboxylate (9)}\). LiOH monohydrate (2.5 mg, 0.06 mmol, 1.4 equiv) was added in one portion to a solution of methylcarbamate oxopiperazine 4\(_m\) (20 mg, 0.04 mmol, 1.0 equiv) in methanol/water (1:1, 1.8 mL) at room temperature. The reaction mixture was stirred for 1 h, diluted with EtOAc (2 mL) and washed with saturated aqueous NaHCO\(_3\) (2 mL). The aqueous phase was extracted with EtOAc (3x3 mL) and the combined organic phases were washed with brine (3 mL), dried over anhydrous Na\(_2\)SO\(_4\), decanted, and concentrated under reduced pressure onto silica gel. The silica-loaded residue was purified by silica gel flash chromatography (hexanes/EtOAc 1:1) to yield lactam 9 as a white foam (14 mg, 92% yield): \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.96 (s, 1H), 5.72 (ddt, \(J = 17.2, 10.2, 7.4\) Hz, 1H), 5.16 – 5.04 (m, 2H), 4.88 (t, \(J = 6.9\) Hz, 1H), 4.26 – 3.91 (m, 1H), 3.82 (s, 1H), 3.60 (dd, \(J = 14.0, 5.9\) Hz, 1H), 3.50 (s, 1H), 3.39 – 2.83 (m, 3H), 2.62 (s, 1H), 1.52 (s, 9H), 1.41 (s, 9H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 172.7, 155.7, 153.9, 132.7, 119.2, 81.2, 79.3, 69.1, 46.0, 43.1, 40.9, 38.9, 28.6, 28.5; IR (Neat Film, NaCl) 3337, 2977, 2360, 1698, 1520, 1367, 1243, 1168, 1085, 1058, 919, 866, 768, 733 cm\(^{-1}\); HRMS (MM: ESI-APCI): m/z calc’d for C\(_{18}\)H\(_{32}\)N\(_3\)O\(_5\) [M+H]\(^+\): 370.2336, found 370.2337; \([\alpha]\)\(_D\)\(^{21,9}\) –5.7 (c 1.0, CHCl\(_3\)).

tert-butyl \((S)-2\text{-allyl}-2-(((\text{tert-butoxycarbonyl})amino)methyl)piperazine-1-carboxylate (10)\). To a solution of lactam 9 (50 mg, 0.14 mmol, 1 equiv) in THF (1.4 mL) at 0 °C was quickly added LAH (8 mg, 0.2 mmol, 1.5 equiv) in one portion. The mixture was stirred at room temperature and three portions of LAH (8 mg, 0.2 mmol, 1.5 equiv) were added over four hours until all starting material was consumed as determined by TLC analysis. The reaction mixture was then cooled to 0 °C and diluted with Et\(_2\)O. H\(_2\)O (40 \(\mu\)L), 15% aqueous NaOH (40 \(\mu\)L), and H\(_2\)O (120 \(\mu\)L) were added successively at 0 °C. The mixture was stirred for 5 minutes at room temperature and then MgSO\(_4\) was added. The mixture was stirred for another 5 minutes at room temperature and then filtered over a pad of celite, rinsing with EtOAc. The solvent was concentrated under reduced pressure and the crude residue was purified by silica gel flash chromatography (MeOH/CH\(_2\)Cl\(_2\), 1 \(\rightarrow\) 2 \(\rightarrow\) 4%) to afford piperazine 10 as a colorless oil (30 mg, 63% yield); \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.84 – 5.66 (m, 1H), 5.28 – 5.01 (m, 3H), 3.75 (dd, \(J = 14.1, 5.6\) Hz, 1H), 3.62 (dt, \(J = 13.6, 4.2\) Hz, 1H), 3.35 (dd, \(J = 14.1, 7.3\) Hz, 1H), 3.24 (ddd, \(J = 13.6, 9.8, 3.8\) Hz,
1H), 3.02 – 2.91 (m, 1H), 2.85 (t, J = 11.1 Hz, 2H), 2.79 – 2.63 (m, 2H), 1.46 (s, 9H), 1.44 (s, 9H); ^13^C NMR (101 MHz, CDCl$_3$) δ 156.8, 156.0, 133.1, 119.1, 80.6, 79.6, 59.9, 50.8, 46.2, 45.1, 42.3, 38.1, 28.6, 28.5; IR (Neat Film, NaCl) 3789, 3662, 3451, 3341, 3074, 2976, 2930, 2284, 1693, 1641, 1502, 1453, 1391, 1365, 1298, 1249, 1169, 1085, 996, 914, 859, 771 cm$^{-1}$; HRMS (MM: ESI-APCI): m/z calc’d for C$_{18}$H$_{34}$N$_3$O$_4$ [M+H]$^+$: 356.2544, found 356.2549; $[^{\alpha}_D]_{22}^{22.8}$ +5.3 (c 0.67, CHCl$_3$).

(S)-1-benzoyl-3-methyl-3-propylpiperazin-2-one 11. Piperazine 4e (80 mg, 0.22 mmol, 1 equiv) was dissolved in MeOH (2.2 mL). The reaction flask was purged with Argon before adding Pd/C (10%, 24 mg, 0.022 mmol, 0.1 equiv). The flask was evacuated and filled with H$_2$ three times, and then sparged with H$_2$ for 5 minutes. The reaction was stirred at room temperature for 6 hours before being filtered through a pad of silica gel while rinsing with EtOAc. The crude hydrogenated product was then dissolved in CH$_2$Cl$_2$ (2.2 mL) and TFA (171 µL, 2.23 mmol, 10 equiv) was added. The reaction was stirred for 16 hours and then quenched with saturated aqueous NaHCO$_3$ (5 mL). The solution was extracted with EtOAc (3x5 mL), dried over Na$_2$SO$_4$, decanted, and concentrated under reduced pressure. The crude piperazinone was purified by silica gel flash chromatography (2.5 → 5% MeOH/CH$_2$Cl$_2$) to afford the desired product 11 (55 mg, 94% yield over two steps): ^1^H NMR (400 MHz, CDCl$_3$) δ 7.58 – 7.50 (m, 2H), 7.54 – 7.46 (m, 1H), 7.46 – 7.36 (m, 2H), 3.92 (ddd, J = 12.6, 5.4, 4.6 Hz, 1H), 3.81 (ddd, J = 12.5, 6.7, 5.4 Hz, 1H), 3.32 – 3.18 (m, 2H), 1.92 (ddd, J = 13.6, 12.1, 4.7 Hz, 1H), 1.62 (ddd, J = 13.6, 12.2, 4.5 Hz, 1H), 1.42 (s, 3H), 1.54 – 1.23 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H); ^13^C NMR (101 MHz, CDCl$_3$) δ 176.7, 174.7, 136.4, 131.6, 128.3, 127.5, 61.2, 48.2, 41.2, 38.7, 25.0, 16.9, 14.5; IR (Neat Film, NaCl) 3331, 2960, 2872, 1681, 1600, 1448, 1378, 1284, 1202, 1176, 1152, 1112, 966, 794, 726, 694, 669 cm$^{-1}$; HRMS (MM: ESI-APCI): m/z calc’d for C$_{15}$H$_{21}$N$_2$O$_2$ [M+H]$^+$: 261.1598, found 261.1596; $[^{\alpha}_D]_{22}^{22.6}$ –59.6 (c 1.35, CHCl$_3$).

(R)-4-benzoyl-6-propyl-1,4-diazabicyclo[4.2.0]octane-5,8-dione (12). To a 10 mL round-bottom flask was added Pd(OPiv)$_2$ (3 mg, 0.0096 mmol, 0.1 equiv), AgOPiv$^7$ (60 mg, 0.29 mmol, 3 equiv), Xantphos (6 mg, 0.0096 mmol, 0.1 equiv), and 1,4-benzoquinone (21 mg, 0.19 mmol, 2 equiv). A solution of piperazine 11 (25 mg, 0.096 mmol, 1 equiv) in toluene (1 mL) was then added and the flask was evacuated and filled with carbon monoxide three times. The flask was then stirred at 80 °C for 16 hours. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc, and filtered through celite while rinsing with additional EtOAc. The solvent was concentrated under reduced
pressure onto silica gel and then purified by silica gel flash chromatography (2:1 hexanes/EtOAc) to provide the β-lactam 12 and as a light yellow oil (15 mg, 55% yield): **1H NMR (400 MHz, CDCl₃)** δ (5:1 ratio of desired product and an inseparable isomer resulting from insertion into another β-C–H) 7.56 – 7.51 (m, 3H), 7.46 – 7.40 (m, 2H), 4.51 (ddd, J = 14.0, 6.1, 2.9 Hz, 1H), 3.94 (ddt, J = 12.3, 10.8, 5.7 Hz, 1H), 3.78 – 3.67 (m, 1H), 3.40 (dddd, J = 12.3, 4.8, 2.8, 1.5 Hz, 1H), 3.27 – 3.10 (m, 2H), 1.98 (ddd, J = 14.2, 11.2, 5.5 Hz, 1H), 1.87 (ddd, J = 14.2, 11.0, 5.7 Hz, 1H), 1.59 – 1.40 (m, 2H), 1.00 (t, J = 7.3 Hz, 3H); **13C NMR (101 MHz, CDCl₃)** δ 174.2, 173.2, 169.1, 135.1, 132.6, 128.6, 128.3, 59.7, 46.7, 41.5, 39.7, 37.8, 17.7, 14.3; **IR (Neat Film, NaCl)** 3374, 2961, 1760, 1688, 1600, 1505, 1449, 1350, 1318, 1279, 1183, 1151, 1118, 1069, 1032, 936, 913, 821, 796, 726, 694, 662 cm⁻¹; **HRMS (MM: ESI-APCI): m/z** calc’d for C₁₆H₁₉N₂O₃ [M+H]⁺: 287.1390, found: 287.1385; [α]D 23.5° – 12.8° (c 0.47, CHCl₃).

(S)-2-benzyl-2-(((tart-butoxycarbonyl)amino)methyl)pent-4-enoic acid (13). To a solution of benzyl tetrahydroprymidinone 6e (200 mg, 0.46 mmol, 1 equiv) in methylene chloride (4.6 mL) was added TFA (352 μL, 4.6 mmol, 10 equiv) dropwise at room temperature. The solution was stirred for 24 hours at room temperature and then quenched with aqueous NaHCO₃ (10 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (4 x 5 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure.

The crude residue was dissolved in MeOH/H₂O (1:1, 5 mL) and LiOH monohydrate (290 mg, 6.9 mmol, 15 equiv) was added. The reaction mixture was heated to 80 °C for 60 hours and then allowed to cool to room temperature. Then, NEt₃ (77 μL, 0.55 mmol, 1.2 equiv) and Boc₂O (110 mg, 0.51 mmol, 1.1 equiv) were added successively at room temperature. The reaction was stirred for 1 hour at room temperature and then acidified with 1 M HCl (4 mL). The solution was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over Na₂SO₄.

The crude Boc-protected β-amino acid was taken up in DMF (2.3 mL). K₂CO₃ (95 mg, 0.69 mmol, 1.5 equiv) and BnBr (66 µL, 0.55 mmol, 1.2 equiv) were added at room temperature. The reaction was stirred at room temperature for 1 hour and then quenched with saturated aqueous NH₄Cl. The solution was extracted with EtOAc (3 x 5 mL) and the combined organic layers were concentrated under reduced pressure and placed under high vacuum until trace DMF had evaporated. The residue was taken up in CH₂Cl₂, concentrated under reduced pressure onto silica gel and purified by silica gel flash chromatography (5 → 10% EtOAc/hexanes) to afford protected β₂,₂-amino acid 13 as a white solid (80 mg, 40% yield): **1H NMR (400 MHz, CDCl₃)** δ 7.42 – 7.27 (m, 5H), 7.20 (dd, J = 4.9, 1.9 Hz, 3H), 7.10 – 6.93 (m, 2H), 5.92 – 5.75 (m, 1H), 5.18 – 5.04 (m, 4H), 4.96 – 4.81 (m, 1H), 3.34 (qd, J = 14.0, 6.5 Hz, 2H), 2.98 (d, J = 13.8 Hz, 1H), 2.86 (d, J = 13.8 Hz, 1H), 2.49 (ddt, J = 14.2, 6.7, 1.4 Hz, 1H), 2.31 (ddt, J = 14.2, 7.9, 1.1 Hz, 1H), 1.43 (s, 9H); **13C NMR (101 MHz, CDCl₃)** δ 175.1, 156.1, 136.6, 135.6, 133.4, 130.2, 128.8, 128.6, 128.5, 128.4, 126.9, 119.2, 79.4, 66.8, 51.6, 44.1, 41.0, 38.8, 28.5; **IR (Neat Film, NaCl)** 3452,
(R)-2-allyl-2-(aminomethyl)pentanedioic acid (14). To a solution of methyl ester tetrahydropyrimidinone 6c (140 mg, 0.325 mmol, 1 equiv) in CH₂Cl₂ (3.1 mL, 0.1 M) was added TFA (250 µL, 3.25 mmol, 10 equiv) dropwise at room temperature. The solution was stirred for 24 h at room temperature and then concentrated under reduced pressure. Remaining TFA was removed with azeotroping with CH₂Cl₂ three times. The crude residue was dissolved in MeOH/H₂O (1:1, 1.1 mL, 0.1 M) and LiOH monohydrate (205 mg, 4.89 mmol, 15 equiv) was added. The reaction mixture was heated to 80 °C for 16 h and then allowed to cool to room temperature. The reaction mixture was then acidified with 4 M HCl in dioxanes (~1 mL) until pH 1. Then, the solvent was concentrated under reduced pressure, resulting in precipitation of a white solid. A minimal amount of DMSO (~1 mL) was added to resolvate this precipitate. This solution was subjected to purification by reverse phase preparatory HPLC (0 → 40% MeCN/H₂O gradient over 11 minutes, 20x250 mm C₁₈ column, 25 mL/min flow rate) to yield β-amino acid 14 (30 mg, 46% yield) as a colorless oil. Note: HPLC fractions were spotted onto a silica TLC plate and eluted in (n-BuOH/H₂O/EtOAc/AcOH, 1:1:1:1), then stained with ninhydrin to identify product-containing fractions. LC-MS was used to verify the fractions containing product. Note: HPLC H₂O solvent contained 0.25% TFA. ¹H NMR (400 MHz, Methanol-d₄) δ 5.88 – 5.68 (m, 1H), 5.32 – 5.13 (m, 2H), 3.18 – 2.99 (m, 2H), 2.51 (ddt, J = 14.4, 7.1, 1.3 Hz, 1H), 2.47 – 2.33 (m, 3H), 1.99 (td, J = 7.6, 1.3 Hz, 2H); ¹³C NMR (101 MHz, MeOD) δ 176.7, 176.6, 153.1, 120.6, 48.3, 43.5, 39.1, 29.38, 29.35; IR (Neat Film, NaCl) 2924, 1678, 1198, 1138 cm⁻¹; HRMS (MM: ESI-APCI): m/z calc’d for C₉H₁₆NO₄ [M+H]⁺: 202.1074, found 202.1075; [α]D²³.⁴ +3.47 (c 1.0, CHCl₃).

(S)-2-allyl-2-(aminomethyl)-4-chloropent-4-enoic acid (15). To a solution of chloroallyl tetrahydropyrimidinone 6d (30 mg, 0.072 mmol, 1 equiv) in CH₂Cl₂ (700 µL, 0.1 M) was added TFA (55 µL, 0.72 mmol, 10 equiv) dropwise at room temperature. The solution was stirred for 5 h at room temperature and then concentrated under reduced pressure. Remaining TFA was removed with azeotroping with CH₂Cl₂ three times. The crude residue was dissolved in MeOH/H₂O (1:1, 700 µL, 0.1 M) and LiOH monohydrate (45 mg, 1.07 mmol, 15 equiv) was added. The reaction mixture was heated to 80 °C for 16 h and then allowed to cool to room temperature. The reaction mixture was then acidified with 4 M HCl in dioxane (~1 mL) until pH 1. Then, the solvent was concentrated under reduced pressure, resulting in precipitation of a white solid. A minimal amount of DMSO (~1 mL) was added to resolvate this precipitate. This solution was subjected to purification by...
reverse phase preparatory HPLC (10 → 40% MeCN/H$_2$O gradient over 11 minutes, 20x250 mm C$_{18}$ column, 25 mL/min flow rate) to yield chloroallyl $\beta$-amino acid 15 (10 mg, 69% yield) as a colorless oil. Note: HPLC fractions were spotted onto a silica TLC plate and eluted in ($n$-BuOH/H$_2$O/EtOAc/AcOH, 1:1:1:1), then stained with ninhydrin to identify product-containing fractions. LC-MS was used to verify the fractions containing product. Note: HPLC H$_2$O solvent contained 0.25% TFA. $^1$H NMR (600 MHz, Methanol-$d_4$) $\delta$ 5.84 (td, $J = 17.2, 7.3$ Hz, 1H), 5.40 (s, 2H), 5.29 (d, $J = 13.5$ Hz, 1H), 3.12 (d, $J = 13.5$ Hz, 1H), 2.94 (d, $J = 15.1$ Hz, 1H), 2.77 (d, $J = 14.8$ Hz, 1H), 2.57 (dd, $J = 14.5, 7.0$ Hz, 1H), 2.47 (dd, $J = 14.5, 7.8$ Hz, 1H); $^{13}$C NMR (101 MHz, MeOD) $\delta$ 176.6, 138.2, 133.1, 120.8, 118.7, 48.4, 44.2, 43.5, 39.6. Note: A $^1$H-$^{13}$C HMBC experiment revealed the chemical shift of the chiral quaternary carbon to be at 48.4 ppm, obscured by the CD$_3$OD resonance. IR (Neat Film, NaCl) 2926, 1673, 1432, 1200, 1140, 900, 836, 800, 722 cm$^{-1}$; HRMS (MM: ESI-APCI): $m/z$ calc’d for C$_9$H$_{15}$ClNO$_2$ [M+H]$^+$: 204.0786, found 204.0787; $[\alpha]_D^{22.5}$ –4.64 (c 0.67, MeOH).

(S)-2-(aminomethyl)-2-fluoropent-4-enoic acid (16). To a solution of fluoro tetrahydropyrimidinone 6h (20 mg, 0.055 mmol, 1 equiv) in 1:1 MeOH/H$_2$O (550 µL, 0.1 M) at room temperature was added KOH (31 mg, 0.55 mmol, 10 equiv). The cloudy solution became clear over seconds and was stirred for 5 min at room temperature until TLC analysis showed complete consumption of starting material. AcOH (~100 µL) was added to acidify the solution, which was then extracted with CH$_2$Cl$_2$ three times. The combined organic layers were dried with Na$_2$SO$_4$ and then concentrated under reduced pressure.

HCl was generated in situ by adding AcCl (205 µL, 2.87 mmol, 52 equiv) dropwise to a separate 1 dram vial containing MeOH (550 µL) at 0 °C. This HCl solution was stirred for 5 min at 0 °C and was then transferred by pipette into a 1 dram vial containing the crude saponified residue. The reaction was stirred at rt for 2 h and was then concentrated under reduced pressure. The crude residue was dissolved in 1:1 H$_2$O/MeCN (2.5 mL) and was then subjected to purification by reverse phase preparatory HPLC (0 → 40% MeCN/H$_2$O gradient over 11 minutes, 20x250 mm C$_{18}$ column, 25 mL/min flow rate) to yield fluoro $\beta$-amino acid 16 (5.0 mg, 65% yield) as a colorless oil. Note: HPLC fractions were spotted onto a silica TLC plate and eluted in ($n$-BuOH/H$_2$O/EtOAc/AcOH, 1:1:1:1), then stained with ninhydrin to identify product-containing fractions. LC-MS was used to verify the fractions containing product. Note: HPLC H$_2$O solvent contained 0.25% TFA. $^1$H NMR (600 MHz, Methanol-$d_4$) $\delta$ 5.80 (ddt, $J = 17.1, 7.3$ Hz, 1H), 5.30 – 5.17 (m, 2H), 3.51 (dd, $J = 26.1, 13.9$ Hz, 1H), 3.38 – 3.32 (dd, $J = 26.1, 13.9$ Hz, 1H), 2.81 – 2.63 (m, 2H); $^{13}$C NMR (101 MHz, MeOD) $\delta$ 170.1 (d, $J_{CF} = 26.2$ Hz), 130.7, 121.3, 95.0 (d, $J_{CF} = 190.2$ Hz), 44.74 (d, $J_{CF} = 22.1$ Hz), 40.44 (d, $J_{CF} = 22.1$ Hz); IR (Neat Film, NaCl) 2924, 1674, 1422, 1202, 1141, 931, 798, 722 cm$^{-1}$; HRMS (MM: ESI-APCI): $m/z$ calc’d for C$_6$H$_{11}$NO$_2$ [M+H]$^+$: 148.0768, found 148.0770; $[\alpha]_D^{22.5}$ –2.47 (c 0.33, MeOH).
Determination of Enantiomeric Excess

*Please note* racemic products were synthesized according to the general procedure, using achiral GlyPHOX ligand instead of (S)-(CF$_3$)$_3$-Bu-PHOX.

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<th>Entry</th>
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<th>Retention time of major isomer (min)</th>
<th>Retention time of minor isomer (min)</th>
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References


$^1$H NMR (500 MHz, CDCl$_3$) of compound 2.
Infrared spectrum (Thin Film, NaCl) of compound 2.

$^{13}$C NMR (126 MHz, CDCl$_3$) of compound 2.
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Infrared spectrum (Thin Film, NaCl) of compound SI-3.

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Infrared spectrum (Thin Film, NaCl) of compound SI-4.

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Infrared spectrum (Thin Film, NaCl) of compound 3b.

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$^1$H NMR (500 MHz, CDCl$_3$) of compound 3c.
Infrared spectrum (Thin Film, NaCl) of compound 3c.

$^{13}$C NMR (126 MHz, CDCl$_3$) of compound 3c.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 3d.
Infrared spectrum (Thin Film, NaCl) of compound 3d.

$^{13}$C NMR (101 MHz, CDCl$_3$) of compound 3d.
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Infrared spectrum (Thin Film, NaCl) of compound 3e.

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Infrared spectrum (Thin Film, NaCl) of compound 3f.

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Infrared spectrum (Thin Film, NaCl) of compound 3h.

$^{13}$C NMR (101 MHz, CDCl$_3$) of compound 3h.
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Infrared spectrum (Thin Film, NaCl) of compound 3i.

$^{13}$C NMR (126 MHz, CDCl$_3$) of compound 3i.
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\[ \text{13C NMR (101 MHz, CDCl}_3\text{) of compound 3j.} \]
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Infrared spectrum (Thin Film, NaCl) of compound 3k.

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$^1$H NMR (500 MHz, CDCl₃) of compound 4d.
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$^{13}$C NMR (126 MHz, CDCl$_3$) of compound 4d.

79
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Infrared spectrum (Thin Film, NaCl) of compound 4e.

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Infrared spectrum (Thin Film, NaCl) of compound 4f.

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Infrared spectrum (Thin Film, NaCl) of compound 4j.

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Infrared spectrum (Thin Film, NaCl) of compound 4k.

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Infrared spectrum (Thin Film, NaCl) of compound 5a.

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Infrared spectrum (Thin Film, NaCl) of compound 5b.

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Infrared spectrum (Thin Film, NaCl) of compound 5c.

$^{13}$C NMR (101 MHz, CDCl$_3$) of compound 5c.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 5d.
Infrared spectrum (Thin Film, NaCl) of compound 5d.

$^{13}$C NMR (101 MHz, CDCl$_3$) of compound 5d.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 5e.
Infrared spectrum (Thin Film, NaCl) of compound 5e.

$^{13}$C NMR (101 MHz, CDCl$_3$) of compound 5e.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 5f.
Infrared spectrum (Thin Film, NaCl) of compound 5f.

$^{13}$C NMR (101 MHz, CDCl$_3$) of compound 5f.
\(^1\)H NMR (400 MHz, CDCl\(_3\)) of compound 5g.
Infrared spectrum (Thin Film, NaCl) of compound 5g.

$^{13}$C NMR (101 MHz, CDCl$_3$) of compound 5g.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 5h.
Infrared spectrum (Thin Film, NaCl) of compound 5h.

$^{13}$C NMR (101 MHz, CDCl$_3$) of compound 5h.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 5i.
Infrared spectrum (Thin Film, NaCl) of compound 5i.

$^{13}$C NMR (101 MHz, CDCl$_3$) of compound 5i.
\[^1\text{H NMR (500 MHz, CDCl}_3\text{)}\) of compound 6a.
Infrared spectrum (Thin Film, NaCl) of compound 6a.

$^{13}$C NMR (101 MHz, CDCl$_3$) of compound 6a.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 6b.
Infrared spectrum (Thin Film, NaCl) of compound 6b.

\[ \text{\textsuperscript{13}C NMR (101 MHz, CDCl}_3\text{) of compound 6b.} \]
$^1$H NMR (400 MHz, CDCl$_3$) of compound 6c.
Infrared spectrum (Thin Film, NaCl) of compound 6c.

$^{13}$C NMR (101 MHz, CDCl$_3$) of compound 6c.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 6d.
Infrared spectrum (Thin Film, NaCl) of compound 6d.

$^{13}$C NMR (101 MHz, CDCl$_3$) of compound 6d.
$^1$H NMR (500 MHz, CDCl$_3$) of compound 6e.
Infrared spectrum (Thin Film, NaCl) of compound 6e.

$^{13}$C NMR (101 MHz, CDCl$_3$) of compound 6e.
$^1$H NMR (500 MHz, CDCl$_3$) of compound 6f.
Infrared spectrum (Thin Film, NaCl) of compound 6f.

$^{13}$C NMR (101 MHz, CDCl$_3$) of compound 6f.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 6g.
Infrared spectrum (Thin Film, NaCl) of compound 6g.

$^{13}$C NMR (101 MHz, CDCl$_3$) of compound 6g.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 6h.
Infrared spectrum (Thin Film, NaCl) of compound 6h.

$^{13}$C NMR (101 MHz, CDCl$_3$) of compound 6h.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 6i.
Infrared spectrum (Thin Film, NaCl) of compound 6i.

$^{13}$C NMR (101 MHz, CDCl$_3$) of compound 6i.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 8.
Infrared spectrum (Thin Film, NaCl) of compound 8.

$^{13}$C NMR (101 MHz, CDCl$_3$) of compound 8.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 9.
Infrared spectrum (Thin Film, NaCl) of compound 9.

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) of compound 9.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 10.
Infrared spectrum (Thin Film, NaCl) of compound 10.

$^{13}$C NMR (101 MHz, CDCl$_3$) of compound 10.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 11.
Infrared spectrum (Thin Film, NaCl) of compound 11.

$^{13}$C NMR (101 MHz, CDCl$_3$) of compound 11.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 12.
Infrared spectrum (Thin Film, NaCl) of compound 12.

$^{13}$C NMR (101 MHz, CDCl$_3$) of compound 12.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 13.
Infrared spectrum (Thin Film, NaCl) of compound 13.

\[ \text{13C NMR (101 MHz, CDCl}_3\text{) of compound 13.} \]
$^1$H NMR (400 MHz, CD$_3$OD) of compound 14.
Infrared spectrum (Thin Film, NaCl) of compound 14.

\(^{13}\text{C} \text{ NMR (101 MHz, CD}_3\text{OD) of compound 14.}\)
$^1$H NMR (600 MHz, CD$_3$OD) of compound 15.
Infrared spectrum (Thin Film, NaCl) of compound 15.

$^{13}$C NMR (101 MHz, CD$_3$OD) of compound 15.
$^1$H-$^{13}$C HMBC (CD$_3$OD) of compound 15
$^1$H NMR (600 MHz, CD$_3$OD) of compound 16.
Infrared spectrum (Thin Film, NaCl) of compound 16.

\[
\begin{align*}
\text{13C NMR (101 MHz, CD}_3\text{OD) of compound 16.}
\end{align*}
\]
Signal 1: DAD1 A, Sig=210.8 Ref=360,100

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Signal 2: DAD1 D, Sig=254.8 Ref=360,100

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Signal 1: DAD1 A, Sig=210,8 Ref=360,100

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(4g)

Signal 4: DAD1 D, Sig=254,8 Ref=360,100

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(4h)
Signal 1: DAD1 A, Sig=210,8 Ref=360,100

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Signal 2: DAD1 B, Sig=235,8 Ref=360,100

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### Data Table

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Signal 3: DAD1 D, Sig=254,8 Ref=360,100

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(6c):
(6d):

BzN \text{N}\text{Boc}

\text{O} \text{Cl}

(6e):

BzN \text{N}\text{Boc}

\text{O} \text{Ph}
Signal 1: DAD1 A, Sig=210,8 Ref=360,100

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Signal 2: DAD1 D, Sig=254,8 Ref=360,100

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### Signal 1: DAD1 A, Sig-210,8 Ref-360,100

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