Supporting Information

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Enantioselective Synthesis of α-Secondary and α-Tertiary Piperazin-2-ones and Piperazines by Catalytic Asymmetric Allylic Alkylation**

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Materials and Methods. Unless otherwise stated, reactions were performed in flame-
dried glassware under an inert atmosphere of argon or nitrogen using dry, deoxygenated
solvents. Reaction progress was monitored by thin-layer chromatography (TLC). THF,
Et₂O, and CH₂Cl₂ were dried by passage through an activated alumina column under
argon. Triethylamine and diisopropylamine were distilled over CaH₂ prior to use. Brine
solutions are saturated aqueous solutions of sodium chloride. Allyl Mander’s reagents
were prepared according to the method of Weber.[1] Allyl 1H-imidazole-1-carboxylate
reagents were prepared according to the method of Trost.[2] Phosphinooxazoline
(PHOX) ligands were prepared by methods described in our previous work.[3] Tris(4,4’-
methoxydibenzylideneacetone)dipalladium(0) [Pd₂(pmdba)₃] was prepared according to
the method of Ibers[4]or Fairlamb.[5] All other reagents were purchased from Sigma-
Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise
stated. Reaction temperatures were controlled by an IKAmag temperature modulator
unless otherwise indicated. Stirring was accomplished with Teflon® coated magnetic stir
bars. Glove box manipulations were performed under a N₂ atmosphere. 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 0.040-0.063 mm) was used for flash column
chromatography. ¹H NMR spectra were recorded on a Varian Inova 500 MHz
spectrometer or Varian Mercury 300 MHz spectrometer and are reported relative to
residual CHCl₃ (δ 7.26 ppm). ¹³C NMR spectra were recorded on a Varian Inova 500
MHz (126 MHz) or Varian Mercury 300 MHz (75 MHz) spectrometer 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, h = heptet,
m = multiplet, br s = broad singlet, br d = broad doublet, app = apparent. Data for 13C
are reported in terms of chemical shifts (δ ppm). IR spectra were obtained using a Perkin
Elmer Spectrum BXII 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 and are reported as: [α]₀T (concentration in g/100 mL, solvent, ee). High-resolution
mass spectra (HRMS) were obtained on an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM: ESI-APCI) ionization mode. Syringe pump additions were performed using a KDS 100 syringe pump from KD Scientific. Preparative HPLC was accomplished using an Agilent 1200 Series HPLC with an Agilent Prep-SIL 30 x 250 mm column. Stereochemistry is assigned by analogy to previous results.[6]

Representative Procedure 1 for the Preparation of 3-Oxopiperazine-2-carboxylates and 1,4-Diazepane-2-carboxylates

Piperazin-2-one (SI2)

To a solution of ethylene diamine (3.34 mL, 50.0 mmol) in EtOH (39 mL) at 0 °C was added ethyl bromoacetate (SI1, 2.76 mL, 25.0 mol) dropwise. The solution was warmed to 23 °C and allowed to stir overnight open to the air. The resulting white solid was removed by filtration, and the filtrate was transferred to a flame dried flask containing sodium ethoxide (3.74 g, 55.0 mmol) under a nitrogen atmosphere. The solution was then heated to 80 °C and allowed to stir for 16 hours under nitrogen atmosphere. The solution was cooled to room temperature and concentrated. Ketopiperazine (SI2) was
isolated by flash column chromatography (SiO₂, 20% MeOH in CH₂Cl₂ to 25% MeOH in CH₂Cl₂) as a yellow solid. 64% yield. Product identity was confirmed by comparison to previously reported characterization data.

**4-Benzylpiperazin-2-one (SI3)**

\[
\text{HN} \quad \text{N}\text{Bn}
\]

A 25 mL round bottom flask was charged with piperazin-2-one (SI2, 3.56 g, 36.3 mmol), triethylamine (8.1 mL, 58.1 mmol), benzyl bromide (3.88 mL, 32.7 mmol), and THF (360 mL) and allowed to stir for 16 hours at 23 °C. The reaction mixture was then concentrated and taken up in a saturated aqueous NaHCO₃ solution. The aqueous solution was extracted with EtOAc (5 x 50 mL) and the organic layers were concentrated to approximately 30 mL at which point SI3 precipitated from the solution. The solid was collected by filtration and dried. 62% yield. Product identity was confirmed by comparison to previously reported characterization data.

**1-Benzoyl-4-benzylpiperazin-2-one (SI4)**

\[
\text{BzN} \quad \text{N}\text{Bn}
\]

Benzyl-protected ketopiperazine (SI3, 1.00 g, 5.26 mmol) was dissolved in 20 mL of THF warmed to 60 °C and added by cannula to a freshly prepared solution of LDA (6.31 mmol, prepared by the addition of 2.53 mL of 2.5 M nBuLi solution to a solution of 1.11 mL of diisopropyl amine in 33 mL THF at 0 °C) cooled to –78 °C. The reaction mixture was allowed to stir at –78 °C for 1.5 hours at which point benzoyl chloride (0.79 mL, 8.84 mmol) was added dropwise. The reaction was stirred at –78 °C for another 4 hours at which point full conversion of the starting material was observed by TLC analysis. The reaction mixture was warmed to 23 °C and poured into 20 mL of H₂O and extracted with EtOAc (4 x 20 mL). The organics were combined, washed once with brine, dried
with MgSO₄, and concentrated under reduced pressure. Ketopiperazine SI4 was isolated by flash column chromatography (SiO₂, 20% EtOAc in hexanes to 25% EtOAc in hexanes) as a pale yellow solid. 83% yield. Rᵣ = 0.5 (35% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.56 (dd, J = 8.3, 1.3 Hz, 2H), 7.53–7.45 (m, 1H), 7.44–7.28 (m, 7H), 3.89–3.80 (m, 2H), 3.64 (s, 2H), 3.31 (s, 2H), 2.90–2.79 (m, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 173.8, 169.4, 136.5, 135.9, 131.9, 129.2, 128.7, 128.2, 128.1, 127.9, 61.8, 58.9, 49.3, 45.2; IR (Neat Film, NaCl) 3062, 3027, 2958, 2903, 2809, 1708, 1683, 1600, 1491, 1450, 1401, 1362, 1237, 1197, 1162, 1136, 1073, 950, 885, 795, 730 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc'd for C₁₈H₁₉N₂O₂ [M+H]⁺: 295.1441, found 295.1446.

**Allyl 4-benzoyl-1-benzyl-3-oxopiperazine-2-carboxylate (10a)**

Ketopiperazine (SI4, 1.40 g, 4.76 mmol) was dissolved in 25 mL of dry THF and added via cannula to a freshly prepared solution of LDA (5.71 mmol) in 23 mL dry THF at −78 °C. The resulting dark red solution was allowed to stir at −78 °C for one hour at which point allyl cyanoformate (58.1 mg, 5.23 mmol) was added neat. After 2.5 hours, the reaction reached completion according to TLC analysis. The reaction mixture was warmed to 23 °C and poured into 20 mL of H₂O and then extracted with EtOAc (4 x 20 mL). The combined organics were washed once with brine, dried with MgSO₄, and concentrated under reduced pressure. Ketopiperazine 10a was isolated by flash column chromatography (SiO₂, 10% EtOAc in hexanes) as a white solid. 63% yield. Rᵣ = 0.4 (20% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.64 (dd, J = 8.3, 1.2 Hz, 2H), 7.53 – 7.45 (m, 1H), 7.41 – 7.33 (m, 5H), 7.31 (td, J = 8.6, 8.1, 3.9 Hz, 2H) 6.06–5.89 (m, 1H), 5.40 (dd, J = 17.2, 1.4 Hz, 1H), 5.31 (dd, J = 10.4, 1.1 Hz, 1H), 4.73 (d, J = 6.0 Hz, 2H), 4.17 (s, 1H), 3.93 (dd, J = 12.5, 8.1, 4.3 Hz, 1H), 3.84 (d, J = 13.4 Hz, 1H), 3.81–3.70 (m, 2H), 3.32 (dd, J = 12.2, 8.1, 3.9 Hz, 1H), 2.80 (dt, J = 12.4, 5.0 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 173.7, 167.7, 166.6, 136.5, 135.2, 132.2, 131.4, 129.1, 128.7, 128.4, 128.3, 128.0, 119.7, 69.7, 66.6, 58.8, 45.0, 44.9; IR (Neat Film, NaCl)
3062, 3029, 2846, 1733, 1494, 1450, 1368, 1281, 1232, 1154, 1091, 1074, 985, 948, 945, 795, 731 cm\(^{-1}\); HRMS (MM: ESI-APCI) \(m/z\) calc’d for C\(_{22}\)H\(_{23}\)N\(_2\)O\(_4\) [M+H]\(^+\): 379.1652, found 379.1664.

**Allyl 4-benzoyl-1-benzyl-2-methyl-3-oxopiperazine-2-carboxylate (8b)**

\[
\begin{align*}
\text{BzN} & \quad \text{Me} \\
\text{Me} & \quad \text{O} \\
\text{O} & \quad \text{BzN}
\end{align*}
\]

Ketopiperazine (10a, 500.0 mg, 1.32 mmol) was dissolved in 8.8 mL of dry DMF along with Cs\(_2\)CO\(_3\) (0.75 g, 2.31 mmol) and methyl iodide (90.0 µL, 1.45 mmol) and allowed to stir for 10.5 hours at 23 °C. The solution was then poured into 10 mL of H\(_2\)O and extracted with EtOAc (4 x 10 mL). The combined organics were washed once with brine, dried with MgSO\(_4\), and concentrated under reduced pressure. Acylated ketopiperazine 8b was isolated by flash column chromatography (SiO\(_2\), 15% EtOAc in hexanes to 20% EtOAc in hexanes) as a white solid. 35% yield. \(R_f=0.4\) (20% EtOAc in hexanes); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.70–7.60 (m, 2H), 7.56–7.45 (m, 1H), 7.44–7.34 (m, 6H), 7.34–7.27 (m, 1H), 6.01 (ddt, \(J=17.1, 10.4, 6.0\) Hz, 1H), 5.50–5.38 (m, 1H), 5.34 (dq, \(J=10.4, 1.1\) Hz, 1H), 4.77 (dt, \(J=6.0, 1.3\) Hz, 2H), 4.01 (d, \(J=14.0\) Hz, 1H), 3.91–3.66 (m, 2H), 3.43 (d, \(J=14.0\) Hz, 1H), 3.15 (ddd, \(J=13.4, 9.3, 4.2\) Hz, 1H), 2.90 (dt, \(J=12.6, 4.2\) Hz, 1H), 1.78 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 173.9, 170.0, 169.3, 137.9, 135.5, 132.0, 131.5, 128.7, 128.6, 128.3, 128.2, 127.8, 119.9, 71.4, 66.6, 54.8, 44.9, 43.0, 20.2; IR (Neat Film, NaCl) 3062, 2943, 2848, 1741, 1685, 1600, 1495, 1449, 1400, 1379, 1315, 1284, 1235, 1150, 1109, 928, 795, 723 cm\(^{-1}\); HRMS (MM: ESI-APCI or EI+) \(m/z\) calc’d for C\(_{23}\)H\(_{25}\)N\(_2\)O\(_4\) [M+H]\(^+\): 393.1809, found 393.1792.

**Allyl 1,4-dibenzoyl-2-methyl-3-oxopiperazine-2-carboxylate (8a)**

\[
\begin{align*}
\text{BzN} & \quad \text{Me} \\
\text{Me} & \quad \text{O} \\
\text{O} & \quad \text{NBz}
\end{align*}
\]
Ketopiperazine 8a was prepared according to representative procedure 1, employing benzoyl chloride instead of benzyl bromide, and was isolated by flash column chromatography (SiO2, 15% EtOAc in hexanes to 25% EtOAc in hexanes) as a colorless solid. $R_f = 0.3$ (20% EtOAc in hexanes); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.59–7.54 (m, 2H), 7.54–7.49 (m, 2H), 7.49–7.45 (m, 4H), 7.41 (dt, $J = 7.8$, 6.5, 1.0 Hz, 2H), 5.98 (dt, $J = 17.2$, 10.4, 5.8 Hz, 1H), 5.39 (dq, $J = 17.2$, 1.5 Hz, 1H), 5.28 (dq, $J = 10.4$, 1.2 Hz, 1H), 4.81–4.70 (m, 2H), 4.20–4.06 (m, 2H), 4.00 (ddd, $J = 14.1$, 5.2, 3.6 Hz, 1H), 3.73–3.63 (m, 1H), 1.99 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 172.3, 170.2, 169.1, 167.3, 134.7, 134.6, 132.4, 131.7, 130.8, 129.0, 128.5, 127.9, 127.0, 119.0, 69.2, 67.2, 44.6, 44.3, 19.6; IR (Neat Film, NaCl) 3583, 2943, 1762, 1700, 1690, 1647, 1600, 1448, 1405, 1370, 1284, 1255, 1209, 1149, 1123, 991, 942, 789, 725 cm$^{-1}$; HRMS (MM: ESI-APCI or EI+) $m/z$ calc'd for C$_{23}$H$_{23}$N$_2$O$_5$ [M+H]$^+$: 407.1607, found 407.1600.

**Allyl 4-benzoyl-1-(4-methoxybenzyl)-2-methyl-3-oxopiperazine-2-carboxylate (8c)**

Ketopiperazine 8c was prepared according to representative procedure 1 employing 4-methoxybenzyl chloride instead of benzyl bromide, and was isolated by flash column chromatography (SiO2, 10% EtOAc in hexanes to 20% EtOAc in hexanes) as a yellow oil. $R_f = 0.4$ (20% EtOAc in hexanes); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.70–7.58 (m, 2H), 7.43–7.33 (m, 2H), 7.30–7.21 (m, 2H), 6.94–6.84 (m, 2H), 6.01 (ddt, $J = 16.4$, 10.4, 6.0 Hz, 1H), 5.43 (dq, $J = 17.2$, 1.4 Hz, 1H), 5.34 (dq, $J = 10.4$, 1.1 Hz, 1H), 4.82–4.72 (m, 2H), 3.90 (d, $J = 13.7$ Hz, 1H), 3.82 (s, 3H), 3.80 (t, $J = 4.0$ Hz, 1H), 3.70 (ddd, $J = 12.5$, 9.8, 4.2 Hz, 1H), 3.32 (d, $J = 13.7$ Hz, 1H), 3.10 (ddd, $J = 13.2$, 9.8, 3.7 Hz, 1H), 2.87 (dt, $J = 12.6$, 4.2 Hz, 1H), 1.75 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 174.0, 170.4, 169.4, 159.2, 135.6, 132.0, 131.6, 130.2, 129.6, 128.2, 128.1, 119.8, 114.0, 71.4, 66.5, 55.4, 54.1, 45.2, 42.7, 20.1; IR (Neat Film, NaCl) 3062, 2997, 2949, 2836, 1742, 1687, 1611, 1512, 1465, 1449, 1378, 1285, 1245, 1171, 1150, 1108, 1034, 926, 825
cm⁻¹; HRMS (MM: ESI-APCI or EI+) m/z calc'd for C₂₄H₂₇N₂O₅ [M+H]⁺: 423.1914, found 423.1890.

**Allyl 1-benzyl-4-(4-fluorobenzoyl)-2-methyl-3-oxopiperazine-2-carboxylate (8d)**

Ketopiperazine 8d was prepared according to representative procedure 1 employing 4-fluoro-benzoyl chloride instead of benzoyl chloride, and was isolated by flash column chromatography (SiO₂, 15% EtOAc in hexanes) as a colorless solid. Rᵣ = 0.5 (20% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.75–7.63 (m, 2H), 7.35 (d, J = 4.4 Hz, 4H), 7.32–7.27 (m, 1H), 7.10–7.02 (m, 2H), 6.01 (ddt, J = 17.1, 10.4, 6.0 Hz, 1H), 5.44 (dd, J = 17.2, 1.4 Hz, 1H), 5.36 (dd, J = 10.4, 1.1 Hz, 1H), 4.84–4.71 (m, 2H), 4.00 (d, J = 14.0 Hz, 1H), 3.83–3.67 (m, 2H), 3.39 (d, J = 14.0 Hz, 1H), 3.10 (ddd, J = 13.5, 9.6, 4.1 Hz, 1H), 2.88 (dt, J = 12.7, 4.1 Hz, 1H), 1.75 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 172.9, 170.4, 169.4, 165.1 (d, ¹JCF = 253.3 Hz), 138.3, 131.6 (d, ⁴JCF = 3.3 Hz), 130.9 (d, ³JCF = 9.1 Hz), 128.7, 128.4, 127.7, 119.9, 115.5 (d, ²JCF = 22.2 Hz), 71.4, 66.5, 54.7, 45.3, 43.0, 20.2; IR (Neat Film, NaCl) 3064, 3028, 3001, 2947, 2902, 2844, 1742, 1689, 1601, 1509, 1454, 1409, 1379, 1316, 1283, 1235, 1150, 1110, 996, 928, 849, 765 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc'd for C₂₃H₂₄FN₂O₄ [M+H]⁺: 411.1715, found 411.1726.

**Allyl 1-benzyl-4-(4-methoxybenzoyl)-2-methyl-3-oxopiperazine-2-carboxylate (8e)**

Ketopiperazine 8e was prepared according to representative procedure 1 employing 4-methoxy-benzoyl chloride instead of benzoyl chloride, and was isolated by flash column chromatography (SiO₂, 20% EtOAc in hexanes) as a white solid. Rᵣ = 0.4 (30% EtOAc
in hexanes); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.74–7.65 (m, 2H), 7.39–7.32 (m, 4H), 7.29 (ddt, $J = 8.6$, 5.5, 2.9 Hz, 1H), 6.91–6.83 (m, 2H), 6.02 (ddt, $J = 16.4$, 10.4, 6.0 Hz, 1H), 5.44 (dq, $J = 17.2$, 1.3 Hz, 1H), 5.34 (dd, $J = 10.4$, 1.1 Hz, 1H), 4.77 (dt, $J = 5.9$, 1.2 Hz, 2H), 3.98 (d, $J = 14.0$ Hz, 1H), 3.85 (s, 3H), 3.78–3.67 (m, 2H), 3.38 (d, $J = 14.0$ Hz, 1H), 3.11 (ddd, $J = 13.2$, 8.4, 5.0 Hz, 1H), 2.87 (dt, $J = 12.6$, 4.1 Hz, 1H), 1.76 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 173.4, 170.1, 169.6, 163.1, 138.4, 131.7, 131.0, 128.7, 128.4, 127.6, 127.4, 119.8, 113.6, 71.3, 66.5, 55.5, 54.8, 45.3, 43.0, 20.2; IR (Neat Film, NaCl) 3583, 2917, 2848, 1740, 1679, 1602, 1511, 1458, 1315, 1256, 1170, 1149, 1109, 1026, 927, 843, 739 cm$^{-1}$; HRMS (MM: ESI-APCI) m/z calc’d for C$_{24}$H$_{27}$N$_2$O$_5$ [M+H]$^+$: 423.1914, found 423.1879.

**Allyl 1-benzyl-4-(2-fluorobenzoyl)-2-methyl-3-oxopiperazine-2-carboxylate (8f)**

![Chemical structure of Allyl 1-benzyl-4-(2-fluorobenzoyl)-2-methyl-3-oxopiperazine-2-carboxylate (8f)](image_url)

Ketopiperazine 8f was prepared according to representative procedure 1 employing 2-fluoro-benzoyl chloride instead of benzyol chloride, and was isolated by flash column chromatography (SiO$_2$, 20% EtOAc in hexanes) as a yellow oil. R$_f$ = 0.4 (20% EtOAc in hexanes); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.49 (td, $J = 7.4$, 1.7 Hz, 1H), 7.43 (dddd, $J = 8.3$, 7.2, 5.2, 1.8 Hz, 1H), 7.38–7.32 (m, 4H), 7.32–7.26 (m, 1H), 7.20 (td, $J = 7.6$, 1.0 Hz, 1H), 7.04 (dddd, $J = 10.1$, 8.3, 0.8 Hz, 1H), 6.04–5.87 (m, 1H), 5.37 (dq, $J = 17.2$, 1.4 Hz, 1H), 5.28 (dq, $J = 10.4$, 1.1 Hz, 1H), 4.83–4.60 (m, 2H), 3.99 (dt, $J = 12.6$, 4.0 Hz, 1H), 3.89 (d, $J = 14.0$ Hz, 1H), 3.67 (ddd, $J = 12.7$, 9.5, 4.3 Hz, 1H), 3.37 (d, $J = 14.0$ Hz, 1H), 3.14 (ddd, $J = 13.0$, 9.5, 3.7 Hz, 1H), 2.86 (dt, $J = 12.7$, 4.4 Hz, 1H), 1.75 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 170.7, 169.4, 168.6, 158.8 (d, $^1$J$_{CF}$ = 250.3 Hz), 138.2, 132.6 (d, $^4$J$_{CF}$ = 8.5 Hz), 131.7, 129.5, 128.7, 128.5, 127.7, 125.4 (d, $^3$J$_{CF}$ = 14.6 Hz), 124.4 (d, $^5$J$_{CF}$ = 3.4 Hz), 119.5, 115.6 (d, $^2$J$_{CF}$ = 21.6 Hz), 71.8, 66.5, 54.5, 44.7, 42.5, 20.3; IR (Neat Film, NaCl) 3066, 3029, 2944, 2847, 1743, 1690, 1614, 1491, 1453, 1379, 1301, 1230, 1146, 928, 755 cm$^{-1}$; HRMS (MM: ESI-APCI) m/z calc’d for C$_{25}$H$_{27}$F$_2$N$_2$O$_5$ [M+H]$^+$: 411.1037, found 411.1715.
3-Allyl 1-benzyl 4-benzyl-3-methyl-2-oxopiperazine-1,3-dicarboxylate (8g)

Ketopiperazine 8g was prepared according to representative procedure 1 employing benzyl chloroformate instead of benzoyl chloride, and was isolated by flash column chromatography (SiO₂, 10% EtOAc in hexanes to 20% EtOAc in hexanes) as a yellow oil. Rᵣ= 0.5 (20% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.38–7.32 (m, 2H), 7.32–7.25 (m, 2H), 7.25–7.21 (m, 5H), 7.21–7.16 (m, 1H), 5.86 (ddt, J = 17.1, 10.5, 5.8 Hz, 1H), 5.30 (dq, J = 17.2, 1.5 Hz, 1H), 5.22 (d, J = 2.6 Hz, 2H), 5.18 (dq, J = 10.4, 1.2 Hz, 1H), 4.74–4.55 (m, 2H), 3.78 (d, J = 14.0 Hz, 1H), 3.70 (dt, J = 12.2, 3.9 Hz, 1H), 3.55–3.46 (m, 1H), 3.23 (d, J = 14.0 Hz, 1H), 2.97 (ddd, J = 13.1, 9.7, 3.7 Hz, 1H), 2.65 (dt, J = 12.7, 4.3 Hz, 1H), 1.68 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 169.5, 168.9, 153.6, 138.2, 135.3, 131.7, 128.7, 128.6, 128.5, 128.4, 128.2, 127.6, 119.2, 72.2, 68.9, 66.2, 54.4, 46.2, 42.5, 20.9; IR (Neat Film, NaCl) 2944, 2848, 1779, 1723, 1495, 1456, 1378, 1315, 1283, 1213, 1112, 1021, 995, 781, 739 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc’d for C₂₄H₂₇N₂O₅ [M+H]⁺: 423.1914, found 423.1913.

Allyl 4-benzoyl-1-benzyl-2-ethyl-3-oxopiperazine-2-carboxylate (8h)

Ketopiperazine 8h was prepared according to representative procedure 1 employing ethyl iodide instead of methyl iodide, and was isolated by flash column chromatography (SiO₂, 10% EtOAc in hexanes to 20% EtOAc in hexanes) as a yellow oil. Rᵣ= 0.6 (20% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.71–7.63 (m, 2H), 7.53–7.46 (m, 1H), 7.42–7.33 (m, 6H), 7.32–7.27 (m, 1H), 6.04 (ddt, J = 17.1, 10.4, 6.0 Hz, 1H), 5.46 (dq, J = 17.2, 1.4 Hz, 1H), 5.37 (dq, J = 10.4, 1.1 Hz, 1H), 4.84–4.75 (m, 2H), 4.08 (d, J = 14.0 Hz, 1H), 3.83 (dt, J = 12.6, 2.8 Hz, 1H), 3.69 (td, J = 12.2, 3.8 Hz, 1H), 3.29 (d, J = 14.0
Hz, 1H), 3.17 (td, J = 12.1, 3.1 Hz, 1H), 2.95 (ddd, J = 12.4, 3.6, 2.5 Hz, 1H), 2.30 (dq, J = 14.6, 7.3 Hz, 1H), 2.15 (dq, J = 14.7, 7.4 Hz, 1H), 1.04 (t, J = 7.3 Hz, 3H); 13C NMR (126 MHz, CDCl3) δ 174.1, 169.2, 169.0, 138.2, 135.7, 132.1, 131.7, 128.8, 128.4, 128.3, 128.2, 127.6, 119.9, 75.0, 66.3, 54.5, 44.9, 43.0, 26.1, 8.4; IR (Neat Film, NaCl) 3063, 3030, 2960, 2839, 1744, 1683, 1600, 1495, 1451, 1400, 1377, 1321, 1284, 1225, 1151, 1119, 1082, 987, 962, 940, 796, 738, 720 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc’d for C24H27N2O4 [M+H]+: 407.1965, found 407.1950.

2-Phenylallyl 4-benzoyl-1-benzyl-2-methyl-3-oxopiperazine-2-carboxylate (8l)

Ketopiperazine 8l was prepared according to representative procedure 1 starting from 10d instead of 10a, and was isolated by flash column chromatography (SiO2, 15% EtOAc in hexanes) as a yellow oil. Rf = 0.4 (15% EtOAc in hexanes) 1H NMR (500 MHz, CDCl3) δ 7.63 (dd, J = 8.2, 1.2 Hz, 2H), 7.56 – 7.44 (m, 3H), 7.42 – 7.35 (m, 4H), 7.35 – 7.30 (m, 3H), 7.30 – 7.26 (m, 1H), 7.23 (d, J = 6.9 Hz, 2H), 5.63 (s, 1H), 5.57 – 5.44 (m, 1H), 5.32 (dd, J = 12.9, 0.9 Hz, 1H), 5.15 – 4.99 (m, 1H), 3.87 (d, J = 14.0 Hz, 1H), 3.69 – 3.56 (m, 2H), 3.12 (d, J = 14.0 Hz, 1H), 2.82 (ddd, J = 13.8, 9.5, 4.5 Hz, 1H), 2.67 (dt, J = 12.7, 3.9 Hz, 1H), 1.72 (s, 3H); 13C NMR (126 MHz, CDCl3) δ 173.9, 170.2, 169.5, 142.5, 138.3, 138.0, 135.6, 131.9, 128.8, 128.6, 128.5, 128.3, 128.2, 128.1, 127.5, 126.4, 117.2, 71.3, 67.3, 54.4, 45.1, 42.6, 20.6; IR (Neat Film, NaCl) 3060, 3029, 3001, 2944, 2900, 2845, 1741, 1686, 1600, 1495, 1466, 1449, 1400, 1379, 1316, 1284, 1236, 1150, 1107, 1028, 918, 780, 723 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc'd for C29H29N2O4 [M+H]+: 469.2122, found 469.2122.
2-Chloroallyl 4-benzoyl-1-benzyl-2-methyl-3-oxopiperazine-2-carboxylate (8m)

Ketopiperazine 8m was prepared according to representative procedure 1 starting from 10c instead of 10a, and was isolated by flash column chromatography (SiO\textsubscript{2}, 5% EtOAc in hexanes to 10% EtOAc in hexanes) as a yellow oil. R\textsubscript{f} = 0.4 (15% EtOAc in hexanes)

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.69 – 7.62 (m, 2H), 7.54 – 7.48 (m, 1H), 7.44 – 7.38 (m, 2H), 7.38 – 7.34 (m, 4H), 7.34 – 7.28 (m, 1H), 5.59 (dt, \(J = 1.9, 1.0\) Hz, 1H), 5.51 (d, \(J = 1.9\) Hz, 1H), 4.88 (d, \(J = 14.0\) Hz, 1H), 4.80 (d, \(J = 13.3\) Hz, 1H), 4.00 (d, \(J = 14.0\) Hz, 1H), 3.86 (dt, \(J = 12.4, 3.8\) Hz, 1H), 3.73 (ddd, \(J = 12.4, 10.0, 4.1\) Hz, 1H), 3.45 (d, \(J = 14.0\) Hz, 1H), 3.19 (ddd, \(J = 13.5, 10.0, 3.6\) Hz, 1H), 2.91 (dt, \(J = 12.7, 4.1\) Hz, 1H), 1.79 (s, 3H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) \(\delta\) 173.9, 170.1, 169.1, 138.3, 135.7, 135.4, 132.0, 128.7, 128.5, 128.3, 128.2, 127.7, 116.9, 71.6, 67.4, 54.7, 45.2, 43.0, 20.5; IR (Neat Film, NaCl) 3062, 3029, 2946, 2846, 1746, 1686, 1639, 1600, 1495, 1450, 1401, 1379, 1316, 1283, 1234, 1177, 1150, 1105, 1027, 1000, 971, 912, 724 cm\textsuperscript{–1}; HRMS (MM: ESI-APCI) \(m/z\) calc'd for C\textsubscript{23}H\textsubscript{24}N\textsubscript{2}O\textsubscript{4}Cl [M+H]\textsuperscript{+}: 427.1419, found 427.1420.

Allyl 4-benzoyl-1-benzyl-2-methyl-3-oxo-1,4-diazepane-2-carboxylate (8o)

1,4-Diazepane 8o was prepared according to representative procedure 1 employing 1,3-diaminopropane instead of ethylene diamine, and was isolated by flash column chromatography (SiO\textsubscript{2}, 10% EtOAc in hexanes to 20% EtOAc in hexanes) as a colorless solid. R\textsubscript{f} = 0.7 (20% EtOAc in hexanes); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.65 (m, 2H), 7.52 – 7.45 (m, 1H), 7.43–7.30 (m, 5H), 7.28 (m, 2H), 6.00 (ddt, \(J = 17.2, 10.4, 6.0\) Hz, 1H), 5.44 (dd, \(J = 17.2, 1.4\) Hz, 1H), 5.33 (dd, \(J = 10.4, 1.4\) Hz, 1H), 4.87–4.70 (m, 2H), 4.29 (ddd, \(J = 14.4, 8.8, 3.0\) Hz, 1H), 3.92 (ddd, \(J = 14.4, 6.1, 3.0\) Hz, 1H), 3.77 (d, \(J =
14.2 Hz, 1H), 3.68 (d, J = 14.2 Hz, 1H), 3.44 (ddd, J = 15.4, 10.9, 4.9 Hz, 1H), 2.89 (ddd, J = 15.4, 6.1, 3.0 Hz, 1H), 1.79 (s, 3H), 1.78–1.73 (m, 1H), 1.69–1.62 (m, 1H); 13C NMR (126 MHz, CDCl3) δ 174.8, 173.7, 170.4, 139.3, 136.2, 131.9, 131.6, 128.6, 128.4, 128.3, 128.1, 127.4, 119.8, 75.1, 66.5, 53.1, 46.8, 42.9, 26.9, 22.7; IR (Neat Film, NaCl) 3062, 3028, 2945, 1742, 1682, 1600, 1494, 1450, 1377, 1357, 1281, 1256, 1139, 1104, 1024, 947, 793, 740, 724 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc'd for C_{24}H_{27}N_{2}O_{4} [M+H]⁺: 407.1965, found 407.1966.

**Representative Procedure 2 for the Preparation of 3-oxopiperazine-2-carboxylates**

![Chemical diagram]

N-Benzylalanine ethyl ester (SI7)

![Chemical structure]

**D,L-Alanine (SI5, 1.50 g, 16.8 mmol)** was dissolved in EtOH (100 mL) and cooled to 0 °C. Thionyl chloride (3.67 mL, 50.5 mmol) was then added dropwise and the resulting solution was heated to reflux for 5 hours. The reaction mixture was then cooled to 23 °C and excess thionyl chloride and ethanol were removed by rotary evaporation to yield
alanine ethyl ester hydrogen chloride salt (SI6) which was used in the following step without further purification. Alanine ester hydrogen chloride salt (SI6) was dissolved in MeOH (17 mL). Then triethylamine (2.6 mL, 18.8 mmol) was added and the solution was allowed to stir for 15 minutes at which point benzaldehyde (1.74 mL, 17.1 mmol) was added neat. The resulting solution was allowed to stir for 10 hours open to air. Then the solution was cooled to 0 °C and NaBH₄ (1.29 g, 34.1 mmol) was added portionwise. The mixture was allowed to stir overnight. The reaction mixture was then carefully poured into 25 mL of 2 N HCl and was washed with Et₂O (1 x 20 mL). The aqueous layer was then basified with 2 N NaOH and was extracted with CH₂Cl₂ (4 x 40 mL). The organic layers were combined and washed once with brine, dried with MgSO₄, and concentrated under reduced pressure to give N-benzylalanine ethyl ester (SI7) in a 90% yield from alanine (SI5). Product identity was confirmed by comparison to previously reported characterization data.

**4-Benzyl-3-methylpiperazin-2-one (SI9)**

![4-Benzyl-3-methylpiperazin-2-one](image)

A solution of N-(2-hydroxyethyl)phthalimide (SI8, 769 mg, 4.00 mmol) in CH₂Cl₂ (4 mL) under argon atmosphere was cooled to 0 °C. Triflic anhydride (0.81 mL, 4.82 mmol) was added dropwise, and the resulting solution was allowed to stir for 10 minutes at 0°C. Then 2,6-lutidine (560 µL, 4.82 mmol) was added and allowed to stir for another 10 minutes before triethylamine (670 µL, 4.82 mmol) and SI7 (suspended in 4 mL of CH₂Cl₂) were added sequentially in dropwise fashion. The solution was warmed to 23 °C and allowed to stir overnight under Ar atmosphere. The reaction mixture was diluted with additional CH₂Cl₂ and washed with 10% aqueous citric acid (2 x 10 mL). The organics were dried with Na₂SO₄ and concentrated. The resulting oil was taken up in MeOH (22 mL), hydrazine hydrate (0.45 mL, 9.20 mmol) was added, and the mixture was allowed to stir overnight. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. Ketopiperazine SI9 was isolated by flash column
chromatography (SiO2, 3% MeOH in CH2Cl2 to 5% MeOH in CH2Cl2) as a yellow solid. 54% yield. Rf = 0.5 (10% MeOH in CH2Cl2); $^1$H NMR (500 MHz, CDCl3) $\delta$ 7.38–7.26 (m, 5H), 6.02 (br s, 1H), 3.94 (d, $J$ = 13.5 Hz, 1H), 3.42 (d, $J$ = 13.5 Hz, 1H), 3.36–3.17 (m, 3H), 2.91 (dt, $J$ = 12.3, 4.8 Hz, 1H), 2.48 (dd, $J$ = 12.3, 7.4, 4.5 Hz, 1H), 1.48 (d, $J$ = 6.9 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl3) $\delta$ 173.0, 138.2, 128.9, 128.5, 127.4, 60.3, 58.3, 45.3, 41.2, 15.5; IR (Neat Film, NaCl) 3203, 3057, 2983, 2953, 2878, 2819, 1667, 1495, 1451, 1345, 1303, 1147, 1088, 1072, 1051, 1024, 890, 822, 750 cm$^{-1}$; HRMS (MM: ESI-APCI) $m/z$ calc'd for C$_{12}$H$_{17}$N$_2$O [M+H]$^+$: 205.1335, found 205.1338.

1-Benzoyl-4-benzyl-3-methylpiperazin-2-one (SI10)

![Chemical Structure]

Ketopiperazine (SI9, 24.7 mg, 1.21 mmol) was dissolved in 6 mL of dry THF and added by cannula to a freshly prepared solution of LDA (1.45 mmol) in 6.1 mL dry THF at –78 °C. The reaction mixture was allowed to stir at −78 °C for 1.5 hours at which point benzoyl chloride (0.18 mL, 1.57 mmol) was added dropwise. The reaction was stirred at −78 °C for another 4 hours at which point full conversion of the starting material was observed by TLC analysis. The reaction mixture was warmed to room temperature and poured into 15 mL of H$_2$O and extracted with EtOAc (4 x 20 mL). The organics were combined and washed once with brine, dried with Na$_2$SO$_4$, and concentrated under reduced pressure. Ketopiperazine SI10 was isolated by flash column chromatography (SiO2, 10% EtOAc in hexanes to 15% EtOAc in hexanes) as a colorless solid. 81% yield. Rf = 0.5 (30% EtOAc in hexanes); $^1$H NMR (500 MHz, CDCl3) $\delta$ 7.54 (app d, $J$ = 7.3 Hz, 2H), 7.52–7.45 (m, 1H), 7.44–7.33 (m, 6H), 7.34–7.27 (m, 1H), 3.99 (d, $J$ = 13.5 Hz, 1H), 3.95–3.83 (m, 1H), 3.77–3.59 (m, 1H), 3.46 (d, $J$ = 13.5 Hz, 1H), 3.37 (app q, $J$ = 6.1 Hz, 1H), 3.18–3.01 (m, 1H), 2.73–2.51 (m, 1H), 1.55 (s, 3H); $^{13}$C NMR (126 MHz, CDCl3) $\delta$ 173.9, 173.5, 136.0, 131.8, 129.9, 129.0, 128.7, 128.3, 128.0, 127.7, 62.3, 58.3, 46.0, 44.7, 15.7; IR (Neat Film, NaCl) 3085, 3062, 3029, 2979, 2942, 2898, 2814, 1693, 1600, 1583, 1455, 1367, 1286, 1228, 1145, 1096, 1075, 1027, 978, 945, 896, 872, 795,
749 cm$^{-1}$; HRMS (MM: ESI-APCI) $m/z$ calc'd for C$_{19}$H$_{21}$N$_2$O$_2$ [M+H]$^+$: 309.1598, found 309.1599.

**Allyl 4-benzoyl-1-benzyl-2-methyl-3-oxopiperazine-2-carboxylate (8b)**

To a cooled solution of KHMDS (64.0 g, 3.19 mmol) in THF (20 mL) at –78 ºC was added a solution of ketopiperazine (SI10, 89.0 g, 2.90 mmol) in THF (10 mL) over a period of 6.5 hours by syringe pump. The resulting solution was allowed to stir for an additional 30 minutes at which point allyl cyanoformate (39.0 g, 3.48 mmol) was added neat. The reaction mixture was stirred at –78 ºC for 2 hours at which point full conversion of the starting material was observed by TLC analysis. The reaction mixture was warmed to 23 ºC, poured into 15 mL of H$_2$O, and extracted with EtOAc (4 x 20 mL). The organics were combined, washed once with brine, dried with Na$_2$SO$_4$, and concentrated under reduced pressure. Ketopiperazine 8b was isolated by flash column chromatography (SiO$_2$, 15% EtOAc in hexanes to 20% EtOAc in hexanes) as a light yellow solid. 61% yield. Product identity was confirmed by comparison to characterization data reported above.

**Allyl 4-benzoyl-1-benzyl-2-isobutyl-3-oxopiperazine-2-carboxylate (8i)**

Ketopiperazine 8i was prepared according to representative procedure 2 starting from D$_L$-leucine instead of D$_L$-alanine, and was isolated by flash column chromatography (SiO$_2$, 10% Et$_2$O in hexanes to 15% Et$_2$O in hexanes) as a white solid. $R_f$ = 0.4 (20% Et$_2$O in hexanes); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.72–7.65 (m, 2H), 7.53–7.46 (m, 1H), 7.41–7.32 (m, 6H), 7.32–7.27 (m, 1H), 6.05 (ddt, $J$ = 17.1, 10.4, 6.0 Hz, 1H), 5.46 (dq, $J$
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= 17.1, 1.4 Hz, 1H), 5.38 (dq, J = 10.4, 1.4 Hz, 1H), 4.85–4.76 (m, 2H), 4.11 (d, J = 14.0 Hz, 1H), 3.86–3.71 (m, 2H), 3.23 (d, J = 14.0 Hz, 1H), 3.15 (ddd, J = 12.4, 10.1, 5.1 Hz, 1H), 2.95 (dt, J = 12.4, 3.0 Hz, 1H), 2.28 (dd, J = 15.0, 4.3 Hz, 1H), 2.18 (dd, J = 15.0, 9.3 Hz, 1H), 2.04 (ddtd, J = 10.1, 9.3, 6.7, 4.3 Hz, 1H), 0.98 (d, J = 6.7 Hz, 3H), 0.86 (d, J = 6.7 Hz, 3H); 13C NMR (126 MHz, CDCl3) δ 174.4, 169.0, 168.8, 137.9, 135.6, 132.1, 131.7, 128.8, 128.5, 128.3, 128.1, 127.6, 120.0, 73.8, 66.4, 54.8, 45.0, 43.0, 40.2, 24.7, 23.8, 22.4; IR (Neat Film, NaCl) 3063, 3030, 2958, 2870, 1739, 1687, 1683, 1601, 1495, 1451, 1368, 1317, 1284, 1227, 1151, 1107, 984, 935, 795, 767, 722 cm–1; HRMS (MM: ESI-APCI) m/z calc’d for C26H31N2O4 [M+H]+: 435.2278, found 435.2291.

Allyl 4-benzoyl-1,2-dibenzyl-3-oxopiperazone-2-carboxylate (8j)

Ketopiperazone 8j was prepared according to representative procedure 2 starting from D,L-phenylalanine instead of D,L-alanine, and was isolated by flash column chromatography (SiO2, 15% Et2O in hexanes) as a white solid. Rf = 0.5 (30% Et2O in hexanes); 1H NMR (500 MHz, CDCl3) δ 7.53–7.44 (m, 3H), 7.40–7.32 (m, 4H), 7.29 (app s, 6H), 7.22 (app d, J = 7.1 Hz, 2H), 6.07 (ddt, J = 17.2, 10.4, 6.0 Hz, 1H), 5.49 (dd, J = 17.2, 1.3 Hz, 1H), 5.39 (dd, J = 10.4, 1.3 Hz, 1H), 4.94–4.77 (m, 2H), 4.29 (d, J = 13.8 Hz, 1H), 3.77–3.64 (m, 1H), 3.61 (d, J = 14.6 Hz, 1H), 3.44 (d, J = 14.6 Hz, 1H), 3.32 (d, J = 13.8 Hz, 1H), 3.19–3.04 (m, 2H), 2.93–2.82 (m, 1H); 13C NMR (126 MHz, CDCl3) δ 173.6, 168.9, 168.6, 137.3, 135.9, 135.5, 132.1, 131.6, 131.0, 128.7, 128.7, 128.4, 128.3, 128.1, 127.6, 127.1, 120.0, 75.5, 66.6, 54.5, 44.1, 43.1, 38.7; IR (Neat Film, NaCl) 3086, 3062, 3030, 2958, 2870, 1739, 1687, 1683, 1601, 1495, 1451, 1368, 1317, 1284, 1227, 1151, 1107, 984, 935, 795, 767, 722 cm–1; HRMS (MM: ESI-APCI) m/z calc’d for C29H29N2O4 [M+H]+: 469.2122, found 469.2133.
**Allyl 4-benzoyl-1-benzyl-2-[(benzyloxy)methyl]-3-oxopiperazine-2-carboxylate (8k)**

![Diagram of 8k](image)

Ketopiperazine 8k was prepared according to representative procedure 2 starting from O-(phenylmethyl)-(L)-serine instead of D,L-alanine, and was isolated by flash column chromatography (SiO₂, 10% EtOAc in hexanes) as a colorless solid. Rf = 0.4 (20% EtOAc in hexanes) ¹H NMR (500 MHz, CDCl₃) δ 7.67 (m, 2H), 7.51–7.43 (m, 1H), 7.42–7.36 (m, 4H), 7.36–7.27 (m, 8H), 5.96 (ddt, J = 17.1, 10.4, 6.0 Hz, 1H), 5.39 (dd, J = 17.1, 1.4 Hz, 1H), 5.35–5.27 (dd, J = 10.4, 1.4 Hz, 1H), 4.77–4.64 (m, 3H), 4.61 (d, J = 12.2 Hz, 1H), 4.20 (d, J = 10.0 Hz, 1H), 4.07 (d, J = 10.0 Hz, 1H), 4.03–3.91 (m, 2H), 3.81–3.66 (m, 1H), 3.50 (d, J = 14.0 Hz, 1H), 3.18 (ddd, J = 12.7, 9.5, 4.2 Hz, 1H), 3.10 (dt, J = 12.2, 4.2 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 173.7, 168.7, 168.0, 138.0, 137.9, 135.5, 132.0, 131.5, 128.7, 128.6, 128.4, 128.4, 128.1, 127.9, 127.8, 127.6, 119.8, 74.7, 74.0, 71.4, 66.4, 54.4, 44.7, 43.5; IR (Neat Film, NaCl) 3062, 3027, 2938, 2853, 1738, 1687, 1600, 1495, 1452, 1376, 1321, 1284, 1226, 1148, 1099, 1047, 973, 940, 795, 743 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc’d for C₃₀H₃₁N₂O₅ [M+H⁺]: 499.2227, found 499.2229.

**Allyl 2-benzoyl-1-oxooctahydro-9aH-pyrido[1,2-a]pyrazine-9a-carboxylate (8n)**

![Diagram of 8n](image)

Bicycle 8n was prepared according to representative procedure 2 starting from pipecolic acid and omitting the benzyl protection operation, and was isolated by flash column chromatography (SiO₂, 15% EtOAc and 1% NEt₃ in hexanes) as a white solid. Rf = 0.3 (25% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.68–7.59 (m, 2H), 7.51–7.44 (m, 1H), 7.40–7.33 (m, 2H), 6.00 (ddt, J = 17.1, 10.4, 6.0 Hz, 1H), 5.41 (dd, J = 17.1, 1.4 Hz, 1H), 5.34 (dd, J = 10.4, 1.4 Hz, 1H), 4.76 (dt, J = 6.0, 1.4 Hz, 2H), 4.04 (td, J = 11.9,
5.5 Hz, 1H), 3.66 (ddd, \(J = 12.6, 4.7, 2.9\) Hz, 1H), 3.49 (ddd, \(J = 12.9, 11.9, 4.7\) Hz, 1H), 3.23–3.07 (m, 1H), 3.07–2.94 (m, 1H), 2.87–2.66 (m, 1H), 2.31–2.15 (m, 1H), 1.88 (m, 1H), 1.75–1.47 (m, 4H); \(^{13}\text{C}\) NMR (126 MHz, CDCl\(_3\)) \(\delta\) 174.4, 169.9, 169.8, 135.7, 131.9, 131.4, 128.2, 128.1, 120.0, 70.3, 66.4, 50.0, 47.2, 44.4, 31.3, 24.7, 20.6; IR (Neat Film, NaCl) 2940, 2860, 1721, 1683, 1600, 1449, 1382, 1355, 1283, 1244, 1150, 1124, 987, 940, 726 cm\(^{-1}\); HRMS (MM: ESI-APCI) \(m/z\) calc'd for \(\text{C}_{19}\text{H}_{23}\text{N}_{2}\text{O}_{4} \ [\text{M}+\text{H}]^{+}\): 343.1652, found 343.1665.

**Procedure for the Preparation of Allyl 4-benzoyl-2-methyl-3-oxo-1-phenylpiperazine-2-carboxylate (8p)**

![Chemical structure](image)

**Ethyl phenylalaninate (SI12)**

![Chemical structure](image)

Ethyl 2-bromopropionate (SI11, 2 mL, 15.4 mmol) was taken up in acetonitrile (18 mL) along with aniline (1.17 mL, 12.8 mmol), potassium carbonate (3.37 g, 24.4 mmol), and potassium iodide (0.26 g, 0.12 mmol) and heated to reflux for 48 hours. The reaction mixture was filtered and the filtrate concentrated. Ethyl phenylalaninate (SI12) was isolated by flash column chromatography (SiO\(_2\), 20% EtOAc in hexanes) as a colorless solid. \(R_f = 0.6\) (30% EtOAc in hexanes). Product identity was confirmed by comparison to previously reported characterization data.
Allyl 4-benzoyl-2-methyl-3-oxo-1-phenylpiperazine-2-carboxylate (8p)

Cyclization, benzoyl protection, and acylation were accomplished as described in representative procedure 2. Ketopiperazine 8p was isolated by preparative HPLC (SiO2, 20% EtOAc in hexanes) as a colorless solid. Rf= 0.4 (10% EtOAc in hexanes); 1H NMR (500 MHz, CDCl3) δ 7.66 (m, 2H), 7.55–7.47 (m, 1H), 7.40 (app t, J = 7.7 Hz, 2H), 7.35–7.27 (m, 2H), 7.12 (app t, J = 7.4 Hz, 1H), 7.10–7.03 (m, 2H), 5.85 (ddt, J = 17.2, 10.4, 7.0 Hz, 1H), 5.30 (dd, J = 17.2, 1.4 Hz, 1H), 5.25 (dd, J = 10.4, 1.1 Hz, 1H), 4.63 (d, J = 7.0 Hz, 2H), 4.10 (ddd, J = 10.8, 4.7, 2.8 Hz, 1H), 4.05–3.92 (m, 2H), 3.55–3.44 (m, 1H), 1.71 (s, 3H); 13C NMR (126 MHz, CDCl3) δ 173.4, 170.5, 169.7, 147.0, 135.4, 132.0, 131.3, 129.1, 128.3, 128.1, 124.6, 123.8, 119.5, 71.9, 66.5, 46.2, 44.9, 21.7; IR (Neat Film, NaCl) 3061, 3028, 2945, 2903, 2862, 1743, 1693, 1599, 1495, 1450, 1398, 1373, 1283, 1179, 1115, 1075, 961, 865, 842, 811, 724 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc'd for C22H23N2O4 [M+H]⁺: 379.1652, found 379.1656.

Procedure for the Preparation of Allyl 4-benzoyl-1,2-dimethyl-3-oxopiperazine-2-carboxylate (8q)
3,4-Dimethylpiperazin-2-one (SI13)

\[
\begin{align*}
\text{HN} & \quad \text{Me} \\
\text{O} & \quad \text{NMe}
\end{align*}
\]

To a solution of ethylene diamine (4.0 mL, 60.0 mmol) in EtOH (23 mL) at 0 °C was added ethyl 2-bromopropionate (SI11, 3.89 mL, 30.0 mmol) dropwise. The solution was warmed to 23 °C and allowed to stir overnight open to air. The resulting white solid was removed by filtration, and the filtrate was transferred to a flame-dried flask containing sodium ethoxide (4.49 g, 66.0 mmol). The solution was then heated to 80 °C and allowed to stir for 16 hours. The solution was cooled to 23 °C and concentrated. Half of the material was then taken up in 13.2 mL of MeOH. Formaldehyde (37%, 0.88 mL, 10.0 mmmol) was then added and the mixture was allowed to stir for 12 hours at 23 °C, at which point NaBH₃CN (0.77 g, 12.2 mmol) was added and the mixture was allowed to stir overnight open to air. N-methyl ketopiperazine SI13 was isolated as a colorless solid by flash chromatography (SiO₂, 5% MeOH in CH₂Cl₂ to 20% MeOH in CH₂Cl₂). 49% yield. Rf = 0.5 (20% MeOH in CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 7.03 (br s, 1H), 3.43 (td, J = 11.0, 10.5, 4.2 Hz, 1H), 3.32–3.10 (m, 1H), 2.87 (dt, J = 12.2, 3.9 Hz, 1H), 2.85–2.79 (m, 1H), 2.51 (ddd, J = 12.1, 10.0, 4.0 Hz, 1H), 2.36 (s, 3H), 1.36 (d, J = 6.8 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 172.8, 62.6, 50.5, 43.3, 40.7, 15.5; IR (Neat Film, NaCl) 3194, 2986, 2951, 2903, 2846, 2799, 1660, 1495, 1455, 1418, 1354, 1316, 1296, 1249, 1223, 1137, 1097, 1034, 893, 854, 826, 782 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc’d for C₆H₁₃N₂O [M+H]+: 129.1022, found 129.1023.

Allyl 4-benzoyl-1,2-dimethyl-3-oxopiperazine-2-carboxylate (8q)

\[
\begin{align*}
\text{BzN} & \quad \text{Me} \\
\text{O} & \quad \text{O} \quad \text{Me} \\
\text{HN} & \quad \text{NMe} \\
\text{O} & \quad \text{BzN}
\end{align*}
\]

Benzoyl protection of and acylation were carried out as described in representative procedure 2. Ketopiperazine 8q was isolated by flash column chromatography (SiO₂, 20% EtOAc in hexanes) as a colorless oil. Rf = 0.5 (40% EtOAc in hexanes); ¹H NMR
(500 MHz, CDCl₃) δ 7.68–7.58 (m, 2H), 7.53–7.43 (m, 1H), 7.42–7.32 (m, 2H), 5.97 (ddt, J = 17.2, 10.4, 6.0 Hz, 1H), 5.40 (dd, J = 17.2, 1.4 Hz, 1H), 5.31 (dd, J = 10.4, 1.1 Hz, 1H), 4.79–4.66 (m, 2H), 3.93–3.82 (m, 2H), 3.28 (dd, J = 12.7, 8.4, 5.5 Hz, 1H), 2.94 (app dt, J = 12.6, 4.2 Hz, 1H), 2.43 (s, 3H), 1.60 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 174.0, 170.3, 169.0, 135.5, 132.0, 131.6, 128.2, 128.1, 119.7, 71.2, 66.4, 47.3, 44.6, 39.1, 19.5; IR (Neat Film, NaCl) 3062, 2994, 2950, 2900, 2811, 1742, 1691, 1601, 1450, 1398, 1372, 1315, 1275, 1219, 1153, 1109, 1046, 929, 887, 795, 754, 724 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc'd for C₁₇H₂₀N₂O₄Na [M+Na]⁺: 339.1315, found 339.1320.

Procedure for the Preparation of 2-Substituted allyl 4-benzoyl-1-benzyl-3-oxopiperazine-2-carboxylates

2-Methylallyl 4-benzoyl-1-benzyl-3-oxopiperazine-2-carboxylate (10b)

LiHMDS (120 mg, 0.61 mmol) was suspended in 1.5 mL of THF and cooled to −78 °C. Then ketopiperazine (SI₄, 150 mg, 0.51 mmol) dissolved in THF (600 µL) was added dropwise to the LiHMDS solution and allowed to stir at −78 °C for 30 minutes, at which point 2-methylallyl 1H-imidazole-1-carboxylate (110 mg, 0.66 mmol) dissolved in 0.5 mL of THF was added dropwise. The reaction mixture was allowed to stir for 6 hours at −78 °C at which point full conversion of the starting material was observed by TLC analysis. The reaction mixture was then warmed to 23 °C and poured into 5 mL of water. The aqueous layer was extracted with EtOAc (4 x 10 mL), the combined organics washed with brine (1 x 10 mL), and dried with Na₂SO₄. 2-Methylallyl 4-benzoyl-1-benzyl-3-oxopiperazine-2-carboxylate (10b) was isolated as a yellow oil by flash column chromatography (SiO₂, 20% EtOAc in hexanes). 14% yield. Rf = 0.3 (20% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.69–7.58 (m, 2H), 7.49 (tt, J = 7.1, 1.2 Hz, 1H), 7.42–7.34 (m, 6H), 7.33–7.27 (m, 1H), 5.03 (d, J = 31.1 Hz, 2H), 4.66 (s, 2H), 4.19
(s, 1H), 3.94 (ddd, J = 12.6, 8.3, 4.3 Hz, 1H), 3.89–3.78 (m, 2H), 3.76 (ddd, J = 12.6, 5.6, 4.0 Hz, 1H), 3.33 (ddd, J = 12.4, 8.3, 3.9 Hz, 1H), 2.82 (dt, J = 12.4, 4.8 Hz, 1H), 1.78 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 173.8, 167.8, 166.6, 139.2, 136.5, 135.3, 132.2, 129.1, 128.7, 128.4, 128.3, 128.0, 114.5, 69.6, 69.2, 58.7, 44.9, 44.8, 19.8; IR (Neat Film, NaCl) 3062, 3030, 2925, 2853, 1740, 1687, 1600, 1494, 1450, 1402, 1381, 1369, 1282, 1233, 1155, 1074, 1028, 990, 950, 907, 793, 731 cm\(^{-1}\); HRMS (MM: ESI-APCI) \(m/z\) calc'd for C\(_{23}\)H\(_{25}\)N\(_2\)O\(_4\) [M+H]\(^+\): 393.1809, found 393.1809.

2-Chloroallyl 4-benzoyl-1-benzyl-3-oxopiperazine-2-carboxylate (10c)

LiHMDS (100 mg, 0.61 mmol) was suspended in 2 mL of THF and cooled to –78 °C. Ketopiperazine (SI4, 150 mg, 0.51 mmol) dissolved in THF (2 mL) was then added dropwise and the solution allowed to stir at –78 °C for 30 minutes. 2-Chloroallyl 1H-imidazole-1-carboxylate (130 mg, 0.66 mmol) dissolved in 1 mL of THF was then added dropwise. The reaction mixture was allowed to stir for 8 hours at –78 °C and then warmed to 23 °C and allowed to stir overnight. The reaction mixture was then poured into 10 mL of water, extracted with EtOAc (4 x 15 mL), the combined organics washed with brine (1 x 15 mL), and dried with Na\(_2\)SO\(_4\). 2-Chloroallyl 4-benzoyl-1-benzyl-3-oxopiperazine-2-carboxylate (10c) was isolated as a yellow oil by flash column chromatography (SiO\(_2\), 10% EtOAc in hexanes to 15% EtOAc in hexanes). 46% yield. 

\(R_f = 0.5\) (20% EtOAc in hexanes); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.68–7.61 (m, 2H), 7.53–7.46 (m, 1H), 7.39 (dd, \(J = 7.8, 1.4\) Hz, 2H), 7.38–7.35 (m, 4H), 7.32 (tttd, \(J = 8.7, 4.3, 3.7, 2.4\) Hz, 1H), 5.54 (dt, \(J = 2.1, 1.1\) Hz, 1H), 5.46 (d, \(J = 1.9\) Hz, 1H), 4.80 (s, 2H), 4.21 (s, 1H), 3.94 (ddd, \(J = 12.5, 8.2, 4.3\) Hz, 1H), 3.90–3.79 (m, 2H), 3.79–3.73 (m, 1H), 3.33 (ddd, \(J = 12.3, 8.1, 3.9\) Hz, 1H), 2.89–2.76 (m, 1H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 173.7, 167.3, 166.3, 136.3, 135.2, 135.0, 132.3, 129.1, 128.8, 128.4, 128.3, 128.1, 116.5, 69.5, 67.2, 58.8, 44.9, 44.9; IR (Neat Film, NaCl) 3060, 3030, 2949, 2898, 2830, 1744, 1689, 1599, 1491, 1448, 1381, 1280, 1232, 1178, 1138, 1074, 1026, 982, 906, 841, 795,
730 cm\(^{-1}\); HRMS (MM: ESI-APCI) \(m/z\) calc'd for C\(_{22}\)H\(_{22}\)ClN\(_2\)O\(_4\) [M+H]\(^+\): 413.1263, found 413.1261.

**2-Phenylallyl 4-benzoyl-1-benzyl-3-oxopiperazine-2-carboxylate (10d)**

![Chemical Structure](image)

LiHMDS (140 mg, 0.83 mmol) was suspended in 3 mL of THF and cooled to –78 °C. Ketopiperazine (SI\(_{14}\), 200 mg, 0.69 mmol) dissolved in THF (3 mL) was then added dropwise to the LiHMDS solution and allowed to stir at –78 °C for 30 minutes. 2-Phenylallyl 1\(H\)-imidazole-1-carboxylate (210 mg, 0.90 mmol) dissolved in 1 mL of THF was then added dropwise. The reaction mixture was allowed to stir for 12 hours at –78 °C and then warmed to 23 °C and poured into 10 mL of water. The aqueous layer was extracted with EtOAc (4 x 15 mL). The combined organics were washed with brine (1 x 15 mL), and dried with Na\(_2\)SO\(_4\). 2-Phenylallyl 4-benzoyl-1-benzyl-3-oxopiperazine-2-carboxylate (10d) was isolated as a yellow oil by flash column chromatography (SiO\(_2\), 5% EtOAc in hexanes). 21% yield. \(R_f = 0.4\) (15% EtOAc in hexanes); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.68–7.60 (m, 2H), 7.52–7.42 (m, 3H), 7.40–7.35 (m, 2H), 7.35–7.31 (m, 3H), 7.31–7.26 (m, 3H), 7.24–7.17 (m, 2H), 5.64–5.57 (m, 1H), 5.46 (d, \(J = 0.9\) Hz, 1H), 5.24–5.10 (m, 2H), 4.13 (s, 1H), 3.87 (dd, \(J = 12.7, 8.5, 4.4\) Hz, 1H), 3.69–3.60 (m, 3H), 3.13 (ddd, \(J = 12.5, 8.5, 3.9\) Hz, 1H), 2.71 (dt, \(J = 12.2, 4.8\) Hz, 1H); \(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 173.7, 167.8, 166.5, 142.2, 137.9, 136.5, 135.3, 132.1, 129.0, 128.9, 128.6, 128.4, 128.3, 127.9, 126.3, 116.9, 69.5, 67.2, 58.4, 44.9, 44.5; IR (Neat Film, NaCl) 3061, 3027, 2925, 2849, 1738, 1688, 1600, 1495, 1450, 1402, 1369, 1281, 1232, 1154, 1074, 1028, 977, 913, 780, 731 cm\(^{-1}\); HRMS (MM: ESI-APCI) \(m/z\) calc'd for C\(_{28}\)H\(_{27}\)N\(_2\)O\(_4\) [M+H]\(^+\): 455.1965, found 455.1965.
Representative Procedure for the Asymmetric Decarboxylative Allylic Alkylation of 3-Oxopiperazine-2-carboxylates, 1,4-Diazepane-2-carboxylates, 1-Oxooctahydro-9aH-pyrido[1,2-a]pyrazine-9a-carboxylates, and 3-Oxo-1,4-diazaspiro[4.5]decane-2-carboxylates

(S)-3-Allyl-1-benzoyl-4-benzyl-3-methylpiperazin-2-one (9b)

In a nitrogen-filled glovebox, an oven-dried 20 mL scintillation vial was charged with [Pd₂(pmdba)₃] (27.4 mg, 0.025 mmol, 0.05 equiv) or [Pd₂(dba)₃] (22.9 mg, 0.025 mmol, 0.05 equiv), (S)-(CF₃)₃-t-BuPHOX (37.0 mg, 0.063 mmol, 0.125 equiv), toluene (15 mL or 13 mL if the substrate is an oil), and a magnetic stir bar. The vial was stirred at ambient glovebox temperature (~28 °C) for 30 min and then the substrate (8b, 182 mg, 0.50 mmol) was added either as a solid or as a solution in toluene (2 mL). The vial thus charged was sealed 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, concentrated under reduced pressure, and purified by flash chromatography to afford the desired alkylated product. Ketopiperazine 9b was isolated as a yellow oil by flash column chromatography (SiO₂, 10% Et₂O and 0.2% Me₂NEt in hexanes). 89% yield. Rₕ = 0.4 (10% EtOAc in hexanes, two developments); ¹H NMR (500 MHz, CDCl₃) δ 7.60–7.53 (m, 2H), 7.52–7.45 (m, 1H), 7.44–7.33 (m, 6H), 7.29 (t, J = 7.2 Hz, 1H), 6.06 (ddt, J = 17.1, 10.3, 7.2 Hz, 1H), 5.24–5.10 (m, 2H), 4.02 (d, J = 13.6 Hz, 1H), 3.87 (d, J = 12.2 Hz, 1H), 3.60 (td, J = 11.9, 4.0 Hz, 1H), 3.43 (d, J = 13.3 Hz,
(S)-(2- Allyl-2- methyl-3- oxopiperazine-1,4-diyl)bis(phenylmethanone) (9a)

Ketopiperazine 9a was isolated as an off-white foam by flash column chromatography (SiO2, 15% EtOAc in hexanes to 25% EtOAc in hexanes). 89% yield. Rf = 0.4 (35% EtOAc in hexanes); 1H NMR (500 MHz, CDCl3) δ 7.59-7.54 (m, 2H), 7.54-7.50 (m, 1H), 7.49-7.37 (m, 7H), 5.85 (dddd, J = 17.0, 10.1, 8.7, 6.2 Hz, 1H), 5.24 (ddt, J = 17.0, 2.3, 1.2 Hz, 1H), 5.20 (dd, J = 10.1, 2.1 Hz, 1H), 4.14 (ddd, J = 13.1, 5.8, 2.9 Hz, 1H), 3.79 (ddd, J = 13.1, 8.9, 2.9 Hz, 1H), 3.71 (ddd, J = 14.2, 5.8, 2.9 Hz, 1H), 3.60 (dd, J = 13.9, 8.7 Hz, 1H), 3.53 (ddd, J = 14.2, 8.9, 2.9 Hz, 1H), 2.88 (ddt, J = 13.9, 6.2, 1.2 Hz, 1H), 2.00 (s, 3H); 13C NMR (126 MHz, CDCl3) δ 173.9, 172.5, 171.2, 137.0, 135.6, 133.0, 131.9, 130.2, 128.9, 128.3, 127.6, 126.7, 119.9, 68.4, 46.6, 44.2, 39.4, 24.3; IR (Neat Film, NaCl) 3057, 2978, 2934, 1685, 1643, 1600, 1448, 1405, 1364, 1286, 1210, 1149, 1075, 990, 934, 828, 788, 716 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc'd for C22H25N2O2 [M+H]⁺: 349.1911, found 349.1898; [α]D²⁵.⁰ −58.4 (c 0.97, MeOH, 91% ee).

(S)-3-Allyl-1-benzoyl-4-(4-methoxybenzyl)-3-methylpiperazin-2-one (9c)

Supporting Information for Stoltz, et al.
Ketopiperazine 9c was isolated as a yellow oil by flash column chromatography (SiO₂, 10% EtOAc in hexanes). 85% yield. Rₜ = 0.4 (20% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.55 (dt, J = 8.4, 1.6 Hz, 2H), 7.51–7.43 (m, 1H), 7.42–7.34 (m, 2H), 7.30 (d, J = 8.6 Hz, 2H), 6.93–6.85 (m, 2H), 6.05 (ddt, J = 17.1, 10.3, 6.9 Hz, 1H), 5.21–5.10 (m, 2H), 3.94 (d, J = 13.4 Hz, 1H), 3.85 (dt, J = 12.3, 3.4 Hz, 1H), 3.82 (s, 3H), 3.55 (ddd, J = 12.2, 10.7, 4.3 Hz, 1H), 3.34 (d, J = 13.4 Hz, 1H), 2.88 (dt, J = 12.7, 3.8 Hz, 1H), 2.85–2.72 (m, 2H), 2.63 (dd, J = 14.9, 6.6 Hz, 1H), 1.43 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 175.2, 174.4, 159.0, 136.3, 134.1, 131.5, 130.8, 129.7, 128.2, 127.7, 118.0, 114.0, 67.2, 55.4, 52.3, 45.2, 41.9, 41.4, 18.6; IR (Neat Film, NaCl) 2938, 2834, 1683, 1611, 1517, 1449, 1377, 1317, 1287, 1245, 1224, 1177, 1153, 1133, 1034, 910, 822 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc'd for C₂₃H₂₇N₂O₃ [M+H]⁺: 379.2016, found 379.1999; [α]D²⁵ -75.0 (c 0.86, CHCl₃, 90% ee).

(S)-3-Allyl-4-benzyl-1-(4-fluorobenzoyl)-3-methylpiperazin-2-one (9d)

Ketopiperazine 9d was isolated as a yellow oil by flash column chromatography (SiO₂, 5% EtOAc in hexanes to 10% EtOAc in hexanes). 86% yield. Rₜ = 0.5 (15% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.59 (dd, J = 8.1, 5.7 Hz, 2H), 7.40 (d, J = 7.5 Hz, 2H), 7.35 (t, J = 7.4 Hz, 2H), 7.29 (t, J = 7.0 Hz, 1H), 7.06 (t, J = 8.5 Hz, 2H), 6.08 (ddt, J = 17.2, 9.9, 6.9 Hz, 1H), 5.17 (t, J = 13.8 Hz, 2H), 4.02 (d, J = 13.7 Hz, 1H), 3.85 (dt, J = 12.1, 3.1 Hz, 1H), 3.57 (td, J = 11.4, 4.2 Hz, 1H), 3.41 (d, J = 13.7 Hz, 1H), 2.89 (dt, J = 12.7, 3.6 Hz, 1H), 2.80 (tt, J = 11.0, 5.1 Hz, 2H), 2.72–2.58 (m, 1H), 1.44 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 175.2, 174.4, 164.8 (d, ¹JC₅ = 252.5 Hz), 138.9, 134.0, 132.3 (d, ²JC₅ = 3.3 Hz), 130.5 (d, ³JC₅ = 9.0 Hz), 128.7, 128.6, 127.5, 118.1, 115.3 (d, ²JC₅ = 22.1 Hz), 67.3, 53.0, 45.3, 42.2, 41.5, 18.7; IR (Neat Film, NaCl) 3065, 3027, 2976, 2942, 2828, 1681, 1602, 1507, 1453, 1408, 1378, 1318, 1285, 1226, 1152, 1134, 1098, 1028, 994, 913, 843, 769, 738 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc'd for
C$_{22}$H$_{24}$FN$_{2}$O$_{2}$ [M+H]$^+$: 367.1816, found 367.1799; [α]$_D^{25.0}$ $-$58.1 (c 1.00, CHCl$_3$, 94% ee).

(S)-3-Allyl-4-benzyl-1-(4-methoxybenzoyl)-3-methylpiperazin-2-one (9e)

Ketopiperazine 9e was isolated as a colorless oil by flash column chromatography (SiO$_2$, 20% EtOAc in hexanes). 87% yield. R$_f = 0.4$ (35% EtOAc in hexanes); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.65–7.55 (m, 2H), 7.44–7.26 (m, 5H), 6.93–6.83 (m, 2H), 6.08 (ddt, J = 17.1, 10.4, 7.1 Hz, 1H), 5.23–5.10 (m, 2H), 4.02 (d, J = 13.7 Hz, 1H), 3.85 (s, 3H), 3.80 (dt, J = 12.1, 3.4 Hz, 1H), 3.57 (dd, J = 12.1, 10.5, 4.3 Hz, 1H), 3.41 (d, J = 13.7 Hz, 1H), 2.95–2.73 (m, 3H), 2.63 (dd, J = 14.9, 6.5 Hz, 1H), 1.45 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 174.9, 173.9, 162.8, 139.0, 134.3, 130.7, 128.6, 128.0, 127.4, 117.9, 113.5, 67.1, 55.5, 53.0, 45.3, 42.3, 41.4, 18.7; IR (Neat Film, NaCl) 3066, 2974, 2838, 1676, 1604, 1579, 1511, 1495, 1452, 1419, 1378, 1363, 1317, 1284, 1224, 1170, 1153, 1134, 1027, 993, 913, 838, 801, 770, 738 cm$^{-1}$; HRMS (MM: ESI-APCI) $m/z$ calc'd for C$_{23}$H$_{27}$N$_2$O$_3$ [M+H]$^+$: 379.2016, found 379.1991; [α]$_D^{25.0}$ $-$36.5 (c 0.70, CHCl$_3$, 93% ee).

(S)-3-Allyl-4-benzyl-1-(2-fluorobenzoyl)-3-methylpiperazin-2-one (9f)

Ketopiperazine 9f was isolated as a yellow oil by flash column chromatography (SiO$_2$, 10% EtOAc in hexanes to 20% EtOAc in hexanes). 86% yield. R$_f = 0.4$ (20% EtOAc in hexanes); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.68–7.59 (m, 1H), 7.50–7.45 (m, 1H), 7.45–7.41 (m, 1H), 7.41–7.37 (m, 2H), 7.38–7.32 (m, 1H), 7.31–7.26 (m, 1H), 7.21 (td, J = 7.5, 1.0 Hz, 1H), 7.05 (ddd, J = 10.2, 8.3, 0.9 Hz, 1H), 5.96 (ddt, J = 17.1, 10.3, 7.0 Hz,
1H), 5.11 (ddt, J = 10.3, 2.1, 1.1 Hz, 1H), 5.07 (dq, J = 17.1, 1.4 Hz, 1H), 3.99 (d, J = 13.7 Hz, 1H), 3.88 (dt, J = 12.5, 3.5 Hz, 1H), 3.60 (ddd, J = 12.5, 10.5, 4.4 Hz, 1H), 3.41 (d, J = 13.7 Hz, 1H), 2.91–2.83 (m, 1H), 2.83–2.75 (m, 2H), 2.59 (dd, J = 14.8, 7.2 Hz, 1H), 1.42 (s, 3H); 13C NMR (126 MHz, CDCl 3) δ 174.6, 169.0, 158.5 (d, JCF = 249.6), 143.3, 138.9, 133.9, 132.0 (d, JCF = 8.4), 129.1 (d, JCF = 2.8), 128.5, 127.3, 126.1 (d, JCF = 14.9), 124.2 (d, JCF = 3.4), 117.7, 115.3 (d, JCF = 21.6), 67.2, 52.8, 44.9, 41.9, 41.5, 18.5; IR (Neat Film, NaCl) 3064, 2828, 1701, 1680, 1616, 1493, 1452, 1399, 1377, 1363, 1261, 1158, 1135, 1103, 1028, 992, 914, 857, 820, 756, 740 cm−1; HRMS (MM: ESI-APCI) m/z calc’d for C22H24FN2O2 [M+H]+: 367.1816, found 367.1824; [α]D25.0 80.9 (c 1.00, CHCl3, 87% ee).

Benzyl (S)-3-allyl-4-benzyl-3-methyl-2-oxopiperazine-1-carboxylate (9g)

Ketopiperazine 9g was isolated as a colorless oil by flash column chromatography (SiO2, 10% EtOAc in hexanes to 20% EtOAc in hexanes). 86% yield. Rf = 0.5 (20% EtOAc in hexanes); 1H NMR (500 MHz, CDCl 3) δ 7.46–7.26 (m, 10H), 5.96 (ddt, J = 17.3, 10.2, 7.1 Hz, 1H), 5.36–5.19 (m, 2H), 5.16–5.00 (m, 2H), 3.96 (d, J = 13.7 Hz, 1H), 3.63 (dt, J = 11.8, 3.3 Hz, 1H), 3.51 (ddd, J = 11.8, 10.3, 5.0 Hz, 1H), 3.32 (d, J = 13.7 Hz, 1H), 2.85–2.73 (m, 1H), 2.73–2.51 (m, 3H), 1.41 (s, 3H); 13C NMR (126 MHz, CDCl 3) δ 173.7, 153.6, 138.9, 135.4, 133.6, 128.5, 128.4, 128.2, 128.0, 127.2, 117.8, 68.4, 68.4, 52.7, 46.7, 42.6, 41.6, 18.2; IR (Neat Film, NaCl) 3064, 3029, 2976, 2827, 1775, 1713, 1454, 1377, 1317, 1282, 1221, 1025, 992 cm−1; HRMS (MM: ESI-APCI) m/z calc’d for C22H27N2O3 [M+H]+: 379.2016, found 379.2016; [α]D25.0 36.0 (c 1.00, CHCl3, 81% ee).
(S)-3-Allyl-1-benzoyl-4-benzyl-3-ethylpiperazin-2-one (9h)

Ketopiperazine 9h was isolated as a colorless oil by flash column chromatography (SiO2, 10% EtOAc in hexanes to 20% EtOAc in hexanes). 85% yield. Rf = 0.5 (20% EtOAc in hexanes); 1H NMR (500 MHz, CDCl3) δ 7.60–7.53 (m, 2H), 7.53–7.45 (m, 1H), 7.37 (ddd, J = 21.1, 8.5, 7.0 Hz, 6H), 7.32–7.26 (m, 1H), 5.99 (ddt, J = 17.3, 10.1, 7.2 Hz, 1H), 5.24–5.08 (m, 2H), 3.92 (d, J = 13.9 Hz, 1H), 3.79 (d, J = 13.9 Hz, 1H), 3.76–3.65 (m, 2H), 3.05 (ddd, J = 12.3, 7.9, 4.3 Hz, 1H), 2.94 (dt, J = 12.7, 4.5 Hz, 1H), 2.77–2.62 (m, 2H), 2.03 (dq, J = 14.7, 7.4 Hz, 1H), 1.85 (dq, J = 14.6, 7.3 Hz, 1H), 1.03 (t, J = 7.4 Hz, 3H); 13C NMR (126 MHz, CDCl3) δ 174.8, 173.5, 139.1, 136.6, 134.6, 131.6, 128.7, 128.4, 128.2, 127.8, 127.4, 118.2, 70.2, 52.7, 45.4, 42.6, 40.1, 28.7, 9.7; IR (Neat Film, NaCl) 3062, 3028, 2976, 2837, 1682, 1601, 1583, 1495, 1450, 1376, 1284, 1152, 1069, 1027, 1002, 967, 915, 879, 793, 722 cm−1; HRMS (MM: ESI-APCI) m/z calc’d for C23H27N2O2 [M+H]+: 363.2067, found 363.2078; [α]D25.0 +26.7 (c 1.00, CHCl3, 97% ee).

(S)-3-Allyl-1-benzoyl-4-benzyl-3-isobutylpiperazin-2-one (9i)

Ketopiperazine 9i was isolated by flash column chromatography (SiO2, 8% Et2O in hexanes to 10% Et2O in hexanes) as a yellow oil. 69% yield. Rf = 0.6 (20% E2O in hexanes); 1H NMR (500 MHz, CDCl3) δ 7.56 (m, 2H), 7.52–7.44 (m, 1H), 7.38 (m, 6H), 7.33–7.27 (m, 1H), 5.95 (ddt, J = 17.1, 10.1, 7.3 Hz, 1H), 5.26–5.11 (m, 2H), 4.00 (d, J = 14.0 Hz, 1H), 3.83–3.73 (m, 2H), 3.71 (d, J = 14.0 Hz, 1H), 3.09 (ddd, J = 13.4, 9.9, 3.8 Hz, 1H), 2.92 (dt, J = 12.7, 3.8 Hz, 1H), 2.79 (dd, J = 14.2, 7.0 Hz, 1H), 2.63 (dd, J = 14.1, 7.6 Hz, 1H), 2.09–1.91 (m, 2H), 1.80–1.67 (m, 1H), 0.89 (d, J = 2.9 Hz, 3H), 0.88
(d, J = 2.9 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 175.0, 173.0, 138.8, 136.6, 134.4, 131.6, 128.8, 128.1, 128.1, 127.9, 127.4, 118.2, 68.6, 53.0, 45.5, 43.9, 42.4, 40.0, 24.7, 24.4, 22.5; IR (Neat Film, NaCl) 3062, 3027, 2955, 2868, 1682, 1600, 1495, 1468, 1450, 1399, 1365, 1284, 1220, 1153, 1113, 1024, 984, 917, 843, 794, 724 cm$^{-1}$; HRMS (MM: ESI-APCI) $m/z$ calc'd for C$_{25}$H$_{31}$N$_2$O$_2$ [M+H]$^+$: 391.2380, found 391.2388; [$\alpha$]$_D$$^{25.0}$ +24.6 (c 1.00, CHCl$_3$, 85% ee).

(R)-3-Allyl-1-benzoyl-3,4-dibenzylpiperazin-2-one (9j)

\[ \text{Ketopiperazine 9j was isolated by flash column chromatography (SiO$_2$, hexanes to 10\% EtOAc in hexanes) as a colorless oil. 99\% yield. R$_f$ = 0.6 (20\% EtOAc in hexanes); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.48 (dd, J = 7.6, 2.6 Hz, 2H), 7.44–7.34 (m, 2H), 7.34–7.14 (m, 11H), 6.06 (ddt, J = 17.3, 10.2, 7.2 Hz, 1H), 5.40–5.06 (m, 2H), 4.14 (d, J = 13.9 Hz, 1H), 3.92 (d, J = 13.9 Hz, 1H), 3.60 (ddd, J = 12.2, 6.0, 3.7 Hz, 1H), 3.49–3.33 (m, 2H), 3.06 (d, J = 14.3 Hz, 1H), 2.97–2.80 (m, 3H), 2.74 (ddd, J = 12.7, 6.0, 3.7 Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 174.4, 173.1, 137.7, 136.5, 134.2, 131.6, 130.8, 128.6, 128.5, 128.3, 128.1, 127.9, 127.4, 126.8, 118.8, 71.5, 52.8, 45.2, 42.5, 42.1, 41.6; IR (Neat Film, NaCl) 3062, 3029, 2929, 2848, 1683, 1622, 1495, 1450, 1339, 1283, 1223, 1153, 1096, 1028, 993, 918 cm$^{-1}$; HRMS (MM: ESI-APCI) $m/z$ calc'd for C$_{28}$H$_{29}$N$_2$O$_2$ [M+H]$^+$: 425.2224, found 425.2224; [$\alpha$]$_D$$^{25.0}$ +31.8 (c 1.00, CHCl$_3$, 97% ee).}

(R)-3-Allyl-1-benzoyl-4-benzyl-3-[(benzyloxy)methyl]piperazin-2-one (9k)

\[ \text{Ketopiperazine 9k was isolated by flash column chromatography (SiO$_2$, 5\% EtOAc in hexanes to 10\% EtOAc in hexanes) as a colorless oil. 56\% yield. R$_f$ = 0.7 (15\% EtOAc
in hexanes); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.68–7.60 (m, 2H), 7.49–7.43 (m, 1H), 7.43–7.26 (m, 12H), 6.00 (ddt, $J = 17.2, 10.2, 7.0$ Hz, 1H), 5.19–5.14 (m, 1H), 5.12 (dd, $J = 17.1, 1.7$ Hz, 1H), 4.64 (d, $J = 11.9$ Hz, 1H), 4.56 (d, $J = 11.9$ Hz, 1H), 4.06 (d, $J = 13.6$ Hz, 1H), 3.94–3.85 (m, 2H), 3.82 (dt, $J = 12.2, 3.1$ Hz, 1H), 3.70–3.58 (m, 2H), 3.41 (td, $J = 11.6, 3.1$ Hz, 1H), 2.85 (dt, $J = 12.0, 3.4$ Hz, 1H), 2.54 (dd, $J = 14.4, 7.4$ Hz, 1H), 2.43 (dd, $J = 14.4, 6.5$ Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 174.4, 173.3, 139.2, 137.9, 136.1, 133.4, 131.6, 128.7, 128.6, 128.6, 128.3, 128.0, 127.8, 127.3, 118.6, 75.8, 73.9, 70.3, 52.9, 45.2, 43.9, 37.9; IR (Neat Film, NaCl) 3063, 3029, 2953, 2923, 2862, 1686, 1601, 1495, 1451, 1403, 1373, 1326, 1284, 1246, 1224, 1154, 1111, 1028, 985, 915, 848, 794, 748 cm$^{-1}$; HRMS (MM: ESI-APCI) m/z calc'd for C$_{29}$H$_{31}$N$_2$O$_3$ [M+H]$^+$: 455.2329, found 455.2325; $\left[\alpha\right]_D^{25.0} -20.3$ (c 1.00, CHCl$_3$, 95% ee).

(S)-1-Benzoyl-4-benzyl-3-methyl-3-(2-phenylallyl)piperazin-2-one (9l)

![Chemical Structure](image)

Ketopiperazine 9l was isolated by flash column chromatography (SiO$_2$, 5% acetone in hexanes) as a colorless oil. 77% yield. R = 0.4 (15% acetone in hexanes) $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.44 (dd, $J = 18.2, 7.6$ Hz, 3H), 7.39 – 7.19 (m, 12H), 5.38 (s, 1H), 5.29 (s, 1H), 4.04 (d, $J = 13.3$ Hz, 1H), 3.61 (d, $J = 12.3$ Hz, 1H), 3.44 (d, $J = 15.6$ Hz, 1H), 3.34 (d, $J = 13.1$ Hz, 1H), 3.29 (d, $J = 3.6$ Hz, 1H), 2.94 (d, $J = 15.6$ Hz, 1H), 2.80 (d, $J = 12.6$ Hz, 1H), 2.74 – 2.62 (m, 1H), 1.47 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 174.2, 173.9, 146.1, 142.2, 138.7, 136.6, 131.3, 128.8, 128.5, 128.1, 128.0, 127.8, 127.5, 127.4, 127.3, 117.3, 67.2, 53.4, 44.9, 42.7, 42.2, 19.6; IR (Neat Film, NaCl) 3059, 3027, 2933, 2829, 1682, 1600, 1494, 1449, 1379, 1363, 1317, 1287, 1223, 1146, 1133, 1074, 1028, 967, 945, 908, 850, 794, 778, 726 cm$^{-1}$; HRMS (MM: ESI-APCI) m/z calc'd for C$_{28}$H$_{29}$N$_2$O$_2$ [M+H]$^+$: 425.2224, found 425.2214; $\left[\alpha\right]_D^{25.0} -73.3$ (c 1.00, CHCl$_3$, 96% ee).
(S)-1-Benzoyl-4-benzyl-3-(2-chloroallyl)-3-methylpiperazin-2-one (9m)

Ketopiperazine 9m was isolated by flash column chromatography (SiO₂, 5% EtOAc in hexanes) as a colorless oil. 60% yield. Rf = 0.4 (20% EtOAc in hexanes).

1H NMR (500 MHz, CDCl₃) δ 7.60 – 7.53 (m, 2H), 7.53 – 7.45 (m, 1H), 7.40 (td, J = 6.8, 1.3 Hz, 4H), 7.34 (td, J = 6.7, 6.2, 1.6 Hz, 2H), 7.31 – 7.27 (m, 1H), 5.27 (t, J = 1.1 Hz, 1H), 5.24 (t, J = 1.3 Hz, 1H), 4.02 (d, J = 13.5 Hz, 1H), 3.80 (dt, J = 13.5 Hz, 1H), 3.73 (ddd, J = 12.3, 9.9, 2.6 Hz, 2H), 1.49 (s, 3H); 13C NMR (126 MHz, CDCl₃) δ 174.3, 174.0, 139.0, 138.5, 136.5, 131.6, 128.7, 128.6, 128.2, 127.9, 127.5, 115.9, 66.0, 53.5, 45.8, 45.0, 42.5, 18.9; IR (Neat Film, NaCl) 3062, 3029, 2938, 2849, 1682, 1633, 1600, 1495, 1449, 1399, 1378, 1364, 1322, 1287, 1242, 1210, 1178, 1157, 1135, 1080, 1062, 1030, 997, 968, 944, 879, 850, 794, 725 cm⁻¹; HRMS (MM: ESI-APCI) m/z calcd for C₂₂H₂₄N₂O₂Cl [M+H]⁺: 383.1521, found 383.1523. [α]D 25.0 -97.0 (c 1.00, CHCl₃, 98% ee).

(S)-9α-Allyl-2-benzoylhexahydro-2H-pyrido[1,2-α]pyrazin-1(6H)-one (9n)

Bicyclic ketopiperazine 9n was isolated by flash column chromatography (SiO₂, 15% EtOAc and 1% NEt₃ in hexanes) as a colorless oil. 68% yield. Rf = 0.4 (25% EtOAc in hexanes).

1H NMR (500 MHz, CDCl₃) δ 7.56–7.49 (m, 2H), 7.50–7.43 (m, 1H), 7.41–7.34 (m, 2H), 5.82 (ddt, J = 16.9, 10.1, 7.6, Hz, 1H), 5.25–5.10 (m, 2H), 4.09 (ddt, J = 12.7, 9.7, 5.2 Hz, 1H), 3.72 (dt, J = 12.7, 4.5 Hz, 1H), 3.39 (ddd, J = 13.8, 9.9, 4.8 Hz, 1H), 3.04 (dt, J = 13.3, 4.6 Hz, 1H), 3.00–2.90 (m, 1H), 2.75 (ddt, J = 21.0, 14.5, 6.9 Hz,
(S)-3-Allyl-1-benzoyl-4-benzyl-3-methyl-1,4-diazepan-2-one (9o)

Ketopiperazine 9o was isolated by flash column chromatography (SiO2, 5% EtOAc in hexanes to 10% EtOAc in hexanes) as a yellow oil. 89% yield. Rf = 0.4 (10% EtOAc in hexanes); 1H NMR (500 MHz, CDCl3) δ 7.64–7.53 (m, 2H), 7.53–7.44 (m, 1H), 7.44–7.31 (m, 6H), 7.31–7.27 (m, 1H), 6.10–5.92 (m, 1H), 5.28–5.15 (m, 2H), 4.30 (ddd, J = 12.0, 8.0, 3.4 Hz, 1H), 4.11 (ddd, J = 14.1, 6.5, 3.8 Hz, 1H), 3.98 (d, J = 13.8 Hz, 1H), 3.85 (d, J = 13.8 Hz, 1H), 2.96 (m, 2H), 2.80 (dd, J = 14.7, 7.0 Hz, 1H), 2.69 (dd, J = 14.7, 7.4 Hz, 1H), 1.81–1.62 (m, 2H), 1.53 (s, 3H); 13C NMR (126 MHz, CDCl3) δ 179.5, 175.6, 140.0, 137.0, 133.8, 131.3, 128.5, 128.5, 128.3, 127.7, 127.3, 118.8, 69.8, 52.4, 45.6, 42.7, 42.4, 26.5, 22.0; IR (Neat Film, NaCl) 3063, 3028, 2976, 2941, 2850, 2252, 1682, 1600, 1583, 1494, 1450, 1376, 1353, 1279, 1228, 1210, 1175, 1076, 1023, 966, 918, 872, 848, 790, 737 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc'd for C23H27N2O2 [M+H]^+: 363.2067, found 363.2066; [α]D 25.0 +2.0 (c 1.00, CHCl3, 59% ee).

(S)-3-Allyl-1-benzoyl-3-methyl-4-phenylpiperazin-2-one (9p)

(S)-3-Allyl-1-benzoyl-4-benzyl-3-methyl-1,4-diazepan-2-one (9o)

Ketopiperazine 9o was isolated by flash column chromatography (SiO2, 5% EtOAc in hexanes to 10% EtOAc in hexanes) as a yellow oil. 89% yield. Rf = 0.4 (10% EtOAc in hexanes); 1H NMR (500 MHz, CDCl3) δ 7.64–7.53 (m, 2H), 7.53–7.44 (m, 1H), 7.44–7.31 (m, 6H), 7.31–7.27 (m, 1H), 6.10–5.92 (m, 1H), 5.28–5.15 (m, 2H), 4.30 (ddd, J = 12.0, 8.0, 3.4 Hz, 1H), 4.11 (ddd, J = 14.1, 6.5, 3.8 Hz, 1H), 3.98 (d, J = 13.8 Hz, 1H), 3.85 (d, J = 13.8 Hz, 1H), 2.96 (m, 2H), 2.80 (dd, J = 14.7, 7.0 Hz, 1H), 2.69 (dd, J = 14.7, 7.4 Hz, 1H), 1.81–1.62 (m, 2H), 1.53 (s, 3H); 13C NMR (126 MHz, CDCl3) δ 179.5, 175.6, 140.0, 137.0, 133.8, 131.3, 128.5, 128.5, 128.3, 127.7, 127.3, 118.8, 69.8, 52.4, 45.6, 42.7, 42.4, 26.5, 22.0; IR (Neat Film, NaCl) 3063, 3028, 2976, 2941, 2850, 2252, 1682, 1600, 1583, 1494, 1450, 1376, 1353, 1279, 1228, 1210, 1175, 1076, 1023, 966, 918, 872, 848, 790, 737 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc'd for C23H27N2O2 [M+H]^+: 363.2067, found 363.2066; [α]D 25.0 +2.0 (c 1.00, CHCl3, 59% ee).
Ketopiperazine 9p was isolated by flash column chromatography (SiO2, 5% EtOAc in hexanes to 10% EtOAc in hexanes) as a colorless oil. 83% yield. R_f = 0.6 (15% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.64–7.55 (m, 2H), 7.48 (tt, J = 6.9, 1.3 Hz, 1H), 7.44–7.36 (m, 2H), 7.33 (td, J = 7.4, 1.9 Hz, 2H), 7.24–7.12 (m, 3H), 6.24–6.10 (m, 1H), 5.26–5.20 (m, 1H), 5.17 (dq, J = 17.2, 1.6 Hz, 1H), 4.11 (ddd, J = 12.3, 4.6, 3.5 Hz, 1H), 3.85 (ddd, J = 12.4, 9.3, 3.9 Hz, 1H), 3.71–3.55 (m, 1H), 3.47 (dt, J = 12.7, 4.2 Hz, 1H), 2.63 (dd, J = 15.2, 7.6 Hz, 1H), 2.56 (ddt, J = 15.2, 5.6, 1.6 Hz, 1H), 1.31 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 175.2, 174.0, 147.9, 136.3, 134.0, 131.6, 128.8, 128.1, 127.8, 126.8, 125.2, 118.6, 68.1, 46.2, 45.3, 42.9, 21.8; IR (Neat Film, NaCl) 3062, 3032, 2975, 2933, 2844, 1683, 1597, 1492, 1449, 1373, 1323, 1284, 1229, 1177, 1128, 1026, 1002, 961, 918, 835, 792, 773, 723 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc'd for C₂₁H₂₃N₂O₂ [M+H]⁺: 335.1754, found 335.1757; [α]D ⁰= +25.2 (c 1.00, CHCl₃, 94% ee).

(S)-3-Allyl-1-benzoyl-3,4-dimethylpiperazin-2-one (9q)

Ketopiperazine 9q was isolated by flash column chromatography (SiO₂, 5% acetone in hexanes) as a colorless oil. 88% yield. R_f = 0.5 (10% acetone in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.53 (dd, J = 8.3, 1.3 Hz, 2H), 7.50–7.43 (m, 1H), 7.42–7.33 (m, 2H), 5.95–5.79 (m, 1H), 5.14–5.10 (m, 1H), 5.10–5.05 (m, 1H), 3.90 (dt, J = 12.3, 3.6 Hz, 1H), 3.73 (ddd, J = 12.3, 10.4, 4.7 Hz, 1H), 3.04 (ddt, J = 14.2, 10.4, 3.9 Hz, 1H), 2.95 (dd, J = 12.8, 4.1 Hz, 1H), 2.73 (dd, J = 14.8, 7.2 Hz, 1H), 2.41 (app s, 4H), 1.32 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 175.1, 174.5, 136.3, 134.0, 131.6, 128.2, 127.7, 117.7, 66.6, 46.7, 44.7, 40.9, 37.4, 17.3; IR (Neat Film, NaCl) 3072, 2977, 2948, 2849, 2809, 1685, 1600, 1450, 1368, 1318, 1286, 1261, 1217, 1153, 1085, 949, 911, 845, 794, 752, 724 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc'd for C₁₆H₂₁N₂O₂ [M+H]⁺: 273.1598, found 273.1598; [α]D ⁰= −66.6 (c 1.00, CHCl₃, 82% ee).
(S)-3-Allyl-1-benzoyl-4-benzylpiperazin-2-one (11a)

Ketopiperazine **11a** was isolated by flash column chromatography (SiO₂, 5% EtOAc in hexanes to 10% EtOAc in hexanes) as a colorless oil. 89% yield. Rᵣ = 0.6 (20% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.61–7.54 (m, 2H), 7.53–7.45 (m, 1H), 7.43–7.34 (m, 6H), 7.34–7.28 (m, 1H), 6.12–5.91 (m, 1H), 5.26–5.16 (m, 2H), 4.08 (d, J = 13.3 Hz, 1H), 4.02 (ddd, J = 12.7, 4.6, 3.7 Hz, 1H), 3.62 (ddd, J = 12.7, 9.6, 4.0 Hz, 1H), 3.43 (d, J = 13.3 Hz, 1H), 3.39–3.32 (m, 1H), 3.14 (dt, J = 12.7, 4.2 Hz, 1H), 2.92–2.80 (m, 1H), 2.80–2.71 (m, 1H), 2.57 (ddd, J = 13.0, 9.6, 3.6 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 173.9, 172.2, 137.5, 136.0, 134.1, 131.7, 129.0, 128.7, 128.1, 127.7, 118.0, 66.8, 58.3, 46.4, 44.0, 34.6; IR (Neat Film, NaCl) 3062, 3028, 2947, 2899, 2811, 1683, 1450, 1283, 1229, 1140, 1072, 1028, 993, 917, 794 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc’d for C₂₁H₂₃N₂O₂ [M+H]⁺: 335.1754, found 335.1758; [α]D₂⁵ 0.0 ± 20.8 (c 1.00, CHCl₃, 98% ee).

(S)-1-Benzoyl-4-benzyl-3-(2-methylallyl)piperazin-2-one (11b)

Ketopiperazine **11b** was isolated as an yellow oil by flash column chromatography (SiO₂, 5% EtOAc in hexanes). 74% yield. Rᵣ = 0.4 (20% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.56–7.55 (m, 2H), 7.49 (tt, J = 6.9, 1.3, 1H), 7.43–7.37 (m, 2H), 7.35 (d, J = 4.8, 4H), 7.32–7.27 (m, 1H), 4.91 (d, J = 15.8, 2H), 4.15–3.89 (m, 2H), 3.76–3.59 (m, 1H), 3.59–3.48 (m, 1H), 3.49–3.36 (m, 1H), 3.33–3.10 (m, 1H), 2.95–2.75 (m, 1H), 2.67 (tq, J = 16.0, 8.9, 2H), 1.74 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 174.1, 172.8, 136.0, 131.8, 129.4, 129.1, 128.7, 128.2, 128.1, 114.0, 110.1, 65.0, 58.4, 45.3, 38.6, 31.1, 22.6; IR (Neat Film, NaCl) 3067, 3027, 2923, 2852, 1685, 1597, 1512, 1449, 1364, 1318, 1283, 1156, 1133, 1073, 1027, 945, 895, 795, 728 cm⁻¹; HRMS (MM: ESI-APCI) m/z
calc'd for C_{22}H_{25}N_{2}O_{2} [M+H]^+: 349.1911, found 349.1914; \[\alpha\]_D^{25.0} -18.3 (c 0.27, CHCl_3, 97% ee).

(S)-1-Benzoyl-4-benzyl-3-(2-chloroallyl)piperazin-2-one (11c)

![Chemical Structure](image)

Ketopiperazine 11c was isolated as an yellow oil by flash column chromatography (SiO_2, 5% acetone in hexanes). 52% yield. R_f = 0.6 (15% EtOAc in hexanes); \(^1\)H NMR (500 MHz, CDCl_3) \(\delta\) 7.59–7.53 (m, 2H), 7.53–7.46 (m, 1H), 7.44–7.27 (m, 7H), 5.38–5.30 (m, 2H), 4.18–4.04 (m, 1H), 4.04–3.93 (m, 1H), 3.80–3.67 (m, 1H), 3.65–3.45 (m, 2H), 3.16 (ddd, \(J\) = 27.2, 8.8, 3.8, 2H), 3.01 (dd, \(J\) = 15.2, 5.4, 1H), 2.65 (ddd, \(J\) = 12.7, 8.8, 3.6, 1H); \(^1^3\)C NMR (126 MHz, CDCl_3) \(\delta\) 173.6, 171.5, 138.8, 135.8, 131.9, 129.1, 128.8, 128.3, 128.1, 127.9, 115.8, 110.1, 64.4, 58.5, 45.8, 43.3, 40.0; IR (Neat Film, NaCl) 3062, 3030, 2953, 2816, 1682, 1634, 1601, 1450, 1383, 1366, 1283, 1227, 1162, 1140, 1073, 1022, 910, 795, 746 cm\(^{-1}\); HRMS (MM: ESI-APCI) \(m/z\) calc'd for C_{21}H_{22}N_{2}O_{2} [M+H]^+: 369.1364, found 369.1371; \([\alpha]\)_D^{25.0} -28.9 (c 0.36, CHCl_3, 87% ee).

(S)-1-Benzoyl-4-benzyl-3-(2-phenylallyl)piperazin-2-one (11d)

![Chemical Structure](image)

Ketopiperazine 11d was isolated as an yellow oil by flash column chromatography (SiO_2, 10% EtOAc in hexanes). 72% yield. R_f = 0.5 (20% EtOAc in hexanes); \(^1\)H NMR (500 MHz, CDCl_3) \(\delta\) 7.55–7.50 (m, 2H), 7.49 (dt, \(J\) = 7.0, 1.5, 1H), 7.44–7.36 (m, 4H), 7.29 (ddd, \(J\) = 12.5, 6.7, 2.8, 6H), 7.25–7.19 (m, 2H), 5.35 (d, \(J\) = 25.9, 2H), 3.93 (ddd, \(J\) = 12.9, 7.3, 4.5, 2H), 3.53 (ddd, \(J\) = 12.3, 7.6, 3.8, 1H), 3.43 (dd, \(J\) = 12.1, 4.1, 2H), 3.23 (qd, \(J\) = 14.9, 5.8, 2H), 3.12 (ddd, \(J\) = 13.0, 6.4, 3.9, 1H), 2.58 (ddd, \(J\) = 12.4, 7.7, 3.8, 1H); \(^1^3\)C NMR (126 MHz, CDCl_3) \(\delta\) 173.6, 172.7, 145.5, 140.4, 137.6, 135.9, 131.6, 128.8, 128.4, 128.1, 127.9, 127.6, 127.4, 126.7, 116.0, 65.3, 58.3, 44.6, 43.1, 37.5;
IR (Neat Film, NaCl) 3059, 3029, 2924, 2852, 1682, 1600, 1494, 1449, 1364, 1283, 1222, 1156, 1073, 1028, 903, 780, 732 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc'd for C₂₇H₂₇N₂O₂ [M+H]⁺: 411.2067, found 411.2070; [α]D 25.0° −7.3 (c 1.00, CHCl₃, 99% ee).

Procedures for Preparation of α-Quaternary Piperazines

(S)-3-Allyl-4-benzyl-3-methylpiperazin-2-one (12)

Ketopiperazine 9b (56.0 mg, 0.16 mmol) was taken up in MeOH (4 mL) and H₂O (4 mL) and stirred with lithium hydroxide monohydrate (10.0 mg, 0.24 mmol) for 16 hours open to air. Reaction mixture was then diluted with EtOAc and washed once with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the organic layers were combined, washed once with brine, dried with Na₂SO₄, and concentrated under reduced pressure to give 12 as a white solid. 76% yield. Rf = 0.3 (50% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.31 (d, J = 7.5, 2H), 7.24–7.13 (m, 1H), 6.13 (s, 1H), 5.99–5.86 (m, 1H), 5.09–4.99 (m, 2H), 3.92 (d, J = 13.7, 1H), 3.26 (d, J = 13.8, 1H), 3.24–3.18 (m, 1H), 2.99 (dq, J = 11.0, 3.3, 1H), 2.83–2.70 (m, 1H), 2.67–2.52 (m, 2H), 2.48 (dd, J = 14.6, 7.3, 1H), 1.31 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 174.6, 139.7, 134.8, 128.6, 128.5, 127.2, 117.1, 65.7, 52.9, 41.9, 41.8, 41.4, 18.2; IR (Neat Film, NaCl) 3435, 3304, 3193, 3077, 2971, 2936, 2809, 1664, 1489, 1451, 1418, 1381, 1361, 1345, 1260, 1202, 1169, 1104, 1085, 1030, 990, 908, 875, 750 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc'd for C₁₅H₂₁N₂O [M+H]⁺: 245.1648, found 245.1638; [α]D 25.0° −32.1 (c 0.90, CHCl₃, 91% ee).
(S)-2-Allyl-1-benzyl-2-methylpiperazine (13)

Ketopiperazine 12 (48.0 mg, 0.20 mmol) was taken up in THF (1.0 mL) and added dropwise to a stirred suspension of LiAlH4 (22.0 g, 0.59 mmol) in 1.0 mL of THF. It was allowed to stir under Ar atmosphere at reflux for 16 hours. The reaction mixture was then cooled to 23 °C and 0.2 mL of water was added dropwise followed by 0.2 mL of 2 N NaOH aqueous solution and 0.6 mL of water. It was allowed to stir for 20 minutes. The reaction mixture was then transferred to a separatory funnel using 10 mL of EtOAc. The organic layer was washed with a saturated solution of Rochelle’s salt (1 x 10 mL) and then the organic layer was washed with brine (1 x 10 mL), dried with Na2SO4, and concentrated under reduced pressure to give 13 as a colorless oil. 99% yield. Rf = 0.3 (5% MeOH in CH2Cl2); 1H NMR (500 MHz, CDCl3) δ 7.28 (d, J = 7.5 Hz, 2H), 7.23 (t, J = 7.5 Hz, 2H), 7.15 (t, J = 7.2 Hz, 1H), 5.85 (ddt, J = 14.7, 10.2, 7.4 Hz, 1H), 5.06 – 4.97 (m, 2H), 3.56 (d, J = 13.8 Hz, 1H), 3.42 (d, J = 12.4 Hz, 1H), 2.79 (d, J = 12.4 Hz, 1H), 2.72 (dt, J = 6.8, 2.9 Hz, 2H), 2.55 (dd, J = 13.9, 7.4 Hz, 1H), 2.49 (d, J = 12.4 Hz, 1H), 2.38 (ddd, J = 11.9, 5.7, 4.1 Hz, 1H), 2.33 – 2.22 (m, 1H), 2.08 (dd, J = 14.0, 7.4 Hz, 1H), 1.04 (s, 3H); The signal of the NH was not detected; 13C NMR (126 MHz, CDCl3) δ 140.6, 134.9, 128.6, 128.3, 126.7, 117.4, 55.6, 55.5, 53.5, 46.9, 46.8, 29.9; IR (Neat Film, NaCl) 3063, 3025, 2929, 2799, 1494, 1452, 1363, 1313, 1139, 1070, 1028, 991, 910, 822, 727 cm–1; HRMS (MM: ESI-APCI) m/z calc'd for C15H23N2 [M+H]+: 231.1856, found 231.1839; [α]D 25.0 –4.6 (c 0.625, CHCl3).

Procedures for the Deprotection and Functionalization of α-Quaternary Piperazin-2-ones
(S)-3-Allyl-4-(4-methoxybenzyl)-3-methylpiperazin-2-one (14)

Ketopiperazine 9c (25.0 mg, 0.07 mmol) was taken up in MeOH (1.5 mL) and H₂O (1.5 mL) and stirred with lithium hydroxide monohydrate (4.0 mg, 0.10 mmol) for 16 hours open to air. Reaction mixture was then diluted with EtOAc and washed once with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the organic layers were combined, washed once with brine, dried with Na₂SO₄, and concentrated under reduced pressure on to silica. Deprotected ketopiperazine 14 was isolated as a white solid by flash column chromatography (SiO₂, 50% EtOAc in hexanes). 93% yield. Rᵣ= 0.3 (50% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.40 – 7.17 (m, 2H), 6.86 (d, J = 8.6 Hz, 2H), 6.34 (s, 1H), 6.00 (ddt, J = 17.1, 10.3, 7.0 Hz, 1H), 5.24 – 4.98 (m, 2H), 3.92 (d, J = 13.5 Hz, 1H), 3.81 (s, 3H), 3.27 (t, J = 9.7 Hz, 2H), 3.06 (dq, J = 10.8, 3.3 Hz, 1H), 2.83 (dd, J = 14.7, 6.5 Hz, 1H), 2.64 (dd, J = 8.9, 3.4 Hz, 2H), 2.56 (dd, J = 14.6, 7.4 Hz, 1H), 1.37 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 174.7, 158.8, 134.9, 131.6, 129.8, 117.0, 113.8, 65.6, 55.4, 52.2, 41.8, 41.7, 41.3, 18.2; IR (Neat Film, NaCl) 3202, 3073, 2935, 2833, 1667, 1611, 1511, 1488, 1455, 1360, 1344, 1301, 1245, 1168, 1104, 1082, 1034, 989, 909, 824, 799, 731 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc’d for C₁₆H₂₃N₂O₂ [M+H]⁺: 275.1754, found 275.1730; [α]D ²⁵.⁰ –21.3 (c 1.00, CHCl₃).

(S)-1,3-Diallyl-4-(4-methoxybenzyl)-3-methylpiperazin-2-one (15)

Ketopiperazine 14 (13.0 mg, 0.05 mmol) was taken up in THF (0.5 mL) and stirred with sodium hydride (3.0 mg, 0.07 mmol) for 5 minutes at 0 °C. Then allyl bromide (0.01 mL,
0.07 mmol) was added neat dropwise and the reaction was allowed to stir at 0 °C until TLC analysis indicated full consumption of the starting material. The reaction mixture was warmed to 23 °C and was then diluted with 5 mL of EtOAc and poured into 5 mL of water. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the organic layers were combined, washed once with brine, dried with Na₂SO₄, and concentrated under reduced pressure on to silica. Allylated ketopiperazine 15 was isolated as a colorless oil by flash column chromatography (SiO₂, 20% EtOAc in hexanes). 65% yield. Rf = 0.6 (50% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.27 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 5.92 (ddt, J = 17.2, 10.2, 7.0 Hz, 1H), 5.82 – 5.66 (m, 1H), 5.19 – 5.12 (m, 2H), 5.12 – 5.02 (m, 2H), 4.07 (dd, J = 15.0, 5.8 Hz, 1H), 3.96 – 3.83 (m, 2H), 3.80 (s, 3H), 3.72 (dd, J = 11.5, 10.0, 5.4 Hz, 1H), 3.22 (d, J = 13.4 Hz, 1H), 2.92 (dt, J = 11.4, 3.1 Hz, 1H), 2.86 (dd, J = 14.6, 6.6 Hz, 1H), 2.63 (tt, J = 7.7, 3.9 Hz, 2H), 2.52 (dd, J = 14.5, 7.3 Hz, 1H), 1.35 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 172.0, 158.8, 135.1, 132.9, 131.6, 129.8, 117.4, 116.9, 113.8, 65.7, 55.4, 52.4, 50.0, 46.7, 41.9, 41.7, 18.2; IR (Neat Film, NaCl) 3072, 2932, 2834, 1716, 1641, 1512, 1485, 1456, 1381, 1360, 1301, 1246, 1169, 1035, 990, 916, 826, 780, 756 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc'd for C₁₉H₂₇N₂O₂ [M+H]+: 315.2067, found 315.2097; [α]D ²⁵.0 –16.6 (c 0.62, CHCl₃).

**Ethyl (S,E)-4-(4-benzoyl-1-(4-methoxybenzyl)-2-methyl-3-oxopiperazin-2-yl)but-2-enoate (16)**

Ketopiperazine 9c (20.0 mg, 0.05 mmol) was taken up in CH₂Cl₂ (0.5 mL) and stirred with trifluoroacetic acid (5.0 mL, 0.06 mmol) for 5 minutes at 23 °C. Then ethyl acrylate (60.0 mL, 0.53 mmol) was added neat dropwise followed by the addition of the o-tolyl-NHC Hoveyda-Grubbs catalyst (3 mg, 0.005 mmol) and the reaction was allowed to stir
at 23 °C for seven days. The reaction mixture was concentrated under reduced pressure directly on to silica. Ketopiperazine 16 was isolated as a colorless oil by flash column chromatography (SiO₂, 10% EtOAc in hexanes to 20% EtOAc in hexanes). 47% yield. 

Rₜ = 0.2 (20% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.55 – 7.51 (m, 2H), 7.51 – 7.45 (m, 1H), 7.43 – 7.36 (m, 2H), 7.26 (d, J = 8.5 Hz, 2H), 7.15 (dt, J = 15.5, 7.3 Hz, 1H), 6.91 – 6.84 (m, 2H), 5.93 – 5.85 (m, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.92 (d, J = 13.3 Hz, 1H), 3.88 – 3.82 (m, 1H), 3.81 (s, 3H), 3.58 (ddd, J = 12.3, 10.8, 4.4 Hz, 1H), 3.35 (d, J = 13.4 Hz, 1H), 3.00 (ddd, J = 15.3, 7.3, 1.3 Hz, 1H), 2.92 – 2.84 (m, 1H), 2.79 (ddd, J = 12.9, 10.8, 3.6 Hz, 1H), 2.72 (ddd, J = 15.3, 7.3, 1.3 Hz, 1H), 1.47 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 174.5, 174.3, 166.3, 159.1, 144.3, 136.2, 131.7, 130.2, 129.6, 128.3, 127.7, 124.1, 114.1, 67.2, 60.5, 55.4, 52.4, 45.1, 42.0, 39.6, 18.5, 14.5; IR (Neat Film, NaCl) 2976, 2935, 2899, 2827, 1718, 1685, 1653, 1610, 1512, 1448, 1366, 1269, 1245, 1222, 1159, 1035, 977, 934, 821, 727, 694 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc'd for C₂₆H₃₁N₂O₅ [M+Na]⁺: 473.2047, found 473.2046; [α]D

²⁵.⁰ – 86.6 (c 0.62, CHCl₃).

(S)-3-Allyl-1-benzoyl-3-methylpiperazin-2-one (17)

To a 20 mL scintillation vial was added ketopiperazine 9c (16.0 mg, 0.04 mmol), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (19.0 mg, 0.08 mmol), 0.6 mL of CH₂Cl₂, 0.06 mL of H₂O, and a magnetic stir bar. The reaction was allowed to stir for 1.5 hours under ambient conditions at which point there was full conversion of the starting material by TLC. The reaction mixture was poured into 5 mL of saturated sodium bicarbonate and extracted with CH₂Cl₂ (4 x 5 mL). The combined organics were washed once with brine, dried with Na₂SO₄, filtered and concentrated under reduced pressure. Ketopiperazine 14 was isolated as a white solid by flash column chromatography (SiO₂, 5% MeOH in CH₂Cl₂). 75% yield. Rₜ = 0.4 (10% MeOH in CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ
7.53 (dd, J = 8.3, 1.3 Hz, 2H), 7.51 – 7.44 (m, 1H), 7.43 – 7.35 (m, 2H), 5.86 – 5.71 (m, 1H), 5.27 – 5.16 (m, 2H), 3.90 (dt, J = 12.6, 4.9 Hz, 1H), 3.79 (dd, J = 12.7, 7.6, 4.9 Hz, 1H), 3.36 – 3.14 (m, 2H), 2.77 (dd, J = 13.7, 6.8 Hz, 1H), 2.32 (dd, J = 13.8, 8.0 Hz, 1H), 1.44 (s, 3H); the signal of the NH was not detected; $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 176.1, 174.6, 136.2, 132.6, 131.7, 128.3, 127.7, 120.4, 60.6, 48.2, 43.0, 38.6, 25.1; IR (Neat Film, NaCl) 3073, 2968, 2926, 2853, 1682, 1601, 1583, 1463, 1449, 1371, 1313, 1285, 1212, 1177, 1152, 1111, 1071, 1022, 1001, 922, 795, 749, 727 cm$^{-1}$; HRMS (MM: ESI-APCI) m/z calc'd for C$_{15}$H$_{19}$N$_{2}$O$_{2}$ [M+H]$^+$: 259.1441, found 259.1432; $[\alpha]^\circ_{D}$ 25.0 $-$ 71.8 (c 0.87, CHCl$_3$).

**Procedures for Preparation of Imatinib Analogs**

**(E)-3-(Dimethylamino)-1-(pyridin-3-yl)prop-2-en-1-one (SI14)**

3-Acetylpyridine (2.42 g, 20.0 mmol), N,N-dimethylformamide diacetal (3.7 g, 31.0 mmol) and acetic acid (0.2 mL) were added to a 15 mL round-bottom flask equipped with a magnetic stirbar. The reaction was heated to 95 °C for 3 hours. It was then cooled to room temperature and poured into 10 mL of H$_2$O. The aqueous phase was extracted with CH$_2$Cl$_2$ (4 x 15 mL) and the combined organics were washed once with brine, dried with Na$_2$SO$_4$, and concentrated to yield SI14 as a red solid. 97% yield. Product identity was confirmed by comparison to previously reported characterization data.

**4-(Pyridin-3-yl)pyrimidin-2-amine (SI15)**
Pyridine **SI14** (2.70 g, 12.5 mmol) was taken up in 12.5 mL of $n$BuOH along with guanidine nitrate (1.53 g, 12.5 mmol) and NaOH (0.50 g, 12.5 mmol). The reaction mixture was refluxed for 20 hours. Upon cooling to room temperature, pyrimidine **SI15** precipitated from the solution and was collected by filtration, washed once with water, and dried under reduced pressure. 76% yield. Product identity was confirmed by comparison to previously reported characterization data.

**N-(2-Methyl-5-nitrophenyl)-4-(pyridin-3-yl)pyrimidin-2-amine (SI16)**

![Chemical structure of N-(2-Methyl-5-nitrophenyl)-4-(pyridin-3-yl)pyrimidin-2-amine (SI16)](image)

In a 50 mL round-bottom flask [Pd$_2$dba$_3$] (80.0 mg, 0.09 mmol), and rac-BINAP (130 mg, 0.21 mmol) were combined in 13 mL of dioxane and heated to 100 °C for 30 minutes under argon atmosphere. The resulting catalyst solution was cooled to room temperature and 2-bromo-1-methyl-4-nitrobenzene (376 mg, 1.74 mmol), prepared according to literature procedure,[7] **SI15** (300 mg, 1.74 mmol), and Cs$_2$CO$_3$ (1.14 g, 3.48 mmol) suspended in 5 mL of dioxane was then added. The reaction mixture was then heated to 100 °C for 24 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and nitro-arene compound **SI16** was isolated by flash column chromatography (SiO$_2$, 100% CH$_2$Cl$_2$ to 1% MeOH in CH$_2$Cl$_2$). 81% yield. Product identity was confirmed by comparison to previously reported characterization data.
6-Methyl-N¹-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (SI17)

In a 100 mL round-bottom flask was added nitro-arene compound SI16 (190 mg, 0.62 mmol) was dissolved in MeOH (50 mL). Then 40.0 mg of 20% Pd on carbon was added. After sparging the reaction mixture with hydrogen for 15 minutes, the reaction mixture was allowed to stir overnight under one atmosphere of hydrogen. The reaction mixture was carefully filtered through a plug of celite and concentrated to give aniline SI17. 99% yield. Product identity was confirmed by comparison to previously reported characterization data.

4-(Chloromethyl)-N-[4-methyl-3-[(4-(pyridin-3-yl)pyrimidin-2-yl)amino]-phenyl]-benzamide (21)

In a 15 mL round-bottom flask was added aniline SI17 (115 mg, 0.42 mmol), 4-(chloromethyl)benzoyl chloride (78.0 mg, 0.42 mmol) and triethylamine (120 µL, 0.83 mmol) were taken up in 4.2 mL of THF and allowed to stir for 3 hours at 23 ºC. Reaction mixture was then poured into 5 mL of H₂O and extracted with EtOAc (4 x 10 mL). The combined organics were washed with brine, dried with Na₂SO₄, filtered, and concentrated. Chloride 21 was isolated by flash column chromatography (SiO₂, 100%
CH$_2$Cl$_2$ to 5% MeOH in CH$_2$Cl$_2$). 64% yield. Product identity was confirmed by comparison to previously reported characterization data.

(S)-4-[(3-Allyl-4-benzyl-3-methylpiperazin-1-yl)methyl]-N-(4-methyl-3-[(4-(pyridin-3-yl)pyrimidin-2-yl)amino]phenyl)benzamide (18)

In a 5 mL round-bottom flask chloride 21 (13.0 mg, 0.03 mmol), piperazine 13 (10.0 mg, 0.04 mmol) and Cs$_2$CO$_3$ (0.020 g, 0.06 mmol) were taken up in 0.3 mL of dry DMF under Ar atmosphere and allowed to stir for 18 hours at room temperature. Imatinib analog 18 was isolated directly by flash column chromatography (SiO$_2$, CH$_2$Cl$_2$ to 3% MeOH in CH$_2$Cl$_2$). 42% yield. R$_f$ = 0.4 (10% MeOH in CH$_2$Cl$_2$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.24 (dd, $J$ = 2.2, 0.7 Hz, 1H), 8.70 (dd, $J$ = 4.8, 1.6 Hz, 1H), 8.59 (d, $J$ = 2.1 Hz, 1H), 8.56 – 8.47 (m, 2H), 8.01 (s, 1H), 7.89 (s, 1H), 7.83 (d, $J$ = 8.3 Hz, 2H), 7.46 (d, $J$ = 8.4 Hz, 2H), 7.44 – 7.38 (m, 1H), 7.38 – 7.26 (m, 4H), 7.25 – 7.14 (m, 2H), 7.04 (s, 1H), 5.93 – 5.71 (m, 1H), 5.11 – 4.92 (m, 2H), 3.66 – 3.41 (m, 3H), 2.95 (s, 2H), 2.88 (s, 2H), 2.79 – 2.60 (m, 1H), 2.61 – 2.39 (m, 3H), 2.35 (s, 3H), 2.10 (dd, $J$ = 13.9, 7.6 Hz, 2H), 1.12 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 165.6, 162.9, 162.7, 160.7, 159.1, 151.6, 148.6, 137.9, 137.9, 136.8, 135.1, 132.8, 130.9, 129.2, 129.0, 128.6, 128.4, 128.3, 127.1, 126.7, 124.3, 123.9, 117.2, 115.5, 113.3, 108.5, 62.7, 56.2, 54.3, 53.1, 46.5, 36.6, 31.6, 29.8, 17.8; IR (Neat Film, NaCl) 3292, 3054, 2923, 2853, 1666, 1579, 1551, 1450, 1417, 1265, 1204, 1114, 1021, 801, 751, 703 cm$^{-1}$; HRMS (MM: ESI-APCI) m/z calc'd for C$_{39}$H$_{42}$N$_7$O [M+H]$^+$: 624.3445, found 624.3456; [$\alpha$]$_{D}^{25.0}$ +2.3 (c 1.00, CHCl$_3$).
N-(4-Methyl-3-[(4-(pyridin-3-yl)pyrimidin-2-yl)amino]phenyl)-4-(piperazin-1-ylmethyl)benzamide (19)

In a 5 mL round bottom flask was added chloride 21 (15.0 mg, 0.04 mmol), piperazine (11.0 mg, 0.13 mmol), Cs₂CO₃ (34.0 mg, 0.11 mmol), and 0.4 mL of dry DMF under Ar atmosphere and allowed to stir for 18 hours at 23 ºC. Des-methyl imatinib (19) was isolated directly by flash column chromatography (SiO₂, 1% MeOH in CH₂Cl₂ to 3% MeOH in CH₂Cl₂). 48% yield. Product identity was confirmed by comparison to previously reported characterization data.

(S)-N-(4-Methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)-4-((3-methyl-3-propylpiperazin-1-yl)methyl)benzamide (20)

Ketopiperazine 13 (22.0 mg, 0.10 mmol) was taken up in 3.2 mL of MeOH and 2 mL of glacial acetic acid in a 10 mL round bottom flask. Pd on CaCO₃ (5.00 mg) was added. The reaction mixture was then sparged for 15 minutes with H₂ and allowed to stir under H₂ atmosphere for 16 hours. The reaction mixture was then carefully filtered through a plug of celite using MeOH and concentrated. Chloride 21 (41.0 mg, 0.10 mmol) and Cs₂CO₃ (124 mg, 0.38 mmol) were then added along with 1 mL of dry DMF. The
reaction was allowed to stir under Ar atmosphere for 48 hours. Imatinib analog 20 was isolated directly by flash column chromatography (SiO₂, CH₂Cl₂ to 5% MeOH and ~1% NMe₂Et in CH₂Cl₂). 4% yield. Rᵣ= 0.4 (15% MeOH and ~1% NMe₂Et in CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 9.24 (dd, J = 2.3, 0.8 Hz, 1H), 8.68 (dd, J = 4.8, 1.7 Hz, 1H), 8.58 (d, J = 1.8 Hz, 1H), 8.54 – 8.42 (m, 2H), 8.03 (s, 1H), 7.85 (d, J = 8.3 Hz, 2H), 7.41 (td, J = 6.3, 1.2 Hz, 3H), 7.31 (dd, J = 8.1, 2.0 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 7.16 (d, J = 5.2 Hz, 1H), 7.06 (s, 1H), 3.65 – 3.47 (m, 2H), 3.15 (t, J = 5.3 Hz, 2H), 2.68 (ddt, J = 17.2, 11.3, 6.5 Hz, 2H), 2.39 (s, 2H), 2.34 (s, 3H), 1.77 (pd, J = 13.1, 4.8 Hz, 2H), 1.38 (s, 4H), 1.21 (dtt, J = 12.8, 9.6, 4.6 Hz, 2H), 0.92 (t, J = 7.2 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 165.3, 162.7, 160.5, 159.0, 151.4, 148.5, 141.8, 137.8, 136.5, 134.9, 134.3, 132.6, 130.8, 129.0, 127.2, 124.3, 123.7, 115.4, 113.2, 108.4, 61.9, 59.8, 56.8, 50.7, 39.8, 17.7, 16.4, 14.4; IR (Neat Film, NaCl) 3247, 2960, 2775, 2481, 2212, 1658, 1581, 1532, 1447, 1418, 1318, 1289, 1046, 1019, 910, 801, 731 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc'd for C₃₂H₃₈N₇O [M+H]⁺: 536.3132, found 536.3138; [α]D 25.0 −8.4 (c 0.17, CHCl₃)

Procedures for the Cell Viability Assay

Human K562 chronic myelogenous leukemia (CML) cells were obtained from the American Type Culture Collection (ATCC). Cells were cultured in RPMI-1640 medium containing 10% fetal bovine serum (FBS) at 37 °C in 5% CO₂. MTS assays were performed for cell viability as instructed by the supplier (Promega, Madison, WI). Briefly, cells (10000/well) were seeded in 96-well plates and exposed to compounds in a cell culture incubator in a dose-dependent manner for 48 h. DMSO was used as the vehicle control. Viable cell numbers were determined by tetrazolium conversion to its formazan and absorbance was monitored at 490 nm using an automated ELISA plate reader. Each experiment was performed in quadruplicate. Data are mean ± SD.

References


### Determination of Enantiomeric Excess

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$^{13}$C NMR (126 MHz, CDCl$_3$) of compound SI4.
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$^{1}$H NMR (500 MHz, CDCl$_3$) of compound 8n.
$^{13}$C NMR (126 MHz, CDCl$_3$) of compound $8n$. 
\( ^1H \) NMR (500 MHz, CDCl\textsubscript{3}) of compound 8p.
$^{13}$C NMR (126 MHz, CDCl$_3$) of compound 8p.
$^1$H NMR (500 MHz, CDCl$_3$) of compound SI13.
$^{13}$C NMR (126 MHz, CDCl$_3$) of compound SI13.
$^1$H NMR (500 MHz, CDCl$_3$) of compound 8q.
$^{13}$C NMR (126 MHz, CDCl$_3$) of compound 8q.
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$^1$H NMR (500 MHz, CDCl$_3$) of compound 10b.
$^{13}$C NMR (126 MHz, CDCl$_3$) of compound 10b.
$^1$H NMR (500 MHz, CDCl$_3$) of compound 10c.
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