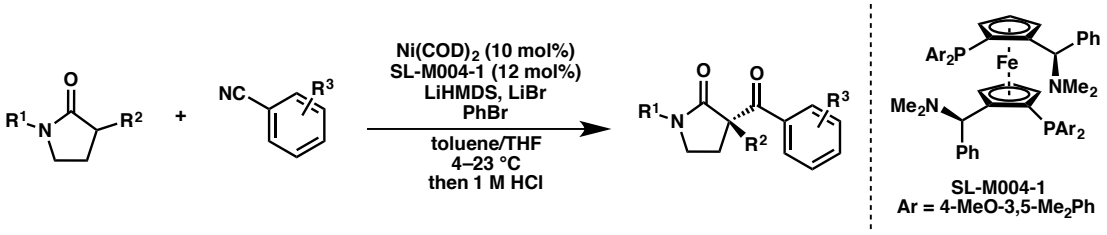
CHAPTER 4

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

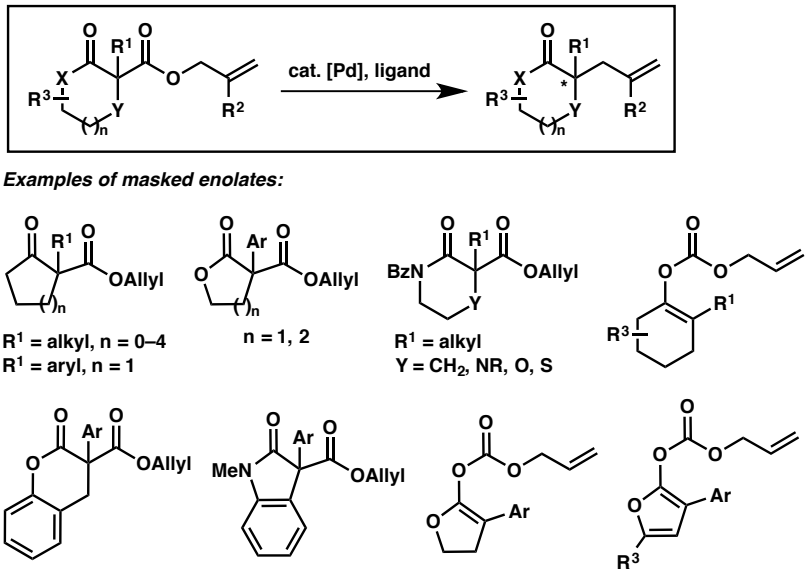


[†]This work was performed in collaboration with Masaki Hayashi, Satoshi Hashimoto, and Chad Eichman and was partially adapted from the publication: Hayashi, M.; Bachman, S.; Hashimoto, S.; Eichman, C. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2016**, *138*, 8997–9000. Copyright 2016 American Chemical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

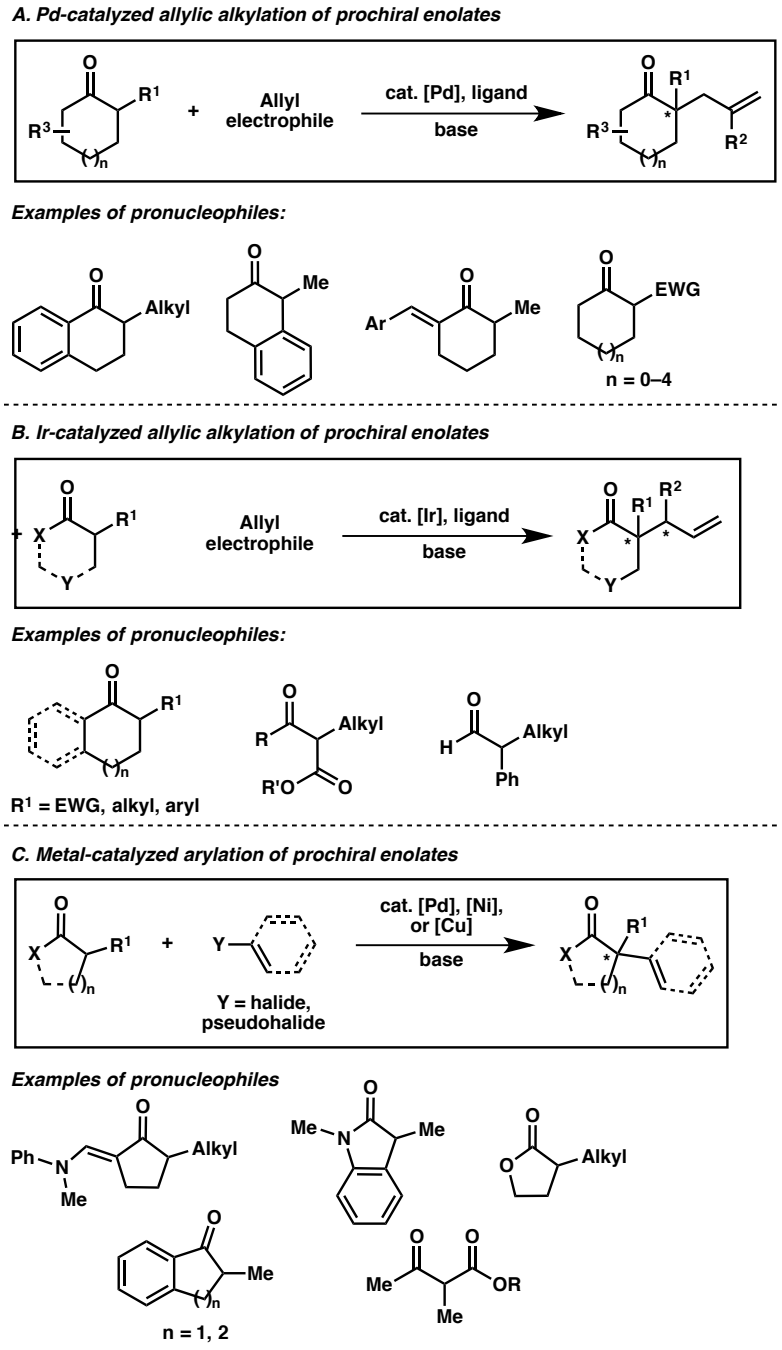
4.1 Introduction

Catalytic enantioselective construction of all-carbon quaternary stereocenters is a particular challenge in organic synthesis.[1] 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).[2] Both Pd[3] and Ir[4] 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[5] and Ni,[6] or Cu catalysis[7] (Scheme 4.2C).[8]

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



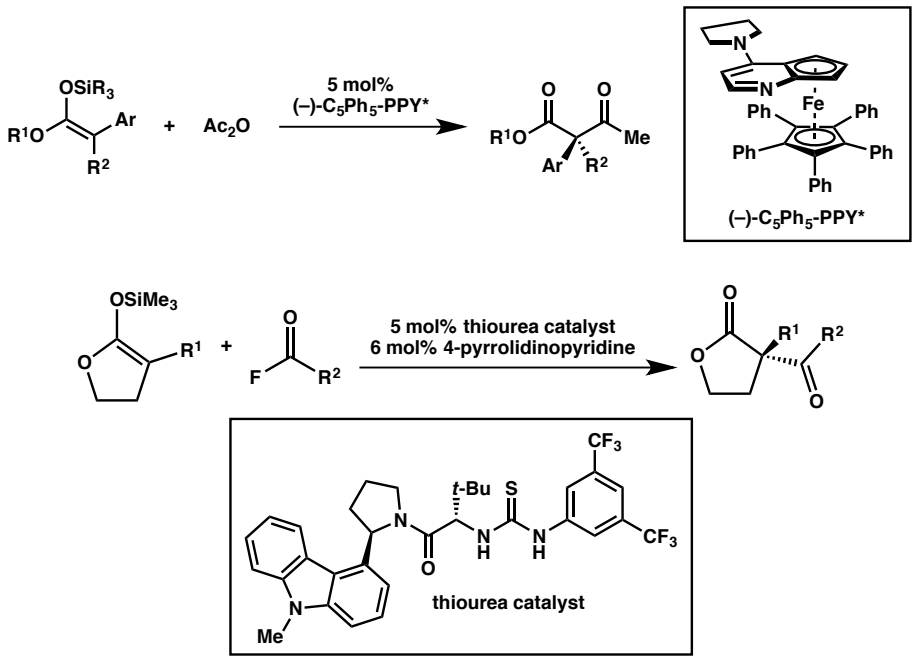
Scheme 4.2 Synthesis of α-quaternary stereocenters via functionalization of in situ-generated prochiral enolates



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,[9] intermolecular *C*-acylation reactions of enolates or enol ethers are more limited. Acylation conditions may result in competitive *O*-acylation of enolates.[10] However, α-acyl quaternary stereocenters have been accessed through organocatalyzed couplings of silyl ketene acetals with acyl derivatives (Scheme 4.3). [11] 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.

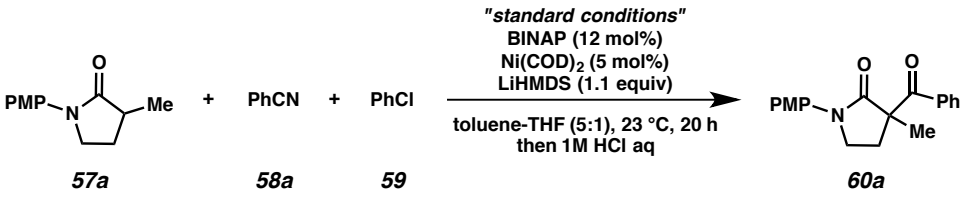
Scheme 4.3 Enantioselective organocatalyzed coupling of silyl ketene acetals with acyl derivatives



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



57a ***58a*** ***59*** ***60a***

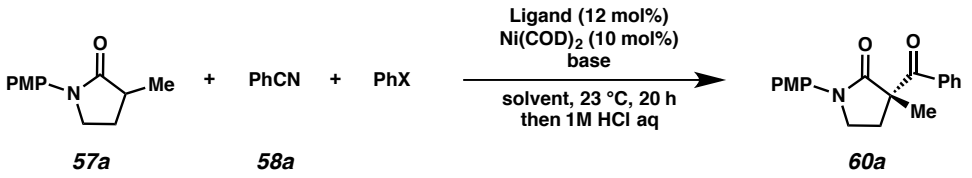
entry	deviation from standard conditions	yield (%)[a]
1	none	31
2	no $Ni(COD)_2$ or (*R*)-BINAP	0
3	no (*R*)-BINAP	3[b]
4	no PhCl	0
5	$Pd(dba)_2$ instead of $Ni(COD)_2$	0
6	$NiCl_2$ instead of $Ni(COD)_2$	0
7	*p*-tolylCl instead of PhCl	41

[a]Conditions: 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.
[b]HPLC 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 **L9** to **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 **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 (**57a**) to an *o*-OMe-phenyl substrate (**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 **57c** and **57d** resulted in moderate to good yield and high ee.

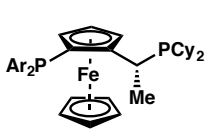
Table 4.2 Effect of base, halide, solvent, and LiBr on Ni-catalyzed C-acylation



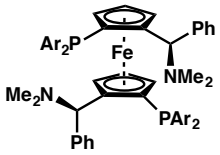
57a ***58a*** ***60a***

entry	ligand	base	PhX	solvent	additive	conversion (%)	ee (%)[a]
1[a]	*L9*	NaHMDS	PhCl	TBME	-	42	0
2[a]	*L9*	KHMDS	PhCl	TBME	-	51	0
3[a]	*L9*	LiHMDS	PhCl	TBME	-	74	–54
4[a]	*L9*	LiHMDS	PhOTf	TBME	-	73	–28
5[a]	*L9*	LiHMDS	PhI	TBME	-	65	–55
6[a]	*L9*	LiHMDS	PhBr	TBME	-	83	–61
7[b]	*L10*	LiHMDS	PhBr	toluene-THF (10:1)	-	55	68
8[b]	*L10*	LiHMDS	PhBr	toluene-THF (10:1)	LiBr (5 equiv)	98	89

[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.

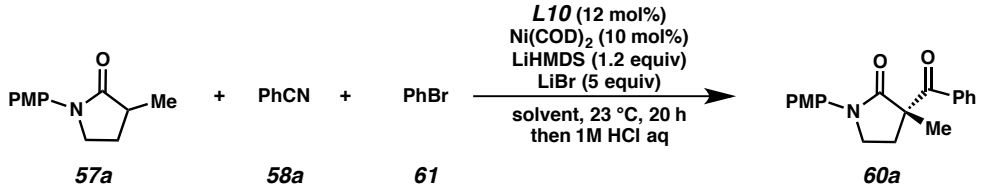


L9: SL-J006-1
Ar = 3,5-$(CF_3)_2$Ph



L10: SL-M004-1
Ar = 4-MeO-3,5-Me_2Ph

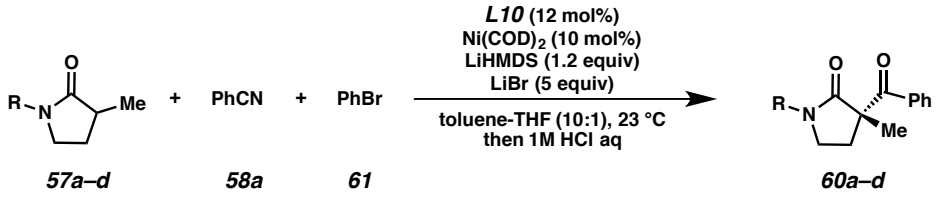
Scheme 4.4 Gram-scale Ni-catalyzed C-acylation



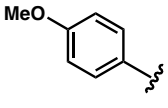
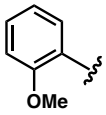
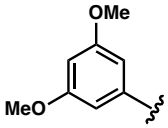
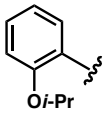
57a ***58a*** ***61*** ***60a***

1.3 equiv 1.0 equiv 1.5 equiv 1.1 g, 69% yield, 90% ee

Scheme 4.5 Effect of N-aryl substituent on Ni-catalyzed C-acylation



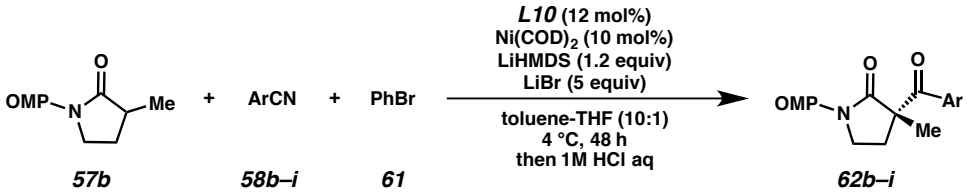
57a–d *58a* *61* *60a–d*

R				
	60a	***60b***	***60c***	***60d***
yield,[a] ee	86%, 88% ee[b]	61%, 92% ee[b] 81%, 92% ee[c]	80%, 85% ee[c]	69%, 86% ee[c]

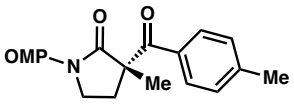
[a]Conditions: lactam (2 equiv), PhCN (1 equiv), PhBr (1.5 equiv), LiHMDS (1.2 equiv), LiBr (5 equiv), $Ni(COD)_2$ (10 mol%), ligand (12 mol%), in toluene/THF (10:1, 0.09 M), then 1 M HCl aq. [b]Reactions were conducted at 23 °C for 24 h. [c]Reactions were conducted at 4 °C for 48 h.

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.

Scheme 4.6 Scope with respect to the benzonitrile coupling partner

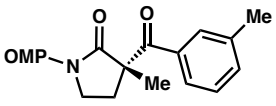


57b *58b–i* *61* *62b–i*



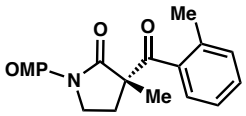
62b

92% yield, 91% ee



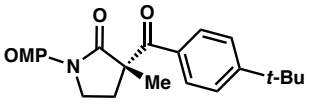
62c

91% yield, 93% ee



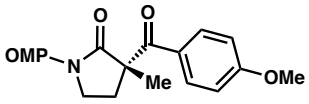
62d

69% yield, 94% ee



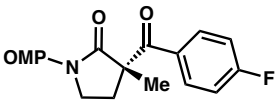
62e

89% yield, 92% ee



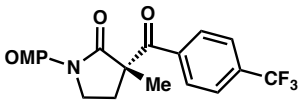
62f

85% yield, 89% ee



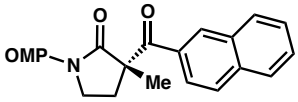
62g

36% yield, 93% ee



62h

23% yield,[b] 87% ee



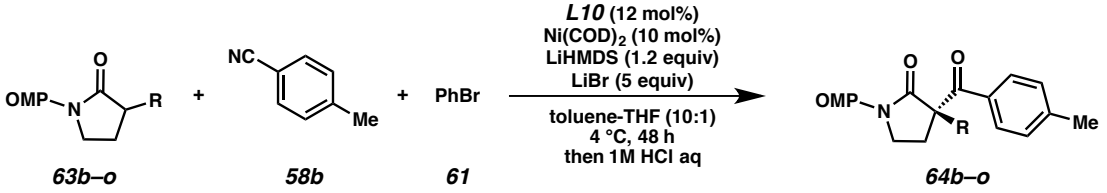
62i

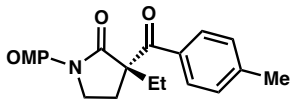
66% yield, 91% ee

[a]Conditions: lactam (2 equiv), ArCN (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. [b]The reaction was carried out at 23 °C for 24 h.

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**).

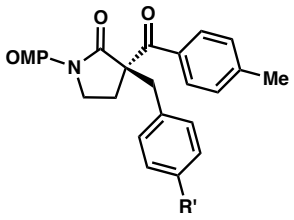
Scheme 4.7 Scope with respect to the lactam α-substituent



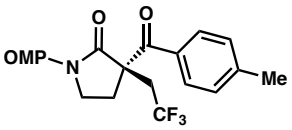


64b

50% yield, 78% ee

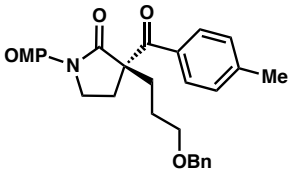


64c (R' = H): 61% yield, 81% ee
64d (R' = OMe): 77% yield, 81% ee
64e (R' = F): 76% yield, 74% ee



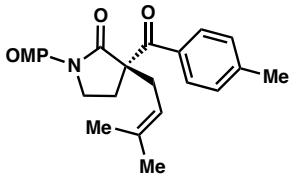
64f

58% yield, 71% ee



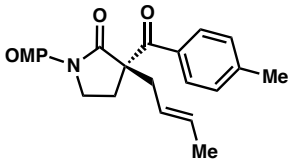
64g

67% yield, 60% ee



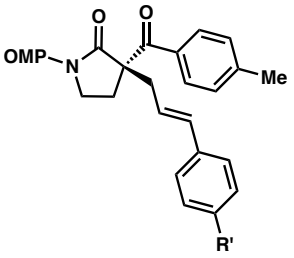
64h

71% yield, 76% ee

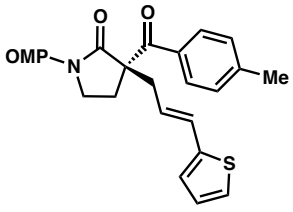


64i

70% yield, 86% ee

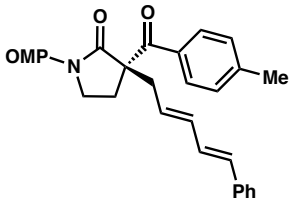


64j (R' = H): 50% yield, 86% ee
64k (R' = Me): 85% yield, 88% ee
64l (R' = OMe): 68% yield, 88% ee
64m (R' = F): 62% yield, 83% ee



64n

76% yield, 83% ee



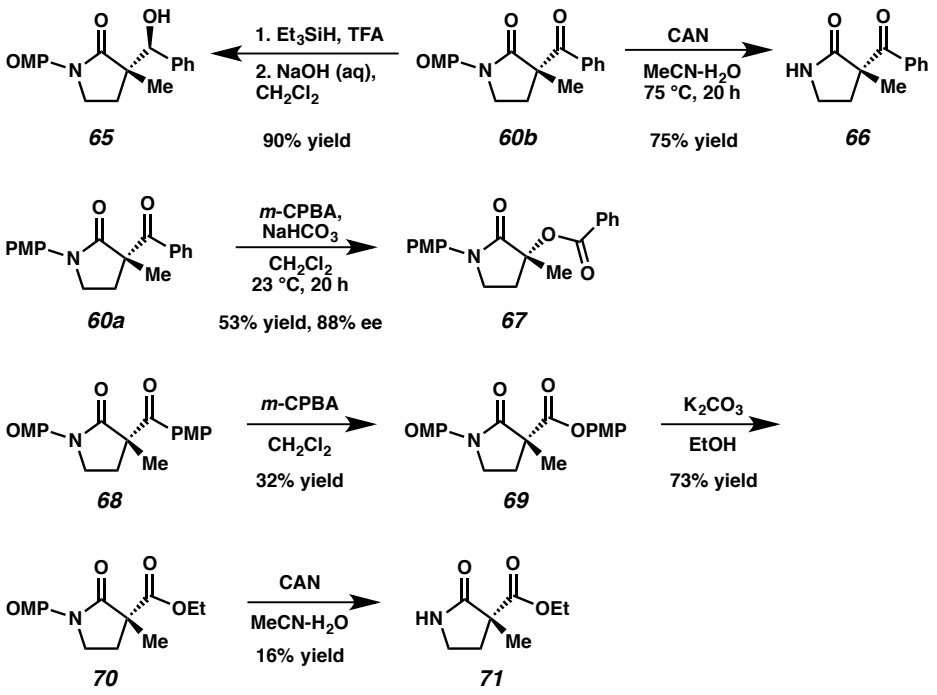
64o

35% yield, 84% ee

[a]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 Et_3SiH 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-aryloxycarbonyl 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.

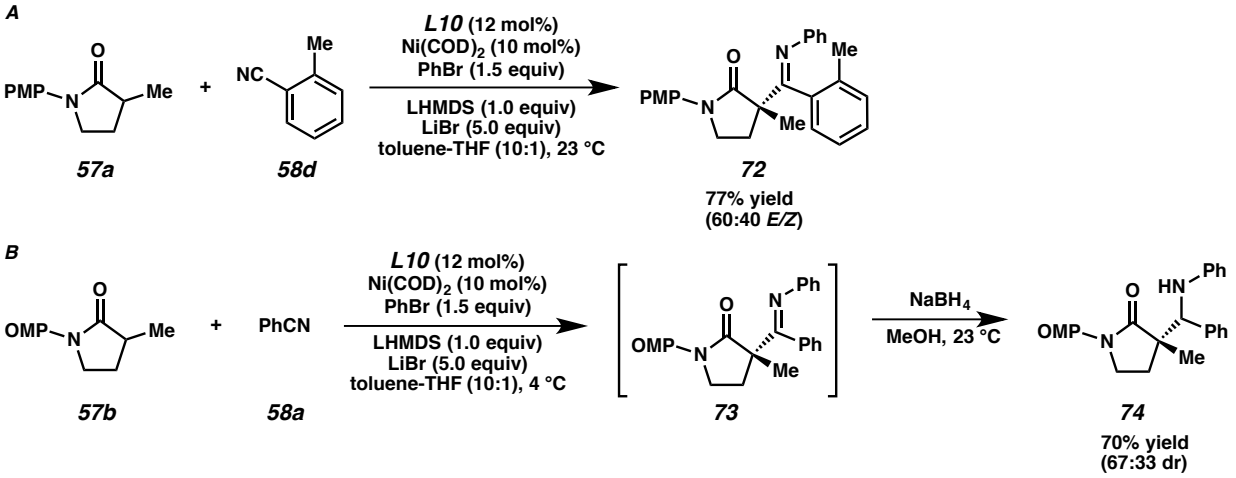
Scheme 4.8 Derivatization of α-acylated lactam products



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

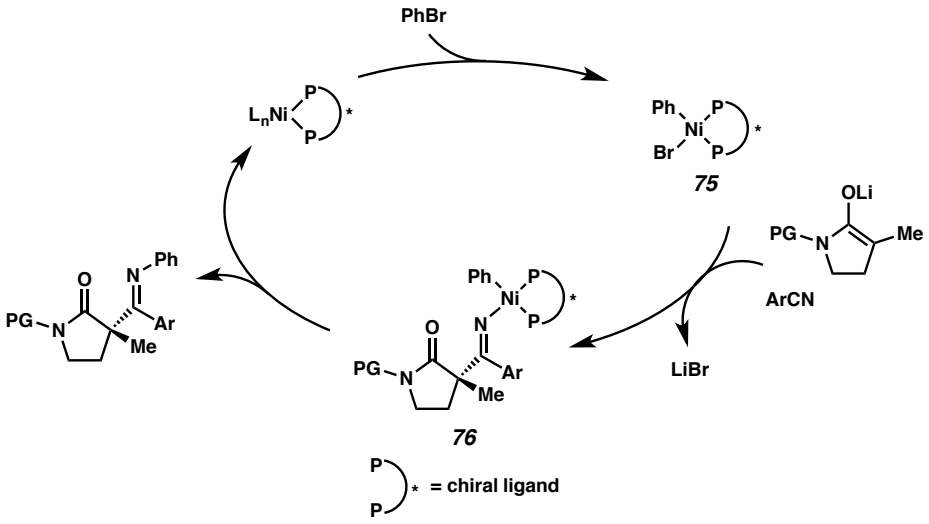
containing lactam **57b** and benzonitrile (**58a**) resulted in the formation of amine **74**. These results are consistent with a reaction pathway involving initial imine formation followed by hydrolysis to reveal the corresponding α-acylated products.

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 Ni^0 species generates $Ni^{II}ArBr$ complex **75**. Subsequent insertion of the benzonitrile and lactam enolate produce Ni^{II}-imino complex **76**. Reductive elimination furnishes the imine product, which is then hydrolyzed upon workup.

Figure 4.1 Possible catalytic cycle for enantioselective Ni-catalyzed C-acylation



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 N_2 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, $KMnO_4$ or PMA (phosphomolybdic acid) staining. Silicycle Silia*Flash* 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 CO_2 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 $CHCl_3$ (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_2O, CH_2Cl_2, toluene, CH_3CN, 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 ((1*E*,3*E*)-5-bromopenta-1,3-dien-1-yl)benzene [18] were prepared by known

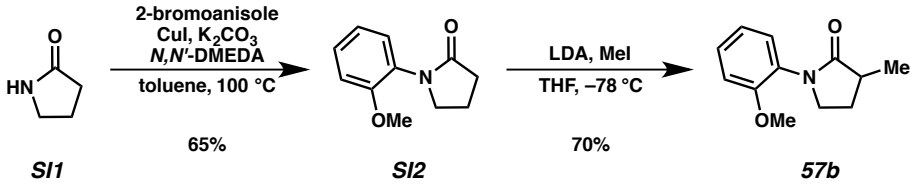
methods and used without purification. (*E*)-3-(3-Chloroprop-1-en-1-yl)thiophene was prepared from (E)-3-(thiophen-3-yl)prop-2-en-1-ol and $SOCl_2$ in CH_2Cl_2 and used without purification.

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'–bis(diphenylphosphino)–1,1'–binaphthyl), LHMDS – lithium hexamethyldisilazide, NaHMDS – sodium hexamethyldisilazide, KHMDS – potasium 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 a-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_2CO_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, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

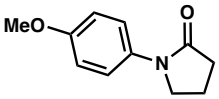
General procedure 2: 1-(2-methoxyphenyl)-3-methylpyrrolidin-2-one (57b)

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_4Cl

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 Na_2SO_4, 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). ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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 $C_{12}H_{16}NO_2$ $[M+H]^+$: 206.1176, found 206.1176.

Spectroscopic Data for *N*-Protected Lactams

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

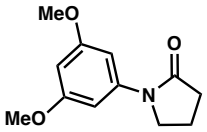


SI3

Lactam **SI3** was prepared according to the general procedure 1, using 4-iodoanisole and K_3PO_4 in place of 2-bromoanisole and K_2CO_3 respectively, and isolated by recrystallization in hexanes/AcOEt (4/1) as a white crystal. 89% yield. ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR

(126 MHz, $CDCl_3$) δ 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.

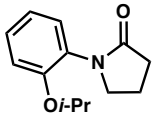
1-(3,5-Dimethoxyphenyl)pyrrolidin-2-one (SI4)



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/AcOEt (5/1) as a white crystal. 89% yield. ^1H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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)

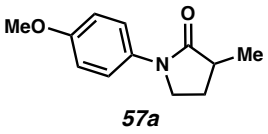


SI5

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, $CDCl_3$) δ 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, $CDCl_3$) δ 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)

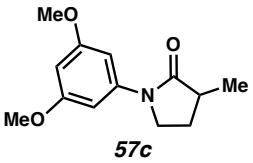


57a

Lactam **57a** was prepared according to the general procedure 2 from **SI3** in place of **SI2**, and isolated by flash column chromatography (1:3 EtOAc:hexanes) on silica gel as a white solid. 82% yield. ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $cdcl_3$) δ 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.

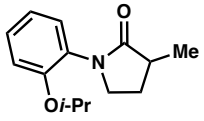
1-(3,5-Dimethoxyphenyl)-3-methylpyrrolidin-2-one (57c)



57c

Lactam **57c** was prepared according to the general procedure 2 from **SI4** in place of **SI2**, and isolated by flash column chromatography (1:4 EtOAc:hexanes) on silica gel as a white solid. 87% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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)

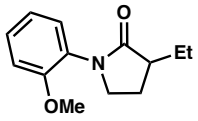


57d

Lactam **57d** was prepared according to the general procedure 2 from **SI5** in place of **SI2**, 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, $CDCl_3$) δ 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}C NMR (126 MHz, $CDCl_3$) δ 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.

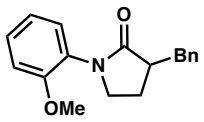
1-(2-Methoxyphenyl)-3-ethypyrrolidin-2-one (63b)



63b

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}H NMR (500 MHz, $CDCl_3$) δ 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}C NMR (126 MHz, $CDCl_3$) δ 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.

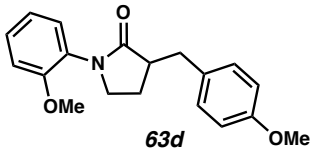
3-Benzyl-1-(2-methoxyphenyl)pyrrolidin-2-one (63c)



63c

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, $CDCl_3$) δ 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, $CDCl_3$) δ 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)

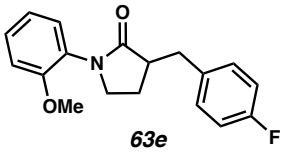


63d

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, $CDCl_3$) δ 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.

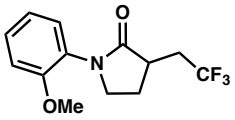
3-(4-Fluorobenzyl)-1-(2-methoxyphenyl)pyrrolidin-2-one (63e)



63e

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.

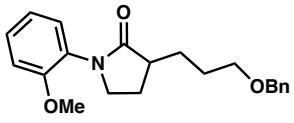
1-(2-Methoxyphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidin-2-one (63f)



63f

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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{13}H_{15}F_3NO_2$ $[M+H]^+$: 274.1049, found 274.1049.

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

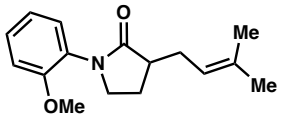


63g

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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{21}H_{26}NO_3$ $[M+H]^+$: 340.1907, found 340.1915.

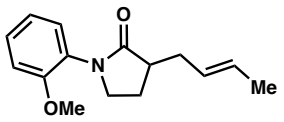
1-(2-Methoxyphenyl)-3-(3-methylbut-2-en-1-yl)pyrrolidin-2-one (63h)



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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{16}H_{22}NO_2$ $[M+H]^+$: 260.1645, found 260.1644.

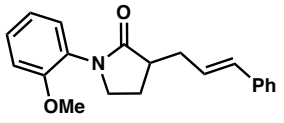
(*E*)-3-(But-2-en-1-yl)-1-(2-methoxyphenyl)pyrrolidin-2-one (63i)



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, $CDCl_3$) δ 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); ^{13}C NMR (126 MHz, $CDCl_3$) δ 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)

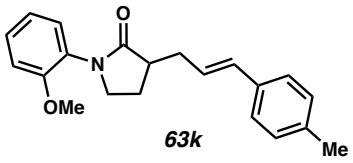


63j

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, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

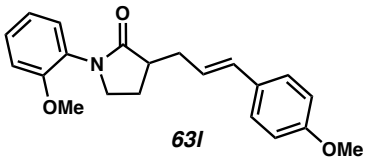
(*E*)-1-(2-Methoxyphenyl)-3-(3-(p-tolyl)allyl)pyrrolidin-2-one (63k)



63k

Lactam **63k** was prepared according to the general procedure 2 using (*E*)-1-(3-chloroprop-1-en-1-yl)-4-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, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

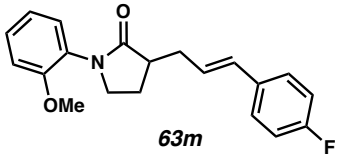
(*E*)-1-(2-Methoxyphenyl)-3-(3-(4-methoxyphenyl)allyl)pyrrolidin-2-one (63l)



63l

Lactam **63l** was prepared according to the general procedure 2 using (*E*)-1-(3-chloroprop-1-en-1-yl)-4-methoxybenzene[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. ^{1}H NMR (500 MHz, $CDCl_3$) 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), 3.81 (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); ^{13}C NMR (126 MHz, $CDCl_3$) 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^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{21}H_{24}NO_3$ $[M+H]^+$: 338.1751, found 338.1748.

(*E*)-3-(3-(4-Fluorophenyl)allyl)-1-(2-methoxyphenyl)pyrrolidin-2-one (63m)

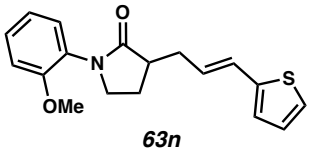


63m

Lactam **63m** was prepared according to the general procedure 2 using (*E*)-1-(3-chloroprop-1-en-1-yl)-4-fluorobenzene[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. ^{1}H NMR (500 MHz, $CDCl_3$) 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, $CDCl_3$) δ 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.

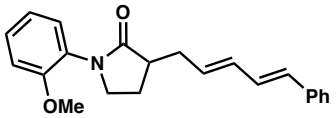
(*E*)-1-(2-Methoxyphenyl)-3-(3-(thiophen-3-yl)allyl)pyrrolidin-2-one (63n)



63n

Lactam **63n** was prepared according to the general procedure 2 using (*E*)-3-(3-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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{18}H_{20}NO_2S$ $[M+H]^+$: 314.1209, found 314.1206.

1-(2-Methoxyphenyl)-3-((2*E*,4*E*)-5-phenylpenta-2,4-dien-1-yl)pyrrolidin-2-one (63o)

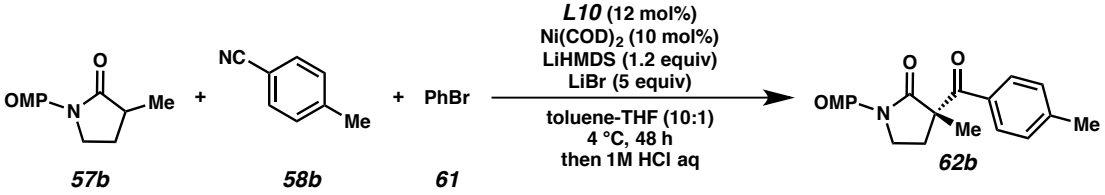


63o

Lactam **63o** was prepared according to the general procedure 2 using ((1*E*,3*E*)-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, $CDCl_3$) δ 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); ^{13}C NMR (126 MHz, $CDCl_3$) δ 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.*



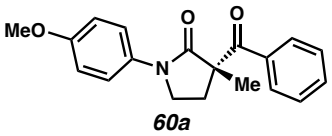
General procedure 3: (*S*)-1-(2-methoxyphenyl)-3-methyl-3-(4-methylbenzoyl) pyrrolidin-2-one (62b)

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 Na_2SO_4, 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). $[a]_D^{25}$ +2.1° (c 1.03, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{20}H_{22}NO_3$ $[M+H]^+$: 324.1594, found 324.1599.

Spectroscopic Data for Ni-Catalyzed C-Acylation Products

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



60a

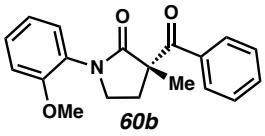
Lactam **60a** was prepared according to the general procedure 3 from **57a** using benzonitrile in place of *p*-tolunitrile, reacting at ambient temperature for 24 h in place of 0 °C for 48 h, and isolated by flash column chromatography (1:10 EtOAc:hexanes) on silica gel as a white solid. 79.9 mg, 86% 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 Na_2SO_4,

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. $[a]_D^{25}$ –27.1° (c 1.45, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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)

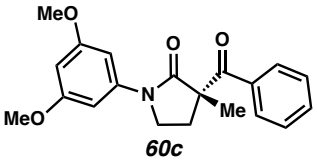


60b

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. $[a]_D^{25}$ +4.0° (c 1.21, $CHCl_3$, 92% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

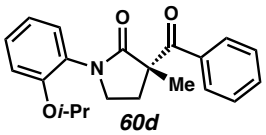
(*S*)-3-Benzoyl-1-(3,5-dimethoxyphenyl)-3-methylpyrrolidin-2-one (60c)



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. $[a]_D^{25}$ –30.0° (c 1.04, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 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); ^{13}C NMR (126 MHz, $CDCl_3$) δ 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.

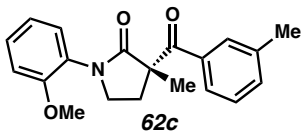
(*S*)-3-Benzoyl-1-(2-isopropoxyphenyl)-3-methylpyrrolidin-2-one (60d)



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. $[a]_D^{25}$ +9.4° (c 1.01, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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, 701cm^{-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)

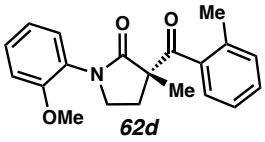


62c

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. $[a]_D^{25}$ +5.5° (c 0.52, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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)

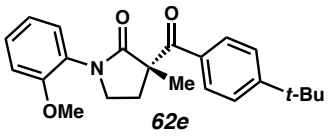


62d

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, $CDCl_3$) δ 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, $CDCl_3$) δ 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,

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.

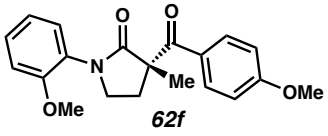
(*S*)-3-(4-(*tert*-Butyl)benzoyl)-1-(2-methoxyphenyl)-3-methylpyrrolidin-2-one (62e)



62e

Lactam **62e** was prepared according to the general procedure 3 from **57b** using 4-(*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. $[a]_D^{25}$ +6.9° (c 1.04, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 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), 2.96 (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, $CDCl_3$) δ 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.

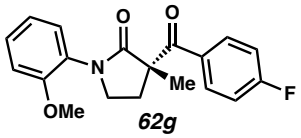
(*S*)-3-(4-Methoxybenzoyl)-1-(2-methoxyphenyl)-3-methylpyrrolidin-2-one (62f)



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, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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 $C_{20}H_{22}NO_4$ $[M+H]^+$: 340.1543, found 340.1547.

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

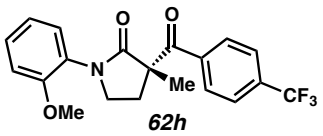


62g

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, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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 $C_{19}H_{19}FNO_3$ $[M+H]^+$: 328.1343, found 328.1353.

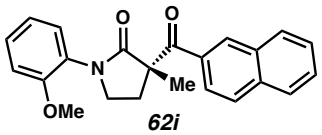
(*S*)-1-(2-Methoxyphenyl)-3-methyl-3-(4-(trifluoromethyl)benzoyl)pyrrolidin-2-one (62h)



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. $[a]_D^{25}$ +2.7° (c 0.71, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{20}H_{19}F_3NO_3$ $[M+H]^+$: 378.1312, found 378.1325.

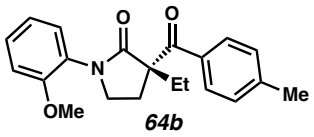
(*S*)-3-(2-Naphthoyl)-1-(2-methoxyphenyl)-3-methylpyrrolidin-2-one (62i)



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. $[a]_D^{25}$ +15.8° (c 0.52, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 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), 3.96 (ddd, *J* = 9.6, 8.3, 4.9 Hz, 1H), 3.90 – 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, $CDCl_3$) δ 198.9, 174.7, 155.0, 135.1, 133.0, 132.4, 131.1, 129.8, 129.0, 128.3, 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.

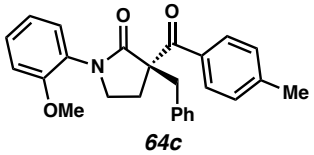
(*S*)-3-Ethyl-1-(2-methoxyphenyl)-3-(4-methylbenzoyl)pyrrolidin-2-one (64b)



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. $[a]_D^{25}$ +14.6° (c 0.81, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 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, $CDCl_3$) 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)

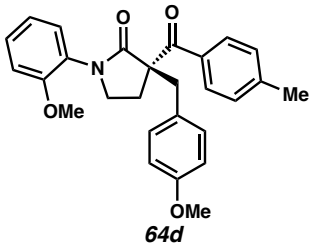


64c

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. $[a]_D^{25}$ +62.3° (c 0.90, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 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, $CDCl_3$) δ 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)

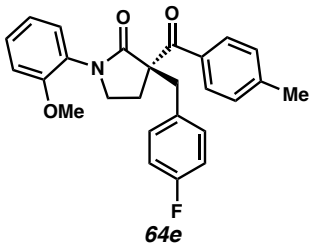


64d

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, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

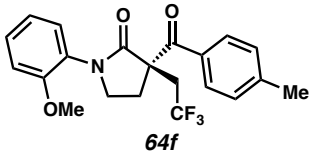
(*S*)-3-(4-Fluorobenzyl)-1-(2-methoxyphenyl)-3-(4-methylbenzoyl)pyrrolidin-2-one (64e)



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. $[a]_D^{25}$ +38.9° (c 3.08, $CHCl_3$); ^1H 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, 1504, 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.

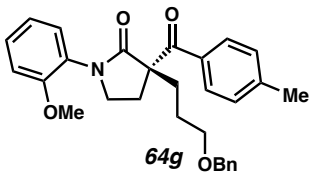
(*R*)-1-(2-Methoxyphenyl)-3-(4-methylbenzoyl)-3-(2,2,2-trifluoroethyl)pyrrolidin-2-one (64f)



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. $[a]_D^{25}$ +10.3° (c 2.16, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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 $C_{21}H_{21}F_3NO_3$ $[M+H]^+$: 392.1468, found 392.1459.

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

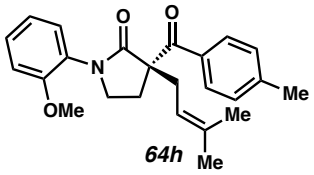


64g

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. $[a]_D^{25}$ +9.3° (c 2.90, $CHCl_3$); ^1H 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, 128.9, 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-Methoxyphenyl)-3-(4-methylbenzoyl)-3-(3-methylbut-2-en-1-yl) pyrrolidin-2-one (64h)

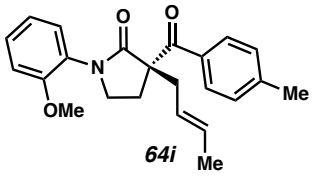


64h

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. $[a]_D^{25}$ +29.6° (c 2.15, $CHCl_3$); ^1H 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, 128.9, 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.

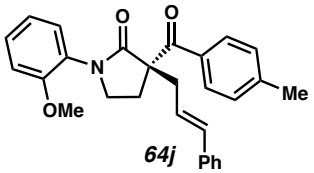
(*S*,*E*)-3-(But-2-en-1-yl)-1-(2-methoxyphenyl)-3-(4-methylbenzoyl)pyrrolidin-2-one (64i)



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. $[a]_D^{25}$ +45.5° (c 2.10, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

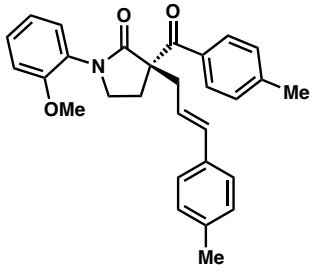
(*S*)-3-Cinnamyl-1-(2-methoxyphenyl)-3-(4-methylbenzoyl)pyrrolidin-2-one (64j)



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. $[a]_D^{25}$ +55.5° (c 0.93, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 197.9, 173.3, 155.0, 143.1, 137.3, 134.2, 133.5, 129.4, 129.0, 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.

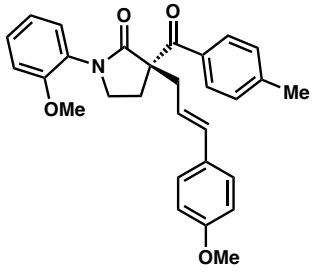
(*S*,*E*)-1-(2-Methoxyphenyl)-3-(4-methylbenzoyl)-3-(3-(p-tolyl)allyl)pyrrolidin-2-one (64k)



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, $CDCl_3$) δ 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, $CDCl_3$) δ 197.9, 173.4, 155.0, 143.1, 137.1, 134.5, 134.0, 133.5, 129.4, 129.2, 129.0, 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.

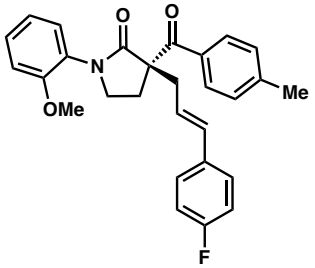
(*S*,*E*)-1-(2-Methoxyphenyl)-3-(3-(4-methoxyphenyl)allyl)-3-(4-methylbenzoyl) pyrrolidin-2-one (64l)



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, $CHCl_3$, 88% ee); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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 $C_{29}H_{30}NO_4$ $[M+H]^+$: 456.2169, found 456.2164.

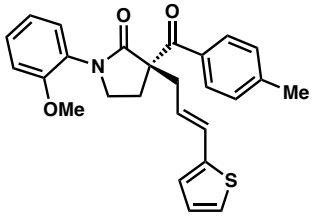
(*S*,*E*)-3-(3-(4-Fluorophenyl)allyl)-1-(2-methoxyphenyl)-3-(4-methylbenzoyl) pyrrolidin-2-one (64m)



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. $[a]_D^{25}$ +40.7° (c 0.55, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{28}H_{27}FNO_3$ $[M+H]^+$: 444.1969, found 444.1969.

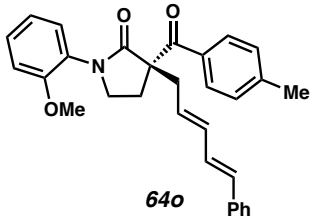
(*S*,*E*)-1-(2-Methoxyphenyl)-3-(4-methylbenzoyl)-3-(3-(thiophen-3-yl)allyl) pyrrolidin-2-one (64n)



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. $[a]_D^{25}$ +46.7° (c 1.17, $CHCl_3$); ^1H 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 $C_{26}H_{25}NO_3S$ $[M+H]^+$: 432.1628, found 432.1622.

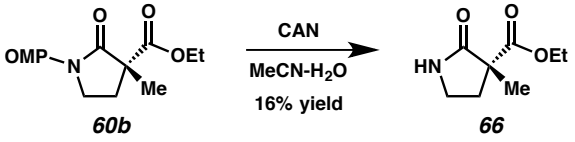
(*S*)-1-(2-Methoxyphenyl)-3-(4-methylbenzoyl)-3-((2*E*,4*E*)-5-phenylpenta-2,4-dien-1-yl)pyrrolidin-2-one (64o)



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, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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 $C_{30}H_{30}NO_3$ $[M+H]^+$: 452.2220, found 452.2220.

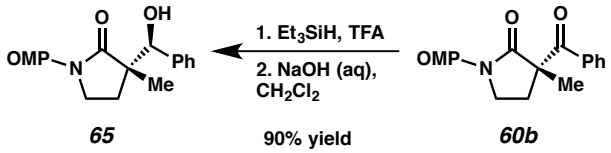
Procedures/Spectroscopic Data for Derivatization of C-Acylation Products



60b ***66***

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

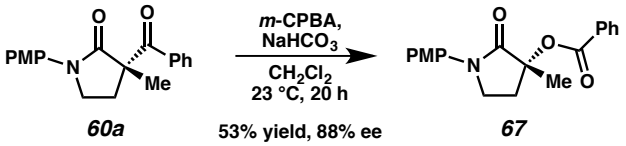
To a solution of lactam **60b** (93% ee, 40.0 mg, 0.129 mmol, 1.00 equiv) in MeCN (0.6 mL) and water (0.6 mL) was added CAN (424 mg, 0.774 mmol, 6.00 equiv) and the reaction mixture was stirred at 70 °C for 24 h. The reaction mixture was allowed to cool to ambient temperature and brine (5 mL) was added. The reaction mixture was extracted with AcOEt (30 mL), dried over Na_2SO_4, 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). $[a]_D^{25}$ +25.7° (c 0.20, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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 $C_{12}H_{14}NO_2$ $[M+H]^+$: 204.1019, found 204.1015.



65 **90% yield** ***60b***

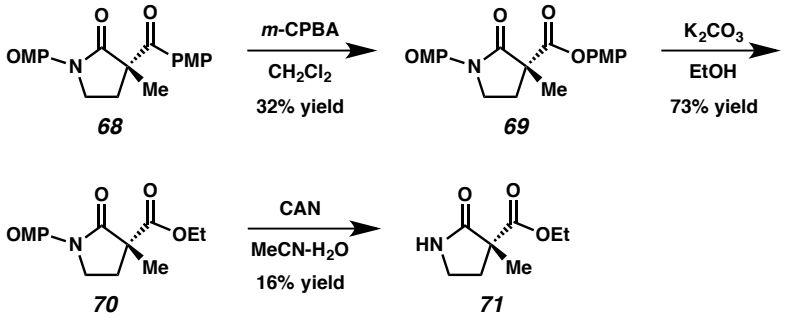
(*S*)-3-((*S*)-Hydroxy(phenyl)methyl)-1-(2-methoxyphenyl)-3-methylpyrrolidin-2-one (65)

To a solution of lactam **60b** (92% ee, 99.5 mg, 0.322 mmol, 1.00 equiv) in TFA (1.6 mL) was added Et_3SiH (0.102 mL, 643 mmol, 2.00 equiv) and the reaction mixture was stirred at ambient temperature for 24 h. CH_2Cl_2 (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 CH_2Cl_2 (30 mL, twice), washed with brine (10 mL), dried over Na_2SO_4, 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). $[a]_D^{25}$ -12.5° (c 1.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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 $C_{19}H_{22}NO_3$ $[M+H]^+$: 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_2Cl_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_2Cl_2 (30 mL, twice), dried over Na_2SO_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). $[a]_D^{25}$ –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-oxopyrrolidine-3-carboxylate (69)

To a solution of lactam **68** (160 mg, 0.471 mmol, 1.00 equiv) in CH_2Cl_2 (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% Na_2SO_3 aqueous solution (30 mL) and saturated $NaHCO_3$ aqueous solution (10 mL) were added. The mixture was extracted with CH_2Cl_2 (130 mL), washed with brine (20 mL), dried over Na_2SO_4, 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). $[a]_D^{25}$ -11.7° (c 0.56, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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 $C_{20}H_{22}NO_5$ $[M+H]^+$: 356.1492, found 356.1489.

(*R*)-Ethyl-1-(2-methoxyphenyl)-3-methyl-2-oxopyrrolidine-3-carboxylate (70)

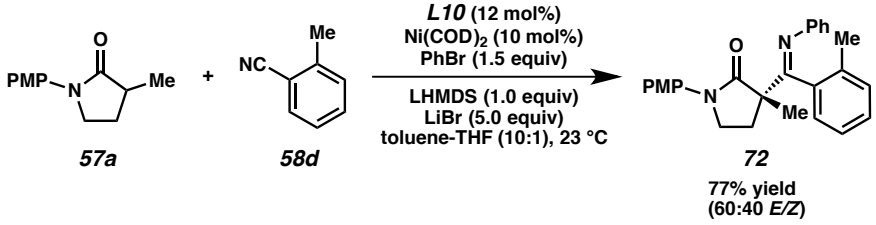
To a solution of lactam **69** (36.0 mg, 0.101 mmol, 1.00 equiv) in EtOH (2.0 mL) was added K_2CO_3 (70.0 mg, 0.506 mmol, 5.00 equiv) and the reaction mixture was stirred at ambient temperature for 30 h. The reaction mixture was concentrated under reduced pressure and brine was added to the residue. The mixture was extracted with AcOEt (15 mL), dried over Na_2SO_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). $[a]_D^{25}$ -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_2SO_3 aqueous solution (3 mL) and brine (3 mL) were added. The reaction mixture was extracted with AcOEt (20 mL, twice),

dried over Na_2SO_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). $[a]_D^{25}$ +19.5° (c 0.09, MeOH) (reported data $[a]_D^{25}$ +19.0° (c 2, MeOH))[19]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_8H_{14}NO_3$ $[M+H]^+$: 171.0968, found 171.0965.

Procedures/Spectroscopic Data for Isolation/Reduction of Imine Intermediates

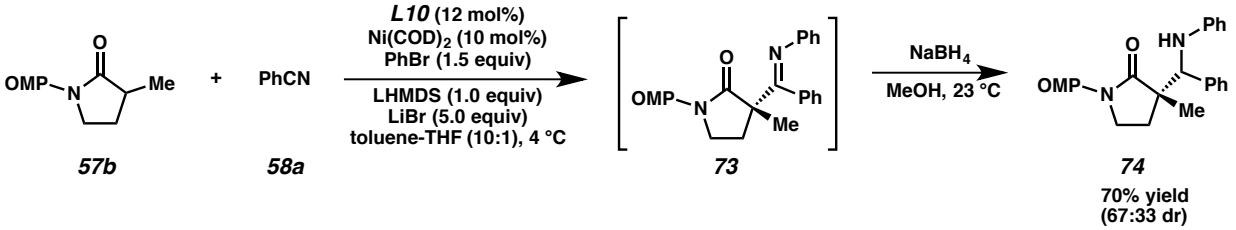


(*S*)-1-(4-Methoxyphenyl)-3-methyl-3-((phenylimino)(*o*-tolyl)methyl)pyrrolidin-2-one (72)

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, 123.56, 123.4, 122.98, 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 $C_{26}H_{27}N_2O_2$ $[M+H]^+$: 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. $NaBH_4$ (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 Na_2SO_4, 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).

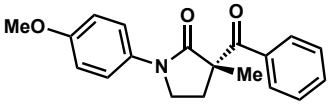
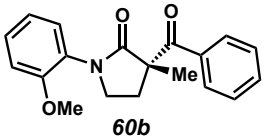
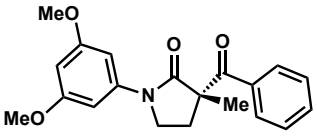
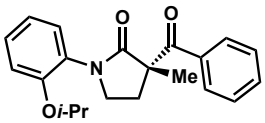
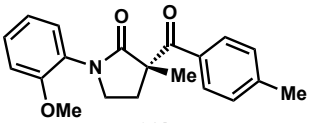
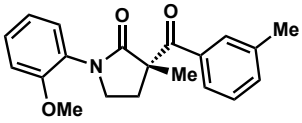
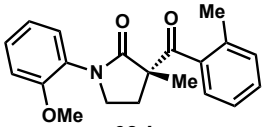
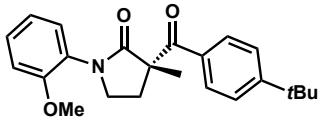
Spectroscopic data for amine **74** was taken after separation of the diastereomers by flash column chromatography on silica gel.

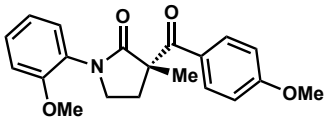
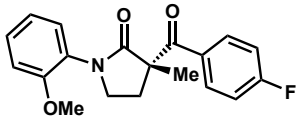
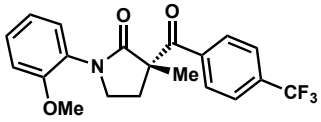
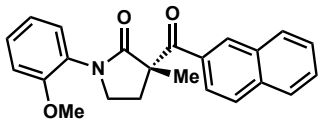
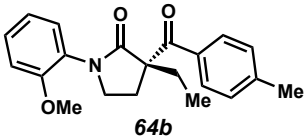
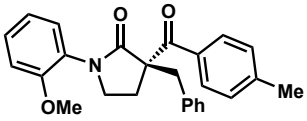
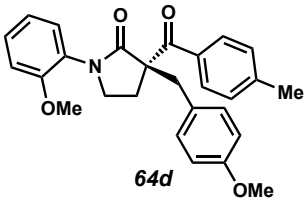
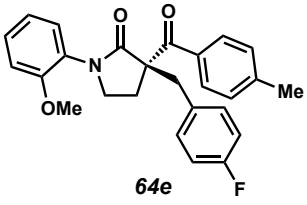
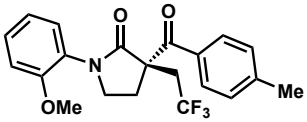
Major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.48 (m, 2H), 7.38 – 7.31 (m, 2H), 7.31 – 7.23 (m, 5H), 7.12 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.06 – 6.99 (m, 2H), 6.99 – 6.88 (m, 2H), 6.62 (t, *J* = 7.3 Hz, 1H), 6.50 (d, *J* = 7.9 Hz, 2H), 5.51 (s, 1H), 4.50 (s,

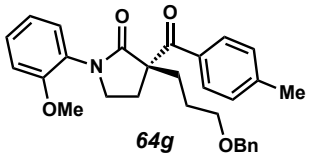
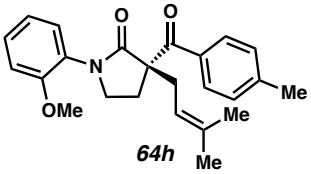
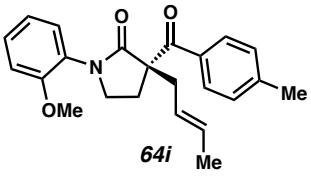
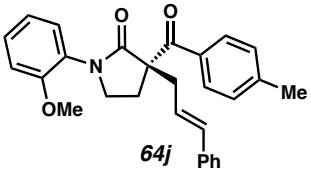
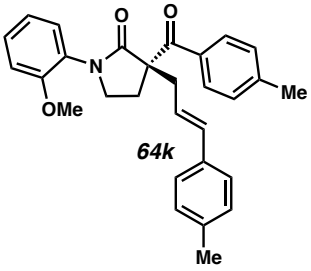
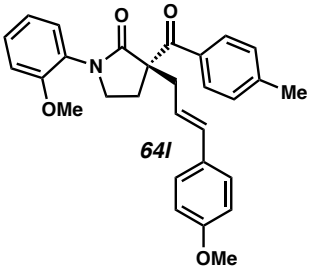
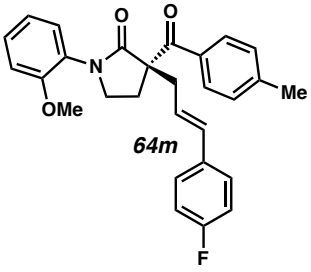
1H), 3.63 – 3.51 (m, 2H), 3.60 (s, 3H), 2.42 (ddd, *J* = 12.7, 7.6, 4.7 Hz, 1H), 1.81 (ddd, *J* = 13.0, 8.3, 6.8 Hz, 1H), 1.34 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.9, 154.9, 148.3, 139.8, 129.0, 128.9, 128.6, 128.6, 128.2, 127.5, 127.0, 120.8, 117.4, 114.1, 112.9, 62.9, 55.4, 47.6, 46.7, 31.0, 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 $C_{25}H_{27}N_2O_2$ $[M+H]^+$: 387.2067, found 387.2070.

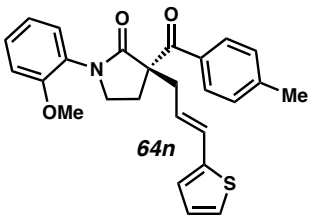
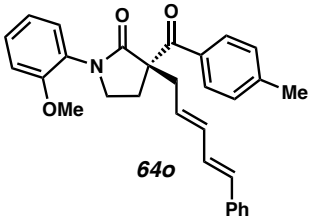
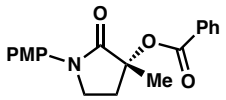
Minor isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.42 (m, 2H), 7.35 – 7.20 (m, 4H), 7.09 – 6.98 (m, 3H), 6.98 – 6.90 (m, 2H), 6.58 – 6.47 (m, 3H), 6.19 (br s, 1H), 4.37 (s, 1H), 3.78 (s, 3H), 3.41 (td, *J* = 9.1, 4.7 Hz, 1H), 2.62 (ddd, *J* = 9.4, 8.4, 6.4 Hz, 1H), 2.27 (ddd, *J* = 13.1, 8.4, 4.7 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 $C_{25}H_{27}N_2O_2$ $[M+H]^+$: 387.2067, found 387.2071.

Determination of Enantiomeric Excess (Table S1)

entry	compound	analytic conditions	ee (%)
1	 ***60a***	**HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min, t_R(min): major 10.56, minor 8.06**	**88**
2	 ***60b***	**HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min t_R(min): major 8.55, minor 7.66**	**92**
3	 ***60c***	**HPLC CHIRALCELL OD, λ = 254 nm 10% IPA/hexanes, 1.0 mL/min t_R(min): major 23.56, minor 16.84**	**85**
4	 ***60d***	**HPLC CHIRALCELL OD, λ = 254 nm 20% IPA/hexanes, 1.0 mL/min t_R(min): major 7.03, minor 6.39**	**86**
5	 ***62b***	**HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min t_R(min): major 10.51, minor 7.66**	**91**
6	 ***62c***	**SFC Chiralpak OJ-H, λ = 254 nm 15% IPA/CO_2, 2.5 mL/min, t_R(min): major 4.20, minor 5.72**	**93**
7	 ***62d***	**HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min t_R(min): major 8.14, minor 6.64**	**94**
8	 ***62e***	**HPLC CHIRALCELL OD, λ = 254 nm 15% IPA/hexanes, 1.0 mL/min t_R(min): major 11.57, minor 9.83**	**92**

entry	compound	analytic conditions	ee (%)
9	 ***62f***	**HPLC** **CHIRALCELL OD, λ = 254 nm** **15% IPA/hexanes, 1.0 mL/min** **t_R(min): major 11.57, minor 9.83**	**89**
10	 ***62g***	**HPLC** **CHIRALCELL OD, λ = 254 nm** **20% IPA/hexanes, 1.0 mL/min** **t_R(min): major 11.36, minor 9.98**	**93**
11	 ***62h***	**HPLC** **CHIRALCELL OD, λ = 254 nm** **30% IPA/hexanes, 1.0 mL/min** **t_R(min): major 7.41, minor 6.76**	**87**
12	 ***62i***	**HPLC** **CHIRALCELL OD, λ = 254 nm** **10% IPA/hexanes, 1.0 mL/min** **t_R(min): major 26.83, minor 23.63**	**91**
13	 ***64b***	**HPLC** **CHIRALCELL OD, λ = 254 nm** **30% IPA/hexanes, 1.0 mL/min** **t_R(min): major 8.24, minor 6.39**	**78**
14	 ***64c***	**SFC** **Chiralpak OJ-H, λ = 254 nm** **2% IPA/CO_2, 2.5 mL/min,** **t_R(min): major 7.25, minor 6.34**	**81**
15	 ***64d***	**HPLC** **CHIRALCELL OD, λ = 254 nm** **30% IPA/hexanes, 1.0 mL/min** **t_R(min): major 11.24, minor 8.72**	**81**
16	 ***64e***	**HPLC** **CHIRALCELL OD, λ = 254 nm** **30% IPA/hexanes, 1.0 mL/min** **t_R(min): major 9.40, minor 7.41**	**74**
17	 ***64f***	**HPLC** **CHIRALCELL OD, λ = 254 nm** **20% IPA/hexanes, 1.0 mL/min** **t_R(min): major 8.40, minor 7.49**	**71**

entry	compound	analytic conditions	ee (%)
18	 ***64g***	**HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min t_R(min): major 11.38, minor 8.47**	**60**
19	 ***64h***	**HPLC CHIRALCELL OD, λ = 254 nm 20% IPA/hexanes, 1.0 mL/min t_R(min): major 9.61, minor 7.13**	**76**
20	 ***64i***	**HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min t_R(min): major 7.31, minor 5.33**	**86**
21	 ***64j***	**HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min t_R(min): major 12.63, minor 8.67**	**86**
22	 ***64k***	**HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min t_R(min): major 11.30, minor 7.58**	**86**
23	 ***64l***	**HPLC CHIRALCELL OD, λ = 254 nm 40% IPA/hexanes, 1.0 mL/min t_R(min): major 11.68, minor 7.70**	**88**
24	 ***64m***	**HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min t_R(min): major 12.54, minor 8.47**	**83**

entry	compound	analytic conditions	ee (%)
25	 ***64n***	**HPLC** **CHIRALCELL OD, λ = 254 nm** **30% IPA/hexanes, 1.0 mL/min** **t_R(min): major 14.39, minor 8.96**	**83**
26	 ***64o***	**HPLC** **CHIRALCELL OD, λ = 254 nm** **30% IPA/hexanes, 1.0 mL/min** **t_R(min): major 11.30, minor 7.58**	**84**
27	 ***67***	**HPLC** **CHIRALCELL OD, λ = 254 nm** **30% IPA/hexanes, 1.0 mL/min** **t_R(min): major 10.42, minor 7.88**	**88**

(1) For reviews, see: (a) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 0369–0396. (b) Christoffers, J.; Mann, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4591–4597. (c) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5363–5367. (d) Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, 181–191. (e) Liu, Y.; Han, S.-J.; Liu, W.-B.; Stoltz, B. M. *Acc. Chem. Res.* **2015**, *48*, 740–751.

(2) (a) Nascimento de Oliveira, M.; Fournier, J.; Areseniyadis, S.; Cossy, J. *Org. Lett.* **2017**, *19*, 14–17. (b) James, J.; Guiry, P. J. *ACS Catal.* **2017**, *7*, 1397–1402. (b) Akula, R.; Guiry, P. J. *Org. Lett.* **2016**, *18*, 5472–5475. (c) Akula, R.; Doran, R.; Guiry, P. J. *Chem. Eur. J.* **2016**, *22*, 9938–9942. (d) Marziale, A. N.; Duquette, D. C.; Craig, R. A.; Kim, K. E.; Liniger, M.; Numajiri, Y.; Stoltz, B. M. *Adv. Synth. Catal.* **2015**, *357*, 2238–2245. (e) Korch, K. M.; Eidamshaus, C.; Behenna, D. C.; Nam, S.; Horne, D.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2015**, *54*, 179–183. (f) Craig, R. A.; Loskot, S. A.; Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Org. Lett.* **2015**, *17*, 5160–5163. (g) Alberch, E.; Brook, C.; Asad, S. A.; Shevyrev, M.; Ulicki, J. S.; Hossain, M. M. *Synlett* **2015**, *26*, 388–392. (h) Liu, W.-B.; Reeves, C. M.; Virgil, S. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2013**, *135*, 10626–10629. (i) Kaiser, T. M.; Yang, J. *Eur. J. Org. Chem.* **2013**, 3983–3987. (j) Fournier, J.; Lozano, O.; Menozzi, C.; Arseniyadis, S.; Cossy, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 1257–1261. (k) Reeves, C. M.; Eidamshaus, C.; Kim, J.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2013**, *52*, 6718–6721. (l) Gartshore, C. J.; Lupton, D. W. *Angew. Chem. Int. Ed.* **2013**, *52*, 4113–4116. (m) Li, Z.; Zhang, S.; Wu, S.; Shen, X.; Zou, L.; Wang, F.; Li, X.; Peng, F.; Zhang, H.; Shao, Z. *Angew. Chem. Int. Ed.* **2013**, *52*, 4117–4121. (n)

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