Ni-Catalyzed Enantioselective C-Acylation of α-Substituted Lactams†

†This work was performed in collaboration with Masaki Hayashi, Satoshi Hashimoto, and Chad Eichman and was partially adapted from the publication: Hayashi, M.; Bachman, S.; Hashimoto, S.; Eichman, C. C.; Stoltz, B. M. J. Am. Chem. Soc. 2016, 138, 8997–9000. Copyright 2016 American Chemical Society.
4.1 Introduction

Catalytic enantioselective construction of all-carbon quaternary stereocenters is a particular challenge in organic synthesis. One successful approach has been stereoselective metal-catalyzed coupling of prochiral tetrasubstituted enolate nucleophiles with alkyl, aryl and alkenyl electrophiles. The nucleophile may be generated via either activation of a masked enolate or enolization of a pronucleophile. For example, Pd-catalyzed decarboxylative asymmetric allylic alkylation reactions provide access to a variety of α-quaternary products (Scheme 4.1). Both Pd and Ir catalysts are effective for asymmetric allylic alkylation of α,α-disubstituted pronucleophiles (Scheme 4.2A, B); Ir catalysis provides access to vicinal quaternary and tertiary stereocenters. Enantioselective α-functionalization of prochiral enolates with aryl and alkenyl (pseudo)halides may be achieved under Pd and Ni, or Cu catalysis (Scheme 4.2C).

Scheme 4.1 Formation of α-quaternary stereocenters via Pd-catalyzed decarboxylative allylic alkylation

Examples of masked enolates:

- R1 = alkyl, n = 0–4
- R1 = aryl, n = 1
- R1 = alkyl
  - Y = CH2NR, O, S
- R1 = Ar
- R1 = MeN
- R1 = Allyl
- R2 = Allyl
- R2 = Ar
- R2 = BzN
- R3 = Allyl
- R3 = Allyl
Scheme 4.2 Synthesis of α-quaternary stereocenters via functionalization of in situ-generated prochiral enolates

**A. Pd-catalyzed allylic alkylation of prochiral enolates**

\[
\begin{align*}
R^1 & + \text{Allyl electrophile} & \rightarrow & \text{Product} \\
\text{cat. [Pd], ligand base} & & & \\
\end{align*}
\]

**Examples of pronucleophiles:**

- ![First Example](image1.png)
- ![Second Example](image2.png)
- ![Third Example](image3.png)

**B. Ir-catalyzed allylic alkylation of prochiral enolates**

\[
\begin{align*}
X & \text{O} & R^1 & \text{Allyl electrophile} & \rightarrow & \text{Product} \\
Y & & & \text{cat. [Ir], ligand base} & & \\
\end{align*}
\]

**Examples of pronucleophiles:**

- ![First Example](image4.png)
- ![Second Example](image5.png)

**C. Metal-catalyzed arylation of prochiral enolates**

\[
\begin{align*}
X & \text{O} & R^1 & \text{Y} & \rightarrow & \text{Product} \\
\text{cat. [Pd], [Ni], or [Cu] base} & & & & & \\
\end{align*}
\]

**Examples of pronucleophiles**

- ![First Example](image6.png)
- ![Second Example](image7.png)

Despite the success of these processes, there are no general methods for stereoselective metal-catalyzed coupling of in situ-generated tetrasubstituted enolates
with *acyl* electrophiles. While intramolecular acyl transfer strategies have been developed, intermolecular *C*-acylation reactions of enolates or enol ethers are more limited. Acylation conditions may result in competitive *O*-acylation of enolates. However, *α*-acyl quaternary stereocenters have been accessed through organocatalyzed couplings of silyl ketene acetals with acyl derivatives (Scheme 4.3). To our knowledge, there have been no reports of intermolecular enantioselective *C*-acylation reactions of carbonyl derivatives other than silyl ketene acetals. Herein, we report a new strategy for catalytic enantioselective formal *C*-acylation that enables the preparation of lactams bearing *α*-quaternary stereocenters.

_Scheme 4.3 Enantioselective organocatalyzed coupling of silyl ketene acetals with acyl derivatives_
4.2 Results and Discussion

During the course of our investigations into enolate functionalization reactions, we observed the formation of α-acylated product 60a under the conditions shown in Table 4.1, entry 1. In the absence of Ni, ligand, or chlorobenzene (59), <5% product was observed (entries 2–4), indicating that direct nucleophilic addition of the lithium enolate derived from lactam 57a to the nitrile 58a is not the predominant reaction pathway. Both Pd(0) and Ni(II) sources were ineffective (entries 5–6). Either chlorobenzene or chlorotoluene resulted in the formation of product 60a, consistent with the phenyl group in the product arising from benzonitrile incorporation (entry 7).

Table 4.1 Effect of various reaction parameters on enantioselective Ni-catalyzed C-acylation

<table>
<thead>
<tr>
<th>entry</th>
<th>deviation from standard conditions</th>
<th>yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>no Ni(COD)2 or (R)-BINAP</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>no (R)-BINAP</td>
<td>3b</td>
</tr>
<tr>
<td>4</td>
<td>no PhCl</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Pd(dba)2 instead of Ni(COD)2</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>NiCl2 instead of Ni(COD)2</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>p-tolyCl instead of PhCl</td>
<td>41</td>
</tr>
</tbody>
</table>

aConditions: lactam (1 equiv), PhCN (2 equiv), aryl chloride (2 equiv), LiHMDS (1.1 equiv), Ni(COD)2 (10 mol%), ligand (12 mol%), in 5:1 toluene/THF (0.2 M) at 23 °C for 20 h, then 1 M HCl aq at 23 °C for 0.5 h. bHPLC conversion
After confirming the involvement of Ni and ligand in this formal lactam α-acylation reaction, we turned our attention to optimization of the reaction parameters. Ferrocene-based ligands were found to be optimal, with both Josiphos and Mandyphos ligand classes providing promising results. In TBME, LiHMDS (Table 4.2, entry 3) provided higher levels of conversion and enantioselectivity than NaHMDS and KHMDS (entries 1 and 2). Using phenyl triflate in place of chlorobenzene resulted in similar conversion but lower levels of enantioselectivity (entry 4), while iodobenzene provided slightly lower conversion and similar enantioselectivity (entry 5). The highest conversion and enantioselectivity were obtained with bromobenzene (entry 6). Switching from \( \text{L9} \) to \( \text{L10} \) and using a 10:1 mixture of toluene/THF resulted in decreased conversion but a small increase in enantioselectivity (entry 7). The addition of excess LiBr was found to substantially increase both conversion and enantioselectivity (entry 8). The synthesis of 1.1 g of product (69% yield, 90% ee) was achieved under conditions using reduced (1.3) equivalents of lactam \( \text{57a} \) (Scheme 4.4).

With optimized conditions in hand, we explored the scope of the reaction with respect to the \( N \)-aryl moiety. Electron-rich aryl rings resulted in generally good yields and high levels of enantioselectivity (Scheme 4.5). Switching from a \( p \)-OMe-phenyl substrate \( \text{57a} \) to an \( o \)-OMe-phenyl substrate \( \text{57b} \) resulted in improved enantioselectivity but lower yield. The yield was improved upon lowering the temperature from 23 °C to 4 °C and increasing the reaction time. Under these lower temperature conditions, both \( \text{57c} \) and \( \text{57d} \) resulted in moderate to good yield and high ee.
Table 4.2 Effect of base, halide, solvent, and LiBr on Ni-catalyzed C-acylation

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>base</th>
<th>PhX</th>
<th>solvent</th>
<th>additive</th>
<th>conversion (%)</th>
<th>ee (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^a$</td>
<td>L9</td>
<td>NaHMDS</td>
<td>PhCl</td>
<td>TBME</td>
<td>-</td>
<td>42</td>
<td>0</td>
</tr>
<tr>
<td>2$^a$</td>
<td>L9</td>
<td>KHMDs</td>
<td>PhCl</td>
<td>TBME</td>
<td>-</td>
<td>51</td>
<td>0</td>
</tr>
<tr>
<td>3$^a$</td>
<td>L9</td>
<td>LiHMDS</td>
<td>PhCl</td>
<td>TBME</td>
<td>-</td>
<td>74</td>
<td>-54</td>
</tr>
<tr>
<td>4$^a$</td>
<td>L9</td>
<td>LiHMDS</td>
<td>PhOTf</td>
<td>TBME</td>
<td>-</td>
<td>73</td>
<td>-28</td>
</tr>
<tr>
<td>5$^a$</td>
<td>L9</td>
<td>LiHMDS</td>
<td>PhI</td>
<td>TBME</td>
<td>-</td>
<td>65</td>
<td>-55</td>
</tr>
<tr>
<td>6$^a$</td>
<td>L9</td>
<td>LiHMDS</td>
<td>PhBr</td>
<td>TBME</td>
<td>-</td>
<td>83</td>
<td>-61</td>
</tr>
<tr>
<td>7$^b$</td>
<td>L10</td>
<td>LiHMDS</td>
<td>PhBr</td>
<td>toluene-THF (10:1)</td>
<td>-</td>
<td>55</td>
<td>68</td>
</tr>
<tr>
<td>8$^b$</td>
<td>L10</td>
<td>LiHMDS</td>
<td>PhBr</td>
<td>toluene-THF (10:1) LiBr (5 equiv)</td>
<td></td>
<td>98</td>
<td>89</td>
</tr>
</tbody>
</table>

$^a$Conditions: lactam (1 equiv), PhCN (2 equiv), PhX (2 equiv), base (1.1 equiv), Ni(COD)$_2$ (10 mol%), ligand (12 mol%), in solvent (0.2 M) at 23 °C for 20 h, then 1 M HCl aq at 23 °C for 0.5 h.

$^b$Conditions: lactam (2 equiv), PhCN (1 equiv), PhX (1 equiv), base (1.2 equiv), Ni(COD)$_2$ (10 mol%), ligand (12 mol%), in solvent (0.2 M) at 23 °C for 20 h, then 1 M HCl aq at 23 °C for 0.5 h.

Scheme 4.4 Gram-scale Ni-catalyzed C-acylation
The scope of the reaction is broad with respect to the benzonitrile (Scheme 4.6). Me-substitution at the para, meta, and ortho positions is well-tolerated (58b–e→62b–e). High levels of enantioselectivity are observed for both electron-poor and electron-rich benzonitriles (58f–h), but electron-poor benzonitriles result in low yields (58g, h). Alkyl nitriles did not result in significant product formation.
The reaction is significantly affected by the nature of the lactam α-substituent. Increasing the steric demand from methyl to ethyl (Scheme 4.7, 63b → 64b) results in both reduced yield and enantioselectivity. Benzyl substituents provide moderate to good yields and levels of enantioselectivity (63c–e → 64c–e). Moderate to high levels of enantioselectivity are also observed for crotyl- and cinnamyl-substituted lactams (63h–n → 64h–n).
Scheme 4.7 Scope with respect to the lactam α-substituent

\[ \text{OMP} \quad \overset{\text{R}}{\text{N}} \quad \overset{\text{O}}{\text{C}} \quad \overset{\text{Me}}{\text{Me}} + \quad \text{NC} \quad \overset{\text{Me}}{\text{Me}} \quad \overset{\text{PhBr}}{\text{Me}} \quad \text{OMP} \quad \overset{\text{L10} \ (12 \text{ mol\%})}{\text{Ni(COD)}_2 \ (10 \text{ mol\%})} \quad \text{LiHMDS} \ (1.2 \text{ equiv}) \quad \text{LiBr} \ (5 \text{ equiv}) \quad \text{toluene-THF} \ (10:1) \quad 4^\circ \text{C}, \ 48 \text{ h} \quad \text{then} \quad 1\text{M HCl aq} \]

\[ \overset{\text{63b–o}}{\text{OMP} \quad \overset{\text{R}}{\text{N}} \quad \overset{\text{O}}{\text{C}} \quad \overset{\text{Me}}{\text{Me}}} + \quad \overset{\text{58b}}{\text{NC} \quad \overset{\text{Me}}{\text{Me}}} \quad \overset{\text{PhBr}}{\text{Me}} \quad \text{OMP} \quad \overset{\text{61}}{\text{OMP} \quad \overset{\text{R}}{\text{N}} \quad \overset{\text{O}}{\text{C}} \quad \overset{\text{Me}}{\text{Me}}} \]

\[ \overset{\text{64b}}{\text{OMP} \quad \overset{\text{Et}}{\text{N}} \quad \overset{\text{O}}{\text{C}} \quad \overset{\text{Me}}{\text{Me}}} \quad 50\% \text{ yield, } 78\% \text{ ee} \]

\[ \overset{\text{64c}}{\text{OMP} \quad \overset{\text{R}}{\text{N}} \quad \overset{\text{O}}{\text{C}} \quad \overset{\text{Me}}{\text{Me}}} \quad 58\% \text{ yield, } 71\% \text{ ee} \]

\[ \overset{\text{64d}}{\text{OMP} \quad \overset{\text{R}}{\text{N}} \quad \overset{\text{O}}{\text{C}} \quad \overset{\text{Me}}{\text{Me}}} \quad (R' = \text{H}): 61\% \text{ yield, } 81\% \text{ ee} \]

\[ \overset{\text{64f}}{\text{OMP} \quad \overset{\text{Me}}{\text{Me}}} \quad (R' = \text{Me}): 58\% \text{ yield, } 71\% \text{ ee} \]

\[ \overset{\text{64e}}{\text{OMP} \quad \overset{\text{R}}{\text{N}} \quad \overset{\text{O}}{\text{C}} \quad \overset{\text{Me}}{\text{Me}}} \quad (R' = \text{OMe}): 77\% \text{ yield, } 81\% \text{ ee} \]

\[ \overset{\text{64g}}{\text{OMP} \quad \overset{\text{Bn}}{\text{N}} \quad \overset{\text{O}}{\text{C}} \quad \overset{\text{Me}}{\text{Me}}} \quad 67\% \text{ yield, } 60\% \text{ ee} \]

\[ \overset{\text{64h}}{\text{OMP} \quad \overset{\text{Me}}{\text{Me}}} \quad 71\% \text{ yield, } 76\% \text{ ee} \]

\[ \overset{\text{64i}}{\text{OMP} \quad \overset{\text{Me}}{\text{Me}}} \quad 70\% \text{ yield, } 86\% \text{ ee} \]

\[ \overset{\text{64j}}{\text{OMP} \quad \overset{\text{Me}}{\text{Me}}} \quad (R' = \text{H}): 50\% \text{ yield, } 86\% \text{ ee} \]

\[ \overset{\text{64k}}{\text{OMP} \quad \overset{\text{Me}}{\text{Me}}} \quad (R' = \text{Me}): 85\% \text{ yield, } 88\% \text{ ee} \]

\[ \overset{\text{64l}}{\text{OMP} \quad \overset{\text{Me}}{\text{Me}}} \quad (R' = \text{OMe}): 68\% \text{ yield, } 88\% \text{ ee} \]

\[ \overset{\text{64m}}{\text{OMP} \quad \overset{\text{Me}}{\text{Me}}} \quad (R' = \text{F}): 76\% \text{ yield, } 83\% \text{ ee} \]

\[ \overset{\text{64n}}{\text{OMP} \quad \overset{\text{Me}}{\text{Me}}} \quad 76\% \text{ yield, } 83\% \text{ ee} \]

\[ \overset{\text{64o}}{\text{OMP} \quad \overset{\text{Me}}{\text{Me}}} \quad 35\% \text{ yield, } 84\% \text{ ee} \]

*Conditions: lactam (2 equiv), p-tolunitrile (0.2 mmol, 1 equiv), PhBr (1.5 equiv), Ni(COD)2 (10 mol%), ligand (12 mol%), in toluene/THF (10:1, 0.09 M) at 4 °C for 48 h, then 1 M HCl aq.*
The enantioenriched α-acylated lactam products were subjected to a variety of further transformations. Lactam 60b was reduced with Et3SiH to a single isomer of alcohol 65 in good yield (Scheme 4.8). Deprotection by CAN oxidation furnished lactam 66. Lactams 60a and 68 were subjected to Baeyer-Villiger oxidation, giving an α-benzoyloxy lactam (67) or an α-aryloxy carbonyl lactam (69), respectively. To determine absolute stereochemistry, lactam 69 was converted to known compound 71 through ester exchange followed by deprotection of the o-methoxyphenyl group.

Scheme 4.8 Derivatization of α-acylated lactam products

When the standard reaction conditions were carried out in the absence of an acidic workup, imine 72 was isolated from the reaction of lactam 57a with o-tolunitrile (58d, Scheme 4.9A). In addition, the in situ reduction of a reaction mixture
containing lactam 57b and benzonitrile (58a) resulted in the formation of amine 74. These results are consistent with a reaction pathway involving initial imine formation followed by hydrolysis to reveal the corresponding α-acylated products.

Scheme 4.9A. Isolation of an imine intermediate B. In situ generation and reduction of an imine intermediate

Although we do not have a complete understanding of the mechanism of this process, a possible catalytic cycle is shown in Figure 4.1. Oxidative addition of the aryl bromide to a Ni0 species generates NiIIArBr complex 75. Subsequent insertion of the benzonitrile and lactam enolate produce NiII-imino complex 76. Reductive elimination furnishes the imine product, which is then hydrolyzed upon workup.
4.3 Conclusion

We have developed the first intermolecular enantioselective C-acylation of lactams via Ni-catalyzed coupling of a lithium enolate, a benzonitrile, and an aryl bromide. The reaction is hypothesized to proceed through initial generation of an imine intermediate followed by hydrolysis to furnish the formal C-acylation product. The use of a Mandyphos-type ligand and LiBr as an additive are essential to achieving high yields and levels of enantioselectivity.
4.4 Experimental Procedures

4.4.1 General Information

Unless otherwise stated, reactions were performed in flame-dried or oven-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. Reaction temperatures were controlled by an IKAmag temperature modulator unless otherwise indicated. 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, p-anisaldehyde, KMnO₄ or PMA (phosphomolybdic acid) staining. Silicycle SiliaFlash P60 Academic Silica gel (particle size 0.040-0.064 mm) was used for flash column chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralcel OD-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 254 nm. Analytical SFC was performed with a Mettler SFC supercritical CO₂ analytical chromatography system utilizing Chiralcel (OJ-H) column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 254 nm. \(^1\)H and \(^{13}\)C NMR spectra were recorded on a Varian Inova 500 (500 MHz and 126 MHz, respectively) and are reported in terms of chemical shift relative to CHCl₃ (δ 7.26 and δ 77.16, respectively). Data for \(^1\)H NMR are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d= broad doublet, app = apparent. Data for \(^{13}\)C are reported in terms of chemical shifts (d ppm). IR spectra were obtained using a Perkin Elmer Paragon 1000
spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm$^{-1}$). High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) or electron ionization (EI+) mode, or Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in g/100 mL, solvent).

Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number.

THF, Et$_2$O, CH$_2$Cl$_2$, toluene, CH$_3$CN, TBME and dioxane were dried by passage through an activated alumina column under argon. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. Brine solutions are saturated aqueous solutions of sodium chloride. Commercially available reagents were purchased from Sigma-Aldrich, Acros Organics, TCI, Oakwood chemicals, Strem, or Alfa Aesar and used as received unless otherwise stated. LiBr was purchased from Aldrich and dried for 3 h at 140 °C in vacuo.

(3-Bromopropoxy)methyl)benzene,$^{12}$ 1-bromo-2-butene,$^{13}$ (E)-1-(3-chloroprop-1-en-1-yl)-4-methylbenzene,$^{14}$ (E)-1-(3-chloroprop-1-en-1-yl)-4-methoxybenzene,$^{15}$ (E)-1-(3-chloroprop-1-en-1-yl)-4-fluoro--benzene,$^{16}$ (E)-3-(thiophen-3-yl)prop-2-en-1-ol,$^{17}$ and ((1E,3E)-5-bromopenta-1,3-dien-1-yl)benzene$^{18}$ were prepared by known
methods and used without purification. \((E)-3-(3\text{-Chloroprop-1-en-1-yl})\text{thiophene was prepared from} (E)-3-(thiophen-3-yl)\text{prop-2-en-1-ol and SOCl}_2 \text{in CH}_2\text{Cl}_2 \text{and used without purification.}

List of Abbreviations:

- ee – enantiomeric excess
- dr – diastereomeric ratio
- HPLC – high-performance liquid chromatography
- SFC – supercritical fluid chromatography
- TLC – thin-layer chromatography
- AcOEt – ethyl acetate
- THF – tetrahydrofuran
- MeOH – methanol
- MeCN – acetonitrile
- IPA – isopropanol
- BINAP – \((2,2'\text{-bis(diphenylphosphino)}-1,1'\text{-binaphthyl})\)
- LHMDS – lithium hexamethyldisilazide
- NaHMDS – sodium hexamethyldisilazide
- KHMDS – potassium hexamethyldisilazide
- PMP – \(p\)-methoxyphenyl
- CAN – ceric ammonium nitrate
- TFA – trifluoroacetic acid
- \(m\)-CPBA – \(m\)-chloroperoxybenzoic acid

4.4.2 Preparation of Materials

General Procedure for \(\alpha\)-Substituted Lactam Substrates
**General procedure 1: 1-(2-methoxyphenyl)pyrrolidin-2-one (SI2)**

To a suspension of lactam SI1 (8.17 g, 96.0 mmol, 1.20 equiv), K$_2$CO$_3$ (22.1 g, 160 mmol, 2.00 equiv) and CuI (1.52 g, 8.00 mmol, 0.10 equiv) in toluene (80 mL) were added 2-bromoanisole (9.84 mL, 80.0 mmol, 1.00 equiv) and N,N’-dimethylethylendiamine (1.68 mL, 16.0 mmol, 0.20 equiv). The reaction mixture was stirred at 100 °C for 18 h then allowed to cool to ambient temperature and filtered through a pad of silica gel eluting with AcOEt (250 mL). The eluate was concentrated under reduced pressure and the residue was purified by flash column chromatography (1:1 EtOAc:hexanes) on silica gel to give lactam SI2 as a pale yellow oil (9.88 g, 65% yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.35 – 7.26 (m, 2H), 7.06 – 6.97 (m, 2H), 3.88 (s, 3H), 3.80 (t, $J$ = 7.0 Hz, 2H), 2.60 (t, $J$ = 8.1 Hz, 2H), 2.23 (p, $J$ = 7.5 Hz, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 175.2, 154.8, 128.7, 128.6, 127.2, 120.9, 112.0, 55.6, 49.9, 31.2, 19.0; IR (Neat Film NaCl) 2968, 2889, 2838, 1694, 1504, 1461, 1408, 1304, 1281, 1253, 1023, 755 cm$^{-1}$; HRMS (MM: ESI-APCI+) $m/z$ calc’d for C$_{11}$H$_{14}$NO$_2$ [M+H]$^+$: 192.1019, found 192.1019.

**General procedure 2: 1-(2-methoxyphenyl)-3-methylpyrrolidin-2-one (57b)**

To a solution of diisopropylamine (3.07 mL, 22.0 mmol, 1.10 equiv) in THF (17 mL) was added a solution of n-BuLi (8.80 mL, 22.0 mmol, 2.5 M in hexanes, 1.10 equiv) dropwise at -78 °C. After 20 min at -78 °C, a solution of lactam SI2 (3.82 g, 20.0 mmol, 1.00 equiv) in THF (50 mL) was added dropwise. After an additional 20 min, a solution of methyl iodide (15.0 mL, 30.0 mmol, 2.0 M in TBME, 1.50 equiv) was added and the reaction mixture was stirred at -78 °C for 3 h. Saturated NH$_4$Cl
aqueous solution (50 mL) was added and the mixture was allowed to ambient
temperature. The mixture was extracted with AcOEt (100 mL), washed with brine
(30 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The residue
was purified by flash column chromatography (1:4 to 1:2 EtOAc:hexanes) on silica
gel to give lactam 57b as a yellow oil (2.86 g, 70% yield). ¹H NMR (500 MHz,
CDCl₃) δ 7.34 – 7.26 (m, 3H), 7.06 – 6.96 (m, 2H), 3.87 (s, 3H), 3.79 – 3.66 (m, 2H),
2.69 (tq, J = 8.7, 7.1 Hz, 1H), 2.41 (dddd, J = 12.2, 8.5, 7.3, 3.5 Hz, 1H), 1.86 (dq, J =
12.4, 8.5 Hz, 1H), 1.36 (d, J = 7.1 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 177.5,
154.8, 128.6, 128.5, 127.6, 120.8, 112.0, 55.6, 47.9, 36.9, 28.1, 16.3; IR (Neat Film
NaCl) 2965, 2932, 2874, 1695, 1504, 1463, 1456, 1403, 1311, 1296, 1277, 1251,
1024, 754 cm⁻¹; HRMS (MM: ESI-APCI⁺) m/z calc'd for C₁₂H₁₆NO₂ [M+H]⁺:
206.1176, found 206.1176.

Spectroscopic Data for N-Protected Lactams

1-(4-Methoxyphenyl)pyrrolidin-2-one (SI3)

Lactam SI3 was prepared according to the general procedure 1, using 4-iodoanisole
and K₃PO₄ in place of 2-bromoanisole and K₂CO₃ respectively, and isolated by
recrystallization in hexanes/AcOEt (4/1) as a white crystal. 89% yield. ¹H NMR
(500 MHz, CDCl₃) δ 7.64 – 7.45 (m, 2H), 7.01 – 6.90 (m, 2H), 3.87 (t, J = 7.0 Hz,
2H), 3.84 (s, 3H), 2.64 (t, J = 8.1 Hz, 2H), 2.20 (tt, J = 15.1, 7.5 Hz, 1H); ¹³C NMR
(126 MHz, CDCl$_3$) $\delta$ 173.9, 156.5, 132.6, 121.8, 114.0, 55.5, 49.2, 32.5, 18.1; IR (Neat Film NaCl) 2952, 2907, 1683, 1517, 1255, 1226, 1182, 1126, 1032, 829 cm$^{-1}$; HRMS (MM: ESI-APCI$^+$) $m/z$ calc'd for C$_{11}$H$_{14}$NO$_2$ [M+H]$^+$: 192.1019, found 192.1021.

**1-(3,5-Dimethoxyphenyl)pyrrolidin-2-one (SI4)**

Lactam SI4 was prepared according to the general procedure 1, using 1-bromo-3,5-dimethoxybenzene in place of 2-bromoanisole, and isolated by recrystallization in hexanes/acetone (5/1) as a white crystal. 89% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.90 (d, $J = 2.2$ Hz, 2H), 6.31 (t, $J = 2.2$ Hz, 1H), 3.87 (t, $J = 7.0$ Hz, 2H), 3.84 (s, 6H), 2.65 (t, $J = 8.1$ Hz, 2H), 2.19 (p, $J = 7.5$ Hz, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 174.4, 160.8, 141.2, 98.4, 96.5, 77.3, 77.0, 76.8, 55.4, 49.0, 33.1, 17.9; IR (Neat Film NaCl) 2959, 1694, 1593, 1474, 1455, 1424, 1397, 1276, 1245, 1198, 1152, 1071, 1056, 922, 840, 825, 683 cm$^{-1}$; HRMS (MM: ESI-APCI$^+$) $m/z$ calc'd for C$_{12}$H$_{16}$NO$_3$ [M+H]$^+$: 222.1125, found 222.1129.

**1-(2-Isopropoxyphenyl)-pyrrolidin-2-one (SI5)**
Lactam **SI5** was prepared according to the general procedure 1, using 1-bromo-2-isopropoxybenzene in place of 2-bromoanisole, and isolated by flash column chromatography (1:2 to 1:1 EtOAc:hexanes) on silica gel as a pale yellow oil. 57% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.33 – 7.23 (m, 2H), 7.03 – 6.96 (m, 2H), 4.58 (hept, $J = 6.0$ Hz, 1H), 3.82 (t, $J = 6.7$ Hz, 2H), 2.59 (t, $J = 7.6$ Hz, 2H), 2.28 – 2.16 (m, 2H), 1.38 (d, $J = 6.0$ Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 175.2, 153.1, 128.9, 128.4, 128.4, 120.8, 114.7, 70.8, 49.9, 31.4, 22.2, 19.2; IR (Neat Film NaCl) 2976, 2933, 1697, 1595, 1500, 1456, 1405, 1385, 1304, 1282, 1251, 1125, 1111, 957, 753 cm$^{-1}$; HRMS (MM: ESI-APCI+) $m/z$ calc’d for C$_{13}$H$_{18}$NO$_2$ [M+H]$^+$: 220.1332, found 220.1328.

**Spectroscopic Data for α-Substituted Lactams**

**1-(4-Methoxyphenyl)-3-methylpyrrolidin-2-one (57a)**

Lactam **57a** was prepared according to the general procedure 2 from **S13** in place of **S12**, and isolated by flash column chromatography (1:3 EtOAc:hexanes) on silica gel as a white solid. 82% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.64 – 7.45 (m, 2H), 7.01 – 6.90 (m, 2H), 3.87 (t, $J = 7.0$ Hz, 2H), 3.84 (s, 3H), 2.64 (t, $J = 8.1$ Hz, 2H), 2.20 (tt, $J = 15.1$, 7.5 Hz, 1H); $^{13}$C NMR (126 MHz, cdcl$_3$) $\delta$ 176.3, 156.4, 133.0, 121.4, 114.0, 55.5, 46.9, 38.1, 27.1, 16.3; IR (Neat Film NaCl) 2952, 2882, 2835, 1682,
1516, 1251, 1225, 1122, 1099, 1030, 829 cm\(^{-1}\); HRMS (MM: ESI-APCI\(^+\)) \(m/z\) calc'd for C\(_{12}\)H\(_{16}\)NO\(_2\) [M+H\(^+\)]: 206.1176, found 206.1177.

1-(3,5-Dimethoxyphenyl)-3-methylpyrrolidin-2-one (57c)

![Structure 57c]

Lactam 57c was prepared according to the general procedure 2 from SI\(_{14}\) in place of SI\(_{12}\), and isolated by flash column chromatography (1:4 EtOAc:hexanes) on silica gel as a white solid. 87% yield. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.96 (d, \(J = 2.2\) Hz, 2H), 6.31 (t, \(J = 2.2\) Hz, 1H), 3.84 (s, 6H), 3.79 (dd, \(J = 8.8, 5.0\) Hz, 2H), 2.78 – 2.66 (m, 1H), 2.45 – 2.35 (m, 1H), 1.86 – 1.74 (m, 1H), 1.35 (d, \(J = 7.1\) Hz, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 176.9, 160.8, 141.5, 97.9, 96.5, 77.3, 77.0, 76.8, 55.4, 46.8, 38.6, 26.9, 16.1; IR (Neat Film NaCl) 2964, 1698, 1597, 1474, 1392, 1273, 1246, 1208, 1154, 1071, 927, 834, 682 cm\(^{-1}\); HRMS (MM: ESI-APCI\(^+\)) \(m/z\) calc'd for C\(_{13}\)H\(_{18}\)NO\(_3\) [M+H\(^+\)]: 236.1281, found 236.1284.

1-(2-Isoproxyphenyl)-3-methylpyrrolidin-2-one (57d)

![Structure 57d]

Lactam 57d was prepared according to the general procedure 2 from SI\(_{15}\) in place of SI\(_{12}\), and isolated by flash column chromatography (1:3 to 1:2 EtOAc:hexanes) on silica gel as a pale yellow oil. 83% yield. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.32 – 7.22
(m, 2H), 7.03 – 6.96 (m, 2H), 4.57 (hept, \(J = 6.1\) Hz, 1H), 3.80 – 3.67 (m, 2H), 2.67 (tq, \(J = 8.4\), 7.1 Hz, 1H), 2.46 – 2.35 (m, 1H), 1.84 (dq, \(J = 12.3\), 8.2 Hz, 1H), 1.37 (d, \(J = 6.1\) Hz, 6H), 1.35 (d, \(J = 7.2\) Hz, 3H);\(^{13}\text{C NMR (126 MHz, CDCl}_3\)) \(\delta\) 177.5, 153.2, 129.0, 128.7, 128.3, 120.8, 114.8, 70.8, 47.9, 36.9, 28.2, 22.2, 22.2, 16.4; IR (Neat Film NaCl) 2974, 2930, 1701, 1595, 1499, 1457, 1405, 1277, 1249, 1124, 1111, 955, 750 cm\(^{-1}\); HRMS (MM: ESI-APCI\(^{+}\)) \(m/z\) calc'd for C\(_{14}\)H\(_{20}\)NO\(_2\) [M+H]\(^{+}\): 234.1489, found 234.1482.

1-(2-Methoxyphenyl)-3-ethylyrroldin-2-one (63b)

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\text{63b}
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Lactam 63b was prepared according to the general procedure 2 using ethyl iodide in place of methyl iodide, and isolated by flash column chromatography (1:3 EtOAc:hexanes) on silica gel as a pale yellow oil. 81% yield. \(^1\text{H NMR (500 MHz, CDCl}_3\)) \(\delta\) 7.29 – 7.19 (m, 2H), 7.01 – 6.92 (m, 2H), 3.82 (s, 3H), 3.76 – 3.69 (m, 1H), 3.69 – 3.60 (m, 1H), 2.53 (qd, \(J = 8.7\), 4.3 Hz, 1H), 2.38 – 2.27 (m, 1H), 2.04 – 1.92 (m, 1H), 1.92 – 1.81 (m, 1H), 1.63 – 1.49 (m, 1H), 1.04 (t, \(J = 7.4\) Hz, 3H);\(^{13}\text{C NMR (126 MHz, CDCl}_3\)) \(\delta\) 176.9, 154.8, 128.7, 128.5, 127.5, 120.8, 112.0, 55.6, 48.2, 43.4, 25.1, 24.2, 11.5; IR (Neat Film NaCl) 2961, 1695, 1596, 1505, 1462, 1404, 1280, 1249, 1024, 752 cm\(^{-1}\); HRMS (MM: ESI-APCI\(^{+}\)) \(m/z\) calc'd for C\(_{13}\)H\(_{18}\)NO\(_2\) [M+H]\(^{+}\): 220.1332, found 220.1334.
3-Benzyl-1-(2-methoxyphenyl)pyrrolidin-2-one (63c)

![Chemical Structure of 63c](image)

Lactam 63c was prepared according to the general procedure 2 using benzyl bromide in place of methyl iodide, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a pale yellow oil. 80% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.44 – 7.08 (m, 7H), 6.99 – 6.90 (m, 2H), 3.80 (s, 3H), 3.63 (dt, $J = 9.5, 7.7$ Hz, 1H), 3.49 (ddd, $J = 9.5, 8.6, 3.7$ Hz, 1H), 3.30 (dd, $J = 13.7, 4.0$ Hz, 1H), 2.93 – 2.83 (m, 1H), 2.77 (dd, $J = 13.6, 9.7$ Hz, 1H), 2.20 – 2.10 (m, 1H), 1.94 – 1.83 (m, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 176.0, 154.8, 139.7, 129.1, 128.6, 128.5, 128.5, 128.4, 127.4, 126.3, 120.9, 112.0, 55.6, 48.0, 43.8, 37.0, 25.1; IR (Neat Film NaCl) 2942, 1694, 1596, 1504, 1454, 1407, 1279, 1252, 1025, 753, 701 cm$^{-1}$; HRMS (MM: ESI-APCI+) $m/z$ calc’d for C$_{18}$H$_{20}$NO$_2$ [M+H]$^+$: 282.1489, found 282.1491.

3-(4-Methoxybenzyl)-1-(2-methoxyphenyl)pyrrolidin-2-one (63d)

![Chemical Structure of 63d](image)

Lactam 63d was prepared according to the general procedure 2 using 4-methoxybenzyl chloride in place of methyl iodide, and isolated by flash column chromatography (1:3 EtOAc:hexanes) on silica gel as a pale yellow oil. 59% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.29 – 7.24 (m, 1H), 7.24 – 7.14 (m, 3H), 7.00 – 6.90 (m, 2H), 6.88 – 6.80 (m, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.62 (dt, $J = 9.5, 7.6$ Hz, 1H),
3.47 (ddd, $J = 9.5, 8.6, 3.8$ Hz, 1H), 3.21 (dd, $J = 13.7, 4.0$ Hz, 1H), 2.90 – 2.80 (m, 1H), 2.74 (dd, $J = 13.8, 9.4$ Hz, 1H), 2.20 – 2.09 (m, 1H), 1.93 – 1.81 (m, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 176.1, 158.1, 154.8, 131.6, 130.1, 128.6, 128.5, 127.4, 120.8, 113.8, 112.1, 55.6, 55.3, 48.1, 43.9, 36.0, 25.0; IR (Neat Film NaCl) 2936, 1696, 1596, 1512, 11506, 1462, 1406, 1300, 1279, 1249, 1179, 1028, 753 cm$^{-1}$; HRMS (MM: ESI-APCI+) m/z calc’d for C$_{19}$H$_{22}$NO$_3$ [M+H]$^+$: 312.1594, found 312.1589.

3-(4-Fluorobenzyl)-1-(2-methoxyphenyl)pyrrolidin-2-one (63e)

![Structure of 3-(4-Fluorobenzyl)-1-(2-methoxyphenyl)pyrrolidin-2-one (63e)](image)

Lactam 63e was prepared according to the general procedure 2 using 4-fluorobenzyl bromide in place of methyl iodide, and isolated by flash column chromatography (1:3 to 1:2 EtOAc:hexanes) on silica gel as a pale yellow oil. 77% yield. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.31 – 7.18 (m, 4H), 7.04 – 6.92 (m, 4H), 3.81 (s, 3H), 3.65 (dt, $J = 9.6, 7.7$ Hz, 1H), 3.50 (ddd, $J = 9.5, 8.6, 3.6$ Hz, 1H), 3.24 (dd, $J = 13.5, 3.8$ Hz, 1H), 2.93 – 2.76 (m, 2H), 2.22 – 2.12 (m, 1H), 1.94 – 1.82 (m, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 175.7, 162.6, 160.6, 154.8, 135.2, 135.1, 130.6, 130.6, 128.6, 128.5, 127.3, 120.9, 115.3, 115.1, 112.0, 55.6, 48.0, 43.7, 36.1, 24.9; IR (Neat Film NaCl) 2942, 1696, 1597, 1507, 1459, 1406, 1252, 1221, 1158, 1025, 752 cm$^{-1}$; HRMS (MM: ESI-APCI+) m/z calc'd for C$_{18}$H$_{19}$FNO$_2$ [M+H]$^+$: 300.1394, found 300.1390.
1-(2-Methoxyphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidin-2-one (63f)

![Chemical Structure](image)

Lactam 63f was prepared according to the general procedure 2 using 2-trifluoroethyl iodide in place of methyl iodide, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a yellow oil. 36% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.29 (ddd, $J = 8.2, 7.5, 1.7$ Hz, 1H), 7.23 (dd, $J = 7.7, 1.7$ Hz, 1H), 7.03 – 6.93 (m, 2H), 3.83 (s, 3H), 3.80 – 3.72 (m, 1H), 3.65 (ddd, $J = 9.7, 8.8, 1.6$ Hz, 1H), 3.04 – 2.93 (m, 1H), 2.93 – 2.84 (m, 1H), 2.56 – 2.46 (m, 1H), 2.14 (s, 1H), 2.07 – 1.95 (m, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 173.8, 154.7, 128.9, 128.5, 128.1, 126.8, 125.9, 120.9, 112.0, 55.6, 48.0, 37.0, 36.9, 35.9, 35.7, 35.4, 35.2, 26.8; IR (Neat Film NaCl) 2946, 1703, 1597, 1505, 1462, 1414, 1282, 1252, 1135, 1039, 753, 615 cm$^{-1}$; HRMS (MM: ESI-APCI+) $m/z$ calc'd for C$_{13}$H$_{15}$F$_3$NO$_2$ [M+H]$^+$: 274.1049, found 274.1049.

3-(3-(Benzyloxy)propyl)-1-(2-methoxyphenyl)pyrrolidin-2-one (63g)

![Chemical Structure](image)

Lactam 63g was prepared according to the general procedure 2 using ((3-bromopropoxy)methyl)benzene$^1$ in place of methyl iodide, and isolated by flash column chromatography (1:3 to 1:2 EtOAc:hexanes) on silica gel as a pale yellow oil. 76% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.36 – 7.18 (m, 7H), 6.99 – 6.90 (m, 2H),
4.50 (s, 2H), 3.80 (s, 3H), 3.73 – 3.64 (m, 1H), 3.64 – 3.58 (m, 1H), 3.58 – 3.46 (m, 2H), 2.63 – 2.53 (m, 1H), 2.36 – 2.25 (m, 1H), 2.05 – 1.94 (m, 1H), 1.90 – 1.80 (m, 1H), 1.80 – 1.68 (m, 2H), 1.64 – 1.52 (m, 1H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 176.7, 154.8, 138.6, 128.6, 128.5, 128.4, 127.7, 127.5, 127.4, 120.8, 112.0, 73.0, 70.4, 55.6, 48.2, 41.8, 28.0, 27.5, 25.8; IR (Neat Film NaCl) 2939, 2860, 1697, 1596, 1504, 1454, 1405, 1279, 1252, 1102, 1026, 749, 699 cm\(^{-1}\); HRMS (MM: ESI-APCI\(^+\)) \(m/z\) calc'd for \(\text{C}_{21}\text{H}_{26}\text{NO}_3\) [M+H]\(^+\): 340.1907, found 340.1915.

1-(2-Methoxyphenyl)-3-(3-methylbut-2-en-1-yl)pyrrolidin-2-one (63h)

Lactam 63h was prepared according to the general procedure 2 using 1-bromo-3-methyl-2-butene in place of methyl iodide, and isolated by flash column chromatography (1:3 EtOAc:hexanes) on silica gel as a pale yellow oil. 75% yield. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.30 – 7.20 (m, 2H), 7.01 – 6.92 (m, 2H), 5.24 – 5.16 (m, 1H), 3.83 (s, 3H), 3.73 – 3.59 (m, 2H), 2.69 – 2.53 (m, 2H), 2.33 – 2.22 (m, 2H), 1.91 – 1.80 (m, 1H), 1.74 (s, 3H), 1.67 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 176.6, 154.8, 133.6, 128.6, 128.5, 127.6, 121.3, 120.8, 112.0, 55.6, 55.6, 48.2, 42.3, 29.5, 25.9, 25.9, 25.1, 18.0; IR (Neat Film NaCl) 2913, 1698, 1596, 1505, 1459, 1405, 1279, 1252, 1025, 751 cm\(^{-1}\); HRMS (MM: ESI-APCI\(^+\)) \(m/z\) calc'd for \(\text{C}_{16}\text{H}_{22}\text{NO}_2\) [M+H]\(^+\): 260.1645, found 260.1644.
(E)-3-(But-2-en-1-yl)-1-(2-methoxyphenyl)pyrrolidin-2-one (63i)

Lactam 63i was prepared according to the general procedure 2 using 1-bromo-2-butene\(^2\) in place of methyl iodide, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a pale yellow oil. 24% yield. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.30 – 7.21 (m, 2H), 7.01 – 6.92 (m, 2H), 5.62 – 5.43 (m, 2H), 3.83 (s, 3H), 3.73 – 3.58 (m, 2H), 2.68 – 2.53 (m, 2H), 2.32 – 2.19 (m, 2H), 1.95 – 1.82 (m, 1H), 1.72 – 1.66 (m, 3H); \(^1\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 176.5, 154.8, 128.6, 128.6, 128.6, 128.1, 127.4, 120.9, 112.1, 55.6, 48.2, 42.0, 34.3, 24.8, 18.1; IR (Neat Film NaCl) 2937, 1699, 1596, 1505, 1456, 1436, 1404, 1298, 1279, 1252, 1107, 1046, 1025, 968, 751 cm\(^{-1}\); HRMS (MM: ESI-APCI+) \(m/z\) calc'd for C\(_{15}\)H\(_{20}\)NO\(_2\) [M+H]\(^+\): 246.1489, found 246.1487.

(E)-3-Cinnamyl-1-(2-methoxyphenyl)pyrrolidin-2-one (63j)

Lactam 63j was prepared according to the general procedure 2 using cinnamyl bromide in place of methyl iodide, and isolated by flash column chromatography (1:5 to 1:2 EtOAc:hexanes) on silica gel as a pale yellow oil. 80% yield. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.41 – 7.36 (m, 2H), 7.36 – 7.17 (m, 5H), 7.02 – 6.93 (m, 2H), 6.51 (d, \(J = 15.7\) Hz, 1H), 6.29 (dt, \(J = 15.7, 7.1\) Hz, 1H), 3.81 (s, 3H), 3.75 – 3.61 (m,
2H), 2.84 – 2.73 (m, 2H), 2.57 – 2.46 (m, 1H), 2.38 – 2.27 (m, 1H), 2.03 – 1.92 (m, 1H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 176.0, 154.8, 137.5, 132.2, 128.6, 128.6, 128.5, 127.5, 127.4, 127.1, 126.1, 120.9, 112.0, 55.6, 48.2, 41.9, 34.7, 24.8; IR (Neat Film NaCl) 2941, 1694, 1596, 1504, 1463, 1407, 1253, 1025, 967, 749, 694 cm\(^{-1}\); HRMS (MM: ESI-APCI+) \(m/z\) calc'd for C\(_{20}\)H\(_{22}\)NO\(_2\) [M+H]\(^+\): 308.1645, found 308.1645.

\((E)-1-(2\text{-methoxyphenyl})-3-(3-(p\text{-tolyl})allyl)pyrrolidin-2\text{-one (63k)}\)

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\begin{array}{c}
\text{O} \\
\text{OMe} \\
63k \\
\text{Me}
\end{array}
\]

Lactam 63k was prepared according to the general procedure 2 using \((E)-1-(3\text{-chloroprop-1-en-1-yl})-4\text{-methylbenzene}^3\) in place of methyl iodide, and isolated by flash column chromatography (1:3 EtOAc:hexanes) on silica gel as a pale yellow oil. 90% yield. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.34 – 7.21 (m, 4H), 7.13 (d, \(J = 7.9\) Hz, 2H), 7.03 – 6.94 (m, 2H), 6.49 (d, \(J = 15.7\) Hz, 1H), 6.24 (dt, \(J = 15.8, 7.1\) Hz, 1H), 3.83 (s, 3H), 3.77 – 3.62 (m, 2H), 2.84 – 2.73 (m, 2H), 2.58 – 2.44 (m, 1H), 2.40 – 2.27 (m, 4H), 2.04 – 1.92 (m, 1H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 176.1, 154.8, 136.9, 134.7, 132.0, 129.2, 128.6, 128.6, 127.4, 126.4, 126.0, 120.9, 112.0, 55.6, 48.2, 41.9, 34.7, 24.8, 21.2; IR (Neat Film NaCl) 2939, 1695, 1596, 1504, 1462, 1405, 1279, 1252, 1181, 1122, 1107, 1045, 1025, 968, 891, 752 cm\(^{-1}\); HRMS (MM: ESI-APCI+) \(m/z\) calc'd for C\(_{21}\)H\(_{24}\)NO\(_2\) [M+H]\(^+\): 322.1802, found 322.1803.

\((E)-1-(2\text{-methoxyphenyl})-3-(3-(4\text{-methoxyphenyl})allyl)pyrrolidin-2\text{-one (63l)}\)
Lactam 63l was prepared according to the general procedure 2 using (E)-1-(3-chloroprop-1-en-1-yl)-4-methoxybenzene\textsuperscript{4} in place of methyl iodide, and isolated by flash column chromatography (1:3 EtOAc:hexanes) on silica gel as a pale yellow oil.

100% yield. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 7.42 – 7.18 (m, 4H), 7.02 – 6.94 (m, 2H), 6.94 – 6.82 (m, 2H), 6.45 (dt, J = 15.8, 1.4 Hz, 1H), 6.14 (dt, J = 15.7, 7.1 Hz, 1H), 3.81 (s, 3H), 3.76 – 3.60 (m, 2H), 2.81 – 2.69 (m, 2H), 2.54 – 2.43 (m, 1H), 2.37 – 2.26 (m, 1H), 2.02 – 1.91 (m, 1H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) δ 176.1, 158.9, 154.8, 131.5, 130.3, 128.6, 128.6, 127.4, 127.2, 125.2, 120.9, 113.9, 112.0, 55.6, 55.3, 48.2, 42.0, 34.7, 24.8; IR (Neat Film NaCl) 2934, 1694, 1606, 1510, 1505, 1463, 1406, 1249, 1175, 1027, 753 cm\textsuperscript{-1}; HRMS (MM: ESI-APCI\textsuperscript{+}) m/z calc'd for C\textsubscript{21}H\textsubscript{24}NO\textsubscript{3} [M+H]\textsuperscript{+}: 338.1751, found 338.1748.

\textit{(E)-3-(3-(4-Fluorophenyl)allyl)-1-(2-methoxyphenyl)pyrroldin-2-one (63m)}

Lactam 63m was prepared according to the general procedure 2 using (E)-1-(3-chloroprop-1-en-1-yl)-4-fluorobenzene\textsuperscript{5} in place of methyl iodide, and isolated by flash column chromatography (1:3 EtOAc:hexanes) on silica gel as a white solid.

52% yield. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 7.37 – 7.30 (m, 2H), 7.30 – 7.21 (m, 2H), 7.05 – 6.93 (m, 4H), 6.51 – 6.43 (m, 1H), 6.20 (dt, J = 15.8, 7.1 Hz, 1H), 3.81 (s, 3H),
3.75 – 3.61 (m, 2H), 2.83 – 2.73 (m, 2H), 2.56 – 2.45 (m, 1H), 2.38 – 2.27 (m, 1H), 1.96 (ddt, \( J = 12.8, 8.6, 7.6 \) Hz, 1H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 176.1, 163.0, 161.1, 154.8, 133.7, 133.6, 131.0, 128.7, 128.6, 127.6, 127.5, 127.3, 127.8, 127.2, 120.9, 115.5, 115.3, 112.0, 55.6, 48.2, 41.9, 34.7, 24.9; IR (Neat Film NaCl) 2942, 1696, 1597, 1507, 1458, 1405, 1279, 1253, 1225, 1158, 1046, 1025, 968, 839, 753 cm\(^{-1}\); HRMS (MM: ESI-APCI+) \( m/z \) calc’d for C\(_{20}\)H\(_{21}\)FNO\(_2\) [M+H]\(^{+}\): 326.1551, found 326.1544.

\((E)-1-(2\text{-methoxyphenyl})-3-(3\text{-thiophen-3-yl)allyl})pyrrolidin-2\text{-one (63n)}\)

[Chemical structure image]

Lactam \( 63n \) was prepared according to the general procedure 2 using \((E)-3\text{-}(3\text{-chloroprop-1-en-1-yl)thiophene in place of methyl iodide, and isolated by flash column chromatography (1:2 EtOAc:hexanes) on silica gel as a pale yellow oil. 62% yield. \(^{1}\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.31 – 7.19 (m, 4H), 7.10 (dd, \( J = 3.1, 1.2 \) Hz, 1H), 7.01 – 6.92 (m, 2H), 6.52 (d, \( J = 15.7 \) Hz, 1H), 6.13 (dt, \( J = 15.7, 7.1 \) Hz, 1H), 3.81 (s, 3H), 3.75 – 3.59 (m, 2H), 2.81 – 2.71 (m, 2H), 2.53 – 2.42 (m, 1H), 2.37 – 2.26 (m, 1H), 2.02 – 1.90 (m, 1H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 176.1, 154.8, 140.1, 128.6, 128.6, 127.3, 127.3, 126.4, 125.9, 125.0, 121.0, 120.9, 112.1, 55.6, 48.2, 41.9, 34.6, 24.9; IR (Neat Film NaCl) 2936, 1694, 1596, 1504, 1463, 1408, 1279, 1252, 1181, 1122, 1046, 1025, 966, 890, 862, 753 cm\(^{-1}\); HRMS (MM: ESI-APCI+) \( m/z \) calc’d for C\(_{18}\)H\(_{20}\)NO\(_2\)S [M+H]\(^{+}\): 314.1209, found 314.1206.
1-(2-Methoxyphenyl)-3-((2E,4E)-5-phenylpenta-2,4-dien-1-yl)pyrrolidin-2-one

(63o)

Lactam 63o was prepared according to the general procedure 2 using ((1E,3E)-5-bromopenta-1,3-dien-1-yl)benzene\(^7\) in place of methyl iodide, and isolated by flash column chromatography (1:2 EtOAc:hexanes) on silica gel as a colorless oil. 73% yield. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.42 – 7.36 (m, 2H), 7.36 – 7.17 (m, 4H), 7.02 – 6.92 (m, 2H), 6.79 (ddd, \(J = 15.7, 10.4, 0.8\) Hz, 1H), 6.49 (d, \(J = 15.7\) Hz, 1H), 6.33 (ddd, \(J = 15.1, 10.4, 0.8\) Hz, 1H), 5.93 – 5.83 (m, 1H), 3.83 (s, 3H), 3.76 – 3.61 (m, 2H), 2.80 – 2.68 (m, 2H), 2.47 – 2.37 (m, 1H), 2.36 – 2.26 (m, 1H), 1.99 – 1.87 (m, 1H); \(^1^3\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 176.0, 154.8, 137.4, 132.8, 132.0, 130.9, 129.0, 128.6, 128.6, 128.6, 127.4, 127.3, 126.2, 120.9, 112.0, 55.6, 48.1, 41.9, 34.6, 25.0; IR (Neat Film NaCl) 2941, 1694, 1596, 1505, 1463, 1407, 1300, 1279, 1252, 1181, 1123, 1107, 1046, 1026, 992, 911, 891, 750, 693 cm\(^{-1}\); HRMS (MM: ESI-APCI\(^+\)) \(m/z\) calc'd for C\(_{22}\)H\(_{24}\)NO\(_2\) [M+H]\(^+\): 334.1802, found 334.1801.
General Procedure for Ni-Catalyzed C-Acylation

Please note that the absolute configuration was determined only for compound 10 by transforming to a known compound. The absolute configuration for all other products has been inferred by analogy. For respective HPLC and SFC conditions, please refer to Table S1.

**General procedure 3:** (S)-1-(2-methoxyphenyl)-3-methyl-3-(4-methylbenzoyl) pyrrolidin-2-one (62b)

In a nitrogen-filled glovebox, to an oven-dried 4 mL vial equipped with a stir bar was added LHMDS (40.2 mg, 0.240 mmol, 1.20 equiv), LiBr (86.9 mg, 1.00 mmol, 5.00 equiv), a solution of lactam 57b (82.1 mg, 0.400 mmol, 2.00 equiv) in toluene (1.0 mL) and THF (0.2 mL), bromobenzene (61, 31.5 µL, 0.300 mmol, 1.50 equiv), and p-tolunitrile 58b (23.4 mg, 0.200 mmol, 1.00 equiv). To a separate oven-dried 4 mL vial equipped with a stir bar was added Ni(COD)$_2$ (5.50 mg, 0.0200 mmol, 0.100 equiv), SL-M004-1 (Solvias, 25.3 mg, 0.0240 mmol, 0.120 equiv), and toluene (1.0 mL). Both the lactam suspension and the Ni/ligand solution were stirred at ambient temperature for several minutes and then cooled to 4 °C. The Ni/ligand solution was added to the lactam suspension at 4 °C, and the vial was closed with a PTFE-lined
septum cap. **Note:** Although this effect has not yet been studied in detail, we have observed lower yields when the vial containing the lactam suspension was first closed with a PTFE-lined septum cap, and then the catalyst solution was added through the septum cap. The reaction mixture was stirred at 4 °C for 48 h and then removed from the glovebox. AcOEt (6 mL) and 1 M HCl aqueous solution (5 mL) were added and the mixture was stirred at ambient temperature for 1 h. The reaction mixture was extracted with AcOEt (24 mL), washed with brine (5 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:5 EtOAc:hexanes) on silica gel to give lactam 62 as a white solid (59.4 mg, 92% yield, 91% ee). \([\alpha]_D^{25} +2.1^\circ (c 1.03, \text{CHCl}_3); \) \(^1\)H NMR (500 MHz, CDCl₃) \(\delta\) 8.09 – 8.02 (m, 2H), 7.33 – 7.20 (m, 4H), 7.03 – 6.95 (m, 2H), 3.94 – 3.87 (m, 1H), 3.85 (s, 3H), 3.84 – 3.78 (m, 1H), 2.94 (ddd, \(J = 12.9, 8.4, 6.4\) Hz, 1H), 2.40 (s, 3H), 2.07 (ddd, \(J = 12.8, 8.0, 4.8\) Hz, 1H), 1.68 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl₃) \(\delta\) 198.4, 174.9, 155.0, 143.2, 133.0, 129.6, 129.0, 129.0, 128.4, 126.9, 120.9, 112.1, 56.6, 55.7, 47.1, 32.5, 21.6; IR (Neat Film NaCl) 2973, 2929, 1701, 1696, 1606, 1503, 1459, 1408, 1272, 1255, 1185, 1121, 1023, 1009, 970, 753 cm⁻¹; HRMS (MM: ESI-APCI+) \(m/z\) calc’d for C₂₀H₂₂NO₃ [M+H]⁺: 324.1594, found 324.1599.
Spectroscopic Data for Ni-Catalyzed C-Acylation Products

(S)-3-Benzoyl-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (60a)

Lactam 60a was prepared according to the general procedure 3 from 57a using benzonitrile in place of p-tolunitrile, reacting at ambient temperature for 24 h in place of 0 °C for 48 h, and isolated by flash column chromatography (1:10 EtOAc:hexanes) on silica gel as a white solid. 79.9 mg, 86% yield, 88% ee.

Gram-scale reaction

In a nitrogen-filled glovebox, to a solution of LHMDS (1.00 g, 6.00 mmol, 1.20 equiv) in toluene (10 mL) at 23 °C, was slowly added a solution of 57a (1.33 g, 6.50 mmol, 1.30 equiv) in toluene (13 mL). The flask containing the solution of 57a was then rinsed with toluene (2 mL), and the rinse was added to the LHMDS/57a solution. LiBr (2.17 g, 25.0 mmol, 5.00 equiv) was dissolved in THF (5 mL) and then added to the reaction mixture, followed by benzonitrile (515 µL, 5.00 mmol, 1.00 equiv) and bromobenzene (785 µL, 7.50 mmol, 1.50 equiv). Then, a solution of Ni(COD)₂ (138 mg, 0.500 mmol, 0.100 equiv) and SL-M004-1 (632 mg, 0.600 mmol, 1.20 equiv) in toluene (23 mL) was added slowly, followed by a 2 mL toluene rinse. The reaction mixture was stirred at 23 °C for 45 h. The reaction mixture was then removed from the glovebox, AcOEt (150 mL) and 1 M HCl aqueous solution (125 mL) were added, and the mixture was stirred at ambient temperature for 1 h. The reaction mixture was extracted with AcOEt (200 mL), washed with brine (100 mL), dried over Na₂SO₄,
and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:3 EtOAc:hexanes) on silica gel to give lactam 60a as an off-white solid. 1.06 g, 69% yield, 90% ee. \([\alpha]_{D}^{25} -27.1^\circ (c 1.45, \text{CHCl}_3)\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 8.07 – 8.00\) (m, 2H), 7.58 – 7.47 (m, 3H), 7.46 – 7.38 (m, 2H), 6.96 – 6.87 (m, 2H), 3.95 (ddd, \(J = 9.5, 7.9, 6.1\) Hz, 1H), 3.86 (ddd, \(J = 9.6, 8.2, 5.1\) Hz, 1H), 3.82 (s, 3H), 2.93 (ddd, \(J = 13.0, 8.0, 5.1\) Hz, 1H), 2.08 (ddd, \(J = 12.9, 8.3, 6.1\) Hz, 1H), 1.68 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta 2930, 199.0, 173.2, 156.9, 135.9, 132.5, 132.4, 129.2, 128.4, 121.8, 114.1, 58.3, 55.5, 46.5, 31.7, 22.0\); IR (Neat Film NaCl) 1685, 1512, 1399, 1268, 1249, 1182, 1090, 1032, 970, 830, 702 cm\(^{-1}\); HRMS (MM: ESI-APCI\(^+\)) \(m/z\) calc’d for C\(_{19}\)H\(_{20}\)NO\(_3\) [M+H]\(^+\): 310.1438, found 310.1442.

(S)-3-Benzoyl-1-(2-methoxyphenyl)-3-methylpyrrolidin-2-one (60b)

Lactam 60b was prepared according to the general procedure 3 from 57b using benzonitrile in place of \(p\)-tolunitrile, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a white solid. 50.3 mg, 81% yield, 92% ee. \([\alpha]_{D}^{25} +4.0^\circ (c 1.21, \text{CHCl}_3, 92%\) ee); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 8.17 – 8.11\) (m, 2H), 7.56 – 7.48 (m, 1H), 7.47 – 7.40 (m, 2H), 7.34 – 7.25 (m, 2H), 7.04 – 6.95 (m, 2H), 3.90 (ddd, \(J = 9.6, 8.4, 4.8\) Hz, 1H), 3.86 – 3.78 (m, 1H), 3.85 (s, 3H), 2.95 (ddd, \(J = 12.9, 8.4, 6.3\) Hz, 1H), 2.08 (ddd, \(J = 12.8, 8.0, 4.8\) Hz, 1H), 1.69 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta 1989.0, 174.7, 155.0, 135.8, 132.4, 129.4, 129.0, 128.3,\)
128.3, 126.8, 121.0, 112.1, 56.8, 55.7, 47.1, 32.4, 21.6; IR (Neat Film NaCl) 2974, 2930, 1701, 1697, 1596, 1503, 1459, 1410, 1305, 1270, 1256, 1121, 1023, 1010, 970, 750, 702 cm\(^{-1}\); HRMS (MM: ESI-APCI\(^+\)) \(m/z\) calc’d for C\(_{19}\)H\(_{20}\)NO\(_3\) [M+H]\(^+\): 310.1438, found 310.1441.

(S)-3-Benzoyl-1-(3,5-dimethoxyphenyl)-3-methylpyrrolidin-2-one (60c)

Lactam 60c was prepared according to the general procedure 3 from 57c using benzonitrile in place of \(p\)-tolunitrile, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a white solid. 54.5 mg, 80% yield, 85% ee. 

\([\alpha]_D^{25} – 30.0^\circ\) (c 1.04, CHCl\(_3\)); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.04 – 7.97 (m, 2H), 7.55 – 7.48 (m, 1H), 7.47 – 7.38 (m, 2H), 6.92 (d, \(J = 2.2\) Hz, 2H), 6.31 (t, \(J = 2.2\) Hz, 1H), 3.97 (ddd, \(J = 9.6, 8.0, 6.0\) Hz, 1H), 3.87 (ddd, \(J = 9.6, 8.3, 5.1\) Hz, 1H), 3.81 (s, 6H), 2.92 (ddd, \(J = 13.1, 8.0, 5.2\) Hz, 1H), 2.07 (ddd, \(J = 12.9, 8.3, 6.0\) Hz, 1H), 1.68 (s, 3H); \(^1^3\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 198.6, 173.8, 160.9, 141.0, 135.7, 132.6, 129.2, 128.4, 98.3, 97.1, 58.7, 55.5, 46.4, 31.4, 22.0; IR (Neat Film NaCl) 2937, 2840, 1696, 1598, 1480, 1393, 1277, 1249, 1206, 1156, 1067, 972, 834, 722, 699, 682, 661 cm\(^{-1}\); HRMS (MM: ESI-APCI\(^+\)) \(m/z\) calc’d for C\(_{20}\)H\(_{22}\)NO\(_4\) [M+H]\(^+\): 340.1543, found 340.1552.
(S)-3-Benzy1-1-(2-isopropoxyphenyl)-3-methylpyrrolidin-2-one (60d)

Lactam 60d was prepared according to the general procedure 3 from 57d using benzonitrile in place of p-tolunitrile, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a white solid. 46.7 mg, 69% yield, 86% ee. 

$[\alpha]_D^{25} +9.4^\circ$ (c 1.01, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.21 – 8.14 (m, 2H), 7.59 – 7.51 (m, 1H), 7.51 – 7.43 (m, 2H), 7.35 – 7.26 (m, 2H), 7.06 – 6.97 (m, 2H), 4.63 (hept, $J$ = 6.1 Hz, 1H), 3.98 (ddd, $J$ = 9.5, 8.2, 4.9 Hz, 1H), 3.85 (ddd, $J$ = 9.6, 8.0, 6.3 Hz, 1H), 3.00 (ddd, $J$ = 12.8, 8.2, 6.3 Hz, 1H), 2.10 (ddd, $J$ = 12.8, 8.0, 4.9 Hz, 1H), 1.73 (s, 3H), 1.36 (d, $J$ = 6.0 Hz, 3H), 1.35 (d, $J$ = 6.0 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 199.0, 174.5, 153.2, 135.9, 132.4, 129.4, 128.8, 128.8, 128.3, 127.7, 120.6, 114.1, 70.4, 56.9, 47.2, 32.6, 22.1, 22.1, 21.6; IR (Neat Film NaCl) 2977, 2930, 1697, 1596, 1500, 1455, 1407, 1281, 1270, 1255, 1124, 954, 750, 701 cm$^{-1}$; HRMS (MM: ESI-APCI+) m/z calc’d for C$_{21}$H$_{24}$NO$_3$ [M+H]$^+$: 338.1751, found 338.1744.

(S)-1-(2-Methoxyphenyl)-3-methyl-3-(3-methylbenzoyl)pyrrolidin-2-one (62c)

Lactam 62c was prepared according to the general procedure 3 from 57b using m-tolunitrile in place of p-tolunitrile, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a colorless oil. 59.1 mg, 91% yield, 93% ee. 

$[\alpha]_D^{25} +5.5^\circ$ (c 0.52, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.97 – 7.90 (m, 1H), 7.89 –
7.88 (m, 1H), 7.33 – 7.26 (m, 4H), 7.04 – 6.95 (m, 2H), 3.90 (ddd, $J = 9.6, 8.4, 4.7$ Hz, 1H), 3.86 – 3.78 (m, 1H), 3.84 (s, 3H), 2.93 (ddd, $J = 12.9, 8.4, 6.5$ Hz, 1H), 2.40 (s, 3H), 2.11 – 2.02 (m, 1H), 1.67 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 199.3, 174.8, 155.06, 138.0, 135.8, 133.1, 129.8, 129.0, 128.3, 128.1, 126.9, 126.5, 121.0, 112.1, 56.8, 55.7, 47.1, 32.4, 21.6, 21.5; IR (Neat Film NaCl) 2973, 2931, 1694, 1598, 1504, 1455, 1409, 1276, 1255, 1182, 1121, 1092, 1044, 1024, 976, 905, 789, 754, cm$^{-1}$; HRMS (MM: ESI-APCI$^+$) $m/z$ calc'd for C$_{20}$H$_{22}$NO$_3$ [M+H]$^+$: 324.1594, found 324.1602.

(S)-1-(2-Methoxyphenyl)-3-methyl-3-(2-methylbenzoyl)pyrrolidin-2-one (62d)

Lactam 62d was prepared according to the general procedure 3 from 57b using o-tolunitrile in place of p-tolunitrile, reacting with aqueous HCl at 70 °C in place of ambient temperature, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a colorless oil. 44.9 mg, 69% yield, 94% ee. [a]$_D^{25}$ = 29.6° (c 0.20, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.64 (dd, $J = 7.6, 1.4$ Hz, 1H), 7.34 – 7.25 (m, 2H), 7.25 – 7.16 (m, 3H), 7.01 – 6.93 (m, 2H), 3.82 (s, 3H), 3.73 (dd, $J = 7.6, 6.3$ Hz, 2H), 2.82 – 2.73 (m, 1H), 2.33 (s, 3H), 2.14 – 2.05 (m, 1H), 1.59 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 205.5, 173.8, 154.9, 139.1, 135.6, 130.9, 129.7, 128.9, 128.4, 126.9, 126.0, 125.2, 120.9, 112.1, 58.4, 55.6, 47.2, 31.9, 21.3, 20.1; IR (Neat Film NaCl) 2971, 2932, 1694, 1597, 1505, 1456, 1409, 1305, 1281, 1256, 1044, 1024, 976, 905, 789, 754, cm$^{-1}$; HRMS (MM: ESI-APCI$^+$) $m/z$ calc'd for C$_{20}$H$_{22}$NO$_3$ [M+H]$^+$: 324.1594, found 324.1602.
1122, 1045, 1025, 969, 755 cm\(^{-1}\); HRMS (MM: ESI-APCI+) \(m/z\) calc'd for C\(_{20}\)H\(_{22}\)NO\(_3\) [M+H]\(^+\): 324.1594, found 324.1601.

\(\text{(S)-3-(4-(\text{tert-Butyl})benzoyl)-1-(2-methoxyphenyl)-3-methylpyrrolidin-2-one (62e)}\)

Lactam 62e was prepared according to the general procedure 3 from 57b using 4-(\text{tert-butyl})benzonitrile in place of \(p\)-tolunitrile, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a white solid. 64.7 mg, 89% yield, 92% ee. \([\alpha]_D^{25} +6.9^\circ\) (c 1.04, CHCl\(_3\)); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.13 – 8.07 (m, 2H), 7.47 – 7.41 (m, 2H), 7.33 – 7.25 (m, 2H), 7.04 – 6.95 (m, 2H), 3.93 – 3.80 (m, 2H), 3.85 (s, 3H), 3.96 (ddd, \(J = 12.9, 8.4, 6.5\) Hz, 1H), 2.08 (ddd, \(J = 12.8, 7.9, 4.8\) Hz, 1H), 1.69 (s, 3H), 1.34 (s, 9H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 198.2, 175.0, 156.0, 155.0, 132.7, 129.5, 128.9, 128.4, 126.9, 125.2, 120.9, 112.1, 56.6, 55.7, 47.1, 35.0, 32.5, 31.1, 21.6; IR (Neat Film NaCl) 2963, 1701, 1676, 1603, 1504, 1459, 1406, 1272, 1255, 1121, 1109, 1023, 971, 752 cm\(^{-1}\); HRMS (MM: ESI-APCI+) \(m/z\) calc'd for C\(_{23}\)H\(_{28}\)NO\(_3\) [M+H]\(^+\): 366.2064, found 366.2072.

\(\text{(S)-3-(4-Methoxybenzoyl)-1-(2-methoxyphenyl)-3-methylpyrrolidin-2-one (62f)}\)
Lactam 62f was prepared according to the general procedure 3 from 57b using 4-methoxybenzonitrile in place of p-tolunitrile, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a colorless oil. 57.8 mg, 85% yield, 89% ee. [a]D 25 −3.7° (c 0.73, CHCl3); 1H NMR (500 MHz, CDCl3) δ 8.24 – 8.17 (m, 2H), 7.32 – 7.27 (m, 2H), 7.03 – 6.88 (m, 4H), 3.93 – 3.87 (m, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.83 – 3.77 (m, 1H), 2.97 (ddd, J = 12.8, 8.2, 6.2 Hz, 1H), 2.07 (ddd, J = 12.9, 8.0, 5.0 Hz, 1H), 1.68 (s, 3H); 13C NMR (126 MHz, CDCl3) δ 196.8, 175.0, 162.9, 155.0, 132.1, 128.9, 128.3, 128.2, 127.0, 120.9, 113.4, 112.1, 56.6, 55.7, 55.4, 47.2, 32.7, 21.8; IR (Neat Film NaCl) 2971, 2933, 1695, 1600, 1504, 1464, 1456, 1410, 1307, 1259, 1174, 1027, 971, 845, 754, 699, 610 cm⁻¹; HRMS (MM: ESI-APCI+) m/z calc'd for C20H22NO4 [M+H]+: 340.1543, found 340.1547.

(S)-3-(4-Fluorobenzoyl)-1-(2-methoxyphenyl)-3-methylpyrrolidin-2-one (62g)

![Structure of 62g]

Lactam 62g was prepared according to the general procedure 3 from 57b using 4-fluorobenzonitrile in place of p-tolunitrile, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a white solid. 23.3 mg, 36% yield, 93% ee. [a]D 25 −1.8° (c 0.77, CHCl3); 1H NMR (500 MHz, CDCl3) δ 8.28 – 8.20 (m, 2H), 7.34 – 7.27 (m, 1H), 7.27 – 7.20 (m, 1H), 7.14 – 7.06 (m, 2H), 7.04 – 6.95 (m, 2H), 3.91 (ddd, J = 9.6, 8.3, 5.0 Hz, 1H), 3.85 – 3.76 (m, 4H), 3.83 (s, 3H), 2.95 (ddd, J = 12.8, 8.3, 6.1 Hz, 1H), 2.12 – 2.03 (m, 1H), 1.68 (s, 3H); 13C NMR (126 MHz, CDCl3) δ 197.1, 174.5, 165.2, 154.9, 132.4, 131.9, 129.1, 128.3, 126.7,
121.0, 115.3, 112.1, 56.9, 55.7, 47.2, 32.5, 21.7; IR (Neat Film NaCl) 2974, 1697, 1684, 1597, 1506, 1457, 1410, 1271, 1256, 1235, 1160, 1024, 972, 848, 754, 609 cm\(^{-1}\); HRMS (MM: ESI-APCI\(^+\)) \(m/z\) calc'd for \(\text{C}_{19}\text{H}_{19}\text{FNO}_3\) [M+H]\(^+\): 328.1343, found 328.1353.

\((S)-1-(2\text{-Methoxyphenyl})-3\text{-methyl}-3-(4\text{-} (\text{trifluoromethyl})\text{benzoyl})\text{pyrrolidin-2-one (62h)}\)

Lactam 62h was prepared according to the general procedure 3 from 57b using 4-trifluoromethylbenzonitrile in place of \(p\)-tolunitrile, reacting at ambient temperature for 24 h in place of 0 °C for 48 h, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a colorless oil. 21.5 mg, 23% yield, 87% ee. \([\alpha]_D^{25}\) +2.7° (c 0.71, CHCl\(_3\)); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.29 – 8.22 (m, 2H), 7.78 – 7.61 (m, 2H), 7.35 – 7.29 (m, 1H), 7.24 (dd, \(J = 7.7, 1.7\) Hz, 1H), 7.05 – 6.95 (m, 2H), 3.91 (ddd, \(J = 9.7, 8.3, 5.0\) Hz, 1H), 3.84 (s, 3H), 3.83 – 3.77 (m, 1H), 2.93 (ddd, \(J = 12.9, 8.3, 6.2\) Hz, 1H), 2.09 (ddd, \(J = 13.0, 8.0, 5.0\) Hz, 1H), 1.69 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 198.4, 174.1, 154.9, 139.0, 133.7, 133.6, 129.7, 129.2, 128.3, 125.3, 123.6, 121.0, 112.1, 57.2, 55.7, 47.2, 32.1, 21.5; IR (Neat Film NaCl) 2975, 2934, 1697, 1505, 1409, 1328, 1316, 1257, 1169, 1127, 1068, 1020, 1009, 973, 858, 753; cm\(^{-1}\); HRMS (MM: ESI-APCI\(^+\)) \(m/z\) calc'd for \(\text{C}_{20}\text{H}_{19}\text{F}_3\text{NO}_3\) [M+H]\(^+\): 378.1312, found 378.1325.
(S)-3-(2-Naphthoyl)-1-(2-methoxyphenyl)-3-methylpyrrolidin-2-one (62i)

Lactam 62i was prepared according to the general procedure 3 from 57b using 2-naphthonitrile in place of p-tolunitrile, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a colorless oil. 47.5 mg, 66% yield, 91% ee. 

$[\alpha]_D^{25} +15.8^\circ$ (c 0.52, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.77 (d, $J = 1.3$ Hz, 1H), 8.14 (dd, $J = 8.6$, 1.8 Hz, 1H), 7.98 – 7.92 (m, 1H), 7.87 (t, $J = 8.4$ Hz, 2H), 7.62 – 7.56 (m, 1H), 7.56 – 7.49 (m, 1H), 7.35 – 7.27 (m, 2H), 7.06 – 6.97 (m, 2H), 3.95 – 3.81 (m, 1H), 3.84 (s, 3H), 3.04 (ddd, $J = 12.9$, 8.3, 6.2 Hz, 1H), 2.17 – 2.08 (m, 1H), 1.75 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 198.9, 174.7, 155.0, 135.1, 133.0, 132.4, 131.1, 129.8, 129.0, 128.3, 128.0, 127.6, 127.0, 126.5, 125.4, 121.0, 112.2, 57.1, 55.7, 47.2, 32.6, 21.8; IR (Neat Film NaCl) 2930, 1694, 1505, 1463, 1409, 1281, 1255, 1120, 1024, 750 cm$^{-1}$; HRMS (MM: ESI-APCI+) $m/z$ calc'd for C$_{23}$H$_{22}$NO$_3$ [M+H]$^+$: 360.1594, found 360.1589.
(S)-3-Ethyl-1-(2-methoxyphenyl)-3-(4-methylbenzoyl)pyrrolidin-2-one (64b)

Lactam **64b** was prepared according to the general procedure 3 from **63b**, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a colorless oil. 33.9 mg, 50% yield, 78% ee. \([\alpha]_D^{25} +14.6^\circ\) (c 0.81, CHCl₃); \(^1\)H NMR (500 MHz, CDCl₃) δ 8.14 (d, \(J = 8.3\) Hz, 2H), 7.31 – 7.18 (m, 4H), 7.01 – 6.92 (m, 2H), 3.90 (ddd, \(J = 9.5, 8.1, 6.7\) Hz, 1H), 3.79 (s, 3H), 3.71 (ddd, \(J = 9.5, 8.7, 4.3\) Hz, 1H), 2.95 (ddd, \(J = 13.0, 8.0, 4.2\) Hz, 1H), 2.41 – 2.30 (m, 4H), 2.17 – 2.05 (m, 2H), 0.97 (t, \(J = 7.5\) Hz, 3H); \(^13\)C NMR (126 MHz, CDCl₃) δ 198.3, 173.5, 154.9, 143.0, 134.0, 129.5, 128.9, 128.9, 128.4, 127.1, 120.9, 112.1, 61.8, 55.6, 47.5, 29.5, 29.1, 21.6, 8.8; IR (Neat Film NaCl) 2962, 1700, 1606, 1504, 1461, 1253, 1159, 1024, 752 cm\(^{-1}\); HRMS (MM: ESI-APCI+) \(m/z\) calc’d for C\(_{21}\)H\(_{24}\)NO\(_3\) [M+H]\(^+\): 338.1751, found 338.1753.

(S)-3-Benzyl-1-(2-methoxyphenyl)-3-(4-methylbenzoyl)pyrrolidin-2-one (64c)

Lactam **64c** was prepared according to the general procedure 3 from **63c**, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a colorless oil. 48.8 mg, 61% yield, 81% ee. \([\alpha]_D^{25} +62.3^\circ\) (c 0.90, CHCl₃); \(^1\)H NMR (500 MHz, CDCl₃) δ 8.13 – 8.06 (m, 2H), 7.31 – 7.16 (m, 8H), 6.93 – 6.83 (m, 3H), 3.77 (s, 3H),...
3.62 (td, $J = 9.1, 4.1$ Hz, 1H), 3.53 (d, $J = 13.7$ Hz, 1H), 3.34 (d, $J = 13.7$ Hz, 1H), 2.90 – 2.72 (m, 2H), 2.37 (s, 3H), 2.26 (ddd, $J = 13.0, 8.4, 4.1$ Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 197.7, 173.1, 154.9, 143.2, 136.7, 133.3, 130.6, 129.7, 129.0, 128.9, 128.4, 127.9, 126.9, 126.7, 120.8, 112.0, 61.4, 55.6, 47.0, 40.9, 28.7, 21.7; IR (Neat Film NaCl) 2928, 1696, 1604, 1502, 1457, 1405, 1240, 1185, 1025, 741, 702 cm$^{-1}$; HRMS (MM: ESI-APCI+) $m/z$ calc'd for C$_{26}$H$_{26}$NO$_3$ [M+H]$^+$: 400.1907, found 400.1919.

(S)-3-((4-Methoxybenzyl)-1-(2-methoxyphenyl)-3-(4-methylbenzoyl)pyrrolidin-2-one (64d)

![Structure](image)

Lactam 64d was prepared according to the general procedure 3 from 63d, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a colorless oil. 65.8 mg, 77% yield, 81% ee. [a]$_D^{25}$ +50.4° (c 1.21, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.16 – 8.09 (m, 2H), 7.30 – 7.18 (m, 5H), 6.99 (dd, $J = 8.0, 1.8$ Hz, 1H), 6.98 – 6.88 (m, 2H), 6.88 – 6.80 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.67 (td, $J = 9.2, 4.2$ Hz, 1H), 3.51 (d, $J = 13.9$ Hz, 1H), 3.32 (d, $J = 13.9$ Hz, 1H), 2.95 (ddd, $J = 9.4, 8.6, 6.5$ Hz, 1H), 2.80 (ddd, $J = 13.3, 9.0, 6.4$ Hz, 1H), 2.40 (s, 3H), 2.27 (ddd, $J = 13.0, 8.6, 4.2$ Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 197.9, 173.2, 158.7, 154.9, 143.1, 133.4, 131.5, 129.7, 129.0, 128.8, 128.6, 127.9, 126.7, 120.8, 113.7, 112.0, 61.5, 55.6, 55.3, 47.0, 40.1, 28.7, 21.6; IR (Neat Film NaCl) 2930, 1694, 1606, 1505,
1463, 1409, 1301, 1248, 1180, 1028, 832, 753 cm$^{-1}$; HRMS (MM: ESI-APCI+) $m/z$ calc'd for C$_{27}$H$_{28}$NO$_4$ [M+H]$^+$: 430.2013, found 430.2006.

(S)-3-(4-Fluorobenzyl)-1-(2-methoxyphenyl)-3-(4-methylbenzoyl)pyrrolidin-2-one (64e)

Lactam 64e was prepared according to the general procedure 3 from 63e, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a white foam. 63.5 mg, 76% yield, 74% ee. [α]$_D^{25}$ +38.9° (c 3.08, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.15 – 8.08 (m, 2H), 7.31 – 7.21 (m, 5H), 7.04 – 6.91 (m, 5H), 3.79 (s, 3H), 3.67 (td, $J = 9.3$, 4.4 Hz, 1H), 3.54 (d, $J = 13.9$ Hz, 1H), 3.34 (d, $J = 13.9$ Hz, 1H), 3.00 (ddd, $J = 9.5$, 8.7, 6.3 Hz, 1H), 2.81 (ddd, $J = 13.4$, 9.1, 6.3 Hz, 1H), 2.41 (s, 3H), 2.26 (ddd, $J = 13.3$, 8.7, 4.4 Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 197.6, 172.9, 163.1, 161.1, 154.8, 143.3, 133.2, 132.4, 132.0, 132.0, 129.6, 129.1, 128.9, 127.8, 126.5, 120.9, 115.3, 115.1, 112.0, 61.4, 55.6, 47.0, 40.1, 28.6, 21.7; IR (Neat Film NaCl) 2931, 1697, 1604, 1465, 1410, 1222, 1185, 1026, 909, 833, 752, 731 cm$^{-1}$; HRMS (MM: ESI-APCI+) $m/z$ calc'd for C$_{26}$H$_{25}$FNO$_3$ [M+H]$^+$: 418.1813, found 418.1806.
(R)-1-(2-Methoxyphenyl)-3-(4-methylbenzoyl)-3-(2,2,2-trifluoroethyl)pyrrolidin-2-one (64f)

Lactam 64f was prepared according to the general procedure 3 from 63f, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a colorless oil. 45.5 mg, 58% yield, 71% ee. [α]D 25 +10.3° (c 2.16, CHCl3); 1H NMR (500 MHz, CDCl3) δ 8.16 – 8.09 (m, 2H), 7.34 – 7.28 (m, 1H), 7.28 – 7.17 (m, 3H), 7.03 – 6.92 (m, 2H), 4.00 (ddd, J = 9.6, 7.7, 6.8 Hz, 1H), 3.78 (s, 3H), 3.72 (ddd, J = 9.6, 8.7, 3.9 Hz, 1H), 3.34 (dq, J = 15.8, 11.1 Hz, 1H), 3.10 – 3.01 (m, 1H), 2.87 (dq, J = 15.7, 11.1 Hz, 1H), 2.40 (s, 4H); 13C NMR (126 MHz, CDCl3) δ 195.1, 171.4, 154.8, 143.5, 133.0, 129.6, 129.3, 129.1, 128.1, 127.5, 126.4, 125.3, 121.0, 112.0, 57.7, 55.6, 47.6, 39.3, 39.1, 38.9, 38.7, 29.1, 29.0, 21.6; IR (Neat Film NaCl) 2952, 1703, 1673, 1505, 1464, 1373, 1299, 1260, 1143, 1021, 753 cm⁻¹; HRMS (MM: ESI-APCI+) m/z calc'd for C21H21F3NO3 [M+H]+: 392.1468, found 392.1459.

(S)-3-(3-(Benzzyloxy)propyl)-1-(2-methoxyphenyl)-3-(4-methylbenzoyl)pyrrolidin-2-one (64g)

Lactam 64g was prepared according to the general procedure 3 from 63g, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a colorless oil.
61.6 mg, 67% yield, 60% ee. $[\alpha]_D^{25} +9.3^\circ$ (c 2.90, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.16 – 8.10 (m, 1H), 7.37 – 7.18 (m, 6H), 7.01 – 6.92 (m, 1H), 4.45 (d, $J = 2.3$ Hz, 1H), 3.88 (ddd, $J = 9.5, 8.0, 6.6$ Hz, 1H), 3.77 (s, 1H), 3.76 – 3.66 (m, 1H), 3.46 (td, $J = 6.4, 1.1$ Hz, 1H), 2.38 (s, 2H), 2.19 – 2.07 (m, 1H), 1.77 – 1.58 (m, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 198.0, 173.4, 154.9, 143.0, 138.5, 133.8, 129.5, 128.9, 128.4, 128.3, 127.6, 127.5, 127.0, 120.9, 112.0, 72.8, 70.3, 61.1, 55.6, 47.5, 32.8, 30.0, 24.8, 21.6; IR (Neat Film NaCl) 2935, 1698, 1606, 1504, 1455, 1408, 1302, 1279, 1252, 1185, 1101, 1027, 750, 699 cm$^{-1}$; HRMS (MM: ESI-APCI+) $m/z$ calc'd for C$_{29}$H$_{32}$NO$_4$ [M+H]$^+$: 458.2326, found 458.2315.

\[(S)-1-(2\text{-}\text{Methoxyphenyl})\text{-}3-(4\text{-}\text{methylbenzoyl})\text{-}3\text{-}(3\text{-}\text{methylbut-2-en-1-yl})\text{pyrrolidin-2-one}~(64h)\]

Lactam 64h was prepared according to the general procedure 3 from 63h, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a pale yellow oil. 53.2 mg, 71% yield, 76% ee. $[\alpha]_D^{25} +29.6^\circ$ (c 2.15, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.14 – 8.07 (m, 2H), 7.32 – 7.25 (m, 2H), 7.25 – 7.18 (m, 2H), 7.02 – 6.92 (m, 2H), 5.23 – 5.15 (m, 1H), 3.88 (ddd, $J = 9.5, 8.5, 5.7$ Hz, 1H), 3.83 (s, 3H), 3.68 (ddd, $J = 9.4, 8.7, 5.1$ Hz, 1H), 3.02 – 2.93 (m, 1H), 2.89 – 2.73 (m, 2H), 2.39 (s, 3H), 2.14 (ddd, $J = 13.0, 8.7, 5.7$ Hz, 1H), 1.72 (s, 3H), 1.59 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 198.2, 173.5, 155.0, 142.9, 135.5, 133.8, 129.5, 128.9, 128.3, 127.1, 120.9, 118.6, 112.1, 61.1, 55.6, 47.5, 34.5, 29.2, 26.1, 21.6, 18.0;
IR (Neat Film NaCl) 2917, 1698, 1606, 1504, 1463, 1408, 1248, 1184, 1123, 1024, 753 cm\(^{-1}\); HRMS (MM: ESI-APCI+) \(m/z\) calc'd for C\(_{24}\)H\(_{28}\)NO\(_3\) [M+H]\(^+\): 378.2064, found 378.2060.

\((S,E)\)-3-(But-2-en-1-yl)-1-(2-methoxyphenyl)-3-(4-methylbenzoyl)pyrrolidin-2-one (64i)

Lactam 64i was prepared according to the general procedure 3 from 63i, and isolated by flash column chromatography (1:8 EtOAc:hexanes) on silica gel as a pale yellow oil. 51.0 mg, 70% yield, 86% ee. [\(\alpha\)]\(_D\)\(^{25}\) +45.5° (c 2.10, CHCl\(_3\)); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.08 (d, \(J=8.3\) Hz, 2H), 7.34 – 7.19 (m, 4H), 7.03 – 6.94 (m, 2H), 5.63 – 5.43 (m, 2H), 3.92 – 3.86 (m, 1H), 3.84 (s, 3H), 3.73 – 3.62 (m, 1H), 2.94 – 2.72 (m, 3H), 2.39 (s, 3H), 2.20 (ddd, \(J=13.2, 8.7, 5.3\) Hz, 1H), 1.68 (dq, \(J=6.3, 1.2\) Hz, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 198.0, 173.5, 155.0, 143.0, 133.7, 129.8, 129.5, 129.5, 128.9, 128.3, 127.0, 125.4, 120.9, 112.1, 60.7, 55.6, 47.4, 39.1, 28.9, 21.6, 18.2; IR (Neat Film NaCl) 2917, 1698, 1606, 1504, 1463, 1408, 1254, 1185, 1122, 1045, 1024, 973, 837, 750 cm\(^{-1}\); HRMS (MM: ESI-APCI+) \(m/z\) calc'd for C\(_{23}\)H\(_{26}\)NO\(_3\) [M+H]\(^+\): 364.1907, found 364.1909.
(S)-3-Cinnamyl-1-(2-methoxyphenyl)-3-(4-methylbenzoyl)pyrrolidin-2-one (64j)

Lactam 64j was prepared according to the general procedure 3 from 63j, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a white foam. 51.1 mg, 60% yield, 86% ee. $[\alpha]_D^{25} +55.5^\circ$ (c 0.93, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.11 – 8.05 (m, 2H), 7.41 – 7.33 (m, 2H), 7.33 – 7.18 (m, 10H), 7.00 – 6.93 (m, 2H), 6.52 (d, $J = 15.8$ Hz, 1H), 6.29 (dt, $J = 15.5$, 7.6 Hz, 1H), 3.92 – 3.82 (m, 1H), 3.80 (s, 3H), 3.75 (ddd, $J = 9.6$, 8.7, 5.7 Hz, 1H), 3.05 (dt, $J = 7.4$, 1.4 Hz, 2H), 2.85 (ddd, $J = 13.3$, 8.9, 5.8 Hz, 1H), 2.41 (s, 2H), 2.30 (ddd, $J = 13.5$, 8.7, 5.0 Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 197.9, 173.3, 155.0, 143.1, 137.3, 134.2, 133.5, 129.4, 129.0, 128.5, 128.3, 127.4, 126.8, 126.2, 124.8, 121.0, 112.1, 60.7, 55.6, 47.3, 39.4, 28.8, 21.6; IR (Neat Film NaCl) 2961, 1698, 1606, 1504, 1463, 1409, 1279, 1255, 1185, 1025, 971, 911, 742, 694 cm$^{-1}$; HRMS (MM: ESI-APCI+) $m/z$ calc'd for C$_{28}$H$_{28}$NO$_3$ [M+H]$^+$: 426.2064, found 426.2067.
(S,E)-1-(2-Methoxyphenyl)-3-(4-methylbenzoyl)-3-(3-(p-tolyl)allyl)pyrrolidin-2-one (64k)

Lactam 64k was prepared according to the general procedure 3 from 63k, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a pale yellow oil. 74.2 mg, 85% yield, 88% ee. [a]$_D^{25}$ +56.0° (c 2.93, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.08 (d, $J$ = 8.3 Hz, 2H), 7.33 – 7.25 (m, 2H), 7.25 – 7.19 (m, 4H), 7.14 – 7.08 (m, 2H), 7.00 – 6.93 (m, 2H), 6.49 (d, $J$ = 15.7 Hz, 1H), 6.23 (dt, $J$ = 15.5, 7.6 Hz, 1H), 3.92 – 3.83 (m, 1H), 3.81 (s, 3H), 3.78 – 3.69 (m, 1H), 3.04 (d, $J$ = 7.6 Hz, 2H), 2.85 (ddd, $J$ = 13.2, 8.9, 5.8 Hz, 1H), 2.40 (s, 3H), 2.39 – 2.25 (m, 4H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 197.9, 173.4, 155.0, 143.1, 137.1, 134.5, 134.0, 133.5, 129.4, 129.2, 129.0, 128.3, 126.8, 126.1, 123.6, 121.0, 112.0, 60.7, 55.6, 47.4, 39.4, 28.8, 21.6, 21.2; IR (Neat Film NaCl) 2920, 1694, 1606, 1505, 1463, 1409, 1279, 1254, 1184, 1121, 1045, 1025, 974, 911, 838, 752 cm$^{-1}$; HRMS (MM: ESI-APCI+) $m/z$ calc'd for C$_{29}$H$_{30}$NO$_3$ [M+H]$^+$: 440.2220, found 440.2220.
(S,E)-1-(2-Methoxyphenyl)-3-(3-(4-methoxyphenyl)allyl)-3-(4-methylbenzoyl)

pyrrolidin-2-one (64l)

Lactam 64l was prepared according to the general procedure 3 from 63l, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a white foam. 62.0 mg, 68% yield, 88% ee. [a]_{D}^{25} +57.6° (c 1.09, CHCl₃, 88% ee); ¹H NMR (500 MHz, CDCl₃) δ 8.11 – 8.05 (m, 2H), 7.34 – 7.26 (m, 3H), 7.26 – 7.17 (m, 3H), 7.00 – 6.93 (m, 2H), 6.87 – 6.81 (m, 2H), 6.46 (d, J = 15.7 Hz, 1H), 6.13 (dt, J = 15.5, 7.5 Hz, 1H), 3.88 (td, J = 9.2, 4.9 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.80 – 3.67 (m, 1H), 3.03 (dt, J = 7.6, 1.4 Hz, 2H), 2.85 (ddd, J = 13.2, 8.9, 5.8 Hz, 1H), 2.40 (s, 3H), 2.35 – 2.23 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 197.9, 173.4, 159.0, 155.0, 143.1, 133.5, 130.1, 129.4, 129.0, 128.9, 128.3, 127.4, 126.8, 122.4, 121.0, 113.9, 112.1, 60.8, 55.6, 55.3, 47.4, 39.4, 28.8, 21.6; IR (Neat Film NaCl) 2957, 1699, 1607, 1505, 1464, 1249, 1175, 1027, 838, 752 cm⁻¹; HRMS (MM: ESI-APCI+) m/z calc'd for C₂₉H₃₀NO₄ [M+H]⁺: 456.2169, found 456.2164.
(S,E)-3-(3-(4-Fluorophenyl)allyl)-1-(2-methoxyphenyl)-3-(4-methylbenzoyl)

pyrrolidin-2-one (64m)

Lactam 64m was prepared according to the general procedure 3 from 63m, and isolated by flash column chromatography (1:10 EtOAc:hexanes) on silica gel as a white foam. 55.3 mg, 62% yield, 83% ee. [α]D<sup>25</sup> +40.7° (c 0.55, CHCl₃); <sup>1</sup>H NMR (500 MHz, CDCl₃) δ 8.07 (d, J = 8.3 Hz, 2H), 7.35 – 7.26 (m, 3H), 7.26 – 7.22 (m, 2H), 7.22 – 7.18 (m, 1H), 7.06 – 6.93 (m, 4H), 6.51 – 6.44 (m, 1H), 6.20 (dt, J = 15.5, 7.6 Hz, 1H), 3.88 (ddd, J = 9.6, 8.9, 5.0 Hz, 1H), 3.79 (s, 3H), 3.78 – 3.69 (m, 1H), 3.04 (ddd, J = 7.2, 3.6, 1.3 Hz, 2H), 2.86 (ddd, J = 13.2, 8.9, 5.7 Hz, 1H), 2.41 (s, 3H), 2.38 – 2.23 (m, 2H); <sup>13</sup>C NMR (126 MHz, CDCl₃) δ 197.8, 173.2, 163.1, 161.2, 154.9, 143.2, 133.5, 132.9, 129.4, 129.1, 129.0, 128.2, 127.7, 126.8, 124.6, 121.0, 115.5, 115.3, 112.1, 60.7, 55.6, 47.3, 39.3, 28.9, 21.6; IR (Neat Film NaCl) 2944, 1693, 1604, 1505, 1460, 1412, 1254, 1228, 1184, 1158, 1045, 1024, 910, 838, 753, 731 cm<sup>–1</sup>; HRMS (MM: ESI-APCI+) m/z calc'd for C<sub>28</sub>H<sub>27</sub>FNO₃ [M+H]<sup>+</sup>: 444.1969, found 444.1969.
(S,E)-1-(2-Methoxyphenyl)-3-(4-methylbenzoyl)-3-(3-(thiophen-3-yl)allyl)

pyrrolidin-2-one (64n)

Lactam 64n was prepared according to the general procedure 3 from 63n, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a pale yellow oil. 65.2 mg, 76% yield, 83% ee. [α]$_D^{25}$ +46.7° (c 1.17, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.12 – 8.01 (m, 2H), 7.33 – 7.14 (m, 6H), 7.10 (dd, $J = 3.0, 1.2$ Hz, 1H), 7.00 – 6.93 (m, 2H), 6.53 (d, $J = 15.7$ Hz, 1H), 6.13 (dt, $J = 15.5, 7.6$ Hz, 1H), 3.88 (td, $J = 9.1, 4.9$ Hz, 1H), 3.81 (s, 3H), 3.79 – 3.68 (m, 1H), 3.01 (dd, $J = 7.7, 1.3$ Hz, 2H), 2.85 (ddd, $J = 13.3, 8.9, 5.8$ Hz, 1H), 2.40 (s, 3H), 2.28 (ddd, $J = 13.5, 8.8, 5.0$ Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 197.8, 173.3, 155.0, 143.2, 139.9, 133.4, 129.4, 129.0, 129.0, 128.4, 128.2, 126.8, 126.0, 125.0, 124.6, 121.5, 121.0, 112.1, 60.7, 55.6, 47.3, 39.3, 28.8, 21.6; IR (Neat Film NaCl) 2958, 1698, 1606, 1504, 1463, 1409, 1302, 1279, 1254, 1184, 1122, 1024, 967, 836, 753 cm$^{-1}$; HRMS (MM: ESI-APCI+) $m/z$ calc'd for C$_{26}$H$_{25}$NO$_3$S [M+H]$^+$: 432.1628, found 432.1622.
(S)-1-(2-Methoxyphenyl)-3-(4-methylbenzoyl)-3-((2E,4E)-5-phenylpenta-2,4-dien-1-yl)pyrrolidin-2-one (64o)

Lactam 64o was prepared according to the general procedure 3 from 63o, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a pale yellow oil. 31.7 mg, 35% yield, 84% ee. [a]D^25 +40.6° (c 1.45, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 8.09 (d, J = 8.3 Hz, 2H), 7.42 – 7.36 (m, 2H), 7.36 – 7.16 (m, 6H), 6.98 (d, J = 7.8 Hz, 2H), 6.76 (ddd, J = 15.7, 10.5, 0.9 Hz, 1H), 6.49 (d, J = 15.7 Hz, 1H), 6.38 – 6.29 (m, 1H), 5.87 (dt, J = 15.2, 7.7 Hz, 1H), 3.90 (ddd, J = 9.5, 8.8, 5.1 Hz, 1H), 3.85 (s, 3H), 3.77 – 3.69 (m, 1H), 3.08 – 2.92 (m, 2H), 2.86 (ddd, J = 13.2, 8.8, 5.6 Hz, 1H), 2.41 (s, 3H), 2.25 (ddd, J = 13.7, 8.8, 5.2 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 197.8, 173.2, 155.0, 143.1, 137.3, 134.8, 133.5, 131.6, 129.5, 129.1, 129.0, 129.0, 128.7, 128.6, 128.4, 127.4, 126.8, 126.3, 121.0, 112.1, 60.8, 55.7, 47.3, 39.3, 29.0, 21.6; IR (Neat Film NaCl) 3024, 1694, 1606, 1505, 1463, 1409, 1304, 1253, 1185, 1122, 1045, 1026, 992, 910, 747, 693 cm⁻¹; HRMS (MM: ESI-APCI+) m/z calc’d for C₃₀H₃₀NO₃ [M+H]^⁺: 452.2220, found 452.2220.
Procedures/Spectroscopic Data for Derivatization of C-Acylation Products

(S)-3-Benzoyl-3-methylpyrrolidin-2-one (66)

To a solution of lactam 60b (93% ee, 40.0 mg, 0.129 mmol, 1.00 equiv) in MeCN (0.6 mL) and water (0.6 mL) was added CAN (424 mg, 0.774 mmol, 6.00 equiv) and the reaction mixture was stirred at 70 °C for 24 h. The reaction mixture was allowed to cool to ambient temperature and brine (5 mL) was added. The reaction mixture was extracted with AcOEt (30 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:2 to 2:1 EtOAc:hexanes) on silica gel to give lactam 66 as a white solid (19.6 mg, 75% yield). [α]D²⁵ +25.7° (c 0.20, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 8.05 – 7.99 (m, 2H), 7.56 – 7.48 (m, 1H), 7.47 – 7.39 (m, 2H), 5.83 (s, 1H), 3.59 – 3.50 (m, 1H), 3.50 – 3.42 (m, 1H), 2.92 (ddd, J = 13.4, 8.1, 5.5 Hz, 1H), 2.08 (ddd, J = 13.3, 8.1, 5.5 Hz, 1H), 1.60 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 199.1, 178.3, 135.7, 132.5, 129.1, 128.4, 55.9, 39.6, 34.5, 21.5; IR (Neat Film NaCl) 3246, 2978, 1667, 1595, 1444, 1307, 1265, 1207, 1008, 973, 782, 701, 651 cm⁻¹; HRMS (MM: ESI-APCI⁺) m/z calc'd for C₁₂H₁₄NO₂ [M+H]⁺: 204.1019, found 204.1015.
(S)-3-((S)-Hydroxy(phenyl)methyl)-1-(2-methoxyphenyl)-3-methylpyrrolidin-2-one (65)

To a solution of lactam 60b (92% ee, 99.5 mg, 0.322 mmol, 1.00 equiv) in TFA (1.6 mL) was added Et₃SiH (0.102 mL, 643 mmol, 2.00 equiv) and the reaction mixture was stirred at ambient temperature for 24 h. CH₂Cl₂ (4 mL) and 2 M NaOH aqueous solution (8 mL) was added and the reaction mixture was stirred at ambient temperature for 3 h. The mixture was extracted with CH₂Cl₂ (30 mL, twice), washed with brine (10 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) on silica gel to give lactam 65 as a white solid (90.2 mg, 90% yield). [α]D²⁵ -12.5° (c 1.10, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.49 – 7.43 (m, 2H), 7.43 – 7.27 (m, 4H), 7.22 (dd, J = 7.7, 1.7 Hz, 1H), 7.03 – 6.94 (m, 2H), 5.18 (br s, 1H), 4.99 (s, 1H), 3.84 (s, 3H), 3.69 (td, J = 9.4, 6.9 Hz, 1H), 3.54 (ddd, J = 9.6, 8.8, 2.2 Hz, 1H), 2.31 (dt, J = 12.6, 9.0 Hz, 1H), 1.54 (ddd, J = 12.6, 6.9, 2.2 Hz, 1H), 1.27 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 180.3, 154.8, 139.4, 129.1, 128.5, 127.9, 127.7, 127.3, 126.5, 120.9, 112.1, 77.8, 55.7, 47.3, 46.9, 30.8, 15.6; IR (Neat Film NaCl) 3400, 2966, 1672, 1596, 1504, 1459, 1413, 1305, 1281, 1256, 1180, 1161, 1121, 1082, 1046, 1026, 917, 885, 753, 725, 703, cm⁻¹; HRMS (MM: ESI-APCI+) m/z calc’d for C₁₉H₂₂NO₃ [M+H]⁺: 312.1594, found 312.1595.
(R)-1-(4-Methoxyphenyl)-3-methyl-2-oxopyrrolidin-3-yl benzoate (67)

To a solution of lactam 60a (88% ee, 30.9 mg, 0.100 mmol, 1.00 equiv) in CH$_2$Cl$_2$ (1 mL) and were added NaHCO$_3$ (42.0 mg, 0.500 mmol, 5.00 equiv) and m-CPBA (75%, 115.0 mg, 0.500 mmol, 5.00 equiv) and the reaction mixture was stirred at ambient temperature for 20 h. 10% NaHCO$_3$ aqueous solution (3 mL) and brine (3 mL) were added and the mixture was extracted with CH$_2$Cl$_2$ (30 mL, twice), dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:5 EtOAc:hexanes) on silica gel to give lactam 67 as a white solid (17.1 mg, 53% yield, 88% ee). [α]$_D^{25}$ –3.3° (c 0.25, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.10 – 8.00 (m, 2H), 7.63 – 7.51 (m, 3H), 7.47 – 7.40 (m, 2H), 6.96 – 6.89 (m, 2H), 3.96 (td, $J$ = 9.6, 3.2 Hz, 1H), 3.82 (s, 3H), 2.84 – 2.74 (m, 1H), 2.40 (ddd, $J$ = 13.3, 8.1, 3.2 Hz, 1H), 1.75 (d, $J$ = 0.7 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 171.2, 165.5, 156.9, 133.2, 132.5, 129.9, 129.9, 128.3, 121.9, 114.1, 81.2, 55.5, 44.9, 30.6, 23.3; IR (Neat Film NaCl) 2963, 1705, 1512, 1451, 1403, 1317, 1292, 1251, 1136, 1116, 1091, 1072, 1032, 828, 715 cm$^{-1}$; HRMS (MM: ESI-APCI$^+$) $m/z$ calc'd for C$_{19}$H$_{20}$NO$_4$ [M+H$^+$]: 326.1387, found 326.1381.
(R)-4-Methoxyphenyl-1-(2-methoxyphenyl)-3-methyl-2-oxypyrrolidin-3-carboxylate (69)

To a solution of lactam 68 (160 mg, 0.471 mmol, 1.00 equiv) in CH₂Cl₂ (9.4 mL) was added m-CPBA (75%, 1.08 g, 4.71 mmol, 10.0 equiv) and the reaction mixture was stirred at ambient temperature for 24 h and then refluxed for 48 h. The reaction mixture was allowed to cool to ambient temperature and 10% Na₂SO₃ aqueous solution (30 mL) and saturated NaHCO₃ aqueous solution (10 mL) were added. The mixture was extracted with CH₂Cl₂ (130 mL), washed with brine (20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:5 EtOAc:hexanes) on silica gel to give lactam 69 as a pale yellow oil (54.2 mg, 32% yield). [α]D²⁵ -11.7° (c 0.56, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.32 – 7.27 (m, 2H), 7.09 – 7.02 (m, 2H), 7.02 – 6.93 (m, 2H), 6.93 – 6.85 (m, 2H), 3.92 – 3.75 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 2.84 (ddd, J = 12.9, 7.8, 4.5 Hz, 1H), 2.21 (ddd, J = 12.9, 8.3, 6.8 Hz, 1H), 1.67 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 172.9, 171.6, 157.3, 154.9, 144.3, 129.0, 128.6, 126.9, 122.2, 120.9, 114.4, 112.1, 55.7, 55.6, 51.8, 47.1, 32.1, 20.2; IR (Neat Film NaCl) 2936, 1760, 1699, 1597, 1505, 1463, 1410, 1305, 1251, 1193, 1112, 1088, 1027, 754 cm⁻¹; HRMS (MM: ESI-APCI+) m/z calc’d for C₂₀H₂₂NO₅ [M+H]⁺: 356.1492, found 356.1489.
(R)-Ethyl-1-(2-methoxyphenyl)-3-methyl-2-oxopyrrolidine-3-carboxylate (70)

To a solution of lactam 69 (36.0 mg, 0.101 mmol, 1.00 equiv) in EtOH (2.0 mL) was added K$_2$CO$_3$ (70.0 mg, 0.506 mmol, 5.00 equiv) and the reaction mixture was stirred at ambient temperature for 30 h. The reaction mixture was concentrated under reduced pressure and brine was added to the residue. The mixture was extracted with AcOEt (15 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) on silica gel to give lactam 70 as a pale yellow oil (20.5 mg, 73% yield). [α]$_D$$^25$ -14.6° (c 0.98, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.31 – 7.24 (m, 2H), 7.03 – 6.88 (m, 2H), 4.31 – 4.17 (m, 2H), 3.83 (s, 3H), 3.82 – 3.70 (m, 2H), 2.64 (ddd, $J$ = 12.8, 7.0, 4.7 Hz, 1H), 2.14 – 2.04 (m, 1H), 1.55 (s, 3H), 1.31 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 173.3, 172.6, 154.9, 128.8, 128.5, 127.1, 120.9, 112.1, 61.5, 55.7, 51.6, 47.1, 32.2, 20.3, 14.2; IR (Neat Film NaCl) 2979, 1738, 1699, 1597, 1505, 1456, 1409, 1257, 1195, 1137, 1090, 1024, 754 cm$^{-1}$; HRMS (MM: ESI-APCI$^+$) m/z calc'd for C$_{15}$H$_{20}$NO$_4$ [M+H]$^+$: 278.1387, found 278.1384.

(R)-Ethyl-3-methyl-2-oxopyrrolidine-3-carboxylate (71)

To a solution of lactam 70 (20.0 mg, 0.0721 mmol, 1.00 equiv) in MeCN (1.5 mL) and water (1.5 mL) was added CAN (237 mg, 0.433 mmol, 6.00 equiv) and the reaction mixture was stirred at 40 °C for 24 h. The reaction mixture was allowed to cool to ambient temperature and 10% Na$_2$SO$_3$ aqueous solution (3 mL) and brine (3 mL) were added. The reaction mixture was extracted with AcOEt (20 mL, twice),
dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (2:1 EtOAc:hexanes) on silica gel to give lactam 7 as a white solid (2.0 mg, 16% yield). $[^{25}\alpha]D +19.5^\circ$ (c 0.09, MeOH) (reported data $[^{25}\alpha]D +19.0^\circ$ (c 2, MeOH))$^{19}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.83 (br s, 1H), 4.21 (m, 2H), 3.53 – 3.44 (m, 1H), 3.40 – 3.31 (m, 1H), 2.65 (ddd, $J = 12.8, 7.8, 4.0$ Hz, 1H), 2.05 (ddd, $J = 13.0, 8.4, 7.0$ Hz, 1H), 1.46 (s, 3H), 1.29 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 2981, 176.6, 172.2, 61.6, 50.5, 39.4, 34.0, 20.1, 14.1; IR (Neat Film NaCl) 3245, 2981, 1703, 1454, 1266, 1196, 1138, 1028 cm$^{-1}$; HRMS (MM: ESI-APCI+) $m/z$ calc'd for C$_8$H$_{14}$NO$_3$ [M+H]$^+$: 171.0968, found 171.0965.

Procedures/Spectroscopic Data for Isolation/Reduction of Imine Intermediates

(S)-1-(4-Methoxyphenyl)-3-methyl-3-((phenylimino)(o-tolyl)methyl)pyrrolidin-2-one (72)

To a suspension of lactam 57a (82.1 mg, 0.400 mmol, 2.00 equiv), o-tolunitrile 58d (23.4 mg, 0.200 mmol, 1.00 equiv), bromobenzene (31.5 mL, 0.300 mmol, 1.5 equiv), LHMDS (40.2 mg, 0.240 mmol, 1.20 equiv) and LiBr (86.9 mg, 1.00 mmol, 5.00 equiv) in toluene (1.0 mL) and THF (0.20 mL) were added a solution of Ni(COD)$_2$
(5.50 mg, 0.0200 mmol, 0.100 equiv) and SL-M004-1 (Solvias, 25.3 mg, 0.0240 mmol, 0.120 equiv) at 25 °C and the reaction mixture was stirred at 25 °C for 24 h. The reaction mixture was filtered through a pad of silica gel eluting with AcOEt (60 mL). The eluate was concentrated under reduced pressure and the residue was purified by flash column chromatography (1:10 EtOAc:hexanes) on silica gel to give imine 72 as a white foam (62 mg, 77% yield, 60/40 mixture of E/Z isomers). $^1$H NMR (500 MHz, CDCl$_3$) for major isomer: δ 7.65 – 6.62 (m, 8H), 3.86 (s, 3H), 3.76 (ddd, J = 9.3, 8.2, 4.6 Hz, 1H), 3.62 (ddd, J = 9.3, 7.9, 6.6 Hz, 1H), 2.68 (ddd, J = 12.6, 7.9, 4.6 Hz, 1H), 2.17 (ddd, J = 12.8, 8.2, 6.6 Hz, 1H), 2.06 (s, 3H), 1.66 (s, 3H); for minor isomer: δ 7.61 – 6.62 (m, 8H), 4.09 (dt, J = 9.1, 7.7 Hz, 1H), 3.85 (s, 3H), 3.82 (td, J = 8.8, 3.6 Hz, 1H), 3.15 (ddd, J = 12.5, 7.8, 3.6 Hz, 1H), 2.27 – 2.20 (m, 1H), 2.07 (s, 3H), 1.66 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) for major and minor isomer: δ 175.1, 174.8, 174.7, 172.2, 156.7, 149.9, 136.1, 135.8, 134.2, 133.3, 132.9, 132.7, 130.1, 129.8, 128.4, 128.3, 128.1, 128.0, 124.8, 124.7, 123.5, 123.4, 122.9, 122.0, 120.59, 120.3, 114.0, 55.8, 55.5, 54.7, 47.0, 46.3, 33.4, 31.2, 22.5, 22.0, 20.5, 20.3; IR (Neat Film NaCl) 2931, 1688, 1512, 1485, 1398, 1289, 1249, 1181, 1090, 1033, 993, 829, 766, 731, 697 cm$^{-1}$; HRMS (MM: ESI-APCI+) m/z calc'd for C$_{26}$H$_{27}$N$_2$O$_2$ [M+H]$^+$: 399.2067, found 399.2072.
(S)-1-(2-Methoxyphenyl)-3-methyl-3-(phenyl(phenylamino)methyl)pyrrolidin-2-one (74)

To a suspension of lactam 57b (82.1 mg, 0.400 mmol, 2.00 equiv), benzonitrile (20.6 mg, 0.200 mmol, 1.00 equiv), bromobenzene (31.5 mL, 0.300 mmol, 1.5 equiv), LHMDS (40.2 mg, 0.240 mmol, 1.20 equiv) and LiBr (86.9 mg, 1.00 mmol, 5.00 equiv) in toluene (1.0 mL) and THF (0.20 mL) were added a solution of Ni(COD)2 (5.50 mg, 0.0200 mmol, 0.100 equiv) and SL-M004-1(Solvias, 25.3 mg, 0.0240 mmol, 0.120 equiv) at 0 °C and the reaction mixture was stirred at 0 °C for 48 h. NaBH4 (45.4 mg, 1.20 mmol, 6 equiv), THF (2 mL) and MeOH (2 mL) were added and the reaction mixture was stirred at 25 °C for 2 days. Water was added and the mixture was extracted with AcOEt (50 mL), dried over Na2SO4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:5 EtOAc:hexanes) on silica gel to give amine 74 as a colorless oil (54.3 mg, 70% yield).

Spectroscopic data for amine 74 was taken after separation of the diastereomers by flash column chromatography on silica gel.

Major isomer: 1H NMR (500 MHz, CDCl3) δ 7.54 – 7.48 (m, 2H), 7.38 – 7.31 (m, 2H), 7.31 – 7.23 (m, 5H), 7.12 (dd, J = 7.7, 1.7 Hz, 1H), 7.06 – 6.99 (m, 2H), 6.99 – 6.88 (m, 2H), 6.62 (t, J = 7.3 Hz, 1H), 6.50 (d, J = 7.9 Hz, 2H), 5.51 (s, 1H), 4.50 (s,
1H), 3.63 – 3.51 (m, 2H), 3.60 (s, 3H), 2.42 (ddd, $J = 12.7, 7.6, 4.7$ Hz, 1H), 1.81 (ddd, $J = 13.0, 8.3, 6.8$ Hz, 1H), 1.34 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 177.9, 154.9, 148.3, 139.8, 129.0, 128.9, 128.6, 128.5, 127.5, 127.0, 120.8, 117.4, 114.1, 112.9, 62.9, 55.4, 47.6, 46.7, 31.0, 19.7; IR (Neat Film NaCl) 3375, 2968, 1678, 1601, 1505, 1455, 1310, 1279, 1260, 1025, 749, 702 cm$^{-1}$; HRMS (MM: ESI-APCI+) m/z calc’d for C$_{25}$H$_{27}$N$_2$O$_2$ [M+H]$^+$: 387.2067, found 387.2070.

Minor isomer: $^1$H NMR (500 MHz, CDCl$_3$) δ 7.48 – 7.42 (m, 2H), 7.35 – 7.20 (m, 4H), 7.09 – 6.98 (m, 3H), 6.98 – 6.90 (m, 2H), 6.58 – 6.47 (m, 3H), 6.19 (br s, 1H), 4.37 (s, 1H), 3.78 (s, 3H), 3.41 (td, $J = 9.1, 4.7$ Hz, 1H), 2.62 (ddd, $J = 9.4, 8.4, 6.4$ Hz, 1H), 2.27 (ddd, $J = 13.1, 8.4, 4.7$ Hz, 1H), 1.98 (ddd, $J = 13.0, 8.9, 6.4$ Hz, 1H), 1.61 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 177.3, 154.6, 147.2, 140.6, 129.0, 128.8, 128.3, 128.3, 127.7, 127.5, 126.8, 120.7, 116.4, 112.9, 112.0, 64.5, 55.6, 47.2, 46.75, 30.8, 24.8; IR (Neat Film NaCl) 3375, 2929, 1674, 1600, 1505, 1455, 1418, 1308, 1256, 1026, 748, 704 cm$^{-1}$; HRMS (MM: ESI-APCI+) m/z calc’d for C$_{25}$H$_{27}$N$_2$O$_2$ [M+H]$^+$: 387.2067, found 387.2071.
### Determination of Enantiomeric Excess (Table S1)

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<th>analytic conditions</th>
<th>ee (%)</th>
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<td><img src="60a.png" alt="image" /></td>
<td>HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min, t&lt;sub&gt;R&lt;/sub&gt;(min): major 10.56, minor 8.06</td>
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<tr>
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<td>HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min t&lt;sub&gt;R&lt;/sub&gt;(min): major 8.55, minor 7.66</td>
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<td>HPLC CHIRALCELL OD, λ = 254 nm 10% IPA/hexanes, 1.0 mL/min t&lt;sub&gt;R&lt;/sub&gt;(min): major 23.56, minor 16.84</td>
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<td>HPLC CHIRALCELL OD, λ = 254 nm 20% IPA/hexanes, 1.0 mL/min t&lt;sub&gt;R&lt;/sub&gt;(min): major 7.03, minor 6.39</td>
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<td>HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min t&lt;sub&gt;R&lt;/sub&gt;(min): major 10.51, minor 7.66</td>
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<td>SFC Chiralpak OJ-H, λ = 254 nm 15% IPA/CO&lt;sub&gt;2&lt;/sub&gt;, 2.5 mL/min, t&lt;sub&gt;R&lt;/sub&gt;(min): major 4.20, minor 5.72</td>
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<td>HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min t&lt;sub&gt;R&lt;/sub&gt;(min): major 8.14, minor 6.64</td>
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<td>HPLC CHIRALCELL OD, λ = 254 nm 15% IPA/hexanes, 1.0 mL/min t&lt;sub&gt;R&lt;/sub&gt;(min): major 11.57, minor 9.83</td>
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<td>HPLC CHIRALCELL OD, $\lambda = 254$ nm 15% IPA/hexanes, 1.0 mL/min $t_R$(min): major 11.57, minor 9.83</td>
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<td>HPLC CHIRALCELL OD, $\lambda = 254$ nm 20% IPA/hexanes, 1.0 mL/min $t_R$(min): major 11.36, minor 9.98</td>
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<td><img src="image" alt="62h" /></td>
<td>HPLC CHIRALCELL OD, $\lambda = 254$ nm 30% IPA/hexanes, 1.0 mL/min $t_R$(min): major 7.41, minor 6.76</td>
<td>87</td>
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<td>12</td>
<td><img src="image" alt="62i" /></td>
<td>HPLC CHIRALCELL OD, $\lambda = 254$ nm 10% IPA/hexanes, 1.0 mL/min $t_R$(min): major 26.83, minor 23.63</td>
<td>91</td>
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<td>13</td>
<td><img src="image" alt="64b" /></td>
<td>HPLC CHIRALCELL OD, $\lambda = 254$ nm 30% IPA/hexanes, 1.0 mL/min $t_R$(min): major 8.24, minor 6.39</td>
<td>78</td>
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<td>14</td>
<td><img src="image" alt="64c" /></td>
<td>SFC Chiralpak OJ-H, $\lambda = 254$ nm 2% IPA/CO$_2$, 2.5 mL/min, $t_R$(min): major 7.25, minor 6.34</td>
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<td><img src="image" alt="64d" /></td>
<td>HPLC CHIRALCELL OD, $\lambda = 254$ nm 30% IPA/hexanes, 1.0 mL/min $t_R$(min): major 11.24, minor 8.72</td>
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<td><img src="image" alt="64e" /></td>
<td>HPLC CHIRALCELL OD, $\lambda = 254$ nm 30% IPA/hexanes, 1.0 mL/min $t_R$(min): major 9.40, minor 7.41</td>
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<td><img src="image" alt="64f" /></td>
<td>HPLC CHIRALCELL OD, $\lambda = 254$ nm 20% IPA/hexanes, 1.0 mL/min $t_R$(min): major 26.83, minor 23.63</td>
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<td>analytic conditions</td>
<td>ee (%)</td>
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<td><img src="image" alt="64g" /></td>
<td>HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min t_R(min): major 11.38, minor 8.47</td>
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<td>HPLC CHIRALCELL OD, λ = 254 nm 20% IPA/hexanes, 1.0 mL/min t_R(min): major 9.61, minor 7.13</td>
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<td>HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min t_R(min): major 7.31, minor 5.33</td>
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<td><img src="image" alt="64j" /></td>
<td>HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min t_R(min): major 12.63, minor 8.67</td>
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<td><img src="image" alt="64k" /></td>
<td>HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min t_R(min): major 11.30, minor 7.58</td>
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<td><img src="image" alt="64l" /></td>
<td>HPLC CHIRALCELL OD, λ = 254 nm 40% IPA/hexanes, 1.0 mL/min t_R(min): major 11.68, minor 7.70</td>
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<td><img src="image" alt="64m" /></td>
<td>HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min t_R(min): major 12.54, minor 8.47</td>
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<td>HPLC CHIRALCELL OD, $\lambda = 254$ nm 30% IPA/hexanes, 1.0 mL/min $t_R$(min): major 14.39, minor 8.96</td>
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<td>HPLC CHIRALCELL OD, $\lambda = 254$ nm 30% IPA/hexanes, 1.0 mL/min $t_R$(min): major 11.30, minor 7.58</td>
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<td><img src="image3" alt="67" /></td>
<td>HPLC CHIRALCELL OD, $\lambda = 254$ nm 30% IPA/hexanes, 1.0 mL/min $t_R$(min): major 10.42, minor 7.88</td>
<td>88</td>
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