CHAPTER 3

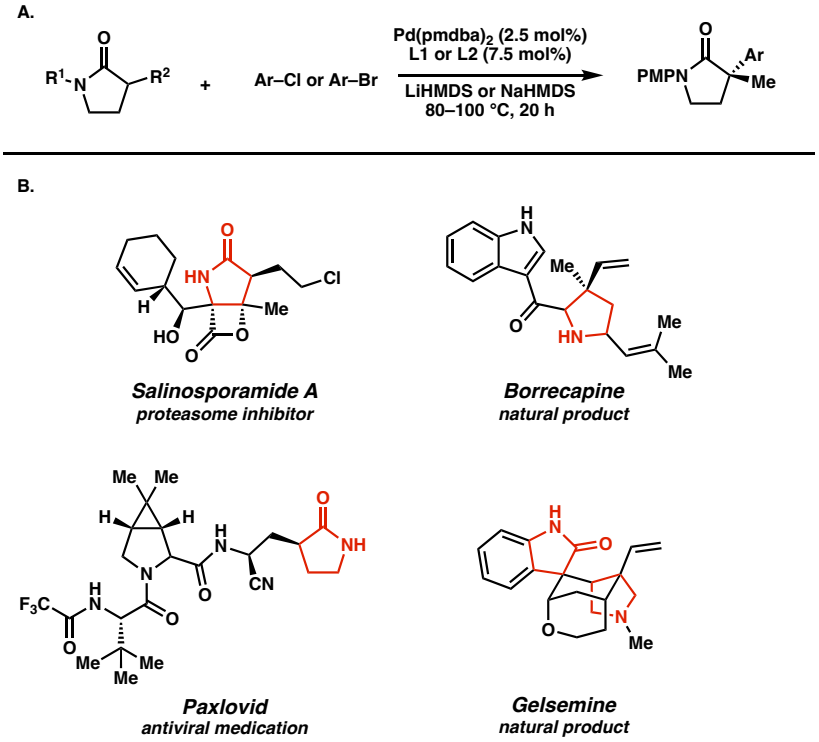
Formation of All-Carbon Quaternary Centers via Enantioselective Pd-Catalyzed α-Vinylation of γ-Lactams[†]

3.1 INTRODUCTION

γ-lactams are ubiquitous heterocyclic motifs found in pharmaceuticals and natural products alike (Figure 3.1).[1] Despite this, the direct vinylation of these and other[2] scaffolds largely remains an unsolved problem in organic synthesis, limiting the feasibility of convenient disconnections in the synthesis of complex scaffolds with potential biological and synthetic applications. Our group previously disclosed a novel, Pd-catalyzed strategy toward the α-arylation of PMP (para-methoxy phenyl)-protected γ-lactams containing substitution at the α-position.[3] As such, we successfully achieved the first asymmetric α-arylation of γ-lactams forming enantioenriched all-carbon quaternary centers. We were next interested in translating this reaction to the unprecedented vinylation of these nucleophiles.

[†]Portions of this chapter have been reproduced with permission from Moghadam M.[†]; , F. A.[†]; Barbor, J. B.[†]; Chan, Jette, C.; Sakurai, S.; Stoltz, B. M. *Org. Lett.* **2024**, *26*, 7551–7554. © 2024 American Chemical Society. [†] denotes equal contribution.

Figure 3.1. *A) Pd-Catalyzed α-Arylation of γ-Lactams B) Selected Examples of γ-Lactams in Pharmaceuticals and Natural Products*

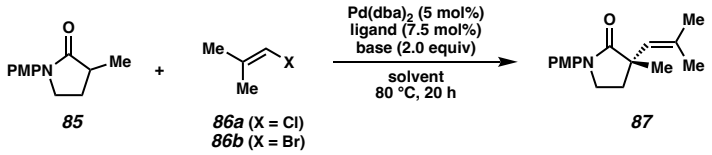


3.2 OPTIMIZATION EFFORTS

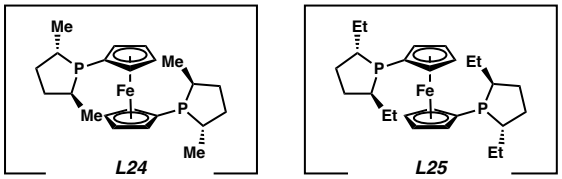
Our investigation commenced by utilizing the same catalytic conditions disclosed in our prior report. Initial efforts illustrated the superiority of vinyl chloride electrophiles and lithium bases (Table 3.1). We observed a dramatic counterion effect, as use of NaHMDS or KHMDS afforded no desired product, whereas LiHMDS afforded a 46% yield of the desired **87** with an excellent 90% ee. Exploration of similar lithium bases, like LiTMP, garnered diminished yields. Similarly, vinyl chlorides were found to be essential for both yield and enantioselectivity, as use of the corresponding vinyl bromide **86b** afforded **87** in a low 27% yield and 77% ee. Use of the more sterically encumbered ligand **L25** did not

improve the reaction further. Although we initially found that CPME (cyclopentyl methyl ether) resulted in a slight improvement of the ee to 92%, we found that 1,4–dioxane was ultimately the optimal solvent for this transformation. Additionally, dilution of the reaction to 0.05 M allowed for an improved 58% yield and 94% ee (entry 10).

Table 3.1. *Reaction Optimization*[a,b,c]



Entry	Ligand	X	Base	Solvent	Yield (%)	ee (%)
1	L24	Cl	NaHMDS	dioxane	0	–
2	L24	Cl	KHMDS	dioxane	0	–
3	L24	Cl	LiHMDS	dioxane	46	90
4	L24	Cl	LiTMP	dioxane	29	ND
5	L24	Br	LiHMDS	dioxane	27	77
6	L25	Cl	LiHMDS	dioxane	43	88
7[b]	L24	Cl	LiHMDS	THF	19	ND
8[b]	L24	Cl	LiHMDS	CPME	43	92
9[c]	L24	Cl	LiHMDS	CPME	38	ND
10[c]	L24	Cl	LiHMDS	dioxane	58	93



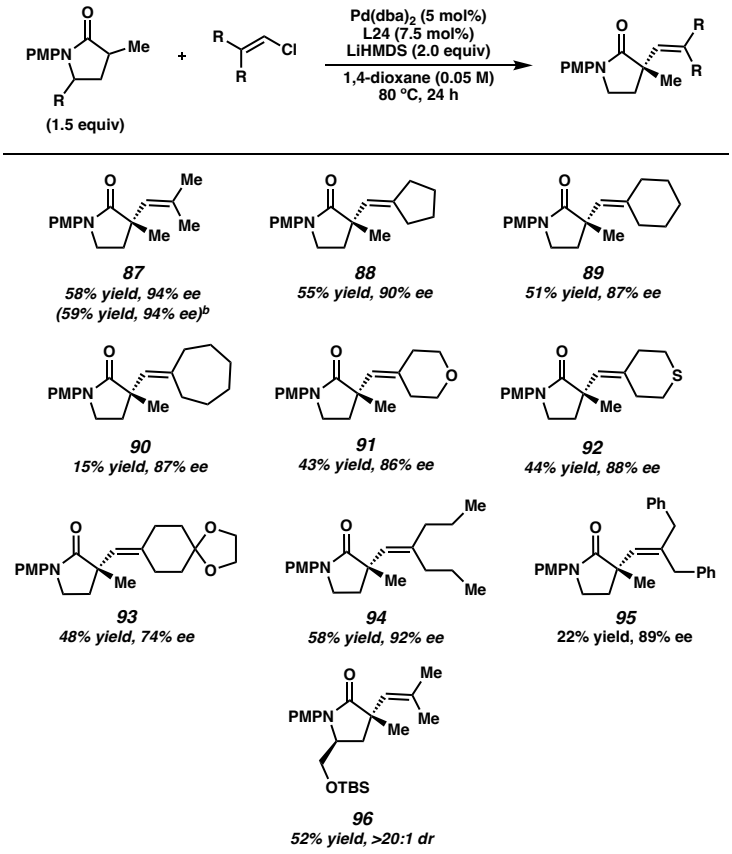
[a]Reactions performed at 0.1 mmol scale and 0.1 M. Yields determined by ^{1}H NMR with CH_2Br_2 internal standard. [b]Reaction performed at 70 °C for 48 h. [c]Reaction performed at 0.05 M concentration.

3.3 SUBSTRATE SCOPE

With optimized conditions in hand, we sought to investigate the range of compatible substitution patterns on the vinyl halide coupling partner (Scheme 3.1). Vinyl electrophiles featuring cyclopentyl, cyclohexyl and cycloheptyl substitution at the 2,2-position of the vinyl chloride afforded products **88**–**90** with high enantioselectivity, although formation of

product **90** was observed in diminished yields likely due to increased steric hindrance. Additionally, saturated heterocyclic moieties, such as a pyran and thiopyran, were well-tolerated (**91** and **92**). Although acyclic product **94** could also be obtained in comparable yield and ee, **95** was isolated in decreased yield. Substitution at the α-position was limited to methyl, but we were pleased to find that pre-existing substitution at the γ-position of the

Scheme 3.1. *Substrate Scope*[a,b,c]



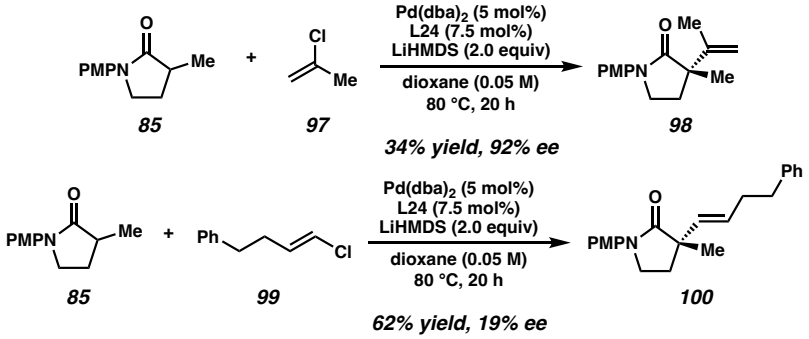
[a]Reactions performed on 0.1 mmol scale. [b]Reaction performed on 3 mmol scale. [c]Yields determined by ^{1}H NMR with CH_2Br_2 internal standard.

lactam resulted in a predictable match/mismatch situation. Enhancement of dr and higher reaction efficiency was observed for product **96**, whereas lower yield and

diastereoselectivity was observed for its epimer ***epi*-96**.[4] We were also able to implement our method at a 3 mmol scale, obtaining over 450 mg of **87** in similar yield and enantioselectivity (59% yield, 94% ee).

While exploring the scope of this transformation, we found that use of 1,1-disubstituted or *trans*-1,2-disubstituted electrophiles resulted in either diminished yield or enantioselectivity, respectively (Figure 3.2). Hypothesizing that reductive elimination is both inner-sphere and enantiodetermining,[5,6] we posit that the diminished yield of the 1,1-disubstituted electrophiles originates from steric congestion at the metal center, which may deter transmetallation of the lithium enolate to palladium. Conversely, we propose that the greatly minimized interactions between the ligand and *trans*-1,2-disubstituted electrophiles result in high conversion but with poor enantiocontrol.

Scheme 3.2. *Reaction with 1,1 and 1,2-Disubstituted Electrophiles*

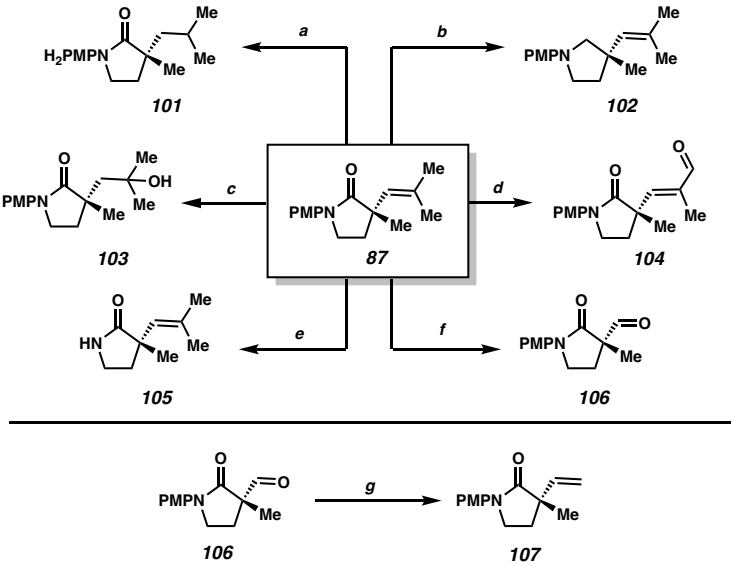


3.4 DERIVATIZATIONS AND CONCLUSION

These enantioenriched heterocycles, characterized by highly substituted quaternary centers, exhibit significant potential for pharmaceutical and total synthetic applications.[7] As a result, we embarked on a series of derivatizations of product **87** to generate

differentially substituted pyrrolidinone derivatives (Scheme 3.3). Our initial strategy involved the hydrogenation of product **87** to yield α-quaternary lactam **101**. Given the inherent challenges associated with enantioselective α-alkylation of lactams using conventional methods, we believe that this approach offers great synthetic value.

Scheme 3.3. *Product Derivitization*



Conditions: a) H_2, Pd/C (10 mol%), MeOH, 12 h, 74% yield. b) LAH (5 equiv), Et_2O, 0–18 °C, 21 h, 84% yield. c) PTSA, AcOH, 70 °C, 12 h, 59% yield. d) SeO_2, 1,4-dioxane, reflux, 15 min, 49% yield. e) CAN, H_2O, 60 ºC, 32 h, 40% yield. f) O_3, PPh_3, CH_2Cl_2, 15 min, 89% yield. g) KO*t*-Bu, methyltriphenylphosphonium bromide, THF, 0 ºC to reflux, 12 h, 84% yield.

Reduction of the lactam with lithium aluminum hydride yields β-quaternary pyrrolidine **102**. This derivative contains a heterocycle of significant pharmaceutical importance,[8] as pyrrolidines are ubiquitous in various existing drug molecules and natural products.[9] Hydration of the newly introduced vinyl group with *p*-TsOH produces tertiary alcohol

103.[10] Allylic oxidation with SeO_2 results in the formation of aldehyde **104**. Additionally, deprotection of the PMP group with ceric ammonium nitrate (CAN) reveals unprotected lactam **105**. Finally, **87** can undergo oxidative cleavage to yield the corresponding aldehyde **106** through ozonolysis. From **106**, a Wittig reaction can be conducted to generate vinylated lactam **107** with no substitution at the terminal position.[11]

In conclusion, our study showcases an enantioselective vinylation method for γ-lactams, yielding α-quaternary centers with up to 58% yield and 94% ee. Notably, the reaction exhibits distinct preferences among different classes of electrophiles. Particularly, we observed that tri-substituted vinyl chlorides outperformed other vinyl halides under these conditions in terms of both yield and ee. Moreover, these highly substituted γ-lactams hold significant synthetic potential, offering diverse functional handles for the synthesis of complex drug molecules or natural products.

3.5 EXPERIMENTAL SECTION

3.5.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. [12] Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 μm) and Teledyne Isco CombiFlash Rf+ UV with Luknova standard silica (avg particle size 50μm) flash columns were used for flash chromatography. ^{1}H NMR spectra were recorded on Varian Inova 500 MHz and Bruker

400 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer (125 MHz) and Bruker 400 MHz spectrometers (100 MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm). Data for ^1H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet. Data for ^{13}C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell. Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing Chiralpak (AD-3, AS-H or IC) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing Chiralpak (IH) or Chiralcel (OD-H) columns (4.6 mm x 25 cm) both obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in field ionization (FI+) or field desorption (FD+) mode, or an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI), or mixed ionization mode (MM: ESI-APCI+). Reagents were purchased from commercial sources and used as received unless otherwise stated.

Low-temperature diffraction data (ϕ-and ω-scans) were collected on a Bruker AXS D8 VENTURE KAPPA diffractometer coupled to a PHOTON II CPAD detector with K_α radiation (λ = 1.54178 Å) from an IμS micro-source for the structure of compound V24190. The structure was solved by direct methods using SHELXS[13] and refined against F^2 on all data by full-matrix least squares with SHELXL-2019[14] using established refinement techniques.[15] All non-hydrogen atoms were refined anisotropically. All hydrogen atoms

were included into the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the *U* value of the atoms they are linked to (1.5 times for methyl groups).

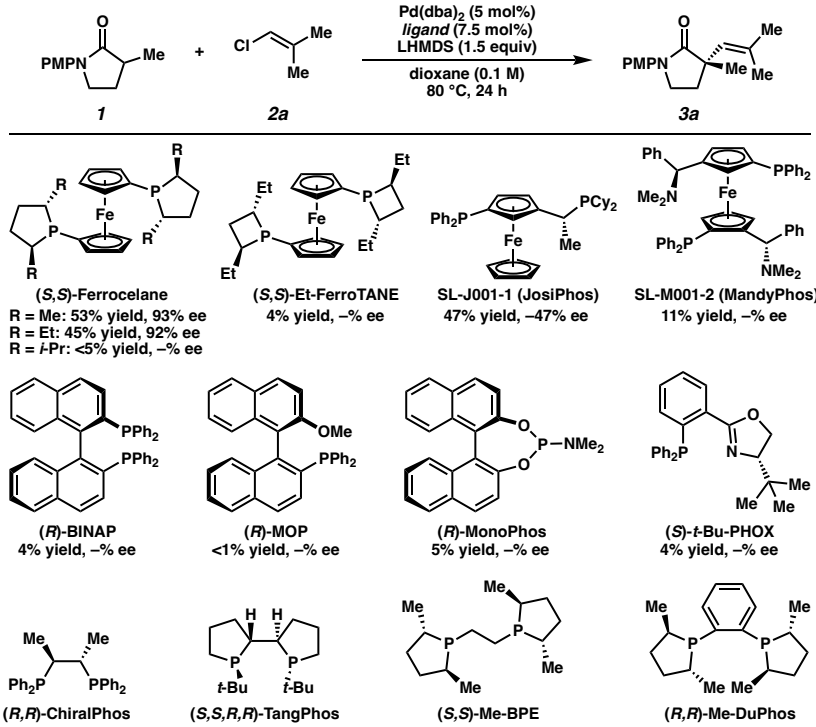
Compound V24190 crystallizes in the orthorhombic space group $P2_12_12_1$ with one molecule in the asymmetric unit.

List of Abbreviations:

ee – enantiomeric excess, SFC – supercritical fluid chromatography, HPLC – high-performance liquid chromatography, TLC – thin-layer chromatography, Dr – dram

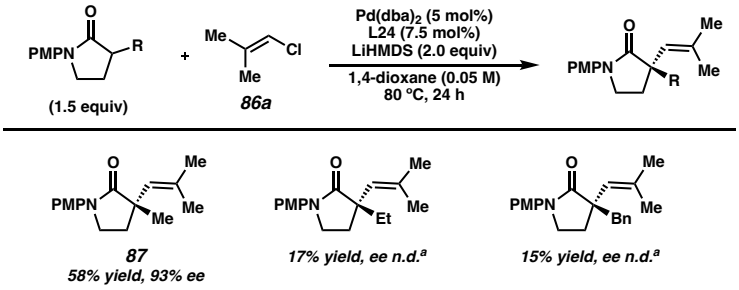
3.5.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

Table 3.2. *Ligand Evaluation*[a]



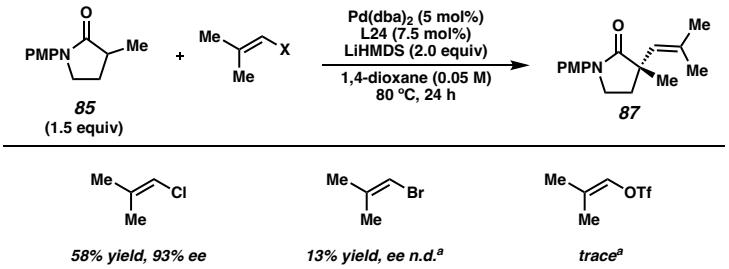
[a]Yields determined by ^{1}H NMR analysis of crude reaction mixture using 1,3,5-trimethoxybenzene as a standard. Enantiomeric excess (ee) was determined by chiral SFC analysis of the isolated product.

Scheme 3.4. *Nucleophile Substitution Patterns*[a]



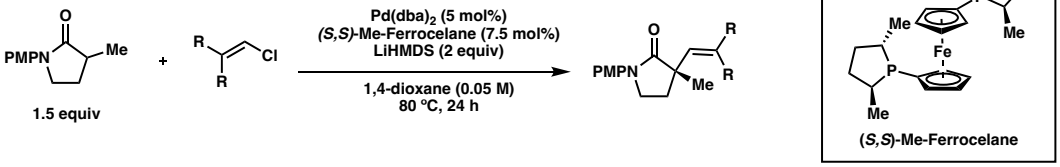
[a]Yields determined by 1H NMR with CH_2Br_2 internal standard.

Scheme 3.5. *Survey of Vinyl Halides and Pseudo-halides*[a]



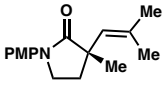
[a]Yields determined by ^{1}H NMR with CH_2Br_2 internal standard. Reaction performed with 1.5 eq of vinyl halide/pseudohalide, 1 equiv lactam, 1 equiv LiHMDS

Pd-catalyzed Vinylation Reactions: General Procedure A



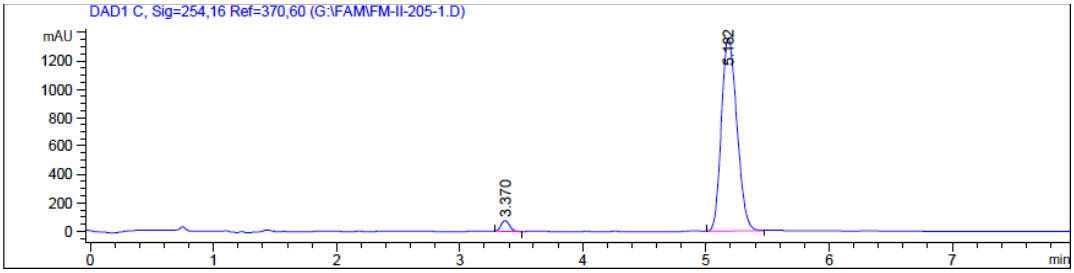
In a nitrogen-filled glovebox, a catalyst solution of $Pd(dba)_2$ (9.6 mg/mL) and *(S,S)-Me-Ferrocelane* (10.4 mg/mL) in 1,4-dioxane was stirred for 20 min at 40 °C. In a vial, the lactam was dissolved in 1,4-dioxane (1.5 equiv, 0.09 M), and subsequently LHMDS (2 equiv) was added. A 2 Dr vial was charged with neat vinyl chloride (0.1 mmol, 1 equiv) and a magnetic stir bar. After the catalyst pre-stir was complete, 0.4 mL of the catalyst solution was added to the vinyl chloride, followed by 1.6 mL of the nucleophile/base

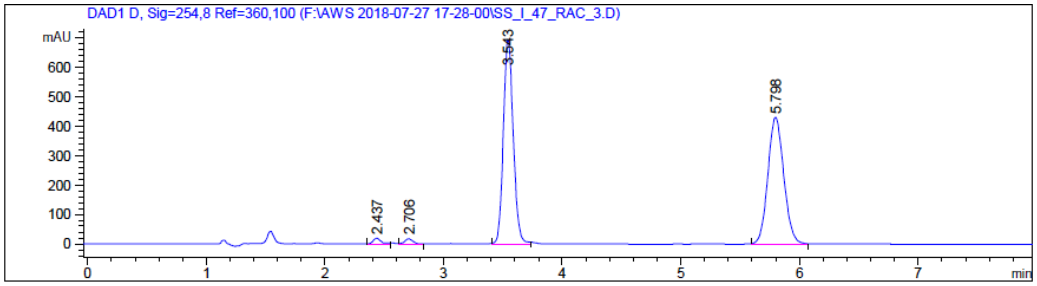
mixture. The vial was sealed with a Teflon-lined cap, removed from the glovebox, and stirred at 80 °C in a metal heating block for 24 h unless noted otherwise. After 24 h, 3 mL 0.5 M HCl or sat. NH_4Cl was added to the crude reaction mixture, which was then extracted three times with ethyl acetate, dried over Na_2SO_4, concentrated, and purified by silica gel flash chromatography to provide the desired vinylation product.



(*S*)-1-(4-methoxyphenyl)-3-methyl-3-(2-methylprop-1-en-1-yl)pyrrolidin-2-one (87)

Prepared according to general procedure A using vinyl chloride **86a** (0.1 mmol) and lactam **85**. Purification by silica gel chromatography (0-30% EtOAc/Hexanes) provided 15 mg (58%, 94% ee) of a yellow oil. The reaction was also performed using 3 mmol vinyl chloride to obtain 456 mg (59%) of a tan solid; $[\alpha]_D^{25}$ –79.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 9.2 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 5.46 (t, *J* = 1.4 Hz, 1H), 3.79 (s, 3H), 3.78 – 3.63 (m, 2H), 2.32 – 2.12 (m, 2H), 1.74 (d, *J* = 1.5 Hz, 3H), 1.69 (d, *J* = 1.4 Hz, 3H), 1.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8, 156.5, 134.6, 133.3, 128.5, 121.6, 114.1, 55.6, 46.3, 45.7, 34.3, 27.1, 24.4, 19.2; IR (Neat Film, NaCl) 2965, 1694, 1513, 1400, 1297, 1250, 1170, 1089, 1063, 1033, 828 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd $C_{16}H_{22}NO_2$ $[M+H]^+$: 260.1645, found 260.1649. SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 3.37, major = 5.18.





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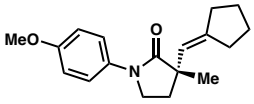
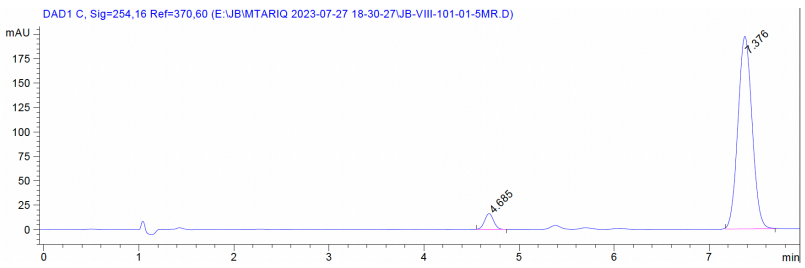
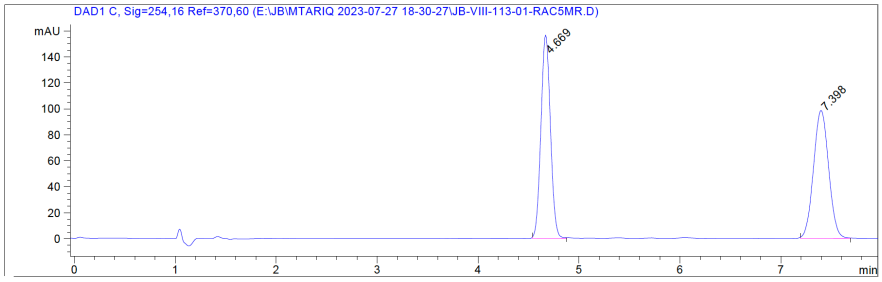


***(S)-3-(cyclopentylidenemethyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one* (88)**

Prepared according to general procedure A using **108**. Purification by column chromatography (0–25 % EtOAc/Hexanes) yielded **88** as a white solid (15.6 mg, 55% yield); 90% *ee*; $[\alpha]_D^{25}$ –56.8 (c 0.75, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 9.1 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 5.53 (p, *J* = 2.3 Hz, 1H), 3.79 (s, 3H), 3.75 – 3.51 (m, 2H), 2.26 (m, 5H), 2.15 – 1.87 (m, 1H), 1.88 – 1.60 (m, 2H), 1.60 – 1.42 (m, 2H), 1.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 156.5, 145.1, 133.3, 123.7, 121.5, 114.1, 55.6, 47.1, 45.8, 35.5, 34.0, 28.9, 27.3, 25.8, 23.9; IR (neat film, NaCl) 3835, 3732, 2951, 2866, 2360, 1693, 1511, 1455, 1395, 1298, 1248, 1181, 1084, 1035, 833, 662 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd for $C_{18}H_{24}NO_2$ $[M+H]^+$: 286.1802, found 286.1815; SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 4.69, major = 7.78.





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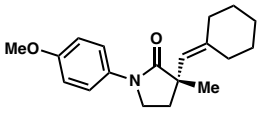
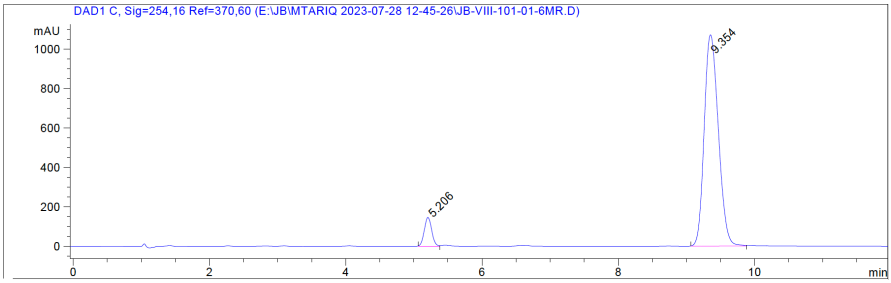
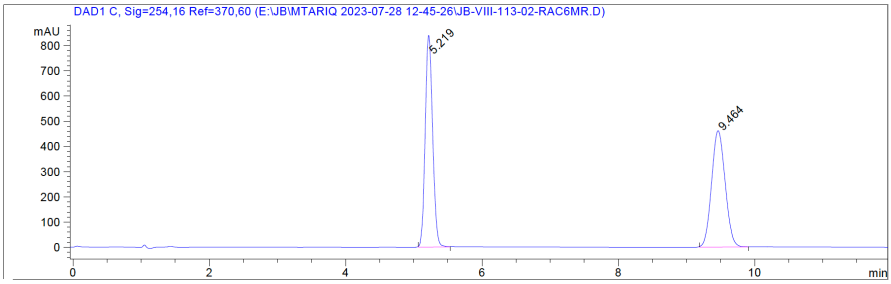


***(S)-3-(cyclohexylidenemethyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one* (89)**

Prepared according to general procedure A using **109**. Purification by column chromatography (0–25 % EtOAc/Hexanes) yielded **89** as a white solid (15.3 mg, 51% yield); 84% *ee*; $[\alpha]_D^{25}$ –64.5 (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 9.1 Hz, 2H), 6.80 (d, J = 9.1 Hz, 2H), 5.36 – 5.31 (m, 1H), 3.69 (s, 3H), 3.67 – 3.34 (m, 2H), 2.12 (m, 2H), 2.08 – 1.94 (m, 4H), 1.55 – 1.32 (m, 6H), 1.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.9, 156.4, 142.7, 133.2, 125.4, 121.5, 114.0, 55.5, 45.9, 45.6, 37.7, 34.6, 30.2, 28.7, 27.6, 26.5, 24.7; IR (neat film, NaCl) 3835, 3745, 2925, 2851, 2359, 1693, 1513, 1443, 1396, 1298, 1248, 1179, 1088, 1035, 828 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd for $C_{19}H_{26}NO_2$ $[M+H]^+$: 300.1958, found 300.1972; SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 5.21, major = 9.35.





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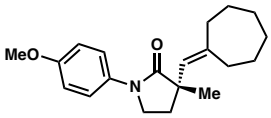
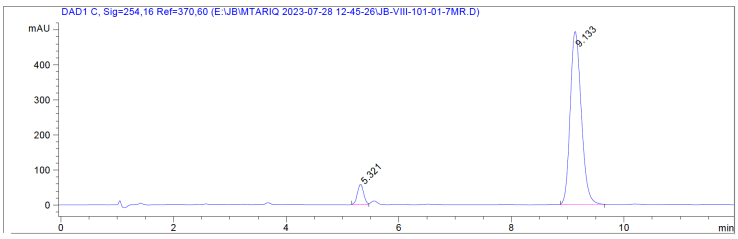
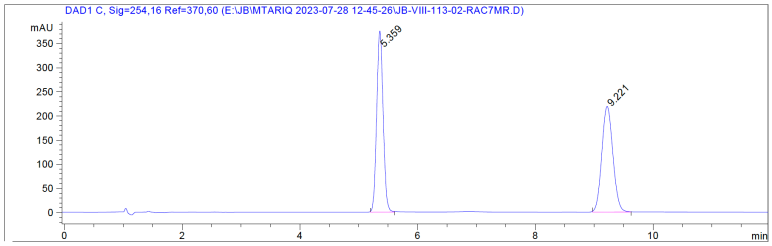


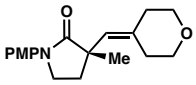
***(S)-3-(cycloheptylidenemethyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one* (90)**

Prepared according to general procedure A using **110**. Purification by column chromatography (0–25 % EtOAc/Hexanes) yielded **90** as a white solid (4.7 mg, 15% yield); 86% *ee*; $[\alpha]_D^{25}$ – 39.4 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 9.2 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 5.52 (p, *J* = 1.4 Hz, 1H), 3.80 (s, 3H), 3.77 – 3.32 (m, 2H), 2.86 – 1.98 (m, 6H), 1.84 – 1.40 (m, 8H), 1.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.9, 156.5, 144.2, 133.3, 128.8, 121.6, 121.6, 114.2, 55.6, 46.3, 45.8, 38.5, 34.1, 31.0, 29.9, 29.7, 29.3, 27.0, 24.4; IR (neat film, NaCl) 3834, 3732, 2923, 2849, 2341, 1693, 1511, 1395, 1298, 1247, 1087, 1035, 827 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd for $C_{20}H_{28}NO_2$ $[M+H]^+$: 314.2115, found 314.2029; SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 5.32, major = 9.13.



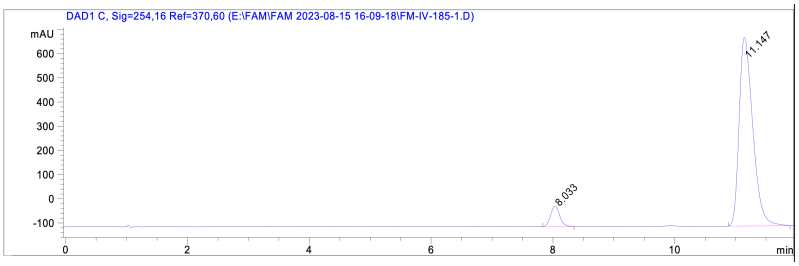


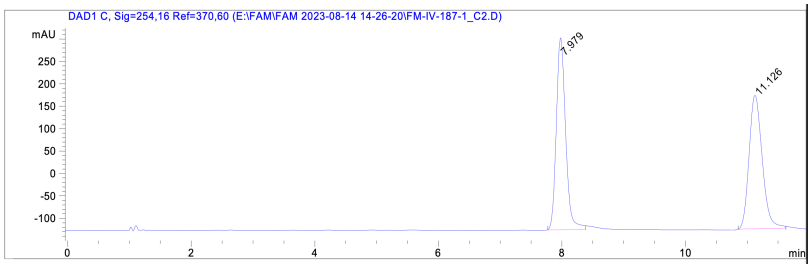
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.321	BV	0.1211	454.95865	58.26056	6.3215
2	9.133	BB	0.2113	6742.08643	493.82556	93.6785



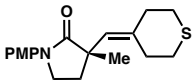
***(S)-3-(tetrahydropyranlidenemethyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one* (91)**

Prepared according to general procedure A using **111**. Purification by column chromatography (0–30% EtOAc/Hexanes) yielded **91** as a colorless oil (13.2 mg, 43%); 86% *ee*; $[\alpha]_D^{25}$ – 41.4 (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 5.54 (d, *J* = 1.3 Hz, 1H), 3.79 (s, 3H), 3.78 – 3.57 (m, 6H), 2.34 (tt, *J* = 5.8, 1.2 Hz, 2H), 2.29 – 2.17 (m, 4H), 1.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 156.6, 137.5, 133.1, 127.5, 121.6, 114.2, 69.8, 68.4, 55.6, 46.0, 45.7, 37.5, 34.9, 31.3, 24.8. IR (neat film, NaCl) 2958, 2839, 1691, 1511, 1462, 1396, 1286, 1269, 1246, 1087, 1032, 831 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd for $C_{18}H_{24}NO_3$ $[M+H]^+$: 302.1751, found 302.1750 ; SFC conditions: 20% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 8.03, major = 11.15.



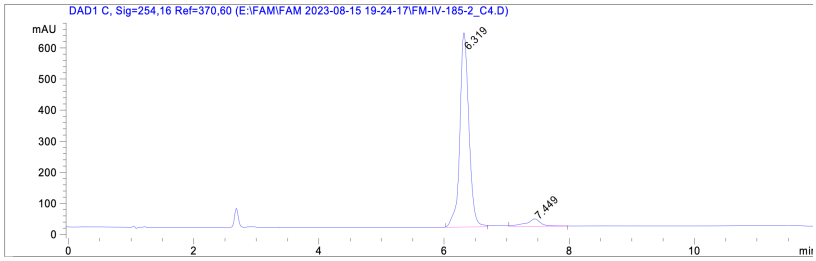


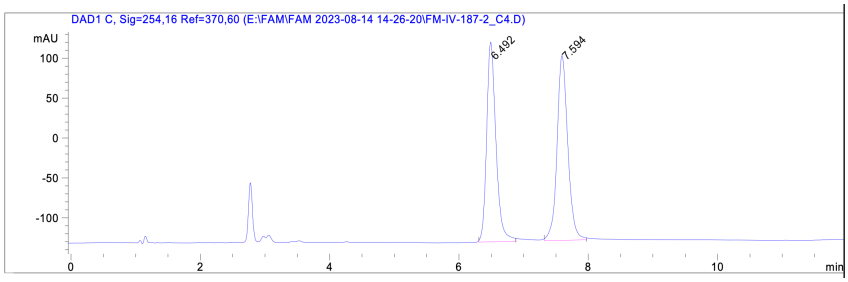
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.033	BB	0.1634	895.48993	84.67880	24.0017
2	11.147	BB	0.2379	1.21628e4	780.28503	325.9983



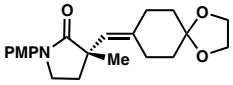
***(S)-3-(tetrahydro-thiopyranlidenemethyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one* (92)**

Prepared according to general procedure A using **112**. Purification by column chromatography (0–25 % EtOAc/Hexanes) yielded **92** as a colorless oil (13.5 mg, 44%); 88% *ee*; $[\alpha]_D^{25}$ –58.3 (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 9.1 Hz, 1H), 6.90 (d, *J* = 9.1 Hz, 1H), 5.55 (t, *J* = 1.0 Hz, 1H), 3.80 (s, 2H), 3.78 – 3.68 (m, 1H), 2.76 – 2.48 (m, 4H), 2.44 (td, *J* = 5.4, 2.5 Hz, 1H), 2.24 – 2.17 (m, 1H), 1.36 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 156.6, 139.6, 133.05, 129.0, 121.6, 114.2, 55.6, 45.9, 45.7, 39.4, 34.8, 32.2, 31.2, 29.9, 24.8. IR (neat film, NaCl) 2953, 1689, 1511, 1428, 1398, 1297, 1247, 1180, 1087, 1034, 821 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd for $C_{18}H_{24}NO_2S$ $[M+H]^+$: 318.1522, found 318.1520; SFC conditions: 20% IPA, 2.5 mL/min, Chiralcel OJ-3 column, λ = 254 nm, tR (min): minor = 7.45, major = 6.32.



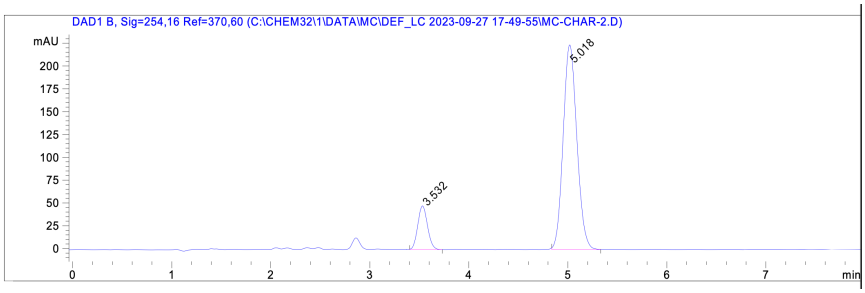


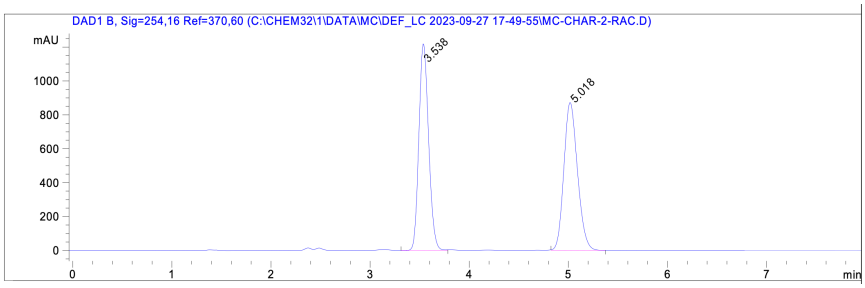
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.319	BB	0.1536	6285.17188	623.72955	328.2187
2	7.449	BB	0.2366	417.09830	24.25278	21.7813



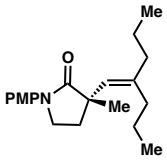
***(S)-3-((1,4-dioxaspiro[4.5]decan-8-ylidene)methyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one* (93)**

Prepared according to general procedure A using **113**. The crude product was purified by silica gel chromatography (30% EtOAc/Hexanes) to afford vinylated lactam **93** (48% yield, 74% ee) as a colorless oil; $[a]_D^{25}$ + 4.5 ° (*c* 0.52, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 9.1 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 5.54 (d, *J* = 1.7 Hz, 1H), 3.95 (s, 3H), 3.80 (s, 3H), 3.76 – 3.60 (m, 2H), 2.40 – 2.29 (m, 2H), 2.31 – 2.16 (m, 4H), 1.71 (td, *J* = 6.7, 3.9 Hz, 3H), 1.68 – 1.62 (m, 1H), 1.60 (s, 1H), 1.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.7, 156.6, 140.0, 133.2, 127.2, 121.6, 114.2, 114.1, 108.7, 77.5, 77.4, 77.2, 76.8, 64.5, 64.5, 55.6, 46.1, 45.7, 36.4, 35.3, 34.7, 34.5, 26.7, 24.7; IR (thin film, NaCl) 3465, 2950, 2886, 2320, 2009, 1902, 1693, 1681, 1513, 1433, 1401, 1298, 1276, 1248, 1226, 1181, 1171, 1120, 1082, 1032, 944, 906, 826, 738, 728 cm^{-1}; HRMS (ESI) m/z calc'd $C_{21}H_{27}NO_4Na$ $[M+Na]^+$: 380.1832, found: 380.1843; SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 3.53, major = 5.02.





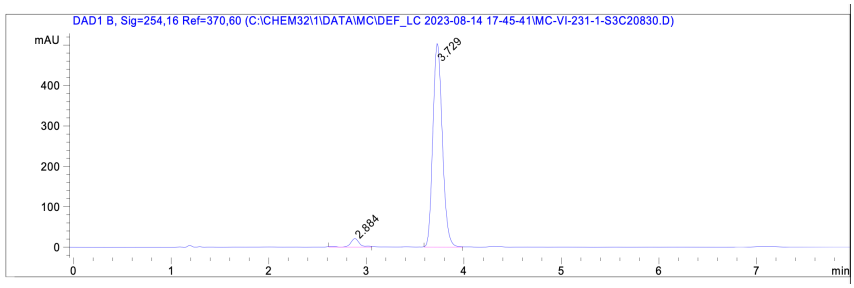
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.532	BB	0.1077	326.17273	47.72661	13.1365
2	5.018	BB	0.1523	2156.76880	223.97276	86.8635



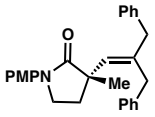
***(S)-1-(4-methoxyphenyl)-3-methyl-3-(2-propylpent-1-en-1-yl)pyrrolidin-2-one* (94)**

Prepared according to general procedure A using **114**. The crude product was purified by silica gel chromatography (30% EtOAc/Hexanes) to afford vinylated lactam **94** (58% yield, 92% ee) as a colorless oil; $[a]_D^{25}$ – 2.5 ° (*c* 0.35, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 9.1 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 5.50 (t, *J* = 1.0 Hz, 1H), 3.80 (d, *J* = 0.7 Hz, 3H), 3.78 – 3.67 (m, 2H), 2.34 – 2.25 (m, 1H), 2.25 – 2.17 (m, 1H), 2.12 – 2.03 (m, 1H), 2.03 – 1.94 (m, 3H), 1.48 – 1.38 (m, 4H), 1.36 (s, 3H), 0.93 – 0.84 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.9, 156.4, 142.4, 133.2, 128.5, 121.4, 114.0, 77.4, 77.2, 77.0, 76.7, 55.5, 46.2, 45.6, 38.8, 34.5, 33.0, 24.7, 21.3, 21.1, 14.6, 13.8. IR (thin film, NaCl) 2958, 2930, 2870, 1694, 1513, 1469, 1454, 1423, 1398, 1299, 1288, 1248, 1181, 1168, 1122, 1087, 1036, 836, 823, 805, 634 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd $C_{20}H_{29}NO_2Na$

$[M+Na]^+$: 338.2091, found: 338.2100; SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 2.88, major = 3.73.



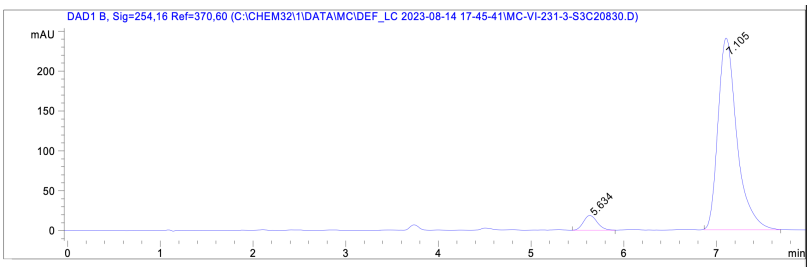
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.884	BB	0.0977	139.83130	21.00225	3.9512
2	3.729	BB	0.1069	3399.10669	502.66321	96.0488



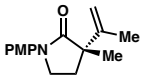
***(S)-3-(2-benzyl-3-phenylprop-1-en-1-yl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one* (95)**

Prepared according to general procedure A using **115**. The crude product was purified by silica gel chromatography (30% EtOAc/Hexanes) to afford vinylated lactam **95** (22% yield, 88% ee) as a colorless oil; $[a]_D^{25}$ – 12.4 ° (*c* 0.56, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 9.1 Hz, 2H), 7.38 – 7.32 (m, 2H), 7.30 – 7.23 (m, 3H), 7.23 – 7.17 (m, 2H), 7.17 – 7.10 (m, 2H), 6.95 (d, *J* = 9.1 Hz, 2H), 6.02 (t, *J* = 1.0 Hz, 1H), 3.86 (s, 3H), 3.84 – 3.74 (m, 2H), 3.54 – 3.38 (m, 2H), 3.27 (t, *J* = 1.6 Hz, 2H), 2.43 (dt, *J* = 12.5, 8.2 Hz, 1H), 2.30 (ddd, *J* = 12.5, 7.2, 3.6 Hz, 1H), 1.52 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 156.5, 139.8, 139.5, 139.0, 132.9, 132.8, 129.0, 128.9, 128.5, 128.3, 128.2, 126.1, 121.6,

114.1, 77.4, 77.2, 77.0, 76.7, 55.5, 46.4, 45.7, 43.3, 35.9, 34.1, 24.8. IR (thin film, NaCl) 3059, 3025, 2930, 2835,m 2340, 1682, 1600, 1520, 1493, 1453, 1398, 1298, 1240, 1181, 1120, 1088, 1031, 829, 734, 702 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd $C_{28}H_{29}NO_2Na$ $[M+Na]^+$: 434.2091, found: 434.2102; SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 5.63, major = 7.11.



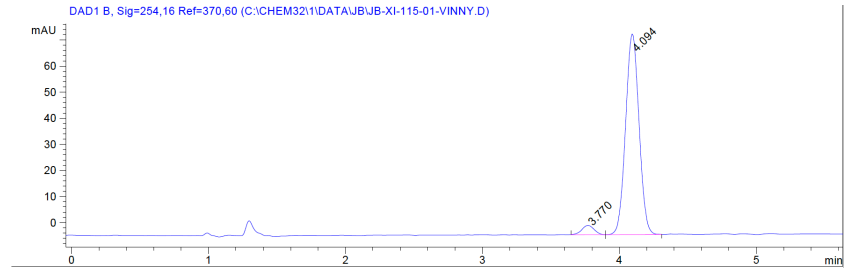
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.634	BB	0.1609	192.02281	18.53370	5.3335
2	7.105	BB	0.2136	3408.32178	240.14082	94.6665



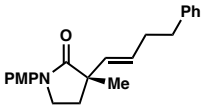
(S)-1-(4-methoxyphenyl)-3-methyl-3-(prop-1-en-2-yl)pyrrolidin-2-one (98)

Prepared according to general procedure A using **97**. The crude product was purified by silica gel chromatography (0–30% EtOAc/Hexanes) to afford vinylated lactam **98** (8.3 mg, 34% yield, 92% ee) as a white solid; $[a]_D^{25}$ – 125.8 ° (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 9.1 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 4.93 (s, 1H), 4.89 (s, 1H), 3.80 (s, 3H), 3.76 – 3.44 (m, 2H), 2.32 (ddd, *J* = 12.7, 7.0, 4.4 Hz, 1H), 1.94 (dt, *J* = 12.7, 7.8 Hz, 1H), 1.83 (d, *J* = 1.3 Hz, 3H), 1.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.3, 156.6, 145.4, 133.1, 121.7, 114.2, 114.1, 111.9, 55.6, 51.2, 45.9, 31.9, 22.5, 19.8; IR (thin film,

NaCl) 2933, 1738, 1693, 1643, 1512, 1455, 1396, 1297, 1248, 1181, 1088, 1034, 892, 828 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd $C_{15}H_{20}NO_2$ $[M+H]^+$: 246.1498, found 246.1495. SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 3.77, major = 4.09.



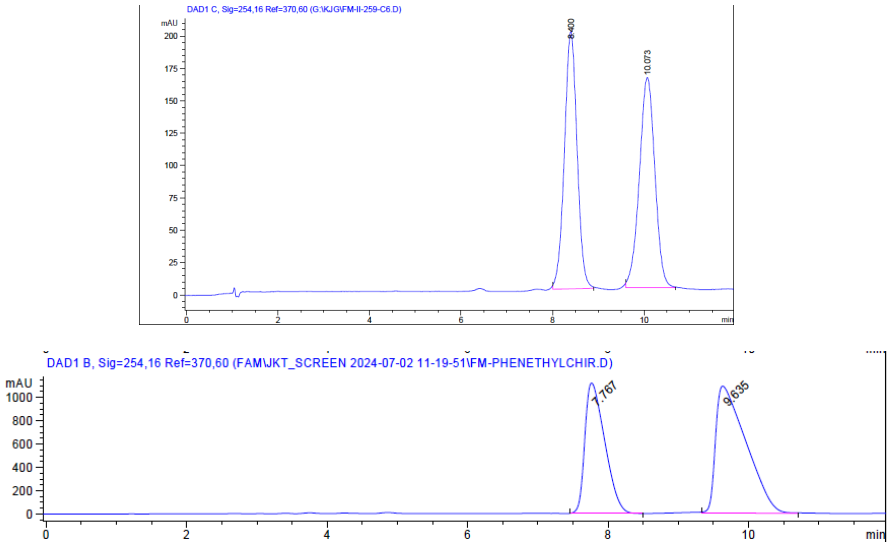
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.770	BV	0.1014	22.07811	3.50927	4.0399
2	4.094	VB	0.1078	524.42456	76.70352	95.9601
Totals :				546.50267	80.21279	



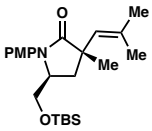
(S,E)-1-(4-methoxyphenyl)-3-methyl-3-(4-phenylbut-1-en-1-yl)pyrrolidin-2-one (100)

Prepared according to general procedure A using **99**. The crude product was purified by silica gel chromatography (0-30% EtOAc/Hexanes) to afford vinylated lactam **100** (20.6 mg, 62% yield, 19% ee) as a colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.38 (m, 2H), 7.22 – 7.12 (m, 2H), 7.12 – 6.99 (m, 3H), 6.89 – 6.73 (m, 2H), 5.57 – 5.38 (m, 2H), 3.72 (s, 3H), 3.63 – 3.49 (m, 2H), 2.66 – 2.53 (m, 2H), 2.35 – 2.19 (m, 2H), 2.07 (ddd, J = 12.4, 6.3, 5.0 Hz, 1H), 1.89 (dt, J = 12.5, 7.7 Hz, 1H), 1.23 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4, 156.5, 141.9, 133.1, 133.1, 129.0, 128.7, 128.4, 125.9, 121.5, 114.1, 55.6,

47.8, 45.6, 35.9, 34.5, 32.7, 23.6; IR (thin film, NaCl) 2928, 1693, 1513, 1461, 1395, 1297, 1249, 1181, 1091, 1032, 974, 830, 798, 739, 700 cm^{-1}; HRMS (FD+) m/z calc'd $C_{22}H_{25}NO_2$ $[M]^{+\bullet}$, 335.1885, found 335.1890. SFC conditions: 20% IPA, 2.5 mL/min, Chiralcel OB-H column, λ = 254 nm, tR (min): minor = 7.77, major = 9.64.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.767	BB	0.3096	2.20195e4	1118.76477	40.2714
2	9.635	BB	0.4339	3.26582e4	1088.92627	59.7286
Totals :				5.46777e4	2207.69104	



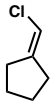
(3S,5S)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1-(4-methoxyphenyl)-3-methyl-3-(2-methylprop-1-en-1-yl)pyrrolidin-2-one (96)

Prepared according to general procedure A using **86a** and lactam **118**. The crude product was purified by silica gel chromatography (0-30% EtOAc/Hexanes) to afford vinylated lactam **96** (21 mg, 52% yield) as a colorless oil; $[a]_D^{25}$ – 36.8 ° (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.21 (m, 2H), 6.92 – 6.86 (m, 2H), 5.41 (h, *J* = 1.4 Hz, 1H), 4.09 (dddd, *J* = 8.6, 5.8, 4.4, 2.8 Hz, 1H), 3.80 (s, 3H), 3.62 – 3.45 (m, 2H), 2.41 (dd, *J* = 12.9, 8.6 Hz, 1H), 2.13 (dd, *J* = 12.9, 5.7 Hz, 1H), 1.70 (dd, *J* = 3.6, 1.4 Hz, 6H), 1.47 (s, 3H),

0.84 (s, 9H), 0.07 (s, 3H), -0.09 (d, J = 13.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.9, 157.8, 134.1, 130.7, 129.8, 126.5, 114.3, 62.6, 58.5, 55.6, 45.3, 37.5, 27.1, 27.0, 26.0, 19.1, 18.4, 1.2, -5.5, -5.5. IR (thin film, NaCl) 2932, 2857, 1693, 1513, 1467, 1401, 1247, 1104, 1043, 826 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd $C_{23}H_{38}NO_3Si$ $[M+H]^+$: 404.2615, found 404.2626.

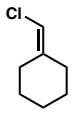
Preparation of Vinyl Chloride Substrates: General Procedure B

To a stirred suspension of (chloromethyl)triphenylphosphonium chloride (2.60 g, 7.50 mmol, 1.5 equiv) in diethyl ether (60 mL) was added sodium bis(hexamethylsilyl)amide (1.38 g, 7.50 mmol, 1.5 equiv) in diethyl ether (15 mL) at –78 °C or 0 ºC, and the resulting mixture was stirred at this temperature for 1 h. Then, ketone (5 mmol, 1.0 equiv) was added dropwise, and the reaction was allowed to slowly warm to room temperature and stirred overnight. After 18 h, the reaction was quenched with water (50 mL), transferred to a separatory funnel, and extracted with diethyl ether (20 mL) three times. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography to provide the desired vinyl chloride.



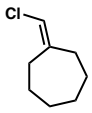
***(chloromethylene)cyclopentane* (108)**

Prepared according to general procedure B using cyclopentanone. Purification by column chromatography (100% Hexanes) yielded **108** as a clear oil (209 mg, 36% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (p, J = 2.4 Hz, 1H), 2.42 – 2.23 (m, 4H), 1.80 – 1.63 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.9, 108.0, 32.6, 30.7, 27.4, 25.8; IR (neat film, NaCl) 3817, 3645, 2955, 2359, 1650, 1455, 772, 653 cm^{-1}; HRMS (FI+) m/z calc'd for C_6H_9Cl $[M]^{+\bullet}$: 116.0400, found 116.0393.



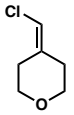
***(chloromethylene)cyclohexane* (109)**

Prepared according to general procedure B using cyclohexanone. Purification by silica gel chromatography (100% Hexanes) yielded **109** as a clear oil (419 mg, 64% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (p, J = 1.2 Hz, 1H), 2.32 (m, 2H), 2.13 (m, 2H), 1.55 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.3, 108.5, 34.2, 28.6, 28.0, 26.8, 26.5; IR (neat film, NaCl) 3817, 3732, 3064, 2937, 2356, 1636, 1541, 1455, 1336, 1293, 1231, 986, 786 cm^{-1}; HRMS (FI+) m/z calc'd for $C_7H_{11}Cl$ $[M]^{+\bullet}$: 130.0549, found 130.0558.



***(chloromethylene)cycloheptane* (110)**

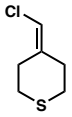
Prepared according to general procedure B using cycloheptanone. Purification by silica gel chromatography (100% Hexanes) yielded **110** as a colorless oil (557 mg, 77% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (p, *J* = 1.5 Hz, 1H), 2.45 – 2.36 (m, 2H), 2.30 – 2.22 (m, 2H), 1.70 – 1.55 (m, 4H), 1.53 – 1.43 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7, 111.7, 35.2, 30.9, 30.2, 29.4, 29.0, 26.2; IR (neat film, NaCl) 3380, 2921, 2859, 2360, 1674, 1506, 1069, 682 cm^{-1}; HRMS (FI+) m/z calc'd for $C_8H_{13}Cl$ $[M]^{+\bullet}$: 144.0712, found 144.0706.



***4-(chloromethylene)tetrahydro-2H-pyran* (111)**

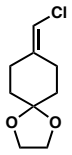
Prepared according to general procedure B using tetrahydro-4*H*-pyran-4-one. The crude product was purified by silica gel chromatography (0-20% EtOAc/Hexanes) to afford vinyl chloride **111** (136 mg, 45%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (t, *J* = 1.3 Hz, 1H), 3.69 (dt, *J* = 7.5, 5.5 Hz, 4H), 2.46 (ddd, *J* = 6.5, 5.3, 1.3 Hz, 2H), 2.27 (ddd,

J = 6.2, 5.0, 1.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.2, 110.6, 68.8, 68.0, 34.3, 29.5; IR (thin film, NaCl) 3069, 2961, 2907, 2848, 2747, 2704, 2360, 1954, 1645, 1466, 1432, 1380, 1356, 1323, 1296, 1228, 1165, 1099, 1021, 1000, 923, 859, 822, 792, 749, 663 cm^{-1}; HRMS (FI+) m/z calc'd for C_6H_9ClO $[M]^{+\bullet}$: 132.0342, found 132.0348.



***4-(chloromethylene)tetrahydro-2H-thiopyran* (112)**

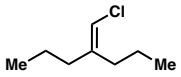
Prepared according to general procedure B using tetrahydro-4*H*-thiopyran-4-one. The crude product was purified by silica gel chromatography (0-20% EtOAc/Hexanes) to afford vinyl chloride **112** (189 mg, 81%) as a colorless, malodorous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (d, *J* = 1.1 Hz, 1H), 2.71 – 2.62 (m, 6H), 2.51 – 2.45 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.3, 111.7, 36.0, 30.5, 30.4, 29.4. IR (thin film, NaCl) 3065, 2949, 2907, 2829, 2360, 1649, 1626, 1425, 1337, 1323, 1291, 1270, 1223, 1171, 991, 975, 938, 822, 797 cm^{-1}; HRMS (FI+) m/z calc'd for C_6H_9ClS $[M]^{+\bullet}$: 148.0114, found 148.0123.



***8-(chloromethylene)-1,4-dioxaspiro[4.5]decane* (113)**

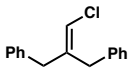
Prepared according to general procedure B using 1,4-dioxaspiro[4.5]decan-8-one. The crude product was purified by silica gel chromatography (100% Hexanes) to afford vinyl chloride **113** (79 yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (d, *J* = 1.4 Hz, 1H), 3.97 (s, 4H), 2.53 – 2.43 (m, 2H), 2.30 (td, *J* = 6.5, 1.3 Hz, 2H), 1.76 – 1.63 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.6, 110.0, 108.6, 77.5, 77.2, 76.8, 64.6, 35.6, 34.5, 30.9, 25.4; IR (thin film, NaCl) 3068, 2950, 2930, 2883, 2685, 2728, 2685, 1718, 1654, 1634, 1443, 1366, 1341, 1295, 1272, 1246, 1225, 1186, 1100, 1080, 1034, 962, 943, 908,

828, 797, 770., 748, 678 cm^{-1}; HRMS (FI+) m/z calc'd $C_9H_{13}ClO_2$ $[M]^{+\bullet}$: 188.0604, found: 188.0619.



***4-(chloromethylene)heptane* (114)**

Prepared according to general procedure B using 4-heptanone. The crude product was purified by silica gel chromatography (100% Hexanes) to afford vinyl chloride **114** (27% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 – 5.73 (m, 1H), 2.21 – 2.14 (m, 2H), 2.03 (td, J = 7.6, 1.3 Hz, 2H), 1.58 – 1.34 (m, 4H), 0.91 (dt, J = 16.5, 7.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7, 112.1, 77.5, 77.2, 76.8, 37.0, 32.2, 21.0, 20.5, 14.1, 13.9; IR (thin film, NaCl) 3066, 2980, 2933, 2872, 1911, 1630, 1465, 1456, 1379, 1319, 1169, 1109, 836, 791, 766 cm^{-1}; HRMS (FI+) m/z calc'd $C_8H_{15}Cl$ $[M]^{+\bullet}$: 146.0862, found: 146.0872.

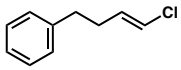


***(2-(chloromethylene)propane-1,3-diyl)dibenzene* (115)**

Prepared according to general procedure B using 1,3-diphenyl-2-propanone. The crude product was purified by silica gel chromatography (100% Hexanes) to afford vinyl chloride **115** (68% yield) as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 4H), 7.32 – 7.28 (m, 2H), 7.27 – 7.23 (m, 2H), 7.19 – 7.14 (m, 2H), 6.07 – 6.01 (m, 1H), 3.56 (s, 2H), 3.32 (d, J = 1.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.2, 138.3, 138.0, 129.1, 128.9, 128.6, 128.5, 126.6, 126.4, 114.9, 77.4, 77.0, 76.7, 40.4, 35.6; IR (thin film, NaCl) 3088, 3062, 3020, 2916, 2845, 2355, 1947, 1872, 1809, 1633, 1601, 1494, 1453, 1433, 1310, 1296, 1178, 1075, 1029, 960, 906, 870, 829,787, 740, 703, 634 cm^{-1}; HRMS (FI+) m/z calc'd $C_{16}H_{15}Cl$ $[M]^{+\bullet}$: 242.0862, found: 242.0889.

Synthesis of Vinyl Chloride 99

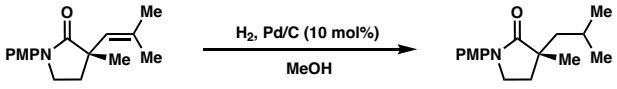
Inspired by a literature protocol, 4-phenyl-1-butyne (523 mg, 4.02 mmol) was dissolved in hexanes (1 M) in a two-neck flask. Under a N_2 atmosphere, neat DIBAL-H (0.788 mL, 1.1 equiv) was added slowly at ambient temperature. The reaction was heated to 50ºC for 2.5 h before being slowly chilled to 18 ºC, at which point Et_2O (2 M) was added. At –78ºC, solid NCS (1.08 g, 2 equiv) was quickly added through one neck of the flask. The reaction was allowed to warm to 18 ºC. After 16h, the reaction mixture was poured into a flask containing 30 mL pentane and 15 mL 6 M HCl with ice. The organic layer was extracted with Et_2O three times, after which it was washed with 10 mL 1 M NaOH then sat. $Na_2S_2O_3$ (10 mL). The organic layer was then dried with Na_2SO_4, filtered, and concentrated, at which point purification by silica gel chromatography (100% Hexanes) yielded the desired vinyl chloride **99** (205 mg, 25% yield).



***(E)-(4-chlorobut-3-en-1-yl)benzene* (99)**

Characterization data in agreement with the literature.[16] ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (dd, J = 8.0, 6.8 Hz, 2H), 7.23 – 7.14 (m, 3H), 6.07 – 5.79 (m, 2H), 2.71 (dd, J = 8.7, 6.7 Hz, 2H), 2.45 – 2.26 (m, 2H).

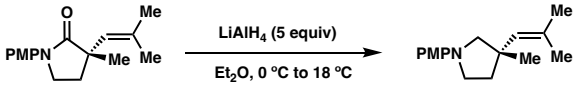
Derivatization of Vinylation Products



***(R)-3-isobutyl-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one* (101)**

A flame-dried one-dram vial was charged with a stir bar and starting material **87** (15 mg, 0.058mmol, 1 equiv) in MeOH (0.421 uL, 0.1M), followed by Pd/C (10%) (6.23mg, 0.058 mmol, 1 equiv). Reaction mixture was purged with N_2 for 5 minutes and then with H_2, and the mixture was stirred overnight with a H_2 balloon. Upon complete consumption of

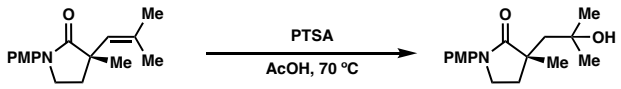
starting material as determined by TLC (30% EtOAc in Hexanes), the reaction was quenched by filtering through a pad of celite with DCM. The filtrate was concentrated in vacuo, and the crude product was purified by prep TLC (25% EtOAc/Hexanes) to afford lactam **101** (7.6 mg, 74% yield) as a pale yellow oil; $[\alpha]_D^{25}$ – 117.2 ° (*c* 0.20, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.44 (m, 2H), 7.04 – 6.81 (m, 2H), 3.80 (s, 3H), 3.77 – 3.65 (m, 2H), 2.17 (ddd, *J* = 12.7, 8.4, 7.0 Hz, 1H), 1.92 (ddd, *J* = 12.6, 7.8, 4.7 Hz, 1H), 1.79 (dqd, *J* = 8.3, 6.6, 4.6 Hz, 1H), 1.68 – 1.58 (m, 2H), 1.49 (dd, *J* = 14.1, 8.3 Hz, 1H), 1.21 (s, 3H), 0.94 (dd, *J* = 17.5, 6.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6, 156.5, 133.3, 121.6, 114.1, 55.6, 46.2, 45.7, 45.2, 31.3, 25.2, 25.0, 23.8, 23.4; IR (thin film, NaCl) 3358, 2953, 2930, 2869, 2837, 2058, 1885, 1700, 1610, 1518, 1461, 1453, 1394, 1366, 1313, 1290, 1252, 1233, 1184, 1168, 1121, 1036, 1011, 830, 805, 743, 722; HRMS (MM:ESI-APCI+) m/z calc'd $C_{16}H_{23}NO_2Na$ $[M+Na]^+$: 284.1621, found: 284.1628.



***(S)-1-(4-methoxyphenyl)-3-methyl-3-(2-methylprop-1-en-1-yl)pyrrolidine* (102)**

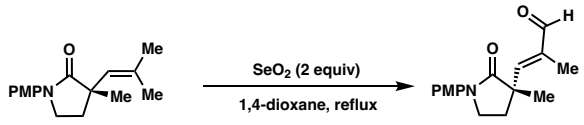
Following our previous report,[17] solid LAH was added to a solution of lactam **87** in Et_2O (0.1 M) at 0 ºC. The solution was stirred at this temperature for 5 min and then was allowed to warm to 18 ºC. After 21 h, the reaction was quenched with H_2O. Extractions were performed with EtOAc seven times, and the crude product was subjected to silica gel chromatography (0-40% EtOAc/Hexanes) to afford the desired product (**102**) as a white solid (22.5 mg, 84% yield). $[a]_D^{25}$ 5.5° (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, CDCl3) δ 6.85 (d, J = 8.5 Hz, 2H), 6.49 (d, J = 8.4 Hz, 2H), 5.34 (s, 1H), 3.76 (s, 3H), 3.35 – 3.13 (m, 4H), 2.10 – 2.00 (m, 1H), 1.92 (s, 1H), 1.73 (d, J = 1.3 Hz, 3H), 1.70 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (101 MHz, CDCl3) δ 132.7, 132.0, 115.2, 112.1, 61.5, 56.2, 47.1, 42.4, 39.7, 27.2,

25.8, 19.4; HRMS (MM:ESI-APCI+) m/z calc'd $C_{16}H_{24}NO$ $[M+H]^+$: 245.1780, found 245.1784.



***(S)-3-(2-hydroxy-2-methylpropyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one* (103)**

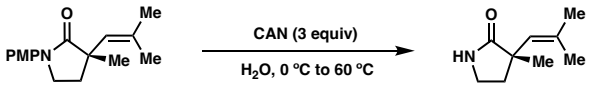
In a one-dram vial, starting material **87** (10.9 mg, 0.042 mmol, 1 equiv) was combined with PTSA (4mg, 0.021 mmol, 0.5 equiv) and acetic acid (700uL, 0.06M). The reaction mixture was heated to 70 ºC overnight, and reaction was tracked by LCMS. After completion, saturated aqueous $NaHCO_3$ was added to quench the reaction, and then extracted with DCM and washed with brine. The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified via prep TLC (50% EtOAc/Hexanes) to afford alcohol **104** (6.3 mg, 59% yield) as a colorless oil; $[\alpha]_D^{25}$ 4.1950 ° (*c* 0.60, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, *J* = 8.9 Hz, 2H), 6.58 (d, *J* = 8.9 Hz, 2H), 3.74 (s, 3H), 3.22 (ddd, *J* = 12.1, 8.7, 5.3 Hz, 1H), 3.12 (ddd, *J* = 12.1, 8.8, 6.7 Hz, 1H), 2.18 (d, *J* = 13.4 Hz, 1H), 2.07 – 1.78 (m, 3H), 1.47 (s, 3H), 1.39 (d, *J* = 5.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.6, 152.5, 142.3, 115.0, 114.4, 81.3, 77.5, 77.4, 77.2, 76.8, 55.9, 46.4, 44.1, 41.0, 38.7, 30.4, 30.2, 26.6; IR (thin film, NaCl) 3369, 2968, 2930, 2834, 2339, 1754, 1681, 1513, 1455, 1401, 1377, 1265, 1249, 182, 1171, 1115, 1098, 1035, 942, 824; HRMS (MM:ESI-APCI+) m/z calc'd $C_{16}H_{24}NO_3$ $[M+H]^+$: 278.1751, found: 278.1771.



***(S,E)-3-(1-(4-methoxyphenyl)-3-methyl-2-oxopyrrolidin-3-yl)-2-methylacrylaldehyde* (104)**

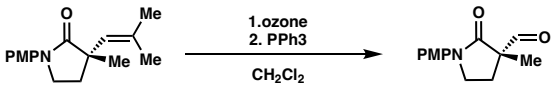
To a solution of **87** (26 mg, 0.1 mmol) in dioxane (0.2 M) was added SeO_2 (22 mg, 0.2 mmol), and the reaction was heated to reflux. After 15 minutes, starting material was

consumed by TLC. The crude reaction was concentrated and passed through a silica plug (ca. 1" silica), eluting with 35% EtOAc/Hexanes, to afford the desired aldehyde **104** as a tan solid (13.4 mg 49% yield); $[\alpha]_D^{25}$ –60.6º (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.53 (d, *J* = 9.2 Hz, 2H), 6.92 (d, *J* = 9.2 Hz, 2H), 6.89 (d, *J* = 1.4 Hz, 1H), 3.88 (m, 1H), 3.81 (s, 4H), 3.78 – 3.35 (m, 1H), 2.43 – 2.31 (m, 2H), 1.84 (d, *J* = 1.4 Hz, 3H), 1.48 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.8, 175.4, 157.0, 156.1, 139.7, 132.5, 121.8, 114.3, 55.6, 47.5, 45.8, 32.5, 22.9, 10.1; IR (neat film, NaCl) 3834, 3732, 2958, 2359, 1688, 1512, 1396, 1299, 1249, 1178, 1090, 1031, 833 cm^{-1}; HRMS (FI+) m/z calc'd for $C_{16}H_{19}NO_3$ $[M]^{+\bullet}$: 273.1365, found 273.1393.



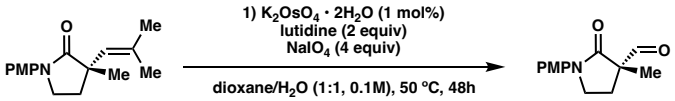
***(S)-3-methyl-3-(2-methylprop-1-en-1-yl)pyrrolidin-2-one* (105)**

A solution of CAN (82 mg, 0.15 mmol) in deionized H_2O (0.05 M) was added dropwise to a solution of **87** (26 mg, 0.1 mmol) at 0 °C, and the reaction was allowed to slowly warm to room temperature. After 12 hours, starting material remained by TLC. CAN (82 mg, 0.15 mmol) added, and the reaction was allowed to continue at 23 °C. After 2 h, the reaction was heated to 60 °C and continued for 18 hours, at which point starting material was consumed by TLC. The reaction was cooled, diluted with ethyl acetate and water, transferred to a separatory funnel, and the organic layer was separated. The aqueous layer was extracted twice with ethyl acetate, the combined organics were dried with Na_2SO_4, filtered, and concentrated. The material was purified with silica gel chromatography (5–10% MeOH/CH_2Cl_2) to afford the desired lactam **105** as a white solid (6.2 mg, 40% yield); $[\alpha]_D^{25}$ –15.7 (c 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.37 – 5.97 (bs, 1H), 5.38 (p, *J* = 1.4 Hz, 1H), 3.32 (ddd, *J* = 8.2, 5.5, 0.9 Hz, 2H), 2.39 – 1.87 (m, 2H), 1.72 (d, *J* = 1.5 Hz, 3H), 1.67 (d, *J* = 1.3 Hz, 3H), 1.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.8, 134.7, 128.1, 44.0, 39.0, 36.8, 27.0, 24.4, 19.1; IR (neat film, NaCl) 3835, 3732, 3229, 2964, 2927, 2358, 1697, 1454, 1281, 1062, 832 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd for $C_9H_{16}NO$ $[M+H]^+$: 154.1226, found 154.1230.



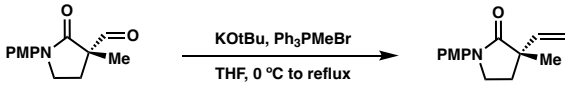
***(S)-1-(4-methoxyphenyl)-3-methyl-2-oxopyrrolidine-3-carbaldehyde* (106)**

Procedure A: A flamed-dried one-dram vial was charged with stir bar, and starting material **87** (50mg, 0.2 mmol, 1 equiv) was added with CH_2Cl_2 (482uL, 0.4M). The reaction mixture was cooled to – 78 ºC in a dry-ice bath, and ozone (1 atm) was bubbled through until all starting material was consumed as indicated by TLC. Then, O_2 gas was bubbled through to quench the residual ozone, and PPh_3 (101.2mg, 0.4 mmol, 2 equiv) was added and reaction was warmed to room temperature. The crude mixture was concentrated in vacuo and purified by silica gel chromatography (30% EtOAc/Hexanes) to afford aldehyde **106** (40 mg, 89% yield) as a white solid. $[a]_D^{25}$ – 26.8 ° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (d, *J* = 0.7 Hz, 1H), 7.56 – 7.43 (m, 2H), 6.96 – 6.83 (m, 2H), 3.93 – 3.67 (m, 5H), 2.75 (ddd, *J* = 12.9, 8.0, 4.8 Hz, 1H), 1.91 (dddd, *J* = 13.1, 8.6, 6.7, 0.7 Hz, 1H), 1.51 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.5, 171.3, 157.1, 132.2, 121.9, 114.3, 58.0, 55.6, 46.0, 25.9, 18.8. IR (thin film, NaCl) 2932, 2358, 1731, 1682, 1520, 1455, 1402, 1297, 1248, 1170, 1092, 1032, 825 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd $C_{13}H_{16}NO_3$ $[M+H]^+$: 234.1125, found 234.1121.



Procedure B[18]: A one dram vial was charged with a stir bar and compound **87**. To this vial, 2,6-lutidine (2 equiv) and K_2OsO_4 • 2 H_2O was added as a solution in dioxane/H_2O. To the stirring mixture, $NaIO_4$ was added and the temperature was increased to 50 ºC. After 24 h, the crude mixture was filtered through a pad of celite, eluting with CH_2Cl_2 and EtOAc. H_2O was added and CH_2Cl_2 was used to perform an extraction. The organic layer was

washed with brine and dried with Na_2SO_4. The crude compound was purified via silica gel chromatography to afford compound **106**.



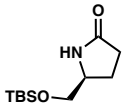
***(S)-1-(4-methoxyphenyl)-3-methyl-3-vinylpyrrolidin-2-one* (107)**

A one-dram vial was flame dried and charged with stir bar. The Ph_3PCH_3Br (51mg, 0.145mmol, 2.5 equiv) was added in THF (300uL, 0.1M) and cooled to 0 ºC. Reaction mixture was then charged with KOtBu (14mg, 0.128 mmol, 2.2 equiv) and stirred at 0 ºC for 20 minutes. Starting material **106** (13.2 mg, 0.057 mmol, 1 equiv) was added with the remaining THF (about 100 μL) and slowly warmed to room temperature and heated to reflux overnight. Second day all starting material was consumed by TLC (50% EtOAc/Hexanes) and reaction was quenched with NH_4Cl and extracted with EtOAc (3x) and washed with brine. The organic extracts were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resultant crude product was the purified by pipette column chromatography (15% EtOAc/Hexanes) to afford vinylated lactam **107** (11 mg, 84% yield) as a pale yellow oil; $[a]_D^{25}$ – 0.6 ° (*c* 0.35, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.48 (m, 2H), 6.95 – 6.80 (m, 2H), 5.97 (dd, *J* = 17.5, 10.6 Hz, 1H), 5.24 – 5.11 (m, 2H), 3.80 (s, 3H), 3.73 (ddt, *J* = 7.8, 5.0, 2.5 Hz, 2H), 2.26 (ddd, *J* = 12.3, 7.0, 5.0 Hz, 1H), 2.12 – 1.96 (m, 1H), 1.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 156.6, 140.6, 133.1, 121.6, 114.2, 114.0, 55.6, 48.6, 45.6, 32.0, 23.1; IR (Neat film, NaCl) 3360, 3077, 2962, 2927, 2060, 1693, 1512, 1504, 1455, 1394, 1315, 1299, 1246, 1182, 1170, 1124, 1111, 1090, 1034, 1005, 924, 913, 883, 825, 807, 731, 636 cm^{-1}; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{14}H_{17}NO_2Na$ $[M+Na]^+$: 254.1151, found 254.1155.

Synthesis of Substrates 118 and 118d

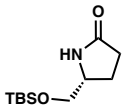
Following a literature protocol, enantiopure 5-(hydroxymethyl)pyrrolidin-2-one was dissolved in CH_2Cl_2 (0.86 M). Iteratively, TBSCl (1.2 equiv) and imidazole (1.5 equiv) were added. The reaction was stirred for 4h, after which it was quenched with H_2O and

separated into layers. The aqueous phase was extracted with CH_2Cl_2 two more times, and the combined organic extracts were dried with Na_2SO_4. The product was isolated as a colorless oil (quant.) and used in the next step without additional purification.



***(S)-5-(((tert-butyldimethylsilyl)oxy)methyl)pyrrolidin-2-one* (116)**

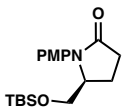
Prepared according to a literature procedure. Characterization data was in agreement with the literature.[19] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71 (s, 1H), 3.92 – 3.70 (m, 1H), 3.63 (dd, *J* = 10.1, 3.8 Hz, 1H), 3.44 (dd, *J* = 10.1, 7.9 Hz, 1H), 2.35 (ddd, *J* = 8.6, 7.2, 2.8 Hz, 2H), 2.25 – 2.09 (m, 1H), 1.73 (dddd, *J* = 13.2, 9.3, 7.7, 5.5 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 6H).



***(R)-5-(((tert-butyldimethylsilyl)oxy)methyl)pyrrolidin-2-one* (116e)**

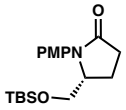
Refer to Compound 13 for ^{1}H NMR data.

In a flask equipped with a magnetic stir bar, CuI (0.5 mmol, 10 mol%) was combined with anhydrous K_2CO_3 (10 mmol, 2 equiv). The vial was purged and backfilled with N_2 three times. At this point, 5 mL of toluene was added, followed by N, N'-dimethylethylenediamine (1 mmol, 20 mol%), intermediate **116** or **116e** (6 mmol, 1.2 equiv), and p-Br anisole (5 mmol). The reaction mixture was allowed to react at 100 ºC for 24h. The crude reaction mixture was concentrated and purified by silica gel chromatography (0-100% EtOAc/Hexanes) to afford the product as a pale yellow oil (1.10 g, 66% yield).



***(S)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1-(4-methoxyphenyl)pyrrolidin-2-one* (117)**

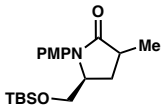
$[\alpha]_D^{25}$ –48.0º (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 4.12 (dtd, *J* = 8.6, 3.6, 2.5 Hz, 1H), 3.80 (3, 2H), 3.68 – 3.43 (m, 2H), 2.68 (ddd, *J* = 16.9, 10.1, 8.1 Hz, 1H), 2.49 (ddd, *J* = 16.9, 10.2, 4.6 Hz, 1H), 2.26 (ddt, *J* = 12.8, 10.1, 8.3 Hz, 1H), 2.09 (dddd, *J* = 12.7, 10.1, 4.6, 3.5 Hz, 1H), 0.86 (s, 9H), -0.04 (d, *J* = 11.3 Hz, 6H);^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 157.9, 130.5, 126.5, 114.5, 63.0, 62.0, 55.6, 31.6, 25.9, 21.5, 18.3, -5.47, -5.51. IR (thin film, NaCl) 2934, 1694, 1513, 1248, 1090, 834, 682 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd $C_{18}H_{30}NO_3Si$ $[M+H]^+$: 336.1989, found 336.1999.



***(R)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1-(4-methoxyphenyl)pyrrolidin-2-one* (117e)**

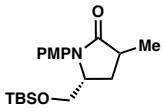
Refer to Compound **14** for ^1H NMR, 13C NMR, IR, and HRMS data. $[\alpha]_D^{25}$ 47.9º (c 1.0, $CHCl_3$).

A solution of LDA was prepared by the slow addition of n-BuLi (1.44 mL, 2.5 M in hexanes) to a solution of diisopropylamine (3.61 mmol) in THF (0.9 M) at -78ºC. After letting the mixture stir for 1h at this temperature, substrate **117** or **117e** was added slowly as a solution in THF (0.3 M). 30 min later, MeI (3.61 mmol) was added slowly to the reaction mixture, and it was allowed to warm up to 18 ºC. After 16h, the reaction was quenched with sat. NH_4Cl solution and extracted with CH_2Cl_2. The crude compound was concentrated and purified by silica gel chromatography (10-60% EtOAc/Hexanes) to afford the product as a dark solid (703 mg, 61% yield).



(5S)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one **(118)**

$[\alpha]_D^{25}$ –30.0º (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 9.1 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 4.15 – 4.01 (m, 1H), 3.81 (s, 3H), 3.68 – 3.43 (m, 2H), 2.81 (td, *J* = 9.1, 7.1 Hz, 1H), 2.33 (ddd, *J* = 12.7, 9.0, 2.0 Hz, 1H), 1.90 (dt, *J* = 12.6, 9.1 Hz, 1H), 1.26 (d, *J* = 7.1 Hz, 3H), 0.86 (s, 9H), -0.03 (d, *J* = 11.9 Hz, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 177.5, 157.5, 131.0, 125.7, 114.4, 63.0, 59.9, 55.6, 36.8, 30.9, 25.9, 18.3, 17.1, -5.45, -5.48; IR (thin film, NaCl) 2928, 1693, 1513, 1463, 1272, 1246, 1171, 1107, 1041, 832, 776, 681 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd $C_{19}H_{32}NO_3Si$ $[M+H]^+$: 350.2146, found 350.2143.



(5R)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one **(118d)**

Refer to Compound **15** for ^1H NMR, ^{13}C NMR, IR, and HRMS data. $[\alpha]_D^{25}$ 32.3º (c 1.0, $CHCl_3$).

3.5.3 CRYSTAL STRUCTURE ANALYSIS OF *(S)*-1-(4-METHOXYPHENYL)-3-METHYL-3-(2 METHYLPROP-1-EN-1-YL)PYRROLIDIN-2-ONE (SAMPLE NO.: V24190)

Compound **87** was crystallized from slow evaporation in hexanes at 23 °C to provide crystals suitable for X-ray analysis. Compound V24190 (CSD 2375577) crystallizes in the orthorhombic space group $P2_12_12_1$ with one molecule in the asymmetric unit.

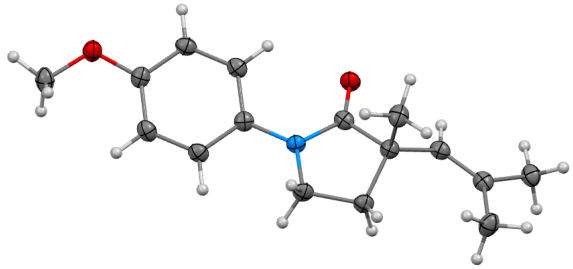


Table 3.3. *Crystal data and structure refinement for V24190.*

Identification code	V24190	
Empirical formula	C16 H21 N O2	
Formula weight	259.34	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.3874(10) Å	a= 90°.
	b = 9.1155(13) Å	b= 90°.
	c = 20.860(3) Å	g = 90°.
Volume	1404.7(3) Å3	
Z	4	
Density (calculated)	1.226 Mg/m3	
Absorption coefficient	0.636 mm-1	
F(000)	560	
Crystal size	0.150 x 0.100 x 0.005 mm3	
Theta range for data collection	4.239 to 74.536°.	
Index ranges	-9<=h<=9, -11<=k<=10, -26<=l<=26	
Reflections collected	21524	
Independent reflections	2879 [R(int) = 0.1102]	
Completeness to theta = 67.679°	99.9 %	

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7538 and 0.6287
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	2879 / 0 / 176
Goodness-of-fit on F2	1.062
Final R indices [I>2sigma(I)]	R1 = 0.0436, wR2 = 0.0947
R indices (all data)	R1 = 0.0574, wR2 = 0.1004
Absolute structure parameter	0.0(3)
Extinction coefficient	n/a
Largest diff. peak and hole	0.173 and -0.182 e.Å-3

Table 3.4. *Atomic coordinates (x 104) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for V24190. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U(eq)
C(1)	4790(4)	5751(3)	3452(1)	21(1)
O(1)	4177(3)	6906(2)	3656(1)	26(1)
C(2)	6222(4)	4815(3)	3796(1)	21(1)
C(5)	5146(4)	3885(3)	4282(1)	28(1)
C(6)	7569(4)	5786(3)	4137(1)	22(1)
C(7)	9203(4)	5434(3)	4356(1)	24(1)
C(8)	10344(4)	6545(3)	4705(1)	27(1)
C(9)	10082(4)	3964(3)	4275(2)	32(1)
C(3)	6944(4)	3841(3)	3251(1)	24(1)
C(4)	5384(4)	3742(3)	2771(1)	25(1)

N(1)	4290(3)	5050(2)	2897(1)	21(1)
C(10)	2709(4)	5361(3)	2530(1)	21(1)
C(11)	2486(4)	4690(3)	1933(1)	24(1)
C(12)	900(4)	4883(3)	1582(1)	25(1)
C(13)	-480(4)	5762(3)	1821(1)	23(1)
O(2)	-2108(3)	6022(2)	1528(1)	28(1)
C(16)	-2465(5)	5246(3)	947(1)	31(1)
C(14)	-238(4)	6463(3)	2410(1)	25(1)
C(15)	1327(4)	6257(3)	2761(1)	24(1)

Table 3.5. *Bond lengths [Å] and angles [°] for V24190.*

C(1)-O(1)	1.222(3)
C(1)-N(1)	1.373(3)
C(1)-C(2)	1.538(4)
C(2)-C(6)	1.509(4)
C(2)-C(3)	1.538(4)
C(2)-C(5)	1.542(4)
C(5)-H(5A)	0.9800
C(5)-H(5B)	0.9800
C(5)-H(5C)	0.9800
C(6)-C(7)	1.329(4)
C(6)-H(6)	0.9500
C(7)-C(9)	1.499(4)
C(7)-C(8)	1.506(4)
C(8)-H(8A)	0.9800

C(8)-H(8B)	0.9800
C(8)-H(8C)	0.9800
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(3)-C(4)	1.529(4)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-N(1)	1.464(4)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
N(1)-C(10)	1.425(4)
C(10)-C(15)	1.394(4)
C(10)-C(11)	1.396(4)
C(11)-C(12)	1.393(4)
C(11)-H(11)	0.9500
C(12)-C(13)	1.389(4)
C(12)-H(12)	0.9500
C(13)-O(2)	1.370(4)
C(13)-C(14)	1.397(4)
O(2)-C(16)	1.427(3)
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800
C(14)-C(15)	1.381(4)
C(14)-H(14)	0.9500
C(15)-H(15)	0.9500
O(1)-C(1)-N(1)	126.5(3)
O(1)-C(1)-C(2)	124.8(2)

N(1)-C(1)-C(2)	108.7(2)
C(6)-C(2)-C(1)	110.3(2)
C(6)-C(2)-C(3)	117.3(2)
C(1)-C(2)-C(3)	102.3(2)
C(6)-C(2)-C(5)	110.6(2)
C(1)-C(2)-C(5)	104.9(2)
C(3)-C(2)-C(5)	110.3(2)
C(2)-C(5)-H(5A)	109.5
C(2)-C(5)-H(5B)	109.5
H(5A)-C(5)-H(5B)	109.5
C(2)-C(5)-H(5C)	109.5
H(5A)-C(5)-H(5C)	109.5
H(5B)-C(5)-H(5C)	109.5
C(7)-C(6)-C(2)	128.2(2)
C(7)-C(6)-H(6)	115.9
C(2)-C(6)-H(6)	115.9
C(6)-C(7)-C(9)	124.8(3)
C(6)-C(7)-C(8)	120.8(3)
C(9)-C(7)-C(8)	114.4(3)
C(7)-C(8)-H(8A)	109.5
C(7)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	109.5
C(7)-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5
C(7)-C(9)-H(9A)	109.5
C(7)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(7)-C(9)-H(9C)	109.5

H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(4)-C(3)-C(2)	104.8(2)
C(4)-C(3)-H(3A)	110.8
C(2)-C(3)-H(3A)	110.8
C(4)-C(3)-H(3B)	110.8
C(2)-C(3)-H(3B)	110.8
H(3A)-C(3)-H(3B)	108.9
N(1)-C(4)-C(3)	104.5(2)
N(1)-C(4)-H(4A)	110.8
C(3)-C(4)-H(4A)	110.8
N(1)-C(4)-H(4B)	110.8
C(3)-C(4)-H(4B)	110.8
H(4A)-C(4)-H(4B)	108.9
C(1)-N(1)-C(10)	125.6(2)
C(1)-N(1)-C(4)	112.4(2)
C(10)-N(1)-C(4)	121.2(2)
C(15)-C(10)-C(11)	118.6(3)
C(15)-C(10)-N(1)	122.1(2)
C(11)-C(10)-N(1)	119.3(2)
C(12)-C(11)-C(10)	120.9(3)
C(12)-C(11)-H(11)	119.6
C(10)-C(11)-H(11)	119.6
C(13)-C(12)-C(11)	120.1(3)
C(13)-C(12)-H(12)	120.0
C(11)-C(12)-H(12)	120.0
O(2)-C(13)-C(12)	125.7(2)
O(2)-C(13)-C(14)	115.2(2)
C(12)-C(13)-C(14)	119.1(3)

C(13)-O(2)-C(16)	117.1(2)
O(2)-C(16)-H(16A)	109.5
O(2)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
O(2)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
C(15)-C(14)-C(13)	120.7(3)
C(15)-C(14)-H(14)	119.7
C(13)-C(14)-H(14)	119.7
C(14)-C(15)-C(10)	120.7(3)
C(14)-C(15)-H(15)	119.6
C(10)-C(15)-H(15)	119.6

Symmetry transformations used to generate equivalent atoms:

Table 3.6. *Anisotropic displacement parameters ($Å^2$ x 10^3) for V24190. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$*

	U11	U22	U33	U23	U13	U12
C(1)	25(1)	17(1)	22(1)	1(1)	2(1)	-4(1)
O(1)	30(1)	19(1)	27(1)	-4(1)	-3(1)	4(1)
C(2)	23(1)	18(1)	24(1)	1(1)	-1(1)	-1(1)
C(5)	27(2)	28(1)	28(1)	6(1)	-2(1)	-4(1)
C(6)	26(1)	16(1)	24(1)	-1(1)	2(1)	-2(1)

C(7)	27(2)	22(1)	23(1)	1(1)	2(1)	-5(1)
C(8)	29(1)	25(1)	28(1)	-2(1)	-2(1)	-5(1)
C(9)	30(2)	25(1)	40(2)	0(1)	-8(1)	3(1)
C(3)	25(1)	18(1)	28(1)	-2(1)	-2(1)	3(1)
C(4)	26(1)	18(1)	30(1)	-3(1)	-1(1)	4(1)
N(1)	24(1)	16(1)	23(1)	0(1)	-1(1)	2(1)
C(10)	25(1)	15(1)	23(1)	3(1)	0(1)	-1(1)
C(11)	29(1)	17(1)	25(1)	-1(1)	0(1)	2(1)
C(12)	33(2)	18(1)	24(1)	-1(1)	-2(1)	-1(1)
C(13)	24(1)	17(1)	27(1)	3(1)	-3(1)	-1(1)
O(2)	29(1)	26(1)	29(1)	-3(1)	-6(1)	2(1)
C(16)	37(2)	24(1)	31(1)	-2(1)	-10(1)	-2(1)
C(14)	28(2)	20(1)	26(1)	-1(1)	3(1)	1(1)
C(15)	29(2)	18(1)	24(1)	-1(1)	0(1)	-1(1)

Table 3.7. *Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for V24190.*

	x	y	z	U(eq)
H(5A)	5974	3226	4510	42
H(5B)	4233	3304	4055	42
H(5C)	4546	4534	4591	42
H(6)	7202	6773	4203	27

H(8A)	9672	7468	4744	41
H(8B)	11465	6717	4466	41
H(8C)	10637	6174	5134	41
H(9A)	9147	3206	4240	47
H(9B)	10851	3759	4648	47
H(9C)	10824	3966	3886	47
H(3A)	8025	4289	3050	28
H(3B)	7271	2855	3414	28
H(4A)	5844	3745	2326	29
H(4B)	4667	2839	2841	29
H(11)	3427	4093	1765	29
H(12)	761	4413	1179	30
H(16A)	-1567	5522	623	46
H(16B)	-3679	5496	793	46
H(16C)	-2394	4189	1027	46
H(14)	-1161	7088	2572	30
H(15)	1463	6731	3163	29

Table 3.8. *Torsion angles [°] for V24190.*

O(1)-C(1)-C(2)-C(6)	-36.0(4)
N(1)-C(1)-C(2)-C(6)	146.0(2)
O(1)-C(1)-C(2)-C(3)	-161.5(3)
N(1)-C(1)-C(2)-C(3)	20.4(3)
O(1)-C(1)-C(2)-C(5)	83.2(3)
N(1)-C(1)-C(2)-C(5)	-94.8(3)

C(1)-C(2)-C(6)-C(7)	-162.8(3)
C(3)-C(2)-C(6)-C(7)	-46.2(4)
C(5)-C(2)-C(6)-C(7)	81.6(4)
C(2)-C(6)-C(7)-C(9)	3.0(5)
C(2)-C(6)-C(7)-C(8)	-178.0(3)
C(6)-C(2)-C(3)-C(4)	-147.2(2)
C(1)-C(2)-C(3)-C(4)	-26.3(3)
C(5)-C(2)-C(3)-C(4)	84.9(3)
C(2)-C(3)-C(4)-N(1)	23.5(3)
O(1)-C(1)-N(1)-C(10)	-14.5(4)
C(2)-C(1)-N(1)-C(10)	163.5(2)
O(1)-C(1)-N(1)-C(4)	175.9(3)
C(2)-C(1)-N(1)-C(4)	-6.1(3)
C(3)-C(4)-N(1)-C(1)	-11.2(3)
C(3)-C(4)-N(1)-C(10)	178.7(2)
C(1)-N(1)-C(10)-C(15)	-11.4(4)
C(4)-N(1)-C(10)-C(15)	157.3(2)
C(1)-N(1)-C(10)-C(11)	172.0(2)
C(4)-N(1)-C(10)-C(11)	-19.3(4)
C(15)-C(10)-C(11)-C(12)	-1.4(4)
N(1)-C(10)-C(11)-C(12)	175.3(3)
C(10)-C(11)-C(12)-C(13)	0.5(4)
C(11)-C(12)-C(13)-O(2)	-179.0(3)
C(11)-C(12)-C(13)-C(14)	1.0(4)
C(12)-C(13)-O(2)-C(16)	4.4(4)
C(14)-C(13)-O(2)-C(16)	-175.7(2)
O(2)-C(13)-C(14)-C(15)	178.3(3)
C(12)-C(13)-C(14)-C(15)	-1.7(4)
C(13)-C(14)-C(15)-C(10)	0.9(4)

C(11)-C(10)-C(15)-C(14)	0.7(4)
N(1)-C(10)-C(15)-C(14)	-175.9(3)

3.6 REFERENCES

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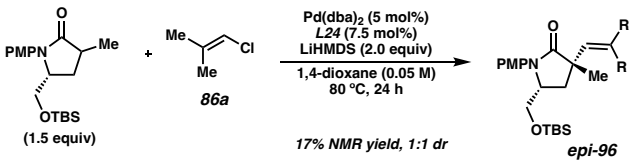
[4] In a matched/mis-matched case, we observed poor efficiency of the reaction to deliver compound ***epi-96***:



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