Supporting Information for

Palladium-Catalyzed Decarboxylative Asymmetric Allylic Alkylation of 1,4-diazepan-5-ones

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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. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching or KMnO₄ staining. Silicycle SiliaFlash® P60 Academic Silica gel (particle size 40–63 nm) was used for flash chromatography. ¹H NMR spectra were recorded on Varian Inova 500 MHz, Varian 400 MHz, and Bruker 400 MHz spectrometers and are reported relative to residual CHCl₃ (δ 7.26 ppm). ¹³C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer (125 MHz), a Varian 400 MHz spectrometer (100 MHz), and Bruker 400 MHz spectrometers (100 MHz) and are reported relative to CHCl₃ (δ 77.16 ppm). Data for ¹H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet. Data for ¹³C NMR are reported in terms of chemical shifts (δ ppm) Some reported spectra include minor solvent impurities of water (δ 1.56 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. Most NMR spectra are complicated by rotational isomerism about amide bonds. This behavior is illustrated by variable-temperature NMR spectra of compound 4e in DMSO (p. S102). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer or Nicolet 6700 FTIR spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm⁻¹). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell. Analytical SFC was performed with a Mettler SFC supercritical CO₂ analytical chromatography system utilizing Chiralpak (AD-H, AS-H or IC) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from 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+). Absolute stereochemistry is assigned by analogy to previous results by our group.²
Reagents were purchased from commercial sources and used as received unless otherwise stated. Ligands (S)-(CF)_3-t-BuPHOX and (S)-Ty-PHOX were prepared according to literature procedures.³,⁴

**List of Abbreviations:**

- ee – enantiomeric excess
- SFC – supercritical fluid chromatography
- TLC – thin-layer chromatography
- IPA – isopropanol
- An = 4-anisoyl
- MeCy = methylcyclohexane

**General Procedure for Pd-Catalyzed Allylic Alkylation Reactions**

In a N₂ filled glovebox, Pd₂dba)₃ (4 mol %) or Pd₂(pmdba)₃ (4 mol %) and (S)-(CF)_3-t-BuPHOX (10 mol %) were suspended in methylcyclohexane (2 mL) in a 20 mL glass vial. After stirring for 20 minutes at 25 °C, the appropriate diazepanone (1.0 equiv) and methylcyclohexane (5.2 mL, total substrate concentration 0.014 M) were added to the pre-stirred catalyst solution. The vial was then sealed and heated to 40 °C. After full consumption of starting material, as monitored by TLC, the reaction mixture was exposed to air. The crude reaction mixture was loaded directly onto a flash column and the product was isolated by silica gel flash chromatography.

**tert-butyl (S)-6-allyl-4-benzoyl-6-benzyl-5-oxo-1,4-diazepane-1-carboxylate (4a)**

Prepared according to the general procedure with allyl ester 3a (51.2 mg, 0.104 mmol, 1.0
Supporting Information for Sercel,‡ Sun,‡ and Stoltz

equiv), Pd₂(pmdba)₃ (4.4 mg, 0.004 mmol, 4 mol %), and (S)-(CF₃)₃-t-BuPHOX (5.9 mg, 0.01 mmol, 10 mol %). Purified by silica gel flash chromatography (15% EtOAc/hexanes) to provide benzyl diazepanone 4a as a colorless oil (43.4 mg, 0.0967 mmol, 93% yield, 90% ee); ¹H NMR (400 MHz, CDCl₃) δ 7.56 – 7.40 (m, 3H), 7.40 – 7.32 (m, 2H), 7.32 – 7.19 (m, 3H), 7.19 – 7.00 (m, 2H), 5.88 (br s, 1H), 5.26 – 5.07 (m, 2H), 4.26 – 4.03 (m, 1H), 3.94 (d, J = 15.4 Hz, 1H), 3.73 (d, J = 42.2 Hz, 1H), 3.54 (d, J = 15.3 Hz, 1H), 3.40 (s, 2H), 3.09 (dd, J = 61.0, 13.7 Hz, 1H), 2.94 – 2.34 (m, 3H), 1.48 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 179.2, 174.8, 156.0, 155.4, 136.6, 136.4, 133.0, 131.5, 130.8, 128.6, 128.4, 127.8, 127.1, 120.0, 119.7, 80.8, 54.3, 53.9, 49.1, 47.4, 46.9, 42.5, 42.0, 41.5, 40.3, 28.5; IR (Neat Film, NaCl) 3062, 2975, 2928, 1693, 1682, 1601, 1452, 1415, 1392, 1365, 1322, 1283, 1246, 1156, 1044, 978, 917, 865, 728, 697 cm⁻¹; HRMS (MM: ESI-APCI): m/z calc’d for C₂₇H₃₃N₂O₄ [M+H]⁺: 449.2435, found 449.2429; [α]D²²⁴ +14.19 (c 0.66, CHCl₃); SFC conditions: 20% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 3.51, minor = 2.71.
**tert-butyl (R)-6-allyl-4-benzoyl-6-methyl-5-oxo-1,4-diazepane-1-carboxylate (4b)**

Prepared according to the general procedure with allyl ester 3b (39.0 mg, 0.0937 mmol, 1.0 equiv), \( \text{Pd}_{2}(\text{pmdba})_{3} \) (4.4 mg, 0.004 mmol, 4 mol %), and \((S)-(CF_{3})_{3}-t-\text{BuPHOX} \) (5.9 mg, 0.01 mmol, 10 mol %). Purified by silica gel flash chromatography (20\% EtOAc/hexanes) to provide methyl diazepanone 4b as a colorless, waxy solid (32.3 mg, 0.868 mmol, 93\% yield, 90\% ee); \(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.54 – 7.43 (m, 3H), 7.43 – 7.32 (m, 2H), 5.74 (ddt, \( J = 17.1, 9.9, 7.4 \) Hz, 1H), 5.19 – 5.06 (m, 2H), 4.30 – 3.89 (m, 3H), 3.85 – 3.69 (m, 1H), 3.66 – 3.34 (m, 2H), 2.63 – 2.20 (m, 2H), 1.50 (s, 9H), 1.30 (s, 3H); \(^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 180.8, 174.5, 155.4, 155.0, 136.3, 132.9, 131.4, 128.3, 127.5, 119.5, 80.7, 50.9, 49.9, 47.2, 46.5, 42.5, 42.1, 41.8, 28.4, 23.5, 23.1; IR (Neat Film, NaCl) 2976, 2933, 1694, 1450, 1418, 1392, 1366, 1323, 1284, 1246, 1146, 1057, 983, 917, 868, 768, 729, 696 cm\(^{-1}\); HRMS (MM: ESI-APCI): \( m/z \) calc’d for \( \text{C}_{21}\text{H}_{29}\text{N}_{2}\text{O}_{4} \) [M+H]\(^+\): 373.2122, found 373.2117; \([\alpha]_{D}^{22.31} \) –12.69 (c 1.0, CHCl\(_3\)); SFC Conditions: 20\% IPA, 2.5 mL/min, Chiralpak IC column, \( \lambda = 210 \) nm, \( t_{R} \) (min): minor = 4.31, major = 5.68.
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tered-butyl (R)-6-allyl-6-methyl-5-oxo-4-(4-(trifluoromethyl)benzoyl)-1,4-diazepane-1-carboxylate (4c)

Prepared according to the general procedure with allyl ester 3c (55.3 mg, 0.114 mmol, 1.0 equiv), Pd$_2$(dba)$_3$ (4.2 mg, 4.57 µmol, 4 mol %), and (S)-(CF$_3$)$_3$-t-BuPHOX (6.7 mg, 0.011 mmol, 10 mol %). Purified by silica gel flash chromatography (20% EtOAc/hexanes) to provide methyl diazepanone 4c as a colorless oil (45.1 mg, 0.102 mmol, 90% yield, 92% ee); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.64 (d, $J = 8.2$ Hz, 2H), 7.55 (d, $J = 8.2$ Hz, 2H), 5.71 (ddt, $J = 17.2$, 10.1, 7.4 Hz, 1H), 5.23 – 5.07 (m, 2H), 4.21 – 4.03 (m, 2H), 4.02 – 3.64 (m, 2H), 3.58 – 3.38 (m, 2H), 2.59 – 2.21 (m, 2H), 1.49 (s, 9H), 1.29 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 181.0, 180.8, 173.1, 155.4, 155.1 140.0, 132.8 (q, $J_{C,F} = 32.9$ Hz), 132.7, 127.6, 125.5 (q, $J_{C,F} = 3.7$ Hz), 123.7 (q, $J_{C,F} = 272.5$ Hz), 119.9, 81.0, 50.9, 50.0, 47.2, 46.4, 42.4, 42.0, 41.8, 28.5, 23.6, 23.3; IR (Neat Film, NaCl) 3366, 3077, 2978, 2934, 1694, 1452, 1410, 1394, 1367, 1326, 1248, 1167, 1147, 1066, 1014, 984, 925, 852, 764 cm$^{-1}$; HRMS (MM: ESI-APCI): m/z calc’d for C$_{22}$H$_{31}$F$_3$N$_3$O$_4$ [M+NH$_4$]$^+$: 458.2261, found 458.2250; [α]$_D^{22.6}$ –12.32 (c 1.0, CHCl$_3$); SFC Conditions: 5% IPA, 2.5 mL/min, Chiralpak AD-H column, $\lambda = 210$ nm, $t_R$ (min): minor = 4.49, major = 5.86.
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**tert-butyl (R)-6-allyl-4-(4-methoxybenzoyl)-6-methyl-5-oxo-1,4-diazepane-1-carboxylate (4d)**

Prepared according to the general procedure with allyl ester 3d (45.8 mg, 0.103 mmol, 1.0 equiv), Pd$_2$(dba)$_3$ (3.7 mg, 0.004 mmol, 4 mol %), and (S)-(CF$_3$)$_3$-t-BuPHOX (5.9 mg, 0.01 mmol, 10 mol %). Purified by silica gel flash chromatography (20% EtOAc/hexanes) to provide methyl diazepanone 4d as a colorless oil (38.9 mg, 0.0966 mmol, 94% yield, 94% ee); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.62 – 7.44 (m, 2H), 6.95 – 6.75 (m, 2H), 5.76 (m, 1H), 5.26 – 4.99 (m, 2H), 4.24 – 3.87 (m, 3H), 3.83 (s, 3H), 3.75 (m, 1H), 3.59 – 3.37 (m, 2H), 2.60 – 2.25 (m, 2H), 1.49 (s, 9H), 1.31 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 180.7, 180.6, 174.3, 162.5, 155.4, 155.0, 133.0, 130.1, 128.1, 119.4, 113.6, 80.7, 55.4, 50.8, 49.8, 47.4, 46.6, 42.7, 42.4, 28.4, 23.5, 23.1; IR (Neat Film, NaCl) 3352, 3076, 2975, 2932, 2841, 2568, 1690, 1605, 1579, 1542, 1511, 1458, 1420, 1392, 1366, 1322, 1284, 1256, 1214, 1168, 1146, 1056, 1032, 984, 924, 868, 842, 807, 762, 743, 736, 650, 633, 621, 608 cm$^{-1}$; HRMS (MM: ESI-APCI): $m/z$ calc’d for C$_{22}$H$_{31}$N$_2$O$_5$ [M+H]+: 403.2227, found 403.2225; $[\alpha]_D^{22.45}$ $-40.51$ (c 1.0, CHCl$_3$); SFC Conditions: 20% MeOH, 2.5 mL/min, Chiralpak IC column, $\lambda = 210$ nm, $t_R$ (min): minor = 5.11, major = 5.66.

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Totals: 1637.72953 150.27887

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**Diagram:**

![Diagram of tert-butyl (R)-6-allyl-4-(4-methoxybenzoyl)-6-methyl-5-oxo-1,4-diazepane-1-carboxylate (4d)](image)
tert-butyl (S)-6-allyl-6-benzyl-4-(4-methoxybenzoyl)-5-oxo-1,4-diazepane-1-carboxylate (4e)

Prepared according to the general procedure with allyl ester 3e (52.3 mg, 0.100 mmol, 1.0 equiv), Pd$_2$(dba)$_3$ (3.7 mg, 0.004 mmol, 4 mol %), and (S)-(CF$_3$)$_3$-t-BuPHOX (5.9 mg, 0.01 mmol, 10 mol %). Purified by silica gel flash chromatography (20% EtOAc/hexanes) to provide benzyl diazepanone 4e as a colorless oil (48.1 mg, 0.100 mmol, >99% yield, 89% ee); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.51 – 7.44 (m, 2H), 7.32 – 7.20 (m, 3H), 7.18 – 7.09 (m, 2H), 6.87 – 6.81 (m, 2H), 5.93 (br s, 1H), 5.26 – 5.12 (m, 2H), 4.09 – 3.88 (m, 2H), 3.84 (s, 3H), 3.78 – 2.41 (m, 8H), 1.48 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 179.0, 174.6, 162.6, 156.0, 155.4, 136.7, 133.1, 130.8, 130.5, 128.5, 128.2, 127.0, 119.9, 119.6, 113.7, 80.9, 80.7, 55.5, 54.2, 53.8, 49.1, 47.5, 47.3, 42.4, 42.0, 41.2, 40.9, 40.0, 28.5; IR (Neat Film, NaCl) 3374, 2974, 2927, 1694, 1604, 1581, 1510, 1454, 1416, 1392, 1365, 1320, 1282, 1256, 1211, 1166, 1028, 979, 925, 838, 762, 742, 705, 678, 636, 610 cm$^{-1}$; HRMS (MM: ESI-APCI): $m/z$ calc’d for C$_{28}$H$_{35}$N$_2$O$_5$ [M+H]$^+$: 479.2540, found 479.2533; $[\alpha]_D^{22.81}$ +19.02 (c 1.0, CHCl$_3$); SFC Conditions: 20% IPA, 2.5 mL/min, Chiralpak AD-H column, $\lambda$ = 210 nm, t$_R$ (min): minor = 3.94, major = 6.20.
tert-butyl (S)-6-allyl-6-(2-chloroallyl)-4-(4-methoxybenzoyl)-5-oxo-1,4-diazepane-1-carboxylate (4f)

Prepared according to the general procedure with allyl ester 3f (48.1 mg, 0.0949 mmol, 1.0 equiv), Pd₂dba₃ (3.7 mg, 0.004 mmol, 4 mol %), and (S)-(CF₃)₃-ᵗ-BuPHOX (5.9 mg, 0.01 mmol, 10 mol %). Purified by silica gel flash chromatography (20% EtOAc/hexanes) to provide alkenyl chloride 4f as a colorless oil (36.7 mg, 0.0793 mmol, 84% yield, 90% ee); ¹H NMR (400 MHz, CDCl₃) δ 7.55 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.93 – 5.71 (m, 1H), 5.36 – 5.07 (m, 4H), 4.36 – 3.84 (m, 4H), 3.83 (s, 3H), 3.82 – 3.51 (m, 2H), 3.00 – 2.33 (m, 4H), 1.50 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 178.2, 174.6, 162.7, 155.8, 155.2, 137.5, 132.9, 130.5, 128.3, 120.1, 118.2, 113.7, 81.1, 80.9, 55.5, 52.6, 49.2, 47.7, 47.4, 47.0, 44.5, 43.8, 42.8, 42.0, 41.8, 40.3, 28.5; IR (Neat Film, NaCl) 2976, 2930, 1694, 1631, 1604, 1580, 1510, 1456, 1421, 1393, 1366, 1320, 1282, 1256, 1212, 1167, 1150, 1030, 980, 928, 840, 765, 682, 636, 610 cm⁻¹; HRMS (MM: ESI-APCI): m/z calc’d for C₂₄H₃₂ClN₂O₅ [M+H]⁺: 463.1994, found 463.2005;
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[α]D22.68 –24.10 (c 0.5, CHCl₃); SFC Conditions: 20% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 2.52, major = 2.77.

tert-butyl (S)-6-allyl-4-benzoyl-6-fluoro-5-oxo-1,4-diazepane-1-carboxylate (4g)

Prepared according to the general procedure with allyl ester 3g (43.2 mg, 0.103 mmol, 1.0 equiv), Pd₂(pmdba)₃ (4.4 mg, 0.004 mmol, 4 mol %), and (S)-(CF₃)₃-t-BuPHOX (5.9 mg, 0.01 mmol, 10 mol %). Purified by silica gel flash chromatography (20% EtOAc/hexanes) to provide alkyl fluoride 4g as a white, amorphous solid (32.6 mg, 0.0866 mmol, 84% yield, 90% ee); ¹H NMR (400 MHz, CDCl₃) δ 7.61 – 7.53 (m, 2H), 7.53 – 7.45 (m, 1H), 7.45 – 7.34 (m, 2H), 5.94 – 5.72 (m, 1H), 5.34 – 5.17 (m, 2H), 4.58 – 4.38 (m, 1H), 4.26 – 4.02 (m, 2H), 3.99 – 3.74 (m, 1H), 3.39 – 3.10 (m, 2H), 2.96 – 2.74 (m, 1H), 2.73 – 2.43 (m, 1H), 1.47 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 173.9, 173.9 (d, J_C-F = 26.3 Hz), 155.1, 135.2, 132.1, 130.3, 128.4, 128.2, 121.0, 97.7 (dd, J_C-F = 193.9, 47.2 Hz), 81.1, 49.8 (dd, J_C-F = 35.3, 23.1 Hz), 47.2, 46.6, 42.6, 39.7 (dd, J_C-F = 27.6, 21.9 Hz), 28.3; IR (Neat Film, NaCl) 2978, 2926, 1694, 1450, 1414, 1393, 1367,
1329, 1246, 1152, 1042, 999, 979, 926, 857, 766, 724, 694, 672, 648 cm⁻¹; HRMS (MM: ESI-APCI): m/z calc’d for C₂₀H₂₉FN₃O₄ [M+NH₄]⁺: 438.2035, found 438.2040; [α]D²².₈⁵ +28.89 (c 1.0, CHCl₃); SFC Conditions: 10% IPA, 2.5 mL/min, Chiralcel OD-H column, λ = 210 nm, tᵣ (min): minor = 6.26, major = 4.99.

**tert-butyl (S)-6-allyl-6-fluoro-4-(4-methoxybenzoyl)-5-oxo-1,4-diazepane-1-carboxylate (4h)**

Prepared according to the general procedure with allyl ester 3h (60 mg, 0.133 mmol, 1.0 equiv), Pd₂(dbca)₃ (4.9 mg, 0.0053 mmol, 4 mol %), and (S)-(CF₃)₃-t-BuPHOX (7.9 mg, 0.013 mmol, 10 mol %). Purified by automated silica gel flash chromatography (0→50% acetone/hexanes) to provide alkyl fluoride 4h as a colorless oil (45 mg, 0.111 mmol, 84% yield, 83% ee); ¹H NMR (400 MHz, CDCl₃) δ 7.61 – 7.53 (m, 2H), 6.92 – 6.84 (m, 2H), 5.93 – 5.78 (m, 1H), 5.30 – 5.21 (m, 2H), 4.35 (t, J = 16.0 Hz, 1H), 4.22 – 4.02 (m, 2H), 3.96 – 3.85 (m, 1H), 3.84 (s, 3H), 3.40 – 3.19 (m, 2H), 2.94 – 2.78 (m, 1H), 2.71 – 2.48 (m, 1H), 1.47 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 173.9, 173.7, 163.1, 155.3, 131.0, 130.6, 127.1, 121.0, 113.8, 97.8 (dd, J_C,F = 193.7,
52.5 Hz), 81.2, 55.5, 49.8 (dd, \(J_{C,F} = 33.5, 23.3\) Hz), 47.5, 46.9, 43.2, 39.8 (dd, \(J_{C,F} = 32.1, 21.8\) Hz), 28.3; IR (Neat Film, NaCl) 2977, 2932, 1696, 1603, 1578, 1511, 1448, 1413, 1366, 1327, 1256, 1169, 1152, 1029, 977, 923, 835, 766 cm\(^{-1}\); HRMS (MM: ESI-APCI): \(m/z\) calc’d for \(C_{21}H_{28}FN_2O_5\) [M+H]: 407.1977, found 407.1973; \([\alpha]_D^{22.5}\) +46.99 (c 1.7, CHCl\(_3\)); SFC conditions: 20% IPA, 2.5 mL/min, Chiralcel OD-H column, \(\lambda = 210\) nm, \(t_R\) (min): major = 2.69, minor = 3.25.

![ chromatogram image ]

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**tert-butyl (S)-6-allyl-4-(4-methoxybenzoyl)-5-oxo-6-(prop-2-yn-1-yl)-1,4-diazepane-1-carboxylate (4i)**

Prepared according to the general procedure with allyl ester 3i (70.0 mg, 0.149 mmol, 1.0 equiv), \(\text{Pd}_2(\text{pmdba})_3\) (5.4 mg, 4.9 \(\mu\)mol, 4 mol %), and (S)-(CF\(_3\))\(_3\)-\(t\)-BuPHOX (8.8 mg, 0.015 mmol, 10 mol %) at 50 °C. Purification by automated silica gel flash chromatography (Teledyne ISCO, 0–40% acetone/hexanes) provided alkyne 4i as a colorless oil (28.0 mg, 0.0656 mmol, 44%
yield, 94% ee; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.59 (d, $J$ = 8.2 Hz, 2H), 6.89 – 6.82 (m, 2H), 5.93 – 5.63 (m, 1H), 5.30 – 5.10 (m, 2H), 4.36 – 4.15 (m, 1H), 4.09 – 3.68 (m, 4H), 3.83 (s, 3H), 3.62 – 3.37 (m, 1H), 2.83 – 2.43 (m, 4H), 2.20 – 1.99 (m, 1H), 1.51 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 177.5, 174.6, 162.9, 155.6, 155.2, 132.1, 130.7, 127.9, 120.0, 113.7, 81.1, 80.9, 80.5, 72.1, 55.6, 52.7, 49.1, 46.9, 47.7, 43.0, 42.3, 39.1, 37.5, 28.5, 26.5, 25.9; IR (Neat Film, NaCl) 3283, 2972, 2922, 1692, 1603, 1511, 1454, 1418, 1365, 1322, 1255, 1169, 1031, 980, 926, 839, 766, 670 cm$^{-1}$; HRMS (MM: ESI-APCI): $m/z$ calc’d for C$_{24}$H$_{31}$N$_2$O$_5$ [M+H]$^+$: 427.2227, found 427.2238; $[\alpha]_D^{22.1}$ $-$ 7.69 (c 1.0, CHCl$_3$); SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak AD-H column, $\lambda$ = 210 nm, $t_R$ (min): major = 10.85, minor = 10.29.

*tert*-butyl (R)-6-allyl-6-(3-methoxy-3-oxopropyl)-4-(4-methoxybenzoyl)-5-oxo-1,4-diazepane-1-carboxylate (4j)
Prepared according to the general procedure with allyl ester 3j (51.9 mg, 0.100 mmol, 1.0 equiv), Pd$_2$(dba)$_3$ (3.7 mg, 0.004 mmol, 4 mol %), and (S)-(CF$_3$)$_3$-t-BuPHOX (5.9 mg, 0.01 mmol, 10 mol %). Purified by silica gel flash chromatography (33% EtOAc/hexanes) to provide methyl ester 4j as a white, amorphous solid (45.8 mg, 0.0965 mmol, 96% yield, 95% ee); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.57 – 7.48 (m, 2H), 6.92 – 6.83 (m, 2H), 5.80 – 5.64 (m, 1H), 5.22 – 5.09 (m, 2H), 4.21 (ddd, $J = 15.7$, 6.6, 2.1 Hz, 1H), 4.13 – 3.85 (m, 3H), 3.83 (s, 3H), 3.62 (s, 3H), 3.51 (d, $J = 15.2$ Hz, 1H), 3.42 – 3.29 (m, 1H), 2.64 – 2.20 (m, 4H), 2.20 – 1.86 (m, 2H), 1.49 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 179.2, 174.7, 173.6, 173.4, 162.7, 155.4, 155.0, 155.0, 132.7, 132.5, 130.3, 128.3, 120.0, 113.8, 81.1, 80.9, 55.5, 51.8, 50.1, 48.9, 47.6, 46.8, 43.2, 42.9, 40.3, 39.7, 29.3, 28.8, 28.5; IR (Neat Film, NaCl) 2975, 2360, 1736, 1694, 1605, 1580, 1510, 1426, 1393, 1366, 1321, 1283, 1254, 1244, 1035, 980, 927, 842, 811, 762, 647, 610 cm$^{-1}$; HRMS (MM: ESI-APCI): $m/z$ calc’d for C$_{25}$H$_{35}$N$_2$O$_7$ [M+H]$^+$: 475.2439, found 475.2438; $[a]_D^{22.52} +7.73$ (c 1.0, CHCl$_3$); SFC conditions: 15% IPA, 2.5 mL/min, Chiralcel OD-H column, $\lambda = 210$ nm, $t_R$ (min): major = 5.27, minor = 4.84.
tert-butyl \((R)\)-6-allyl-6-(2-cyanoethyl)-4-(4-methoxybenzoyl)-5-oxo-1,4-diazepane-1-carboxylate (4k)

Prepared according to the general procedure with allyl ester 3k (62.2 mg, 0.128 mmol, 1.0 equiv), Pd\(_2\)(dba)\(_3\) (4.7 mg, 0.00512 mmol, 4 mol %), and (S)-(CF\(_3\))\(_3\)-t-BuPHOX (7.6 mg, 0.0128 mmol, 10 mol %), using 9:1 methylcyclohexane-toluene as the reaction solvent. Purified by silica gel flash chromatography (33% EtOAc/hexanes) to provide nitrile 4k as a white, amorphous solid (48.6 mg, 0.110 mmol, 86% yield, 84% ee); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.59 – 7.47 (m, 2H), 6.96 – 6.85 (m, 2H), 5.82 – 5.64 (m, 1H), 5.30 – 5.11 (m, 2H), 4.09 – 3.93 (m, 2H), 3.93 – 3.72 (m, 2H), 3.85 (s, 3H), 3.70 – 3.38 (m, 2H), 2.60 – 2.25 (m, 4H), 2.22 – 1.93 (m, 2H), 1.50 (s, 9H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 178.0, 174.5, 163.0, 155.6, 154.9, 131.7, 130.3, 127.9, 120.7, 119.7, 113.9, 81.4, 55.6, 52.2, 49.6, 48.0, 47.4, 46.8, 43.0, 42.6, 39.9, 39.0, 32.1, 31.5, 28.4, 12.4; IR (Neat Film, NaCl) 2975, 2931, 2361, 2246, 1690, 1604, 1579, 1510, 1456, 1419, 1366, 1321, 1256, 1168, 1148, 1031, 980, 926, 840, 811, 766, 607 cm\(^{-1}\); HRMS (MM: ESI-APCI): \(m/z\) calc’d for C\(_{24}\)H\(_{35}\)N\(_4\)O\(_5\) [M+NH\(_4\)]\(^+\): 459.2602, found 459.2602; \([\alpha]_D^{22.4}\) +9.31 (c 0.5, CHCl\(_3\)); SFC conditions: 20% IPA, 2.5 mL/min, Chiralcel OD-H column, \(\lambda\) = 310 nm, \(t_R\) (min): major = 8.33, minor = 6.18.
**Supporting Information for Sercel,‡ Sun,‡ and Stoltz**

**tert-butyl (S)-6-allyl-4-benzoyl-6-(((tert-butoxycarbonyl)amino)methyl)-5-oxo-1,4-diazepane-1-carboxylate (4l)**

Prepared according to the general procedure with allyl ester 3l (53 mg, 0.0997 mmol, 1.0 equiv) and Pd$_2$(dba)$_3$. Purification by automated silica gel flash chromatography (0→50% EtOAc/hexanes) provided carbamate 4l as a white foam (37 mg, 0.0759 mmol, 76% yield, 93% ee). ¹H NMR (400 MHz, CDCl$_3$) δ 7.55 – 7.44 (m, 3H), 7.44 – 7.35 (m, 2H), 5.74 (ddt, $J = 15.7, 10.5, 7.4$ Hz, 1H), 5.35 (br s, 0.5H), 5.21 – 5.06 (m, 2H), 4.79 (br s, 0.5H), 4.48 – 4.28 (m, 1H), 4.14 – 3.09 (m, 7H), 2.69 – 2.18 (m, 2H), 1.50 (s, 9H), 1.44 (s, 9H); ¹³C NMR (100 MHz, CDCl$_3$) δ 179.3, 178.8, 174.5, 156.3, 155.9, 155.1, 136.3, 132.1, 131.7, 128.5, 127.7, 120.1, 81.3, 81.1, 79.5, 54.8, 48.9, 47.3, 46.8, 46.3, 42.6, 41.1, 38.7, 37.1, 28.5, 28.5; IR (Neat Film, NaCl) 2977, 1687, 1502, 1422, 1391, 1365, 1282, 1245, 1168, 978, 916, 753 cm$^{-1}$; HRMS (MM: ESI-APCI): $m/z$ calc’d for C$_{26}$H$_{37}$N$_3$O$_6$ [M+H]$^+$: 488.2755, found 488.2747; $[\alpha]_D^{23.2}$ −3.70 (c 1.85, CHCl$_3$); SFC conditions: 20% IPA, 2.5 mL/min, Chiralpak IC column, $\lambda = 254$ nm, $t_R$ (min): major = 5.85, minor = 4.65.
Procedure for the large scale preparation of diazepanone 4e

To a 500 mL Schlenk flask was added Pd$_2$(dba)$_3$ (37 mg, 0.04 mmol, 4 mol %), (S)-(CF$_3$)$_3$t-BuPHOX (59 mg, 0.1 mmol, 10 mol %), and MeCy (20 mL). After stirring for 20 minutes at 25 °C, allyl ester 3e (523 mg, 1.0 mmol, 1.0 equiv) and methylcyclohexane (52 mL, total substrate concentration 0.014 M) were added to the pre-stirred catalyst solution. After stirring for 23 h at 40 °C, the reaction mixture was directly loaded onto a flash column and purified by silica gel flash chromatography (20% EtOAc/hexanes) to provide benzyl diazepanone 4e as a colorless oil (393 mg, 0.82 mmol, 82% yield, 83% ee); All characterization data matched those reported above for compound 4e; $[\alpha]_D^{21.96} +14.757$ ($c$ 1.0, CHCl$_3$); SFC Conditions: 20% IPA, 2.5 mL/min, Chiralpak AD-H column, $\lambda = 210$ nm, $t_R$ (min): minor = 3.76, major = 5.90.
Supporting Information for Sercel,‡ Sun,‡ and Stoltz

Synthesis of Allylic Alkylation Substrates

tert-butyl 4-oxo-1,4-diazepane-1-carboxylate (SI1)

To a solution of tert-butyl 5-oxo-1,4-diazepane-1-carboxylate (5.00 g, 23.3 mmol, 1.0 equiv) in THF (230 mL, 0.1 M) at −78 °C was slowly added n-BuLi (2.18 M in hexanes, 12.8 mL, 27.9 mmol, 1.2 equiv). The opaque mixture was allowed to warm to ambient temperature until the solution became homogeneous, at which point it was again cooled to −78 °C. Then, benzoyl chloride (3.52 mL, 30.3 mmol, 1.3 equiv) was added dropwise and the reaction turned light orange over several minutes. The reaction was stirred for 1 h at −78 °C, then poured into saturated aqueous NH₄Cl (200 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated. The crude product was purified by silica gel flash chromatography (20% acetone/hexanes) to afford benzoyl-protected lactam SI1 as a white solid (7.43 g, 23.3 mmol, >99% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.57 − 7.49 (m, 2H), 7.49 − 7.41 (m, 1H), 7.41 − 7.32 (m, 2H), 4.03 − 3.96 (m, 2H), 3.71 (m, 4H), 2.82 − 2.75 (m, 2H), 1.47 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 175.6, 173.7, 154.5, 135.9, 131.7, 128.2, 127.9, 80.7, 47.8, 47.10, 45.4, 41.6, 41.0, 40.6, 28.3; IR (Neat Film, NaCl) 2976, 2932, 2251, 1682, 1599, 1582, 1450, 1422, 1392, 1366, 1327, 1285, 1247, 1229, 1157, 1115, 1032, 1018, 976, 954, 915, 862, 793, 769, 729, 696, 647 cm⁻¹; HRMS (MM: ESI-APCI): m/z calc’d for C₁₇H₂₆N₅O₄ [M+NH₄]⁺: 336.1918, found 336.1912.

tert-butyl 5-oxo-4-(4-(trifluoromethyl)benzoyl)-1,4-diazepane-1-carboxylate (SI2)
To a solution of tert-butyl 5-oxo-1,4-diazepane-1-carboxylate (500 mg, 2.33 mmol, 1 equiv) in THF (25 mL, 0.1 M) at −78 °C was slowly added n-BuLi (2.5 M in hexanes, 1.02 mL, 2.56 mmol, 1.1 equiv), and the reaction mixture was stirred at −78 °C for 15 min. Then, 4-trifluoromethylbenzoyl chloride (450 µL, 3.03 mmol, 1.3 equiv) was added dropwise, and the reaction was stirred for 30 min at −78 °C. The reaction mixture was then poured into saturated aqueous NH₄Cl (20 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (25% EtOAc/hexanes) to afford the title compound as a white solid (698 mg, 1.81 mmol, 77% yield);

1H NMR (400 MHz, CDCl₃) δ 7.66 (d, J = 8.2 Hz, 2H), 7.60 (d, J = 8.1 Hz, 2H), 4.14 – 4.02 (m, 2H), 3.84 – 3.66 (m, 4H), 2.91 – 2.77 (m, 2H), 1.50 (s, 9H); 13C NMR (100 MHz, CDCl₃) δ 175.7, 172.5, 154.6, 139.6, 133.0 (q, J_C-F = 32.8 Hz), 130.6, 128.0, 125.5 (q, J_C-F = 3.8 Hz), 123.7 (q, J_C-F = 272.6 Hz), 81.2, 47.7 (br), 45.3, 41.4 (br), 40.8, 28.5; IR (Neat Film, NaCl) 2981, 1689, 1455, 1367, 1230, 1159, 1127, 1066, 1028, 1015, 977, 955, 852, 832, 769 cm⁻¹; HRMS (MM: ESI-APCI): m/z calc’d for C₁₈H₂₅F₃N₃O₄ [M+NH₄]⁺: 404.1742, found 404.1797.

**tert-butyl 4-(4-methoxybenzoyl)-5-oxo-1,4-diazepane-1-carboxylate (SI3)**

To a solution of tert-butyl 5-oxo-1,4-diazepane-1-carboxylate (800 mg, 3.73 mmol, 1 equiv) in THF (37 mL, 0.1 M) at −78 °C was slowly added n-BuLi (2.5 M in hexanes, 1.64 mL, 4.1 mmol, 1.1 equiv). The opaque mixture was allowed to warm to ambient temperature until the solution became homogeneous, at which point it was again cooled to −78 °C. Then, 4-methoxybenzoyl chloride (657 µL, 4.85 mmol, 1.3 equiv) was added dropwise and the reaction was stirred for 30 min at −78 °C. The reaction mixture was then poured into saturated aqueous NH₄Cl (30 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→100% EtOAc/hexanes) to afford the title compound as a white solid (1.2 g, 3.44 mmol, 92%...
yield; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.62 – 7.54 (m, 2H), 6.93 – 6.84 (m, 2H), 4.00 – 3.93 (m, 2H), 3.83 (s, 3H), 3.78 – 3.69 (m, 4H), 2.85 – 2.78 (m, 2H), 1.48 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 175.7, 173.4, 162.9, 154.6, 130.9, 130.6, 127.7, 113.7, 80.8, 55.5, 48.0, 47.4, 46.1, 41.9, 41.3, 40.8, 28.5; IR (Neat Film, NaCl) 2974, 2936, 1774, 1687, 1604, 1578, 1510, 1458, 1420, 1391, 1366, 1327, 1284, 1249, 1166, 1114, 1023, 977, 956, 916, 860, 842, 809, 767, 632 cm$^{-1}$; HRMS (MM: ESI-APCI): $m/z$ calc’d for C$_{18}$H$_{25}$N$_2$O$_5$ [M+H]$^+$: 349.1758, found 349.1760.

6-allyl 1-(tert-butyl) 4-benzoyl-5-oxo-1,4-diazepane-1,6-dicarboxylate (2a)

To a solution of diisopropylamine (266 µL, 1.88 mmol, 1.2 equiv) in THF (10 mL) at –78 °C in a flame-dried round-bottom flask was added n-BuLi (2.5 M in hexanes, 792 µL, 1.73 mmol, 1.1 equiv), the resulting solution was stirred at –78 °C for 45 min. To this solution was then added lactam SI1 (500 mg, 1.57 mmol, 1.0 equiv) in THF (6 mL, 0.1 M total concentration) dropwise while stirring at –78 °C. The reaction mixture was stirred for 75 min at –78 °C. Allyl cyanoformate (201 µL, 1.88 mmol, 1.2 equiv) was then added dropwise at –78 °C. After stirring for 3 h at –78 °C, the reaction mixture was poured into saturated aqueous NH$_4$Cl (10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were concentrated under reduced pressure onto silica (4 g). The silica-adsorbed crude mixture was purified by silica gel flash chromatography (20→30% EtOAc/hexanes) to provide allyl ester 2a as an off-white solid (550 mg, 1.37 mmol, 87% yield); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.65 – 7.57 (m, 2H), 7.53 – 7.45 (m, 1H), 7.42 – 7.34 (m, 2H), 5.92 (ddt, $J$ = 17.2, 10.4, 5.9 Hz, 1H), 5.40 – 5.22 (m, 2H), 4.79 – 4.59 (m, 2H), 4.33 – 4.03 (m, 2H), 4.02 – 3.88 (m, 3H), 3.87 – 3.66 (m, 1H), 3.55 – 3.40 (m, 1H), 1.48 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 173.7, 171.4, 167.5, 154.7, 135.3, 132.2, 131.4, 128.4, 119.5, 81.3, 66.6, 56.0, 46.7 (br), 44.5, 43.3 (br), 28.4; IR (Neat Film, NaCl) 3374, 3062, 2977, 2934, 1746, 1694, 1600, 1582, 1450, 1419, 1393, 1367, 1327, 1246, 1156, 1037, 1020, 995, 968, 939, 857, 792, 769, 727, 695, 616 cm$^{-1}$; HRMS (MM: ESI-APCI): $m/z$ calc’d for C$_{21}$H$_{30}$N$_3$O$_6$ [M+NH$_4$]$^+$: 420.2129, found 420.2109.
6-allyl 1-(tert-butyl) 5-oxo-4-(4-(trifluoromethyl)benzoyl)-1,4-diazepane-1,6-dicarboxylate (2b)

To a solution of lactam S12 (500 mg, 1.29 mmol, 1.0 equiv) in THF (8 mL, 0.1 M total concentration) at −78 °C was added LiHMDS (303 mg, 1.81 mmol, 1.4 equiv) in THF (5 mL) dropwise. The resulting yellow reaction mixture was stirred for 15 min at −78 °C. Then, allyl cyanoformate (166 µL, 1.55 mmol, 1.2 equiv) was added dropwise at −78 °C, after which the solution slowly became colorless. After stirring for 1 h at −78 °C, the reaction was poured into 2 M HCl (20 mL) and extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and NaHCO₃, passed through filter paper, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (20→33% EtOAc/hexanes) to provide allyl ester 2b as a white solid (266 mg, 0.565 mmol, 44% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.69 (d, J = 8.3 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 5.92 (ddt, J = 17.2, 10.4, 5.9 Hz, 1H), 5.42 – 5.23 (m, 2H), 4.79 – 4.59 (m, 2H), 4.46 – 3.63 (m, 6H), 3.52 (m, 1H), 1.47 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 172.4, 171.4, 167.4, 154.6, 138.9, 133.3 (q, J_C-F = 32.6 Hz), 131.2, 128.3, 125.4 (q, J_C-F = 3.8 Hz), 123.7 (q, J_C-F = 272.5 Hz), 119.8, 81.5, 66.8, 56.0, 47.4, 46.3, 44.2, 43.0, 28.4; IR (Neat Film, NaCl) 3377, 3083, 2980, 2935, 2463, 2358, 1928, 1798, 1747, 1694, 1652, 1619, 1584, 1513, 1455, 1414, 1394, 1368, 1327, 1246, 1156, 1131, 1067, 1034, 1016, 994, 970, 940, 879, 853, 824, 770, 723, 679, 639, 630, 612 cm⁻¹; HRMS (MM: ESI-APCI): m/z calc’d for C₂₂H₂₉F₃N₃O₆ [M+NH₄]⁺: 488.2003, found 488.2022.

6-allyl 1-(tert-butyl) 4-(4-methoxybenzoyl)-5-oxo-1,4-diazepane-1,6-dicarboxylate (2c)

To a solution of lactam S13 (1.00 g, 2.87 mmol, 1.0 equiv) in THF (20 mL, 0.1 M total concentration) at −78 °C was added LiHMDS (528 mg, 3.16 mmol, 1.1 equiv) in THF (9 mL)
dropwise. The resulting pale yellow reaction mixture was stirred for 15 min at −78 °C. Allyl cyanooformate (368 µL, 3.44 mmol, 1.2 equiv) was then added dropwise at −78 °C, resulting in a clear solution. After stirring for 1.5 h at −78 °C, the reaction was poured into 1 M HCl (10 mL) and diluted with ethyl acetate (20 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and NaHCO₃, filtered, and concentrated under reduced pressure onto silica. The silica-adsorbed crude mixture was purified by silica gel flash chromatography (10→20% EtOAc/hexanes) to provide allyl ester 2c as a colorless oil (600 mg, 1.39 mmol, 48% yield; ¹H NMR (400 MHz, CDCl₃) δ 7.72 – 7.60 (m, 2H), 6.91 – 6.79 (m, 2H), 5.92 (ddt, J = 17.3, 10.4, 5.9 Hz, 1H), 5.42 – 5.20 (m, 2H), 4.77 – 4.56 (m, 2H), 4.40 – 3.92 (m, 4H), 3.92 – 3.62 (m, 2H), 3.82 (s, 3H), 3.58 – 3.24 (m, 1H), 1.46 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 173.1, 171.3, 167.6, 163.2, 154.6, 131.4, 131.2, 127.0, 119.4, 113.7, 81.1, 66.5, 55.9, 55.4, 47.7 and 46.7, 45.1, 43.3, 42.8, 28.3; IR (Neat Film, NaCl) 2977, 1746, 1693, 1603, 1578, 1511, 1454, 1419, 1392, 1366, 1234, 1255, 1168, 1025, 995, 965, 842, 766 cm⁻¹; HRMS (MM: ESI-APCI): m/z calc’d for C₂₂H₂₈N₂O₇ [M+H]+: 433.1969, found 433.1966.

6-allyl 1-(tert-butyl) 4-benzoyl-6-benzyl-5-oxo-1,4-diazepane-1,6-dicarboxylate (3a)

To a flame-dried round bottom flask containing a solution of allyl ester 2a (1.00 g, 2.49 mmol, 1.0 equiv) in THF (25 mL, 0.1 M) at 0 °C was added NaH (60% dispersion in mineral oil, 107 mg, 2.74 mmol, 1.1 equiv) and the mixture was stirred at 0 °C for 30 min. BnBr (1.50 mL, 12.45 mmol, 5.0 equiv) was then added dropwise and the reaction mixture was warmed to 45 °C. After 16 h, the temperature was further increased to 53 °C due to sluggish reactivity. After another 45 min of stirring at 53 °C, the reaction mixture was cooled to 23 °C and poured into saturated aqueous NH₄Cl (25 mL), the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (20% EtOAc/hexanes) to provide the title compound as a colorless foam (922 mg, 1.87 mmol, 75% yield; ¹H NMR (400 MHz, CDCl₃) δ 7.68 (d, J = 7.6 Hz, 2H), 7.55 –
7.46 (m, 1H), 7.37 (t, J = 7.7 Hz, 2H), 7.31 – 7.25 (m, 3H), 7.24 – 7.12 (m, 2H), 5.86 (tq, J = 22.8, 6.5 Hz, 1H), 5.42 – 5.26 (m, 2H), 4.71 – 4.55 (m, 2H), 4.22 (dd, J = 75.3, 15.5 Hz, 1H), 4.05 – 3.57 (m, 4H), 3.57 – 3.36 (m, 2H), 3.22 (dd, J = 68.5, 13.7 Hz, 1H), 1.45 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) (174.4, 174.0, 172.2, 172.0, 170.8, 170.2, 155.5, 155.0, 135.7, 135.6, 135.5, 132.0, 130.9, 130.8, 128.5, 128.3, 127.5, 127.4, 120.6, 120.2, 81.2, 81.0, 67.0, 66.9, 62.6, 62.2, 47.3, 46.7, 46.2, 45.8, 42.4, 42.1, 42.0, 28.5; IR (Neat Film, NaCl) 3063, 3030, 2977, 2933, 1694, 1601, 1583, 1495, 1450, 1416, 1393, 1366, 1325, 1280, 1247, 1154, 1132, 1092, 1041, 1023, 980, 939, 868, 796, 768, 728, 703, 662 cm\(^{-1}\); HRMS (MM: ESI-APCI): m/z calc’d for C\(_{22}\)H\(_{22}\)N\(_2\)O\(_6\) [M+H]+: 437.1707, found 437.1697.

6-allyl 1-(tert-buty1) 4-benzoyl-6-methyl-5-oxo-1,4-diazepane-1,6-dicarboxylate (3b)

To a solution of allyl ester 2a (240 mg, 0.596 mmol, 1.0 equiv) in THF (6 mL, 0.1 M) at 0 °C was added 60 % NaH (26 mg, 0.657 mmol, 1.1 equiv). The solution was stirred at 0 °C for 40 min, after which MeI (186 µL, 2.98 mmol, 5.0 equiv) was added rapidly. The reaction was heated to 45 °C and stirred for 16 h, cooled to 23 °C, poured into saturated aqueous NH\(_4\)Cl (5 mL), and extracted with EtOAc (3 x 3 mL). The combined organic extracts were dried over Na\(_2\)SO\(_4\) and concentrated onto silica gel. The silica-adsorbed crude product was purified by silica gel flash chromatography (20% EtOAc/hexanes) to afford the title compound as a light yellow oil (200 mg, 0.480 mmol, 81% yield). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.78 – 7.63 (m, 2H), 7.58 – 7.43 (m, 1H), 7.38 (t, J = 7.6 Hz, 2H), 5.96 (ddt, J = 16.6, 10.4, 6.0 Hz, 1H), 5.49 – 5.26 (m, 2H), 4.85 – 4.64 (m, 2H), 4.46 – 4.22 (m, 1H), 4.10 (br d, J = 14.8 Hz, 1H), 3.86 – 3.42 (m, 4H), 1.57 (s, 3H), 1.45 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 174.5 174.1, 173.0, 171.7, 155.1, 154.9, 135.7, 132.0, 131.2, 128.3, 128.2, 120.2, 81.1, 66.9, 57.7, 49.8, 49.0, 47.1, 46.0, 43.2, 28.4, 23.6; IR (Neat Film, NaCl) 3077, 1693, 1449, 1416, 1366, 1325, 1281, 1249, 1139, 1104, 1047, 983, 938, 768, 727, 694 cm\(^{-1}\); HRMS (MM: ESI-APCI): m/z calc’d for C\(_{24}\)H\(_{25}\)N\(_2\)O\(_6\) [M+H]+: 417.2020, found 417.2010.
6-allyl 1-(tert-butyl) 6-methyl-5-oxo-4-(4-(trifluoromethyl)benzoyl)-1,4-diazepane-1,6-dicarboxylate (3c)

To a suspension of allyl ester 2b (150 mg, 0.319 mmol, 1.0 equiv) and Cs$_2$CO$_3$ (208 mg, 0.638 mmol, 2.0 equiv) in acetonitrile (3.2 mL, 0.1 M) was added MeI (99 µL, 1.59 mmol, 5.0 equiv) at 23 °C. The reaction was heated to 45 °C and stirred for 5 h, then cooled to 23 °C, poured into saturated aqueous NH$_4$Cl (6 mL), and extracted with EtOAc (3 x 3 mL). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (15% EtOAc/petroleum ether) to provide the title compound as a colorless oil (146 mg, 0.301 mmol, 95% yield); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.75 (d, $J = 8.1$ Hz, 2H), 7.63 (d, $J = 8.1$ Hz, 2H), 5.97 (ddt, $J = 17.3, 10.3, 6.1$ Hz, 1H), 5.48 – 5.29 (m, 2H), 4.84 – 4.68 (m, 2H), 4.49 – 4.30 (m, 1H), 4.18 – 3.98 (m, 1H), 3.90 – 3.39 (m, 4H), 1.57 (s, 3H), 1.45 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 173.2, 172.7, 171.7, 154.9, 139.2, 133.1 (q, $J_{C,F} = 32.5$ Hz), 131.1, 128.2, 125.4, 123.8 (q, $J_{C,F} = 272.7$ Hz), 120.5, 81.3, 67.0, 57.7, 49.7, 49.0, 46.9, 45.8, 43.1, 42.9, 28.4, 23.7; IR (Neat Film, NaCl) 3384, 3083, 2979, 2937, 1698, 1619, 1584, 1514, 1478, 1453, 1416, 1394, 1367, 1326, 1285, 1250, 1207, 1166, 1136, 1110, 1066, 1022, 1012, 985, 938, 855, 832, 817, 790, 769, 740, 722, 680 cm$^{-1}$; HRMS (MM: ESI-APCI): m/z calc’d for C$_{23}$H$_{28}$F$_3$N$_2$O$_6$ [M+H]$^+$: 485.1894, found 485.1907.

6-allyl 1-(tert-butyl) 4-(4-methoxybenzoyl)-6-methyl-5-oxo-1,4-diazepane-1,6-dicarboxylate (3d)

To a suspension of allyl ester 2c (200 mg, 0.462 mmol, 1.0 equiv), Cs$_2$CO$_3$ (301 mg, 0.925 mmol, 2.0 equiv) in acetonitrile (4.6 mL, 0.1 M) was added MeI (143 µL, 2.31 mmol, 5.0 equiv) at 23 °C. The reaction was heated to 45 °C and stirred for 40 min, then cooled to 23 °C, poured
into saturated aqueous NH₄Cl (10 mL), and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→90% EtOAc/hexanes) to provide the title compound as a colorless oil (70 mg, 0.157 mmol, 34% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.75 – 7.65 (m, 2H), 6.90 – 6.82 (m, 2H), 5.96 (ddt, J = 17.3, 10.4, 6.0 Hz, 1H), 5.44 – 5.29 (m, 2H), 4.77 – 4.66 (m, 2H), 4.27 – 4.15 (m, 1H), 4.14 – 4.04 (m, 1H), 3.83 (s, 3H), 3.80 – 3.70 (m, 1H), 3.67 – 3.58 (m, 2H), 3.56 – 3.46 (m, 1H), 1.57 (s, 3H), 1.44 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 174.0, 173.6, 172.9, 172.0, 171.8, 162.9, 155.2, 154.9, 131.2, 131.0, 127.6, 120.1, 120.0, 113.6, 81.0, 66.8, 57.5, 55.5, 49.6, 48.9, 47.2, 46.1, 43.7, 28.4, 23.7; IR (Neat Film, NaCl) 2974, 2937, 1698, 1604, 1578, 1511, 1453, 1416, 1392, 1366, 1324, 1280, 1256, 1169, 1139, 1103, 1031, 1001, 983, 929, 840, 768, 733 cm⁻¹; HRMS (MM: ESI-APCI): m/z calc’d for C₂₃H₃₁N₂O₇ [M+H]⁺: 447.2126, found 447.2128.

6-allyl 1-(tert-butyl) 6-benzyl-4-(4-methoxybenzoyl)-5-oxo-1,4-diazepane-1,6-dicarboxylate (3e)

To a flame-dried round bottom flask containing a solution of allyl ester 2c (300 mg, 0.694 mmol, 1.0 equiv) in THF (7 mL, 0.1 M) at 0 °C was added NaH (60% dispersion in mineral oil, 38 mg, 0.972 mmol, 1.4 equiv) and the mixture was stirred at 0 °C for 15 min and then allowed to warm to 23 °C over 15 min. BnBr (412 µL, 3.47 mmol, 5.0 equiv) was then added dropwise and the reaction mixture was heated to 50 °C. After stirring for 8 h, the reaction mixture was allowed to cool to 23 °C and poured into saturated aqueous NH₄Cl (5 mL), the layers were separated, and the aqueous phase was extracted with ethyl acetate (3 x 2 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (20% EtOAc/hexanes) to provide the title compound as a colorless foam (303 mg, 0.580 mmol, 84% yield); ¹H NMR (500 MHz, CDCl₃) δ 7.72 (d, J = 8.5 Hz, 2H), 7.31 – 7.12 (m, 5H), 6.90 – 6.80 (m, 2H), 5.95 – 5.75 (m, 1H), 5.41 – 5.26 (m, 2H), 4.69 – 4.54 (m, 2H), 4.21 – 4.05 (m, 1H), 4.02 – 3.86 (m, 2H), 3.83 (s, 3H),
3.78 – 3.62 (m, 2H), 3.56 – 3.49 (m, 1H), 3.43 – 3.10 (m, 2H), 1.45 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 173.7, 173.4, 172.0, 171.7, 170.8, 170.2, 162.9, 155.4, 154.8, 135.7, 135.6, 131.1, 130.9, 130.7, 130.5, 128.5, 128.3, 128.2, 127.5, 127.3, 127.0, 120.2, 119.9, 113.5, 80.9, 80.7, 66.6, 62.4, 62.0, 55.3, 47.1, 46.8, 46.0, 45.8, 42.8, 42.5, 41.9, 28.3; IR (Neat Film, NaCl) 2976, 2359, 1698, 1604, 1512, 1455, 1416, 1366, 1324, 1258, 1155, 1028, 979, 840, 741, 703, 671, 634 cm$^{-1}$; HRMS (MM: ESI-APCI): m/z calc’d for C$_{29}$H$_{38}$N$_2$O$_7$ [M+H]$^+$: 523.2439, found 523.2446.

6-allyl 1-(tert-butyl) 6-(2-chlorallyl)-4-(4-methoxybenzoyl)-5-oxo-1,4-diazepane-1,6-dicarboxylate (3f)

To a suspension of allyl ester 2c (300 mg, 0.694 mmol, 1.0 equiv) and Cs$_2$CO$_3$ (453 mg, 1.39 mmol, 2.0 equiv) in acetonitrile (7 mL, 0.1 M) was added 2,3-dichloropropene (320 µL, 3.47 mmol, 5.0 equiv) at 23 °C. The reaction mixture was heated to 50 °C and stirred for 19 h, after which starting material remained as judged by TLC. Tetraethylammonium iodide (25.6 mg, 0.0694 mmol, 0.1 equiv) was added and the reaction mixture was stirred at 50 °C for an additional 9 h, then allowed to cool to 23 °C. The mixture was filtered through a cotton plug and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (20% EtOAc/petroleum ether) to provide the title compound as a colorless oil (196 mg, 0.387 mmol, 56% yield); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.71 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.9 Hz, 2H), 6.12 – 5.94 (m, 1H), 5.60 – 5.25 (m, 4H), 4.78 (qdt, J = 12.8, 6.0, 1.2 Hz, 2H), 4.25 (br t, J = 13.9 Hz, 1H), 4.17 – 3.87 (m, 3H), 3.84 (s, 3H), 3.76 – 3.51 (m, 1H), 3.48 – 3.30 (m, 1H), 3.29 – 2.99 (m, 2H), 1.43 (d, J = 16.9 Hz, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 173.9, 173.3, 170.3, 163.1, 155.9, 155.1, 137.0, 136.7, 131.1, 127.2, 120.6, 120.3, 119.4, 118.4, 113.6, 81.4, 81.0, 67.5, 60.0, 55.5, 47.1, 45.9, 46.0, 45.2, 45.6, 44.7, 43.1, 42.8, 28.4; IR (Neat Film, NaCl) 3356, 3080, 2977, 2933, 2841, 2568, 2254, 1700, 1629, 1605, 1579, 1512, 1456, 1417, 1393, 1367, 1326, 1281, 1257, 1217, 1196, 1153, 1029, 988, 910, 842, 811, 780, 757, 732, 668, 634, 621 cm$^{-1}$; HRMS (MM: ESI-APCI): m/z calc’d for C$_{25}$H$_{32}$ClN$_2$O$_7$ [M+H]$^+$: 507.1893, found 507.1902.
6-allyl 1-( tert -butyl) 4-benzyol-6-fluoro-5-oxo-1,4-diazepane-1,6-dicarboxylate (3g)

To a 20 mL vial containing allyl ester 2a (250 mg, 0.621 mmol, 1.0 equiv) in THF (7.4 mL, 0.1 M) at 23 °C was added NaH (60% dispersion in mineral oil, 27.3 mg, 0.683 mmol, 1.1 equiv). After stirring for 12 min, Selectfluor™ (264 mg, 0.745 mmol, 1.2 equiv) was added in a single portion, and the reaction mixture was warmed to 50 °C and stirred for 24 h, after which starting material remained as judged by TLC. Additional Selectfluor™ (264 mg, 0.745 mmol, 1.2 equiv) was then added, and the reaction mixture was stirred for an additional 8 h at 50 °C. The reaction mixture was allowed to cool to 23 °C and water (5 mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over anhydrous Na2SO4, concentrated under reduced pressure, and purified by silica gel flash chromatography (25% EtOAc/hexanes) to provide the title compound (167 mg, 0.397 mmol, 64% yield); 1H NMR (500 MHz, CDCl3) δ 7.64 – 7.56 (m, 2H), 7.52 – 7.43 (m, 1H), 7.36 (t, J = 7.7 Hz, 2H), 5.99 – 5.80 (m, 1H), 5.43 – 5.19 (m, 2H), 4.83 – 4.56 (m, 2H), 4.52 – 4.17 (m, 3H), 4.03 – 3.56 (m, 2H), 3.27 – 3.08 (m, 1H), 1.47 (s, 9H); 13C NMR (125 MHz, CDCl3) δ 173.1, 169.6, 169.4, 164.8, 164.6, 154.9, 154.3, 132.5, 130.7, 128.5, 128.4, 119.7, 95.7 (d, J = 204.8 Hz), 81.5, 67.2, 47.6 (dd, JCP = 137.5, 24.1 Hz), 47.3, 46.4, 42.8, 28.3; IR (Neat Film, NaCl) 2978, 2926, 1694, 1450, 1414, 1393, 1367, 1329, 1246, 1152, 1042, 999, 979, 926, 857, 766, 724, 694, 672, 648 cm⁻¹; HRMS (MM: ESI-APCI): m/z calc’d for C21H25FN3O6 [M+NH4]⁺: 438.2035, found 438.2040.

6-allyl 1-( tert -butyl) 6-fluoro-4-(4-methoxybenzoyl)-5-oxo-1,4-diazepane-1,6-dicarboxylate (3h)

To a 20 mL vial containing allyl ester 2c (320 mg, 0.740 mmol, 1.0 equiv) and NaH (60% dispersion in mineral oil, 32.5 mg, 0.814 mmol, 1.1 equiv) was added THF (7.4 mL, 0.1 M) at 23 °C. After stirring for 30 min, Selectfluor™ (315 mg, 0.889 mmol, 1.2 equiv) was added in a
single portion, and the reaction mixture was warmed to 50 °C and stirred for 5 h. The crude reaction mixture was then concentrated under reduced pressure and purified by silica gel flash chromatography (30% acetone/hexanes) to provide the title compound (290 mg, 0.644 mmol, 87% yield); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.66 – 7.58 (m, 2H), 6.90 – 6.82 (m, 2H), 5.91 (ddt, $J$ = 16.3, 10.9, 5.7 Hz, 1H), 5.43 – 5.21 (m, 2H), 4.84 – 4.40 (m, 3H), 4.40 – 4.16 (m, 2H), 4.00 – 3.86 (m, 1H), 3.82 (s, 3H), 3.77 – 3.56 (m, 1H), 3.22 – 3.09 (m, 1H), 1.47 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.6, 169.6 (dd, $J_{C-F}$ = 48.2, 25.4 Hz), 164.9 (d, $J_{C-F}$ = 25.8 Hz), 163.4, 155.0, 131.3, 130.8, 126.1, 119.8, 113.9, 95.7 (dd, $J_{C-F}$ = 205.6, 14.6 Hz), 81.5, 67.3, 55.5, 47.5 (dd, $J_{C-F}$ = 109.0, 23.7 Hz), 47.2 (d, $J_{C-F}$ = 92.2 Hz), 43.4, 28.3; IR (Neat Film, NaCl) 2976, 2936, 2844, 1759, 1698, 1578, 1512, 1449, 1414, 1367, 1327, 1258, 1168, 1151, 1076, 1030, 997, 977, 942, 929, 841, 817, 770, 760, 730, 698 cm$^{-1}$; HRMS (MM: ESI-APCI): m/z calc’d for C$_{22}$H$_{28}$FN$_2$O$_7$ [M+H]$^+$: 451.1875, found 451.1877.

6-allyl 1-(tert-butyl) 4-(4-methoxybenzoyl)-5-oxo-6-(prop-2-yn-1-yl)-1,4-diazepane-1,6-dicarboxylate (3i)

To a solution of allyl ester 2c (250 mg, 0.578 mmol, 1.0 equiv) in THF (5.8 mL, 0.1 M) was added NaH (60% dispersion in mineral oil, 25 mg, 0.636 mmol, 1.1 equiv) at 0 °C. After stirring for 30 min at 0 °C, propargyl bromide (80% wt/wt in toluene, 125 µL, 1.16 mmol, 2.0 equiv) was added at 0 °C. The reaction mixture was heated to 50 °C and stirred for 16 h. The mixture was allowed to cool to 23 °C, quenched with aqueous NaHCO$_3$ (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→50% acetone/hexanes) to provide propargyl allyl ester 3i as a colorless oil (220 mg, 0.468 mmol, 81% yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.73 – 7.59 (m, 2H), 6.84 (d, $J$ = 8.6 Hz, 2H), 5.99 (ddt, $J$ = 17.3, 10.4, 6.0 Hz, 1H), 5.54 – 5.27 (m, 2H), 4.85 – 4.69 (m, 2H), 4.33 – 3.85 (m, 4H), 3.82 (s, 3H), 3.76 – 3.56 (m, 1H), 3.56 – 3.39 (m, 1H), 3.14 – 2.90 (m, 2H), 2.08 (s, 1H), 1.42 (d, $J$ = 14.3 Hz, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 173.7, 173.2, 170.5, 170.3, 169.7, 169.3, 163.0, 155.6, 154.9, 131.2, 131.0, 127.1, 120.3, 120.0,
6-allyl 1-(tert-butyl) 6-(3-methoxy-3-oxopropyl)-4-(4-methoxybenzoyl)-5-oxo-1,4-diazepane-1,6-dicarboxylate (3j)

To a 20 mL vial containing allyl ester 2c (300 mg, 0.694 mmol, 1.0 equiv) and K₂CO₃ (480 mg, 3.47 mmol, 5.0 equiv) was added acetone (2.8 mL, 0.25 M) and methyl acrylate (126 µL, 1.39 mmol, 2.0 equiv) at 23 °C. The vessel was sealed and heated to 50 °C. After stirring for 5 h, additional methyl acrylate (126 µL, 1.39 mmol, 2.0 equiv) was added and the reaction was stirred for an additional 14 h. The reaction mixture was then filtered through a plug of cotton, concentrated under reduced pressure, and purified by silica gel flash chromatography (33% EtOAc/petroleum ether) to provide diester 3j as a colorless, waxy solid (185 mg, 0.357 mmol, 51% yield); ¹H NMR (500 MHz, CDCl₃) δ 7.77 – 7.65 (m, 2H), 6.92 – 6.79 (m, 2H), 5.96 (ddt, J = 17.2, 10.3, 6.1 Hz, 1H), 5.48 – 5.27 (m, 2H), 4.82 – 4.63 (m, 2H), 4.32 – 3.84 (m, 3H), 3.83 (s, 3H), 3.81 – 3.66 (m, 1H), 3.62 (s, 3H), 3.58 – 3.40 (m, 2H), 2.56 – 2.13 (m, 4H), 1.44 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 173.8, 173.5, 173.0, 171.9, 170.9, 170.6, 163.0, 155.1, 154.8, 151.4, 141.6, 139.3, 1367, 1260, 1168, 1030, 982, 916, 843, 811, 782, 766, 732, 648, 634 cm⁻¹; IR (Neat Film, NaCl) 3354, 2976, 2843, 2568, 2255, 2044, 1694, 1605, 1579, 1556, 1513, 1416, 1393, 1260, 1168, 1030, 982, 916, 843, 811, 782, 766, 732, 648, 634 cm⁻¹; HRMS (MM: ESI-APCI): m/z calc’d for C₂₆H₃₈N₃O₉ [M+H]⁺: 536.2603, found 536.2603.
6-allyl 1-(tert-butyl) 6-(2-cyanoethyl)-4-(4-methoxybenzoyl)-5-oxo-1,4-diazepane-1,6-dicarboxylate (3k)

To a 20 mL vial containing allyl ester 2c (300 mg, 0.694 mmol, 1.0 equiv) and K₂CO₃ (480 mg, 3.47 mmol, 5.0 equiv) was added acetone (2.8 mL, 0.25 M) and acrylonitrile (182 µL, 2.78 mmol, 4.0 equiv) at 23 °C. The vessel was sealed and heated to 50 °C. After 17 h of stirring, the reaction mixture was filtered through a plug of cotton, concentrated under reduced pressure, and purified by silica gel flash chromatography (33% EtOAc/petroleum ether) to provide 3k as a colorless foam (176 mg, 0.362 mmol, 52% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.74 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.9 Hz, 2H), 6.01 (ddt, J = 16.7, 10.3, 6.3 Hz, 1H), 5.51 – 5.36 (m, 2H), 4.89 – 4.75 (m, 2H), 4.32 – 3.88 (m, 3H), 3.86 (s, 3H), 3.86 – 3.34 (m, 3H), 2.71 – 2.09 (m, 4H), 1.53 – 1.34 (m, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 170.8, 170.3, 163.2, 155.3, 131.0, 130.6, 127.1, 121.4, 121.1, 119.1, 113.7, 81.4, 67.5, 60.2, 55.5, 47.5, 46.8, 43.6, 32.9, 28.3, 13.6; IR (Neat Film, NaCl) 2975, 2934, 2250, 1694, 1605, 1579, 1512, 1494, 1419, 1393, 1367, 1326, 1255, 1164, 1031, 1000, 979, 941, 916, 842, 813, 781, 762, 733, 648, 634 cm⁻¹; HRMS (MM: ESI-APCI): m/z calc’d for C₂₅H₃₅N₄O₇ [M+NH₄]⁺: 503.2500, found 503.2505.

6-allyl 1-(tert-butyl) 4-benzoyl-6-(((tert-butoxycarbonyl)amino)methyl)-5-oxo-1,4-diazepane-1,6-dicarboxylate (3l)

A solution of allyl ester 2a (200 mg, 0.497 mmol, 1.0 equiv) and tert-butyl ((phenylsulfonyl)methyl)carbamate⁵,⁶ (162 mg, 0.597 mmol, 1.2 equiv) in CH₂Cl₂ (2.5 mL, 0.2 M) at 23 °C was stirred for 5 min, after which time Cs₂CO₃ (405 mg, 1.24 mmol, 2.5 equiv) was added at the same temperature. After an additional 30 min of stirring, saturated aqueous NH₄Cl (1 mL) was added and the biphasic mixture was vigorously stirred for 20 min. The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (3 x 3 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure onto silica gel (2 g). The silica-adsorbed crude reaction mixture was purified by automated silica gel flash chromatography (Teledyne ISCO, 10→40% acetone/hexanes) to provide carbamate 3l
as a white foam (200 mg, 0.376 mmol, 76% yield): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.83 – 7.71 (m, 2H), 7.59 – 7.46 (m, 1H), 7.46 – 7.36 (m, 2H), 6.00 (ddt, $J$ = 16.6, 10.3, 6.1 Hz, 1H), 5.51 – 5.25 (m, 2H), 5.17 (br s, 1H), 4.79 – 4.64 (m, 2H), 4.48 – 4.23 (m, 1H), 4.14 – 3.20 (m, 7H), 1.44 (s, 9H), 1.42 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.1, 173.8, 172.7, 170.1, 169.6, 156.0, 155.2, 154.7, 135.5, 132.2, 131.4, 128.5, 128.4, 120.2, 81.4, 79.6, 67.4, 62.7, 47.1, 46.8, 45.9, 43.2, 28.5, 28.4; IR (Neat Film, NaCl) 3457, 2977, 2934, 2253, 1704, 1600, 1503, 1450, 1417, 1392, 1325, 1283, 1248, 1158, 1042, 980, 913, 860, 767, 729, 693, 663 cm$^{-1}$; HRMS (MM: ESI-APCI): $m/z$ calc’d for C$_{27}$H$_{38}$N$_3$O$_8$ [M+H]$^+$: 532.2653, found 532.2664.

Derivatization of Allylic Alkylation Products

![Image of 2-bromo-5-chlorobenzo[d]oxazole (6)]

2-bromo-5-chlorobenzo[d]oxazole (6)

Prepared according to the literature procedure by Mangion and coworkers$^7$ and used directly in the synthesis of 7.

![Image of 5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoic acid (8)]

5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoic acid (8)

Prepared according to the literature procedure by Mangion and coworkers.$^7$ All characterization data matched those reported in the literature.

**tert-butyl (S)-6-allyl-6-benzyl-5-oxo-1,4-diazepane-1-carboxylate (SI4)**

To a flask containing benzoyl-protected diazepanone $^4$a (460 mg, 1.03 mmol, 1.0 equiv) was added isopropyl alcohol (100 mL, 0.01 M) and water (10 mL), followed by LiOH·H$_2$O (61 mg, 1.45 mmol, 1.5 equiv) at 23 °C. After stirring for 4 h at 23 °C, the isopropyl alcohol was removed under reduced pressure and the resulting aqueous mixture extracted with EtOAc (4 x 50
mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated under reduced pressure to yield a crude oil (400 mg) that was used without further purification.

**tert-butyl (R)-6-allyl-6-benzyl-1,4-diazepane-1-carboxylate (5)**

Crude lactam SI4 (350 mg [theoretical maximum 310 mg lactam], 0.903 mmol, 1 equiv) was dissolved in THF (10.2 mL, 0.1 M) and cooled to 0 °C. LiAlH₄ (77 mg, 2.03 mmol, 2.25 equiv) was then added, and the reaction mixture was stirred at 0 °C for 4 h, over the course of which an additional 3.37 equiv (116 mg, 3.05 mmol) of LiAlH₄ were added in total (77 mg, followed by 39 mg, at equal intervals). The reaction mixture was then diluted with diethyl ether (10 mL) and water (300 µL) was added. After gas generation subsided, 15% aqueous NaOH (300 µL) was added, followed by additional water (900 µL). After stirring at 0 °C for 15 min, anhydrous MgSO₄ was added, and the mixture was stirred for an additional 10 min, whereafter it was filtered through celite and concentrated under reduced pressure. Purification by automated silica gel flash chromatography (Teledyne ISCO, 0→20% MeOH/CH₂Cl₂) provided the product as a light yellow oil (130 mg, 0.393 mmol, 44% yield; ¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.14 (m, 5H), 6.01 (dq, J = 17.1, 7.8 Hz, 1H), 5.18 (d, J = 15.9 Hz, 2H), 3.67 – 3.30 (m, 4H), 2.97 (m, 2H), 2.88 – 2.48 (m, 4H), 2.30 – 2.06 (m, 3H), 1.50 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 155.8, 138.1, 134.6, 130.7, 128.0, 126.2, 118.2, 79.8, 79.5, 57.9, 57.2, 55.3, 54.2, 50.9, 49.8, 49.3, 43.5, 41.3, 39.8, 39.4, 28.5; IR (Neat Film, NaCl) 3357, 3066, 3028, 2976, 2928, 1694, 1602, 1464, 1455, 1416, 1391, 1365, 1334, 1302, 1248, 1166, 1031, 996, 952, 912, 866, 771, 733, 703, 685, 672, 659, 644, 612 cm⁻¹; HRMS (MM: ESI-APCI): m/z calc’d for C₂₀H₃₁N₂O₂ [M+H]⁺: 331.2380, found 331.2399; [α]D²⁴ – 6.496 (c 2.0, CHCl₃).

**tert-butyl (R)-6-allyl-6-benzyl-4-(5-chlorobenzo[d]oxazol-2-yl)-1,4-diazepane-1-carboxylate (SI5)**

To a 1 dram vial containing diazepane 5 (9.5 mg, 0.0287 mmol, 1.0 equiv), aryl bromide 6 (10.0 mg, 0.0431 mmol, 1.5 equiv), and K₂CO₃ (7.9 mg, 0.0574 mmol, 2 equiv) was added
S33

MeCN (0.3 mL, 0.1 M) at 23 °C. After stirring for 24 h at 23 °C, saturated aqueous NH₄Cl (1 mL) was added, and the mixture was extracted with EtOAc (3 x 1 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude material (15.4 mg) thus obtained was carried forward without further purification.

(S)-2-(6-allyl-6-benzyl-1,4-diazepan-1-yl)-5-chlorobenzo[d]oxazole (7)

Crude carbamate SI5 was dissolved in MeOH (0.3 mL, 0.1 M) and AcCl (20.5 µL, 0.288 mmol, 10 equiv) was added at 23 °C. After stirring for 5 h at 23 °C, the reaction mixture was concentrated under reduced pressure and purified by silica gel flash chromatography (66% EtOAc/benzene + 1% Et₃N) to provide 7 as a beige, amorphous solid (4.3 mg, 0.0113 mmol, 39% yield from 5) of sufficient purity for use in the next reaction, however, further purification was possible by silica gel flash chromatography with 2% Et₃N in Et₂O; ¹H NMR (400 MHz, CDCl₃) δ 7.34 – 7.27 (m, 3H), 7.25 – 7.17 (m, 3H), 7.12 (d, J = 8.4 Hz, 1H), 6.94 (dd, J = 8.4, 2.3 Hz, 1H), 5.99 (ddt, J = 14.5, 10.4, 7.2 Hz, 1H), 5.30 (d, J = 3.1 Hz, 1H), 5.20 – 5.10 (m, 1H), 3.87 – 3.61 (m, 3H), 3.15 – 3.00 (m, 2H), 2.90 – 2.66 (m, 3H), 2.57 (d, J = 13.9 Hz, 1H), 2.22 – 2.10 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 147.5, 137.8, 134.1, 130.8, 129.4, 128.2, 126.4, 120.1, 118.8, 116.2, 109.2, 57.8, 56.5, 53.3, 49.2, 43.8, 41.3, 39.8; IR (Neat Film, NaCl) 2922, 1638, 1570, 1458, 1249, 1167, 921, 792, 710 cm⁻¹; HRMS (MM: ESI-APCI): m/z calc’d for C₂₂H₂₅ClN₃O [M+H]⁺: 382.1681, found 382.1695; [α]D²¹⁺89 +7.524 (c 0.07, CHCl₃).

(R)-(6-allyl-6-benzyl-4-(5-chlorobenzo[d]oxazol-2-yl)-1,4-diazepan-1-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone (9)

To a vial containing carboxylic acid 8 (35 mg, 0.172 mmol, 1.0 equiv) in CH₂Cl₂ (1.8 mL) at 23 °C was added DMF (4 µL, 0.0517 mmol, 0.3 equiv) and oxalyl chloride (18 µL, 0.207 mmol, 1.2 equiv). After stirring for 1 h, Et₃N (48 µL, 0.344 mmol, 2.0 equiv) was added, followed by amine 7 (60 mg, 0.155 mmol, 0.9 equiv) in CH₂Cl₂ (1.8 mL, 0.05 M total concentration). After stirring for an additional 1 h at 23 °C, the reaction mixture was quenched with saturated aqueous NaHCO₃ (3 mL), the layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (3
x 2 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, concentrated under reduced pressure, and purified by automated silica gel flash chromatography (Teledyne ISCO, 0→40% Et₂O/hexanes) to provide amide 9 as a beige oil (29.6 mg, 0.0522 mmol, 34% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.73 (s, 1H), 7.55 (s, 1H), 7.34 – 7.27 (m, 6H), 7.20 – 7.09 (m, 3H), 7.04 – 6.92 (m, 2H), 6.11 (ddt, J = 17.6, 10.4, 7.3 Hz, 1H), 5.26 – 5.12 (m, 2H), 4.24 – 4.07 (m, 1H), 3.96 – 3.75 (m, 1H), 3.70 – 3.40 (m, 4H), 3.38 – 3.12 (m, 2H), 2.99 – 2.80 (m, 2H), 2.43 – 2.38 (m, 2H), 2.38 – 2.33 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 170.7, 170.5, 170.0, 163.0, 147.2, 144.4, 138.7, 138.6, 133.6, 133.5, 133.2, 132.9, 130.9, 130.8, 130.6, 130.4, 129.9, 129.5, 129.5, 129.0, 129.0, 128.3, 128.3, 128.2, 128.2, 128.2, 128.1, 128.1, 126.6, 126.6, 122.2, 122.0, 121.9, 120.5, 120.5, 119.2, 119.1, 119.0, 116.3, 116.3, 109.3, 109.2, 56.2, 56.1, 55.5, 54.3, 52.9, 52.2, 49.5, 49.3, 49.2, 48.9, 47.6, 45.0, 43.5, 43.1, 42.4, 42.2, 42.0, 41.8, 39.5, 39.5, 37.6, 21.0, 21.0, 20.9; IR (Neat Film, NaCl) 3431, 2923, 2854, 2356, 1644, 1634, 1574, 1568, 1538, 1505, 1462, 1454, 1428, 1372, 1308, 1251, 1054, 952, 921, 822, 794, 737, 704 cm⁻¹; HRMS (MM: ESI-APCI): m/z calc’d for C₃₂H₃₂ClN₆O₂ [M+H]⁺: 567.2270, found 567.2294; [α]D²²⁺ +41.90 (c 1.0, CHCl₃).

References


NMR and IR Spectra of New Compounds

$^1$H NMR (400 MHz, CDCl$_3$) of compound 4a.
Infrared spectrum (Thin Film, NaCl) of compound 4a.

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 4a.
Supporting Information for Sercel,‡ Sun,‡ and Stoltz

$^1$H NMR (400 MHz, CDCl$_3$) of compound 4b.

BzN NBoc O Me

\[ \text{Diagram of compound 4b} \]
Supporting Information for Sercel, Sun, and Stoltz

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

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 4b.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 4c.
Infrared spectrum (Thin Film, NaCl) of compound 4c.

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 4c.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 4d.
Infrared spectrum (Thin Film, NaCl) of compound 4d.

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 4d.
An NMR spectrum is shown for compound 4e, labeled as 

\[ ^1H \text{NMR (400 MHz, CDCl}_3\text{) of compound 4e.} \]
Infrared spectrum (Thin Film, NaCl) of compound 4e.

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 4e.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 4f.
Supporting Information for Sercel,‡ Sun,‡ and Stoltz

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

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 4f.
Supporting Information for Sercel, Sun, and Stoltz

$^1$H NMR (400 MHz, CDCl$_3$) of compound 4g.

$\text{BzN}$

$\text{NBoc}$

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

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 4g.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 4h.
Infrared spectrum (Thin Film, NaCl) of compound 4h.

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 4h.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 4i.
Infrared spectrum (Thin Film, NaCl) of compound 4i.

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 4i.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 4j.
Infrared spectrum (Thin Film, NaCl) of compound 4j.

$^{13}$C NMR (100 MHz, CDCl₃) of compound 4j.
Supporting Information for Sercel,‡ Sun,‡ and Stoltz

$^1$H NMR (400 MHz, CDCl$_3$) of compound 4k.

Diagram showing the NMR spectrum and chemical structure of compound 4k.
Supporting Information for Sercel,‡ Sun,‡ and Stoltz

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

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 4k.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 4l.
Infrared spectrum (Thin Film, NaCl) of compound 4l.

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 4l.
Supporting Information for Sercel, Sun, and Stoltz

$^1$H NMR (400 MHz, CDCl$_3$) of compound S11.
Infrared spectrum (Thin Film, NaCl) of compound SI1.

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound SI1.
$^1$H NMR (400 MHz, CDCl$_3$) of compound SI2.
Infrared spectrum (Thin Film, NaCl) of compound S12.

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound S12.
$^1\text{H} \text{NMR (400 MHz, CDCl}_3\text{) of compound SI3.}
Infrared spectrum (Thin Film, NaCl) of compound S13.

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound S13.
$^1$H NMR (500 MHz, CDCl$_3$) of compound 2a.
Infrared spectrum (Thin Film, NaCl) of compound 2a.

$^{13}$C NMR (125 MHz, CDCl$_3$) of compound 2a.


$^1$H NMR (400 MHz, CDCl$_3$) of compound 2b.
Infrared spectrum (Thin Film, NaCl) of compound 2b.

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 2b.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 2c.
Infrared spectrum (Thin Film, NaCl) of compound 2c.

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 2c.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 3a.
Infrared spectrum (Thin Film, NaCl) of compound 3a.

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 3a.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 3b.
Infrared spectrum (Thin Film, NaCl) of compound 3b.

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) of compound 3b.
Supporting Information for Sercel,‡ Sun,‡ and Stoltz

$^1$H NMR (400 MHz, CDCl$_3$) of compound 3c.
Infrared spectrum (Thin Film, NaCl) of compound 3c.

$^{13}$C NMR (100 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 (100 MHz, CDCl$_3$) of compound 3d.
Supporting Information for Sercel, Sun, and Stoltz

$^1$H NMR (500 MHz, CDCl$_3$) of compound 3e.
Supporting Information for Sercel,‡ Sun,‡ and Stoltz

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

$^{13}$C NMR (125 MHz, CDCl$_3$) of compound 3e.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 3f.
Infrared spectrum (Thin Film, NaCl) of compound 3f.

\[ ^{13} \text{C NMR (100 MHz, CDCl}_3 \text{)} \text{ of compound 3f.} \]
$^1$H NMR (500 MHz, CDCl$_3$) of compound 3g.
Infrared spectrum (Thin Film, NaCl) of compound 3g.

$^{13}$C NMR (125 MHz, CDCl$_3$) of compound 3g.
$^{1}$H NMR (400 MHz, CDCl$_3$) of compound 3h.
Infrared spectrum (Thin Film, NaCl) of compound 3h.

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 3h.
$^1$H NMR (500 MHz, CDCl$_3$) of compound 3i.
Infrared spectrum (Thin Film, NaCl) of compound 3i.

$^{13}$C NMR (125 MHz, CDCl$_3$) of compound 3i.
Supporting Information for Sercel,‡ Sun,‡ and Stoltz

$^1$H NMR (500 MHz, CDCl$_3$) of compound 3j.
Supporting Information for Sercel,‡ Sun,‡ and Stoltz

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

$^{13}$C NMR (125 MHz, CDCl$_3$) of compound 3j.
Supporting Information for Sercel,‡ Sun,‡ and Stoltz

H NMR (400 MHz, CDCl₃) of compound 3k.

1H NMR (400 MHz, CDCl₃) of compound 3k.
Supporting Information for Sercel,‡ Sun,‡ and Stoltz

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

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 3k.
\(^1\)H NMR (400 MHz, CDCl\(_3\)) of compound 3l.
Infrared spectrum (Thin Film, NaCl) of compound 3l.

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) of compound 3l.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 5.
Supporting Information for Sercel,‡ Sun,‡ and Stoltz

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

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 5.
H NMR (400 MHz, CDCl₃) of compound 7.
Supporting Information for Sercel,‡ Sun,‡ and Stoltz

Infrared spectrum (Thin Film, NaCl) of compound 7.

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 7.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 9.
Infrared spectrum (Thin Film, NaCl) of compound 9.

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 9.
Variable-Temperature NMR of Diazepanone 4e
Supporting Information for Sercel, ‡ Sun, ‡ and Stoltz

$^1$H NMR (400 MHz, DMSO-$d_6$, 80 °C) of compound 4e.
$^{13}$C NMR (100 MHz, DMSO-$d_6$, 80 °C) of compound 4e.