CHAPTER 2

Palladium-Catalyzed Enantioselective Decarboxylative Allylic Alkylation of Lactam Enolates for the Construction of Quaternary N-Heterocycles[÷]

2.1 Introduction

Nitrogen-containing heterocycles are ubiquitous in natural products, [1] pharmaceuticals,[2] and materials science.[3,4,5] Stereoselective methods for the synthesis of 3,3-disubstituted pyrrolidinones, piperidinones, and caprolactams, in addition to the corresponding amines, are valuable for the preparation of a wide array of important structures in these areas of research (Figure 2.1). Despite the prevalence of such architectures and the potential of lactam enolate alkylation as a direct method for their

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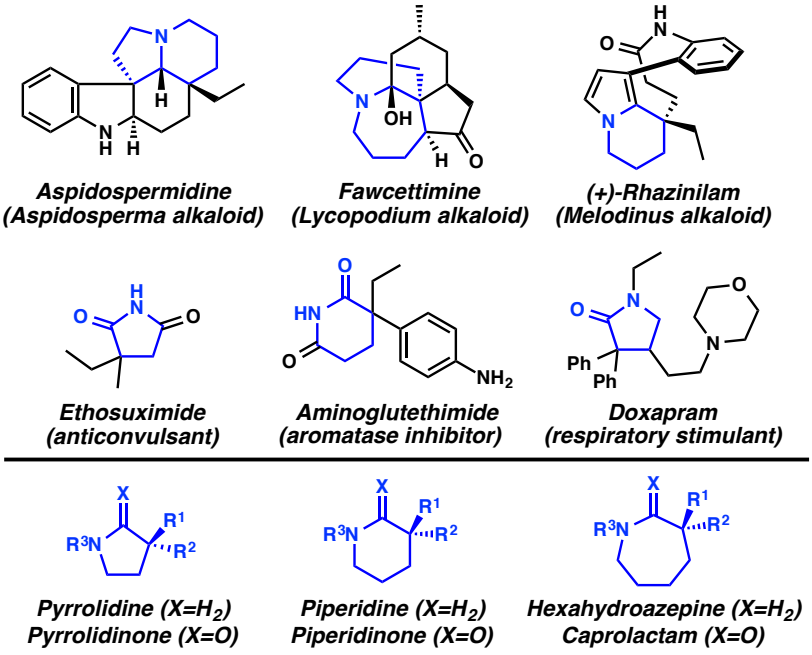
[÷] This work was performed in collaboration with Dr. Doug Behenna, Taiga Yurino, Dr. Jimin Kim, and Guillermo A. Guerrero-Vásquez, and was partially adapted from the publication: Behenna, D. C.; Liu, Y.; Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nature Chem.* **2012**, *4*, 130–133. Copyright 2011 Macmillan Publishers Limited.

synthesis, a paucity of enantioselective lactam alkylations leading to C(α)-quaternary centers are known. While most methods rely on chiral auxiliary chemistry,[6,7,8] the few catalytic examples that exist are specific to the oxindole lactam nucleus[9,10,11] or cyclic imides.[12] Importantly, enolate stabilization is critical for success in both of these catalytic systems, thereby limiting the scope of each transformation. To the best of our knowledge, there are no examples of catalytic asymmetric alkylations of simple piperidinone, pyrrolidinone, and caprolactam scaffolds for the formation of C(α)-quaternary or C(α)-tetrasubstituted tertiary centers. Herein, we describe the stereoselective synthesis of a wide range of structurally-diverse, functionalized lactams by palladium-catalyzed enantioselective enolate alkylation. The importance of this chemistry to the synthesis of bioactive alkaloids is specifically demonstrated, and the potential utility of this transformation for the construction of novel building blocks for medicinal and polymer chemistry can be readily inferred.

Figure 2.1 Natural products and pharmaceuticals containing chiral N-heterocycles



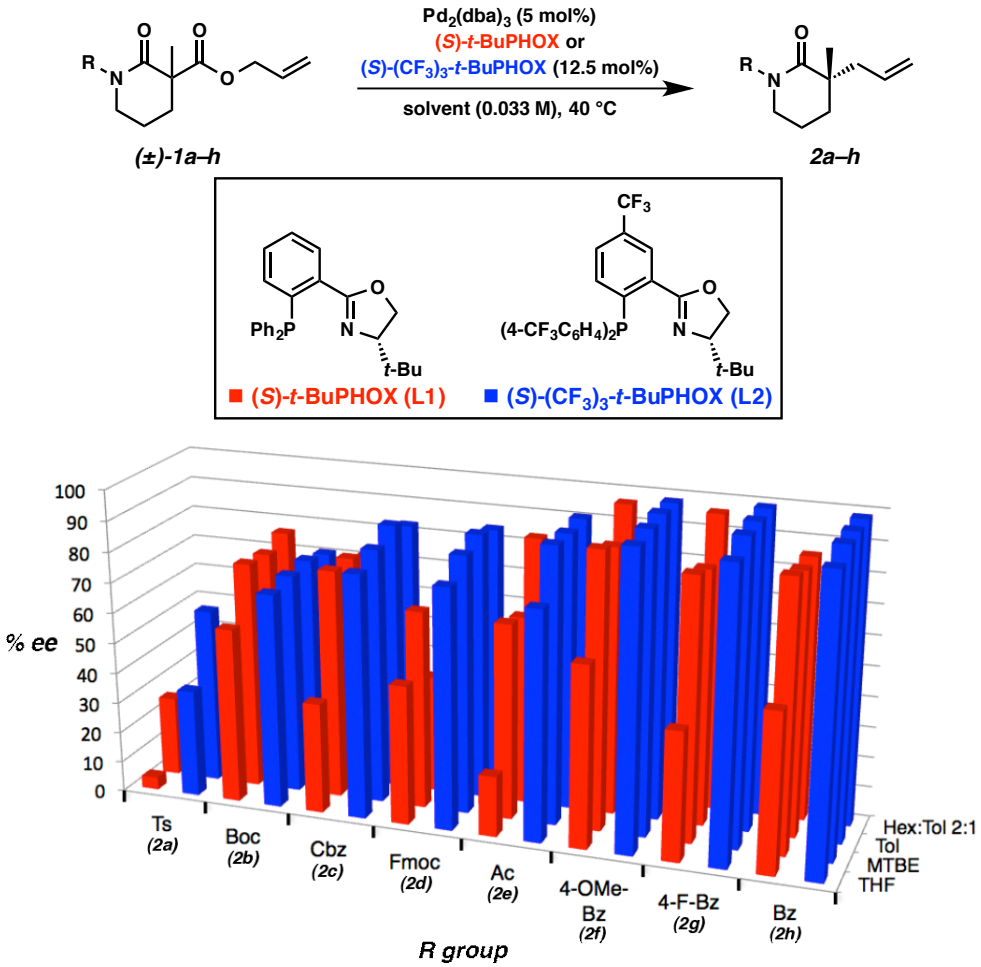
2.2 Reaction Development and Optimization

Transition metal-catalyzed allylic alkylation is a key method for the enantioselective preparation of chiral substances and ranks among the best general techniques for the catalytic alkylation of prochiral enolates.[13,14,15,16] We sought to develop a general method for catalytic asymmetric α-alkylation, given the importance of α-quaternary lactams (vide supra). Over the past seven years, our laboratory has reported an array of methods for the synthesis of α-quaternary ketones[17,18,19,20] and demonstrated the use of these methods in a number of complex molecule syntheses.[21,22,23,24] In the course of our investigations of the ketone enolate allylic alkylation and other alkylation processes, we have often encountered interesting ligand electronic effects and, in certain cases, pronounced solvent effects.[25] In keeping with our ultimate goal of *N*-heterocycle alkylation, we set out to further probe these subtle effects by examining enolate reactivity in a lactam series that would be amenable to both steric and electronic fine-tuning.

We prepared a collection of racemic lactam substrates (i.e., **1a–h**) for palladium-catalyzed decarboxylative allylic alkylation and performed a reactivity and enantioselectivity screen across an array of solvents employing two chiral ligands, (*S*)-*t*-BuPHOX (**L1**) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**L2**).[26,27,28] Preliminary data suggested that electron rich *N*-alkyl lactam derivatives were poor substrates for decarboxylative alkylation due to low reactivity. Thus, electron withdrawing *N*-protecting groups were chosen in our study. We screened these substrates across a series of four solvents (THF, MTBE, toluene, and 2:1 hexane–toluene) while employing two electronically distinct ligands on Pd. The results of this broad screen were highly encouraging (Table 2.1, see also Experimental Section). Reactivity across all substrates with either ligand was

uniformly good, as all of the compounds were completely converted to the desired product. Strikingly, as the *N*-substituent group was changed from sulfonyl to carbamoyl to acyl functionalities, the enantioselectivity rose from nearly zero to nearly perfect. There was also a substantial difference between the two ligands, and electron poor (*S*)-$(CF_3)_3$-*t*-BuPHOX was clearly the superior choice. As the solvent system became less polar, a distinct increase in enantiomeric excess was observed, however, this effect was substantially less pronounced for reactions employing the electron poor ligand and for reactions varying the *N*-substituent. Ultimately, with the *N*-benzoyl group (Bz) on the substrate (i.e., **1h**) and (*S*)-$(CF_3)_3$-*t*-BuPHOX as ligand, the reaction produced lactam **2h** in >96% ee in each of the four solvents.

Table 2.1 Solvent, protecting-group, and ligand screen [a]



[a] Conditions: Reactions were performed with lactam **1a–h** (33.6 μmol), $Pd_2(dba)_3$ (5 mol%), and ligand (12.5 mol%) in solvent (1.0 mL) at 40 °C for 72 h. In all cases, complete consumption of starting material and product formation was observed by thin layer chromatography on silica gel. $Pd_2(pmdba)_3$ (5 mol%) was used for lactams **1a,b** at 50 °C. Enantiomeric excess (ee) was determined by chiral GC, SFC, or HPLC. See Experimental Section for details.

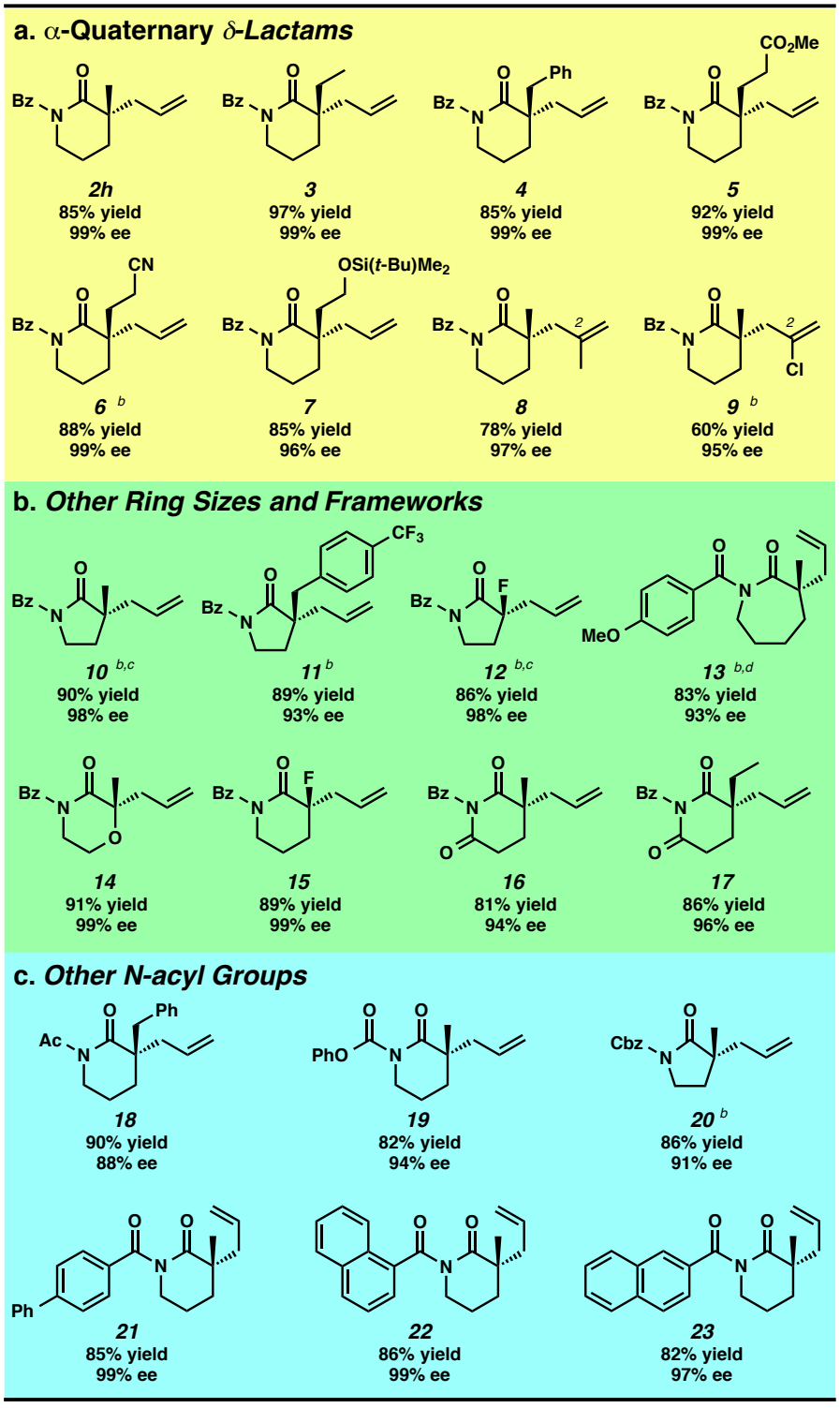
2.3 Study of Reaction Scope

With these stunning results in hand, we initiated efforts to investigate the reaction scope by exploring a range of substituted *N*-acyl lactam derivatives (Table 2.2). Importantly, reproducing the screening reaction on preparative scale furnishes *N*-Bz piperidinone **2h** in 85% isolated yield and 99% ee (Table 2.2a). Alteration of the C(α)-group to other alkyl and functionalized alkyl units (e.g., $–CH_2CH_3$ and $–CH_2Ph$), as well as to moieties possessing additional acidic protons (e.g., $–CH_2CH_2CO_2Me$ and –

CH_2CH_2CN) leads to high yields of lactams **3–6** in uniformly excellent enantioenrichment (99% ee). Common silyl protecting groups are tolerated in the transformation and lactam **7** is furnished in 85% yield and 96% ee. Substituted allyl groups can be incorporated, however only at C(2), leading to products such as methallyl lactam **8** and chloroallyl lactam **9** in good yield and outstanding enantioselectivity (≥95% ee).

Beyond piperidinones, we have demonstrated that pyrrolidinones and caprolactams are also exceptional substrate classes, leading to heterocycles **10–13** in excellent yield and ee (Table 2.2b). Additionally, morpholine-derived product **14**, which contains a C(α)-tetrasubstituted tertiary center, is produced in 91% yield and 99% ee. C(α)-Fluoro substitution is readily introduced into the 1,3-dicarbonyl starting material and is viable in the enantioselective reaction leading to fluoropyrrolidinone **12** (86% yield, 98% ee) and fluoropiperidinone **15** (89% yield, 99% ee). Moreover, *N*-Bz glutarimides serve as outstanding substrates, smoothly reacting to provide cyclic imides **16** and **17** in high yield and enantioselectivity. Finally, alteration of the *N*-Bz group is possible (Table 2.2c), leading to lactams with an *N*-acetyl group (**18**), *N*-carbamates (**19** and **20**), and a variety of *N*-aroyl derivatives (**21–23**).

Table 2.2 Palladium-catalyzed decarboxylative alkylation of lactams: reaction scope [a]

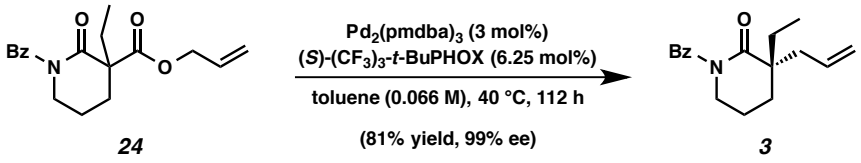


[a] Conditions: Reactions were performed with lactam substrate (0.50 mmol), $Pd_2(pmdba)_3$ (5 mol%), and (*S*)-$(CF_3)_3$-*t*-BuPHOX (12.5 mol%) in toluene (15 mL) at 40 °C for 11–172 h. In all cases, complete consumption of starting material and product formation was observed by thin layer chromatography on silica gel. Isolated yields are reported. Enantiomeric excess (ee) was determined by chiral GC, SFC, or HPLC. See Supplementary Information for details. [b] $Pd_2(dba)_3$ was employed. [c] Reaction performed at 50 °C. [d] Reaction performed in MTBE as solvent.

2.4 Large-Scale Alkylation Reaction

To test the scalability of our palladium-catalyzed enantioselective alkylation reaction, we conducted gram-scale experiments (Scheme 2.1). Using 4.73 g (15 mmol) of starting material **24**, the reaction proceeded smoothly to afford the desired quaternary lactam **3** in 81% isolated yield (3.87 g) and 99% ee. This result establishes the practical utility of our chemistry in organic synthesis.

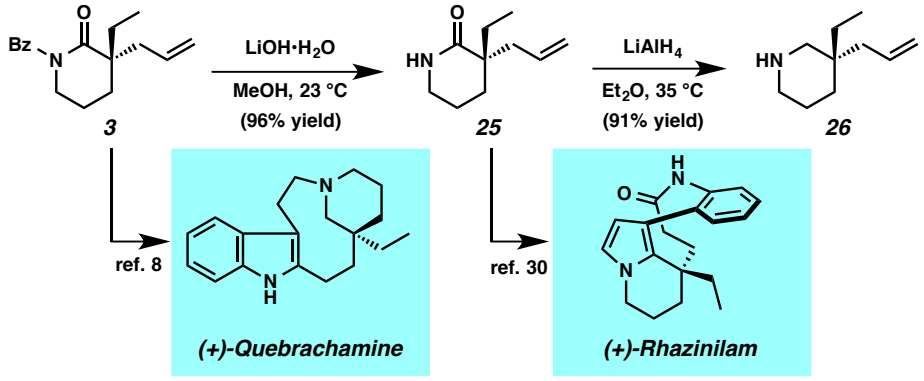
Scheme 2.1 Gram-scale alkylation reactions



2.5 Derivatization of Alkylated Lactam Products

The enantioenriched lactam products formed by our catalytic asymmetric alkylation chemistry are envisioned to be of broad utility in synthetic chemistry. To illustrate this point, lactam **3** can be transformed into the *Aspidosperma* alkaloid (+)-quebrachamine by modification of a previous route that employed a chiral auxiliary.[8] Additionally, cleavage of the *N*-Bz group of lactam **3** produces chiral lactam **25**, a compound previously used as a racemate in the synthesis of rhazinilam, a microtubule-disrupting agent that displays similar cellular characteristics to paclitaxel (Scheme 2.2).[29,30] Finally, reduction of lactam **25** produces the C(3)-quaternary piperidine (**26**) and demonstrates access to the corresponding amine building blocks.

Scheme 2.2 Synthetic utility of lactam products



2.6 Concluding Remarks

In summary, we have reported the first method for catalytic enantioselective alkylation of monocyclic 5-, 6-, and 7-membered lactam enolate derivatives to form α-quaternary and α-tetrasubstituted tertiary lactams. The reaction discovery process was enabled by parallel screening of reaction parameters and led to the identification of a sterically and electronically tuned system for highly enantioselective alkylation. We have applied this method to the catalytic asymmetric synthesis of key intermediates previously employed for the construction of *Aspidosperma* alkaloids. Finally, the asymmetric products formed in this investigation are envisioned to be widely useful as building blocks for the preparation of range of nitrogen containing heterocycles in materials science, medicinal chemistry and natural products synthesis.

2.7 Experimental Section

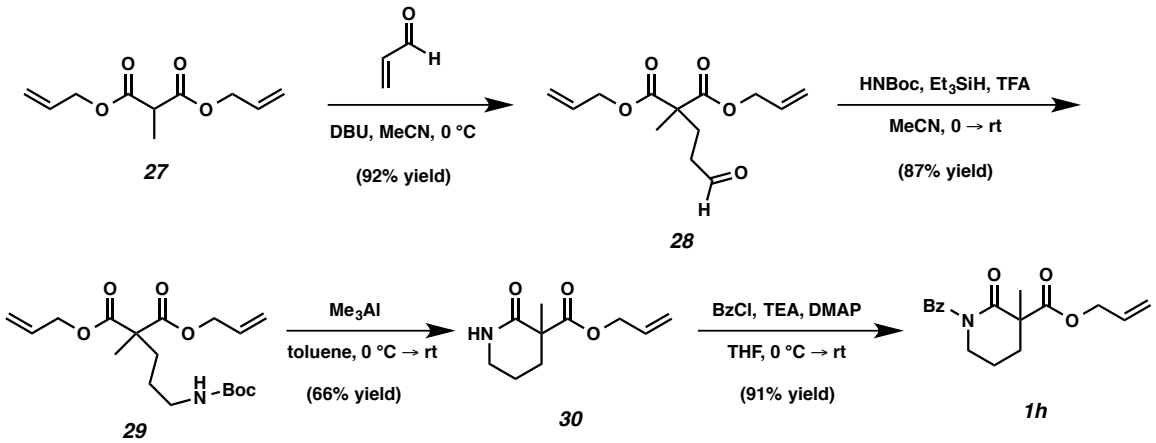
2.7.1 Materials and Methods

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. Brine solutions are saturated aqueous sodium chloride solutions. Tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) was purchased from Strem and stored in a glove box. Lithium bis(trimethylsilyl)amide was purchased from Aldrich and stored in a glove box. Tris[bis(*p*-methoxybenzylidene*)*-acetone]dipalladium(0) ($Pd_2(pmdba)_3$) was prepared by known methods and stored in a glovebox.[1] (*S*)-*t*-BuPHOX, (*S*)-$(CF_3)_3$-*t*-BuPHOX, and allyl cyanoformate were prepared by known methods.[2,3,4] Selectfluor, methyl iodide, and ethyl iodide were purchased from Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. Sodium hydride (NaH) was purchased as a 60% dispersion in mineral oil from Acros and used as such unless otherwise stated. Triethylamine was distilled from CaH_2 prior to use. Acrolein, acrylonitrile, methyl acrylate, and benzoyl chloride were distilled prior to use. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized by UV fluorescence quenching, anisaldehyde, $KMnO_4$, or CAM staining. ICN Silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak (AD-H or AS) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 220 or 254 nm. Analytical chiral SFC was performed with a JACSO 2000 series instrument utilizing Chiralpak (AD-H or AS-H) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm), or a Chiralpak IC column (4.6 mm x 10 cm) obtained from Daicel Chemical Industries, Ltd with visualization at 210 or 254 nm. Optical rotations were measured with a Jasco P-

2000 polarimeter at 589 nm. 1H and 13C NMR spectra were recorded on a Varian Inova 500 (at 500 MHz and 126 MHz, respectively) or a Mercury 300 (at 300 MHz and 75 MHz, respectively), and are reported relative to residual protio solvent ($CDCl_3$ = 7.26 and 77.0 ppm and C_6D_6 = 7.16 and 128.0 ppm, respectively). Data for 1H NMR spectra are reported as follows: chemical shift (d ppm) (multiplicity, coupling constant (Hz), integration). IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm-1). High resolution mass spectra were obtained using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MM) ionization mode or from the Caltech Mass Spectral Facility.

2.7.2 Representative Procedures for the Preparation of Lactam Substrates



Aldehyde 28: To a cooled (0 °C) solution of diallyl 2-methylmalonate (**27**)[31] (17.0 g, 84.7 mmol, 1.00 equiv) and acrolein (6.23 mL, 93.2 mmol, 1.10 equiv) in MeCN (282 mL) was added DBU (253 mL, 1.70 mmol, 0.02 equiv). After 15 min, the reaction mixture was diluted with saturated aqueous NH_4Cl (200 mL) and EtOAc (100 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 x 200 mL)

and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (8 x 16 cm SiO_2, 10 to 20% EtOAc in hexanes) to afford aldehyde **28** as a colorless oil (19.7 g, 92% yield). R_f = 0.32 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (t, *J* = 1.2 Hz, 1H), 5.83 (ddt, *J* = 17.2, 10.5, 5.7 Hz, 2H), 5.26 (dq, *J* = 17.2, 1.5 Hz, 2H), 5.19 (dq, *J* = 10.4, 1.3 Hz, 2H), 4.57 (dt, *J* = 5.6, 1.4 Hz, 4H), 2.55–2.45 (m, 2H), 2.20–2.10 (m, 2H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.6, 171.2, 131.3, 118.5, 65.9, 52.8, 39.2, 27.7, 20.3; IR (Neat Film NaCl) 2988, 2945, 1732, 1230, 1186, 1116, 984, 935 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{13}H_{19}O_5$ $[M+H]^+$: 255.1227, found 255.1223.

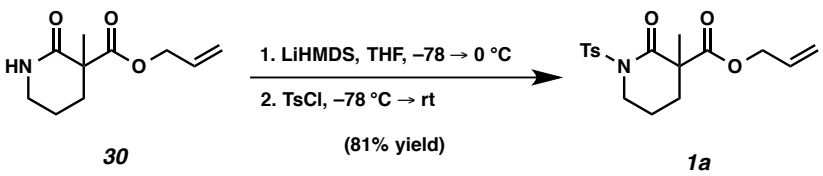
Carbamate 29: To a cooled (0 °C) solution of aldehyde **28** (19.7 g, 77.5 mmol, 1.00 equiv), $BocNH_2$[32] (22.7 g, 194 mmol, 2.50 equiv), and Et_3SiH (31.0 mL, 194 mmol, 2.50 equiv) in MeCN (310 mL) was added trifluoroacetic acid (12.1 mL, 163 mmol, 2.10 equiv) dropwise over 5 min. The reaction mixture was stirred at 0° C for 2 h and at ambient temperature for an additional 18 h, at which point the reaction mixture was cooled (0 °C), treated with saturated aqueous $NaHCO_3$ (150 mL), stirred for 40 min, and concentrated under reduced pressure to remove MeCN (~250 mL). The remaining material was diluted with Et_2O (200 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (4 x 100 mL) and EtOAc (1 x 150 mL), and the combined organic phases were washed with brine (2 x 150 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (8 x 25 cm SiO_2, 5 to 15% EtOAc in hexanes) to afford carbamate **29** as a colorless oil (23.0 g, 87% yield). R_f = 0.32 (20% EtOAc in hexanes); ^{1}H NMR (300

MHz, $CDCl_3$) δ 5.88 (ddt, *J* = 17.3, 10.4, 5.7 Hz, 2H), 5.30 (dq, *J* = 17.2, 1.6, 1.5 Hz, 2H), 5.23 (dq, *J* = 10.4, 1.3, 1.3 Hz, 2H), 4.61 (dt, *J* = 5.6, 1.4 Hz, 4H), 4.55 (br s, 1H), 3.12 (q, *J* = 6.7 Hz, 2H), 2.00–1.75 (m, 2H), 1.44 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 155.8, 131.5, 118.4, 79.0, 65.7, 53.4, 40.4, 32.7, 28.3, 24.9, 19.9; IR (Neat Film NaCl) 3403, 2977, 2939, 1734, 1517, 1366, 1250, 1173, 985, 934 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{29}NO_6Na$ $[M+Na]^+$: 378.1887, found 378.1892.

Lactam 30: To a cooled (0 °C) solution of carbamate **29** (10.4 g, 30.6 mmol, 1.00 equiv) in toluene (306 mL) was added trimethylaluminum (11.7 mL, 61.1 mmol, 2.00 equiv) dropwise over 10 min. After 5 h the reaction was allowed to warm to ambient temperature and stirred for an additional 17 h. The reaction was cooled (0 °C), treated with brine (100 mL, *CAUTION: Gas evolution and exotherm*) in a dropwise manner over 30 min, and stirred until gas evolution ceased. The reaction mixture was then treated with saturated aqueous sodium potassium tartrate (200 mL) and stirred for 4 h. The phases were separated and the aqueous phase was extracted with EtOAc (5 x 150 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (5 x 16 cm SiO_2, 45 to 65% EtOAc in hexanes) to afford lactam **30** as a colorless oil (3.99 g, 66% yield). R_f = 0.41 (100% EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (s, 1H), 6.00–5.75 (m, 1H), 5.30 (d, *J* = 17.1 Hz, 1H), 5.20 (d, *J* = 10.4 Hz, 1H), 4.70–4.50 (m, 2H), 3.40–3.20 (m, 2H), 2.30–2.15 (m, 1H), 1.94–1.59 (m, 3H), 1.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 172.0, 131.7, 118.1, 65.7, 50.1, 42.3, 33.0, 22.4, 19.3; IR (Neat Film

NaCl) 3207, 3083, 2942, 2873, 1737, 1668, 1254, 1194, 1132 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{10}H_{16}NO_3$ $[M+H]^+$: 198.1125, found 198.1117.

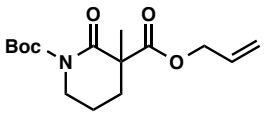
Benzoyl Lactam 1h: To a cooled (0 °C) solution of lactam **30** (394 mg, 2.00 mmol, 1.00 equiv), triethylamine (840 mL, 6.00 mmol, 3.00 equiv), and DMAP (25.0 mg, 205 mmol, 0.102 equiv) in THF (8.00 mL) was added benzoyl chloride (470 mL, 4.00 mmol, 2.00 equiv) dropwise over 5 min. The reaction mixture was allowed to warm to ambient temperature and stirred for 14 h. The reaction mixture was then diluted with brine (10 mL) and EtOAc (10 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (3 x 15 mL), and the combined organic phases were washed with brine (2 x 30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (3 x 25 cm SiO_2, 15 to 25% Et_2O in hexanes) to afford benzoyl lactam **1h** as an amorphous solid (550 mg, 91% yield). R_f = 0.38 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78–7.63 (m, 2H), 7.52–7.42 (m, 1H), 7.42–7.32 (m, 2H), 5.98 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.40 (dq, *J* = 17.2, 1.4 Hz, 1H), 5.33 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.72 (dt, *J* = 6.0, 1.3 Hz, 2H), 3.93–3.82 (m, 1H), 3.83–3.73 (m, 1H), 2.56–2.43 (m, 1H), 2.13–1.90 (m, 2H), 1.87–1.76 (m, 1H), 1.49 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 172.8, 172.4, 135.9, 131.6, 131.4, 128.0, 127.9, 119.5, 66.5, 52.9, 46.8, 33.8, 22.5, 20.2; IR (Neat Film NaCl) 3063, 2941, 2873, 1735, 1681, 1449, 1276, 1040, 942, 724 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{20}NO_4$ $[M+H]^+$: 302.1387, found 302.1388.



30 ***1a***

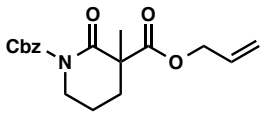
Tosyl Lactam 1a: To a cooled (–78 °C) solution of LiHMDS (385 mg, 2.30 mmol, 1.15 equiv) in THF (8.0 mL) was added lactam **30** (394 mg, 2.00 mmol, 1.00 equiv). The reaction mixture warmed to 0 °C and stirred for 30 min, then cooled to –78 °C and treated with TsCl (572 mg, 3.00 mmol, 1.50 equiv). After 5 min, the reaction mixture was allowed to warm to ambient temperature for 30 min and treated with saturated aqueous NH_4Cl (10 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (3 x 30 cm SiO_2, 4:1:1 hexanes-EtOAc-DCM) to afford tosyl lactam **1a** as a colorless oil (571 mg, 81% yield). R_f = 0.58 (33% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93–7.83 (m, 2H), 7.35–7.27 (m, 2H), 5.68 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.17 (dq, *J* = 9.1, 1.4 Hz, 1H), 5.14 (q, *J* = 1.4 Hz, 1H), 4.47 (qdt, *J* = 13.2, 5.6, 1.4 Hz, 2H), 3.98 (ddd, *J* = 12.8, 6.9, 6.1 Hz, 1H), 3.90 (ddt, J = 12.4, 6.0, 0.8 Hz, 1H), 2.42 (s, 3H), 2.34–2.26 (m, 1H), 1.95 (tt, *J* = 6.5, 5.5 Hz, 2H), 1.71 (ddd, *J* = 14.2, 8.1, 6.6 Hz, 1H), 1.41 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 169.9, 144.6, 135.7, 131.1, 129.2, 128.6, 118.7, 66.1, 52.8, 46.4, 32.4, 22.3, 21.6, 20.4; IR (Neat Film NaCl) 2942, 1740, 1691, 1353, 1284, 1167, 1090 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{21}NO_5SNa$ $[M+Na]^+$: 374.1033, found 374.1042.

2.7.3 Characterization Data for Lactam Substrates Used in Table 2.1



1b

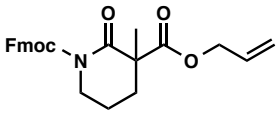
Boc Lactam 1b: Prepared in a manner analogous to tosyl lactam **1a** using lactam **30** (394 mg, 2.00 mmol, 1.00 equiv) and Boc_2O (873 mg, 4.00 mmol, 2.00 equiv). Boc lactam **1b** (407 mg, 68% yield) was isolated as an amorphous solid by flash chromatography (SiO_2, 9 to 11% Et_2O in hexanes). R_f = 0.54 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95–5.81 (m, 1H), 5.33 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.22 (dq, *J* = 10.5, 1.5 Hz, 1H), 4.64 (m, 2H), 3.80–3.70 (m, 1H), 3.63–3.49 (m, 1H), 2.43–2.33 (m, 1H), 1.98–1.77 (m, 2H), 1.75–1.66 (m, 1H), 1.52 (s, 9H), 1.50 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 170.9, 153.1, 131.5, 118.4, 83.0, 65.9, 53.1, 46.0, 32.6, 28.0, 22.9, 20.1; IR (Neat Film NaCl) 2981, 2939, 1772, 1719, 1457, 1393, 1294, 1282, 1254, 1152, 988, 945, 852 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{15}H_{23}NO_5Na$ $[M+Na]^+$: 320.1468, found 320.1470.



1c

Cbz Lactam 1c: Prepared in a manner analogous to tosyl lactam **1a** using lactam **30** (394 mg, 2.00 mmol, 1.00 equiv) and CbzCl (682 mg, 4.00 mmol, 2.00 equiv). Cbz lactam **1c** (325 mg, 49% yield) was isolated as a colorless oil by flash chromatography (SiO_2, 14 to 17% Et_2O in hexanes). R_f = 0.34 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.40 (m, 2H), 7.39–7.28 (m, 3H), 5.85 (ddt, *J* = 17.1, 10.5, 5.6 Hz,

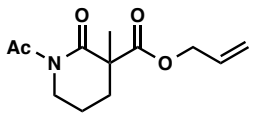
1H), 5.30 (dq, *J* = 10.5, 1.3 Hz, 1H), 5.29 (s, 2H), 5.19 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.69–4.54 (m, 2H), 3.86–3.79 (m, 1H), 3.71–3.60 (m, 1H), 2.44–2.37 (m, 1H), 1.98–1.78 (m, 2H), 1.73 (ddd, *J* = 14.0, 9.1, 5.1 Hz, 1H), 1.52 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 170.9, 154.4, 135.4, 131.3, 128.5, 128.2, 128.0, 118.7, 68.6, 66.1, 53.3, 46.4, 32.5, 22.8, 20.0; IR (Neat Film NaCl) 2943, 2876, 1776, 1721, 1456, 1378, 1270, 1191, 1167, 1125, 1002, 941, 739, 698 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{21}NO_5Na$ $[M+Na]^+$: 354.1312, found 354.1310.



1d

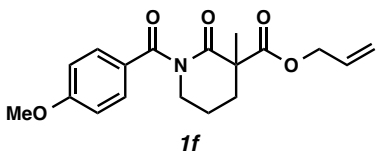
Fmoc Lactam 1d: Prepared in a manner analogous to tosyl lactam **1a** using lactam **30** (394 mg, 2.00 mmol, 1.00 equiv) and FmocCl (621 mg, 2.40 mmol, 1.20 equiv). Fmoc lactam **1d** (352 mg, 42% yield) was isolated as a colorless oil by flash chromatography (SiO_2, 2 to 12% Et_2O in hexanes). R_f = 0.28 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (dt, *J* = 7.6, 0.9 Hz, 2H), 7.73 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 2H), 7.43–7.38 (m, 2H), 7.32 (tdd, *J* = 7.4, 4.8, 1.2 Hz, 2H), 5.91 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.36 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.25 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.69 (ddt, *J* = 5.6, 2.8, 1.4 Hz, 2H), 4.56–4.43 (m, 2H), 4.33 (t, *J* = 7.5 Hz, 1H), 3.86–3.79 (m, 1H), 3.73–3.61 (m, 1H), 2.44 (dddd, *J* = 13.8, 6.8, 5.0, 0.9 Hz, 1H), 2.00–1.83 (m, 2H), 1.78 (ddd, *J* = 14.0, 9.1, 5.0 Hz, 1H), 1.59 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 170.9, 154.5, 143.6, 141.2, 131.4, 127.8, 127.1, 125.4, 119.9, 118.7, 69.3, 66.1, 53.4, 46.6, 46.4, 32.6, 22.9, 20.0; IR (Neat Film NaCl) 2948, 2892, 1776, 1721, 1451, 1378, 1269, 1191, 997, 759,

742 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{25}H_{25}NO_5Na$ $[M+Na]^+$: 442.1625, found 442.1610.



1e

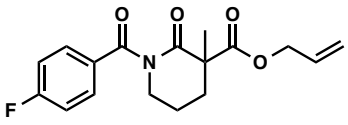
Acetyl Lactam 1e: Prepared in a manner analogous to benzoyl lactam **1h** using lactam **30** (394 mg, 2.00 mmol, 1.00 equiv), acetic anhydride (940 mL, 10.0 mmol, 5.00 equiv), and triethylamine (2.80 mL, 20.0 mmol, 10.0 equiv). Acetyl lactam **1e** (347 mg, 72% yield) was isolated as a colorless oil by flash chromatography (SiO_2, 12 to 25% Et_2O in hexanes). R_f = 0.44 (25% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 5.88 (ddt, *J* = 17.1, 10.4, 5.7 Hz, 1H), 5.31 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.25 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.66–4.60 (m, 2H), 3.78 (ddd, *J* = 13.1, 7.6, 5.3 Hz, 1H), 3.71–3.62 (m, 1H), 2.49 (s, 3H), 2.44–2.37 (m, 1H), 1.93–1.77 (m, 2H), 1.78–1.70 (m, 1H), 1.52 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0, 173.5, 172.4, 131.3, 119.1, 66.2, 53.2, 44.0, 32.9, 27.0, 22.7, 19.9; IR (Neat Film NaCl) 2985, 2942, 1739, 1699, 1457, 1368, 1301, 1261, 1190, 1132, 1048, 990, 959, 936 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{12}H_{18}NO_4$ $[M+H]^+$: 240.1230, found 240.1237.



1f

4-Methoxybenzoyl Lactam 1f: Prepared in a manner analogous to benzoyl lactam **1h** using lactam **30** (394 mg, 2.00 mmol, 1.00 equiv), 4-methoxybenzoyl chloride (682 mg,

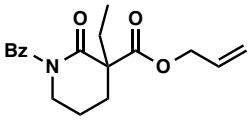
4.00 mmol, 2.00 equiv), and triethylamine (840 mL, 6.00 mmol, 3.00 equiv). 4-Methoxybenzoyl lactam **1f** (425 mg, 64% yield) was isolated as a colorless oil by flash chromatography (SiO_2, $CHCl_3$-hexanes-Et_2O 6.5:5:1). R_f = 0.76 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81–7.67 (m, 2H), 6.93–6.79 (m, 2H), 6.05–5.88 (m, 1H), 5.39 (dq, *J* = 17.2, 1.4 Hz, 1H), 5.31 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.71 (dt, *J* = 6.0, 1.3 Hz, 2H), 3.90–3.77 (m, 1H), 3.82 (s, 3H), 3.76–3.63 (m, 1H), 2.48 (ddd, *J* = 13.7, 5.7, 4.3 Hz, 1H), 2.06–1.89 (m, 2H), 1.80 (ddd, *J* = 13.5, 10.0, 5.0 Hz, 1H), 1.49 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 172.6, 172.6, 162.7, 131.4, 130.7, 127.7, 119.3, 113.3, 66.3, 55.3, 52.8, 46.9, 33.7, 22.5, 20.2; IR (Neat Film NaCl) 3080, 2941, 1732, 1682, 1604, 1512, 1456, 1390, 1257, 1173, 1139, 1029, 939, 844, 770 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{22}NO_5$ $[M+H]^+$: 332.1492, found 332.1501.



1g

4-Fluorobenzoyl Lactam 1g: Prepared in a manner analogous to benzoyl lactam **1h** using lactam **30** (394 mg, 2.00 mmol, 1.00 equiv), 4-fluorobenzoyl chloride (470 mL, 4.00 mmol, 2.00 equiv), and triethylamine (840 mL, 6.00 mmol, 3.00 equiv). 4-Fluorobenzoyl lactam **1g** (557 mg, 87% yield) was isolated as an amorphous white solid by flash chromatography (SiO_2, 15 to 25% Et_2O in hexanes). R_f = 0.37 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84–7.72 (m, 2H), 7.12–6.97 (m, 2H), 5.99 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.41 (dq, *J* = 17.2, 1.4 Hz, 1H), 5.35 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.73 (dt, *J* = 6.0, 1.3 Hz, 2H), 3.89–3.82 (m, 1H), 3.81–3.75 (m, 1H), 2.57–2.42 (m, 1H), 2.09–1.91 (m, 2H), 1.89–1.75 (m, 1H), 1.50 (s, 3H); ^{13}C NMR (126 MHz,

$CDCl_3$) δ 173.8, 172.9, 172.5, 164.8 (d, $J_{C\text{-}F}$ = 252.5 Hz), 131.8 (d, $J_{C\text{-}F}$ = 3.3 Hz), 131.3, 130.7 (d, $J_{C\text{-}F}$ = 9.0 Hz), 119.5, 115.2 (d, $J_{C\text{-}F}$ = 22.0 Hz), 66.5, 52.9, 47.0, 33.8, 22.4, 20.2; IR (Neat Film NaCl) 3079, 2943, 2874, 1734, 1684, 1602, 1508, 1277, 1240, 1193, 1140, 939, 849, 770 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{19}NO_4F$ $[M+H]^+$: 320.1293, found 320.1297.



24

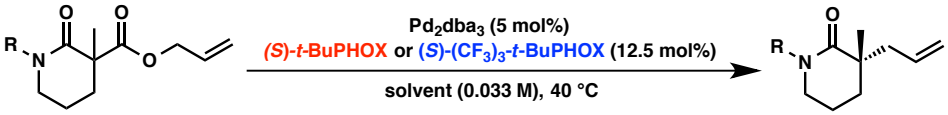
Benzoyl Lactam 24: Prepared in a manner analogous to benzoyl lactam **1h** using diallyl 2-ethylmalonate as a starting material. Benzoyl lactam **24** was isolated by flash chromatography (SiO_2, 15 to 25% Et_2O in hexanes) as a colorless oil. R_f = 0.38 (35% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.72–7.67 (m, 2H), 7.51–7.43 (m, 1H), 7.37 (dd, *J* = 8.3, 7.1 Hz, 2H), 5.99 (ddt, *J* = 17.3, 10.4, 5.9 Hz, 1H), 5.40 (dq, *J* = 17.2, 1.4 Hz, 1H), 5.33 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.73 (dt, *J* = 6.0, 1.3 Hz, 2H), 3.93–3.63 (m, 2H), 2.43 (ddt, *J* = 13.7, 4.4, 1.4 Hz, 1H), 2.17–1.65 (m, 5H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, CDCl3) δ 175.0, 172.0, 171.8, 135.9, 131.6, 131.4, 128.0, 128.0, 119.5, 66.4, 56.9, 46.4, 29.8, 28.6, 20.3, 9.0; IR (Neat Film NaCl) 3062, 2943, 2882, 1732, 1678, 1449, 1385, 1268, 1188, 1137, 980, 937, 723, 693, 660 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{22}NO_4$ $[M+H]^+$: 316.1543, found 316.1545.

2.7.4 General Procedure for Allylic Alkylation Screening Reactions

All reagents were dispensed as solutions using a Symyx Core Module within a nitrogen-filled glovebox. Oven-dried half-dram vials were charged with a solution of the palladium source (Pd_2dba_3 or Pd_2pmdba_3, 1.68 μmol, 0.05 equiv) in THF (368 μL). The palladium solutions were evaporated to dryness under reduced pressure using a Genevac centrifugal evaporator within the glovebox, and stirbars were added to the vials. The reaction vials were then charged with the desired reaction solvent (500 mL) and a solution of the PHOX ligand (4.20 μmol, 0.125 equiv) in the reaction solvent (250 μL) and stirred at ambient glovebox temperature (~28 °C). After 30 min, solutions of the lactam substrate (33.6 μmol, 1.0 equiv) in the reaction solvent (250 μL) were added. The reaction vials were tightly capped and heated to the desired temperature. When complete consumption of the starting material was observed by colorimetric change (from light green to red-orange) and confirmed by thin-layer chromatography on SiO_2 (typically less than 72 h), the reaction mixtures were removed from the glovebox, concentrated under reduced pressure, resuspended in an appropriate solvent for analysis (e.g., hexanes), filtered, and analyzed for enantiomeric excess (see Methods for the Determination of Enantiomeric Excess).

2.7.5 Results of Screening Various Reaction Parameters

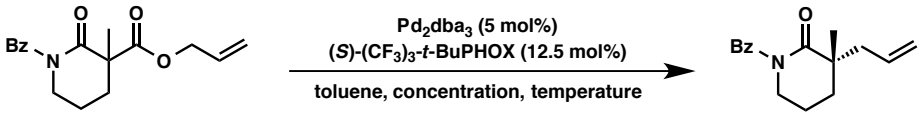
Table 2.3 Influences of solvent, protecting group, and ligand



	% ee			
	THF	MTBE	Toluene	Hex:Tol 2:1
R = Ts[a]	4.1 35.2	25.9 57.2	6.5 37.2	31.4 44.2
R = Boc[a]	57.3 70.3	74.5 72.1	73.6 73.0	76.7 71.0
R = Cbz	36.3 79.9	75.2 83.5	75.1 87.3	71.5 83.2
R = Fmoc	45.7 78.9	64.9 84.6	38.3 87.1	44.9 84.6
R = Ac	20.0 75.1	64.1 90.6[b]	61.6 90.2[b]	83.2 90.9[b]
R = 4-MeO-Bz	59.5 97.1	90.7 98.3	87.4 99.0	96.8 98.5
R = 4-F-Bz	42.3 95.3	85.8 99.0	83.2 99.3	96.4 99.4
R = Bz	52.2 96.2	88.3 99.2	85.8 99.0	96.4 98.8

[a] Reactions performed at 50 °C. [b] Reaction performed at 60 °C.

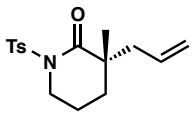
Table 2.4 Influence of temperature and concentration



0.1 mmol

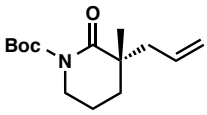
entry	temperature (°C)	concentration (M)	time (h)	% ee
1	40	0.033	43	99.2
2	45	0.033	22	98.9
3	50	0.033	12	98.7
4	55	0.033	6	98.2
5	40	0.10	43	98.9
6	40	0.20	43	97.4

2.7.6 Characterization Data for Lactam Products in Table 2.1



2a

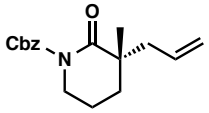
Tosyl Lactam 2a: Reaction performed in MTBE at 40 °C. Tosyl lactam **2a** was isolated by flash chromatography (SiO_2, 3 to 15% Et_2O in hexanes) as a light yellow solid. 90.0% yield. R_f = 0.29 (35% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89–7.84 (m, 2H), 7.33–7.27 (m, 2H), 5.41 (dddd, *J* = 16.9, 10.2, 8.1, 6.7 Hz, 1H), 4.99–4.86 (m, 2H), 3.99 (dddd, *J* = 11.9, 5.9, 4.9, 1.3 Hz, 1H), 3.82–3.71 (m, 1H), 2.42 (s, 3H), 2.41–2.34 (m, 1H), 2.07 (ddt, *J* = 13.6, 8.1, 1.0 Hz, 1H), 1.98–1.83 (m, 2H), 1.83–1.75 (m, 1H), 1.55–1.48 (m, 1H), 1.12 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7, 144.4, 136.2, 132.9, 129.2, 128.5, 118.9, 47.6, 44.2, 44.0, 32.1, 25.5, 21.6, 20.1; IR (Neat Film NaCl) 3074, 2938, 1689, 1597, 1454, 1351, 1283, 1171, 1103, 1089, 1039, 921, 814, 748 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{21}NO_3SNa$ $[M+Na]^+$: 330.1134, found 330.1141; $[\alpha]_D^{25}$ –69.2° (c 1.16, $CHCl_3$, 75% ee).



2b

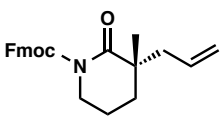
Boc Lactam 2b: Reaction performed in toluene at 40 °C. Boc lactam **2b** was isolated by flash chromatography (SiO_2, 8 to 9% Et_2O in hexanes) as a colorless oil. 87.1% yield. R_f = 0.57 (35% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (dddd, *J* = 17.1, 10.4, 7.8, 7.0 Hz, 1H), 5.14–5.02 (m, 2H), 3.71–3.61 (m, 1H), 3.58–3.48 (m, 1H), 2.48 (dd, *J* = 13.6, 7.0 Hz, 1H), 2.26 (dd, *J* = 13.6, 7.9 Hz, 1H), 1.87–1.76 (m, 3H), 1.61–1.52

(m, 1H), 1.50 (s, 9H), 1.22 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.1, 153.7, 133.7, 118.5, 82.5, 47.4, 44.5, 44.2, 33.0, 28.0, 25.4, 19.7; IR (Neat Film NaCl) 3076, 2978, 2936, 1768, 1715, 1457, 1392, 1368, 1298, 1280, 1252, 1149, 999, 917, 854 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{14}H_{23}NO_3Na$ $[M+Na]^+$: 276.1570, found 276.1574; $[\alpha]_D^{25}$ –73.6° (c 1.025, $CHCl_3$, 81% ee).



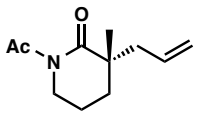
2c

Cbz Lactam 2c: Reaction performed in toluene at 40 °C. Cbz lactam **2c** was isolated by flash chromatography (SiO_2, 8 to 10% Et_2O in hexanes) as a colorless oil. 84.6% yield. R_f = 0.49 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.40 (m, 2H), 7.36 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 2H), 7.33–7.29 (m, 1H), 5.74 (dddd, *J* = 16.6, 10.5, 7.8, 6.9 Hz, 1H), 5.26 (s, 2H), 5.13–5.02 (m, 2H), 3.80–3.72 (m, 1H), 3.67–3.58 (m, 1H), 2.51 (dd, *J* = 13.6, 7.0 Hz, 1H), 2.26 (dd, *J* = 13.6, 7.9 Hz, 1H), 1.90–1.77 (m, 3H), 1.62–1.53 (m, 1H), 1.25 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.0, 154.8, 135.6, 133.4, 128.5, 128.2, 128.0, 118.8, 68.3, 47.8, 44.8, 44.2, 32.8, 25.5, 19.6; IR (Neat Film NaCl) 2940, 1772, 1712, 1456, 1377, 1296, 1270, 1218, 1161, 1001, 918 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{20}NO_3Na$ $[M+Na]^+$: 310.1414, found 310.1414; $[\alpha]_D^{25}$ –65.8° (c 1.48, $CHCl_3$, 86% ee).



2d

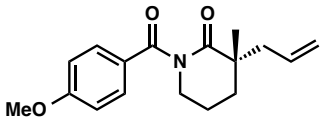
Fmoc Lactam 2d: Reaction performed in toluene at 40 °C. Fmoc lactam **2d** was isolated by flash chromatography (SiO_2, 6 to 8% Et_2O in hexanes) as a colorless oil. 82.4% yield. R_f = 0.45 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (dt, *J* = 7.6, 1.0 Hz, 2H), 7.71 (ddd, *J* = 7.5, 3.6, 1.0 Hz, 2H), 7.41 (tt, *J* = 7.5, 0.9 Hz, 2H), 7.33 (ddt, *J* = 7.5, 2.0, 1.2 Hz, 2H), 5.80 (dddd, *J* = 17.9, 8.7, 7.9, 6.9 Hz, 1H), 5.18–5.10 (m, 2H), 4.53–4.42 (m, 2H), 4.33 (t, *J* = 7.4 Hz, 1H), 3.80–3.71 (m, 1H), 3.65–3.57 (m, 1H), 2.58 (dd, *J* = 13.6, 7.0 Hz, 1H), 2.32 (ddt, *J* = 13.6, 7.8, 1.1 Hz, 1H), 1.93–1.79 (m, 3H), 1.64–1.57 (m, 1H), 1.31 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.0, 154.9, 143.7, 141.2, 133.5, 127.7, 127.1, 125.4, 119.9, 118.8, 68.9, 47.7, 46.7, 44.8, 44.2, 32.8, 25.5, 19.6; IR (Neat Film NaCl) 3067, 2945, 1770, 1712, 1478, 1451, 1377, 1297, 1269, 1161, 1000, 759, 740 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{24}H_{26}NO_3$ $[M+H]^+$: 376.1907, found 376.1914; $[\alpha]_D^{25}$ –38.5° (c 2.17, $CHCl_3$, 89% ee).



2e

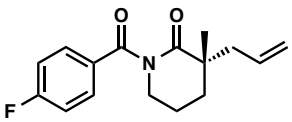
Acetyl Lactam 2e: Reaction performed in toluene at 40 °C. Acetyl lactam **2e** was isolated by flash chromatography (SiO_2, 8 to 10% Et_2O in hexanes) as a colorless oil. 47.2% yield. R_f = 0.38 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (dddd, *J* = 16.6, 10.4, 7.8, 7.0 Hz, 1H), 5.14–5.04 (m, 2H), 3.82–3.72 (m, 1H), 3.60–3.49 (m, 1H), 2.50 (ddt, *J* = 13.6, 7.0, 1.2 Hz, 1H), 2.44 (s, 3H), 2.25 (ddt, *J* = 13.6, 7.7, 1.1 Hz, 1H), 1.91–1.71 (m, 3H), 1.64–1.52 (m, 1H), 1.25 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.3, 174.4, 133.3, 118.9, 45.4, 44.8, 44.4, 32.8, 27.2, 25.7, 19.4; IR (Neat Film NaCl) 2941, 1694, 1387, 1367, 1293, 1248, 1177, 1114, 1046, 920 cm^{-1}; HRMS

(MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{18}NO_2$ $[M+H]^+$: 196.1332, found 196.1329; $[\alpha]_D^{25}$ – 100.9° (c 0.99, $CHCl_3$, 91% ee).



2f

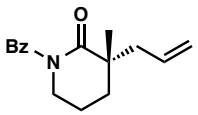
4-Methoxybenzoyl Lactam 2f: Reaction performed in toluene at 40 °C. 4-Methoxybenzoyl lactam **2f** was isolated by flash chromatography (SiO_2, 15% EtOAc in hexanes) as a colorless oil. 92.7% yield. R_f = 0.36 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60–7.48 (m, 2H), 6.92–6.82 (m, 2H), 5.76 (dddd, *J* = 17.2, 10.3, 7.7, 7.0 Hz, 1H), 5.19–5.03 (m, 2H), 3.83 (s, 3H), 3.80 (ddd, *J* = 12.1, 5.3, 1.4 Hz, 1H), 3.73–3.64 (m, 1H), 2.57 (ddt, *J* = 13.6, 7.1, 1.2 Hz, 1H), 2.29 (ddt, *J* = 13.7, 7.6, 1.1 Hz, 1H), 2.05–1.91 (m, 3H), 1.72–1.63 (m, 1H), 1.32 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.0, 174.9, 162.4, 133.4, 130.1, 128.4, 118.9, 113.5, 55.4, 47.3, 43.9, 43.4, 33.3, 25.3, 19.6; IR (Neat Film NaCl) 2937, 1675, 1604, 1511, 1254, 1164, 1029, 922, 840, 770 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{22}NO_3$ $[M+H]^+$: 288.1594, found 288.1595; $[\alpha]_D^{25}$ –94.2° (c 1.00, $CHCl_3$, 99% ee).



2g

4-Fluorobenzoyl Lactam 2g: Reaction performed in toluene at 40 °C. 4-Fluorobenzoyl lactam **2g** was isolated by flash chromatography (SiO_2, 9% Et_2O in hexanes) as a colorless oil. 89.4% yield. R_f = 0.41 (17% EtOAc in hexanes); ^{1}H NMR (500 MHz,

$CDCl_3$) δ 7.59–7.47 (m, 2H), 7.12–6.99 (m, 2H), 5.74 (ddt, *J* = 17.0, 10.4, 7.3 Hz, 1H), 5.18–5.05 (m, 2H), 3.89–3.77 (m, 1H), 3.77–3.63 (m, 1H), 2.55 (dd, *J* = 13.7, 7.0 Hz, 1H), 2.28 (dd, *J* = 13.7, 7.6 Hz, 1H), 2.07–1.88 (m, 3H), 1.76–1.62 (m, 1H), 1.31 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.1, 174.2, 164.6 (d, $J_{C\text{-}F}$ = 252.4 Hz), 133.2, 132.5 (d, $J_{C\text{-}F}$ = 3.4 Hz), 123.0 (d, $J_{C\text{-}F}$ = 8.9 Hz), 119.1, 115.3 (d, $J_{C\text{-}F}$ = 22.1 Hz), 47.3, 44.0, 43.3, 33.3, 25.2, 19.5; IR (Neat Film NaCl) 3076, 2940, 1679, 1602, 1507, 1384, 1280, 1145, 922, 844, 769 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{19}NO_2F$ $[M+H]^+$: 276.1394, found 276.1392; $[\alpha]_D^{25}$ –85.5° (c 1.02, $CHCl_3$, 99% ee).



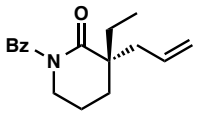
2h

Benzoyl Lactam 2h: Reaction performed in toluene at 40 °C. Benzoyl lactam **2h** was isolated by flash chromatography (SiO_2, 5 to 9% Et_2O in pentane) as a colorless oil. 84.7% yield. R_f = 0.55 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54–7.50 (m, 2H), 7.49–7.43 (m, 1H), 7.40–7.35 (m, 2H), 5.75 (dddd, *J* = 17.1, 10.2, 7.7, 7.0 Hz, 1H), 5.19–5.03 (m, 2H), 3.92–3.78 (m, 1H), 3.72 (ddt, *J* = 12.6, 6.4, 6.0, 1.2 Hz, 1H), 2.55 (ddt, *J* = 13.7, 7.0, 1.2 Hz, 1H), 2.29 (ddt, *J* = 13.7, 7.7, 1.1 Hz, 1H), 2.07–1.87 (m, 3H), 1.75–1.60 (m, 1H), 1.31 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.0, 175.3, 136.5, 133.3, 131.3, 128.1, 127.4, 118.9, 47.1, 44.0, 43.3, 33.3, 25.1, 19.5; IR (Neat Film NaCl) 3074, 2939, 2870, 1683, 1478, 1449, 1386, 1282, 1151, 919, 726, 695 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{20}NO_2$ $[M+H]^+$: 258.1489, found 258.1491; $[\alpha]_D^{25}$ –91.2° (c 1.07, $CHCl_3$, 99% ee).

2.7.7 General Procedure for Preparative Allylic Alkylation Reactions

In a nitrogen-filled glovebox, an oven-dried 20 mL vial was charged with Pd_2pmdba_3 (27.4 mg, 0.025 mmol, 0.05 equiv) or Pd_2dba_3 (22.9 mg, 0.025 mmol, 0.05 equiv),[33] (*S*)-$(CF_3)_3$-*t*-BuPHOX (37.0 mg, 0.0625 mmol, 0.125 equiv), toluene (15 mL or 13 mL if the substrate is an oil), and a magnetic stir bar. The vial was stirred at ambient glovebox temperature (~28 °C) for 30 min and the substrate (0.50 mmol, 1.00 equiv) was added either as a solid or as a solution of an oil dissolved in toluene (2 mL). The vial was sealed and heated to 40 °C. When complete consumption of the starting material was observed by colorimetric change (from light green to red-orange) and confirmed by thin layer chromatography on SiO_2, the reaction mixtures were removed from the glovebox, concentrated under reduced pressure, and purified by flash chromatography to afford the desired alkylated product.

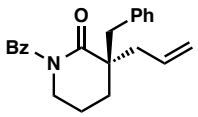
2.7.8 Characterization Data for Lactam Products in Table 2.2



3

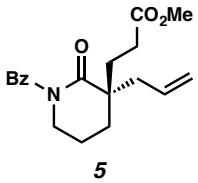
Benzoyl Lactam 3: Benzoyl lactam **3** was isolated by flash chromatography (SiO_2, 15 to 20% Et_2O in hexanes) as a colorless oil. 97.2% yield. R_f = 0.39 (20% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53–7.49 (m, 2H), 7.48–7.43 (m, 1H), 7.41–7.34 (m, 2H), 5.74 (dddd, *J* = 16.7, 10.4, 7.6, 7.0 Hz, 1H), 5.19–5.02 (m, 2H), 3.84–3.70 (m, 2H), 2.51 (ddt, *J* = 13.8, 7.0, 1.3 Hz, 1H), 2.28 (ddt, *J* = 13.8, 7.6, 1.2 Hz, 1H), 2.06–1.91 (m, 2H), 1.91–1.74 (m, 3H), 1.74–1.63 (m, 1H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.0, 175.6, 136.7, 133.6, 131.2, 128.1, 127.4, 118.6, 47.4, 46.9, 41.3, 30.3,

30.3, 19.6, 8.3; IR (Neat Film NaCl) 3072, 2970, 2941, 2880, 1678, 1448, 1384, 1283, 1147, 916, 725, 694 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{22}NO_2$ $[M+H]^+$: 272.1645, found 272.1649; $[\alpha]_D^{25}$ –28.6° (c 1.15, $CHCl_3$, 99% ee).



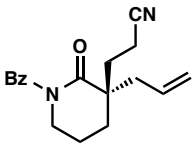
4

Benzoyl Lactam 4: Benzoyl lactam **4** was isolated by flash chromatography (SiO_2, 10% Et_2O in hexanes) as a white solid. 84.8% yield. R_f = 0.48 (35% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 8.1, 1.4 Hz, 2H), 7.52–7.46 (m, 1H), 7.43–7.37 (m, 2H), 7.32–7.22 (m, 3H), 7.18–7.11 (m, 2H), 5.80 (dddd, *J* = 16.8, 10.1, 7.6, 6.8 Hz, 1H), 5.21–5.06 (m, 2H), 3.70 (ddd, *J* = 12.2, 7.0, 4.8 Hz, 1H), 3.63 (ddd, *J* = 12.5, 7.7, 4.4 Hz, 1H), 3.34 (d, *J* = 13.4 Hz, 1H), 2.73–2.64 (m, 1H), 2.68 (d, *J* = 13.3 Hz, 1H), 2.25 (ddt, *J* = 13.8, 7.7, 1.1 Hz, 1H), 2.03–1.91 (m, 1H), 1.91–1.83 (m, 1H), 1.81 (dd, *J* = 6.7, 5.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.4, 175.5, 136.9, 136.6, 133.2, 131.4, 130.8, 128.2, 128.1, 127.6, 126.7, 119.3, 48.8, 46.8, 43.0, 42.9, 28.9, 19.6; IR (Neat Film NaCl) 3061, 3028, 2942, 1679, 1449, 1286, 1149, 919, 724, 704, 695 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{22}H_{24}NO_2$ $[M+H]^+$: 334.1802, found 334.1800; $[\alpha]_D^{25}$ +48.1° (c 0.825, $CHCl_3$, 99% ee).



5

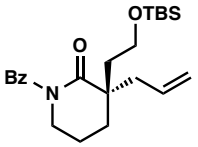
Benzoyl Lactam 5: Benzoyl lactam **5** was isolated by flash chromatography (SiO_2, 25% Et_2O in hexanes) as a light yellow oil. 91.8% yield. R_f = 0.39 (35% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.53–7.49 (m, 2H), 7.49–7.44 (m, 1H), 7.41–7.31 (m, 2H), 5.72 (ddt, *J* = 17.4, 10.3, 7.3 Hz, 1H), 5.23–5.05 (m, 2H), 3.78 (t, *J* = 6.0 Hz, 2H), 3.67 (s, 3H), 2.58–2.47 (m, 1H), 2.42–2.24 (m, 3H), 2.08–1.97 (m, 4H), 1.93 (ddd, *J* = 14.0, 7.8, 4.6 Hz, 1H), 1.78 (ddd, *J* = 13.9, 7.1, 4.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.4, 175.5, 173.7, 136.5, 132.6, 131.4, 128.2, 127.4, 119.4, 51.7, 47.0, 46.6, 41.2, 32.2, 31.2, 29.0, 19.4; IR (Neat Film NaCl) 3073, 2950, 2874, 1736, 1679, 1448, 1281, 1150, 920, 727, 696, 665 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{19}H_{24}NO_4$ $[M+H]^+$: 330.1700, found 330.1704; $[\alpha]_D^{25}$ +14.0° (c 0.72, $CHCl_3$, 99% ee).



6

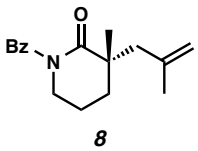
Benzoyl Lactam 6: Benzoyl lactam **6** was isolated by flash chromatography (SiO_2, 15 to 25% EtOAc in hexanes) as a colorless oil. 88.2% yield. R_f = 0.43 (35% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.52–7.47 (m, 3H), 7.41 (ddt, *J* = 8.7, 6.6, 1.0 Hz, 2H), 5.71 (ddt, *J* = 17.4, 10.1, 7.3 Hz, 1H), 5.28–5.15 (m, 2H), 3.88–3.79 (m, 1H), 3.76 (ddd, *J* = 12.9, 8.7, 4.2 Hz, 1H), 2.57 (ddt, *J* = 14.1, 7.3, 1.2 Hz, 1H), 2.44–2.29 (m, 3H), 2.13–2.04 (m, 2H), 2.03–1.89 (m, 3H), 1.87–1.78 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.8, 175.2, 136.2, 131.7, 131.5, 128.3, 127.3, 120.3, 119.5, 47.0, 46.5, 41.1, 32.7, 30.8, 19.2, 12.5; IR (Neat Film NaCl) 3074, 2945, 2876, 1678, 1448, 1389, 1282,

1151, 922, 727, 696 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{21}N_2O_2$ $[M+H]^+$: 297.1598, found 297.1603; $[\alpha]_D^{25}$ +46.9° (c 0.83, $CHCl_3$, 99% ee).



7

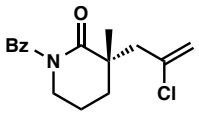
Benzoyl Lactam 7: Benzoyl lactam **7** was isolated by flash chromatography (SiO_2, 5 to 15% Et_2O in hexanes) as a colorless oil. 85.4% yield. R_f = 0.32 (10% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.54–7.48 (m, 2H), 7.48–7.42 (m, 1H), 7.41–7.33 (m, 2H), 5.76 (ddt, *J* = 17.3, 10.2, 7.3 Hz, 1H), 5.18–5.06 (m, 2H), 3.81–3.75 (m, 2H), 3.75–3.64 (m, 2H), 2.55 (ddt, *J* = 13.8, 7.1, 1.2 Hz, 1H), 2.33 (ddt, *J* = 13.8, 7.5, 1.1 Hz, 1H), 2.10–1.94 (m, 4H), 1.94–1.85 (m, 1H), 1.81 (ddd, *J* = 13.9, 7.3, 5.6 Hz, 1H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.6, 175.5, 136.8, 133.4, 131.2, 128.1, 127.4, 118.9, 59.2, 46.9, 46.3, 42.2, 39.7, 30.8, 25.9, 19.6, 18.2, –5.4; IR (Neat Film NaCl) 2953, 2928, 2884, 2856, 1681, 1280, 1257, 1151, 1093, 836, 776, 725, 694 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{23}H_{36}NO_3Si$ $[M+H]^+$: 402.2459, found 402.2467; $[\alpha]_D^{25}$ –3.71° (c 1.40, $CHCl_3$, 96% ee).



8

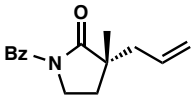
Benzoyl Lactam 8: Benzoyl lactam **8** was isolated by flash chromatography (SiO_2, 5 to 9% EtOAc in hexanes) as a colorless oil. 78.0% yield. R_f = 0.54 (25% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.54–7.50 (m, 2H), 7.48–7.43 (m, 1H), 7.41–

7.35 (m, 2H), 4.89 (t, *J* = 1.8 Hz, 1H), 4.70 (dt, *J* = 2.1, 1.0 Hz, 1H), 3.94–3.84 (m, 1H), 3.74–3.63 (m, 1H), 2.75 (dd, *J* = 13.8, 1.3 Hz, 1H), 2.13 (dd, *J* = 13.8, 0.8 Hz, 1H), 2.08–1.94 (m, 3H), 1.69 (s, 3H), 1.68–1.61 (m, 1H), 1.37 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.8, 175.5, 141.9, 136.5, 131.3, 128.1, 127.4, 115.5, 47.2, 46.2, 44.0, 32.9, 26.9, 24.7, 19.8; IR (Neat Film NaCl) 3070, 2940, 1678, 1448, 1274, 1144, 726 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{22}NO_2$ $[M+H]^+$: 272.1645, found 272.1655; $[\alpha]_D^{25}$ –105.6° (c 0.99, $CHCl_3$, 97% ee).



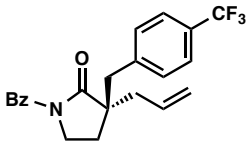
9

Benzoyl Lactam 9: Benzoyl lactam **9** was isolated by flash chromatography (SiO_2, 8 to 10% Et_2O in hexanes) as a colorless oil. 60.3% yield. R_f = 0.39 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55–7.49 (m, 2H), 7.49–7.43 (m, 1H), 7.42–7.34 (m, 2H), 5.32 (d, *J* = 1.7 Hz, 1H), 5.18 (s, 1H), 3.92 (ddt, *J* = 12.7, 4.8, 1.7 Hz, 1H), 3.75–3.66 (m, 1H), 3.04 (dd, *J* = 14.5, 1.0 Hz, 1H), 2.50 (d, *J* = 14.5 Hz, 1H), 2.16 (ddd, *J* = 13.4, 10.2, 4.4 Hz, 1H), 2.12–1.98 (m, 2H), 1.86–1.77 (m, 1H), 1.43 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.9, 175.3, 138.3, 136.4, 131.4, 128.1, 127.4, 117.1, 47.0, 47.0, 44.2, 32.8, 26.3, 19.7; IR (Neat Film NaCl) 2944, 2872, 1679, 1628, 1448, 1386, 1277, 1151, 894, 726 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{19}NO_2Cl$ $[M+H]^+$: 292.1099, found 292.1102; $[\alpha]_D^{25}$ –91.4° (c 0.94, $CHCl_3$, 95% ee).



10

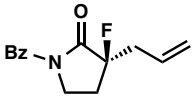
Benzoyl Lactam 10: Benzoyl lactam **10** was isolated by flash chromatography (SiO_2, 5 to 10% Et_2O in hexanes) as a colorless oil. 90.3% yield. R_f = 0.35 (35% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58–7.54 (m, 2H), 7.53–7.48 (m, 1H), 7.43–7.38 (m, 2H), 5.78 (dddd, *J* = 17.1, 10.2, 7.8, 7.0 Hz, 1H), 5.22–5.09 (m, 2H), 3.87 (dd, *J* = 7.7, 6.7 Hz, 2H), 2.36 (dd, *J* = 13.8, 7.0 Hz, 1H), 2.24 (dd, *J* = 13.7, 7.8 Hz, 1H), 2.15 (dt, *J* = 12.9, 7.6 Hz, 1H), 1.85 (dt, *J* = 13.1, 6.7 Hz, 1H), 1.22 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.6, 170.8, 134.4, 133.0, 131.8, 128.8, 127.7, 119.3, 46.2, 42.8, 41.8, 29.3, 22.8; IR (Neat Film NaCl) 3075, 2974, 2902, 1742, 1674, 1448, 1377, 1357, 1306, 1243, 1156, 921, 860, 731, 694, 656 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{15}H_{18}NO_2$ $[M+H]^+$: 244.1332, found 244.1336; $[\alpha]_D^{25}$ –31.6° (c 1.04, $CHCl_3$, 98% ee).



11

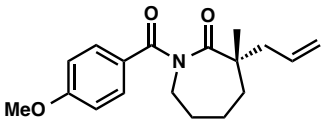
Benzoyl Lactam 11: Benzoyl lactam **11** was isolated by flash chromatography (SiO_2, 10 to 20% Et_2O in hexanes) as a colorless oil. 89.3% yield. R_f = 0.24 (20% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60–7.56 (m, 2H), 7.56–7.51 (m, 1H), 7.49–7.45 (m, 2H), 7.42 (ddt, *J* = 7.8, 6.7, 1.0 Hz, 2H), 7.31 (d, *J* = 7.7 Hz, 2H), 5.83 (dddd, *J* = 17.1, 10.1, 7.8, 6.9 Hz, 1H), 5.28–5.10 (m, 2H), 3.70 (dt, *J* = 11.4, 7.5 Hz, 1H), 3.39 (dt, *J* = 11.4, 6.9 Hz, 1H), 3.10 (d, *J* = 13.4 Hz, 1H), 2.76 (d, *J* = 13.5 Hz, 1H), 2.48 (dd, *J* = 13.8, 7.0 Hz, 1H), 2.32 (dd, *J* = 13.8, 7.8 Hz, 1H), 2.05 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR

(126 MHz, $CDCl_3$) δ 177.1, 170.5, 140.9, 134.2, 132.3, 131.9, 130.7, 129.4 (q, $J_{C\text{-}F}$ = 32.5 Hz), 128.7, 127.7, 125.3 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.1 (q, $J_{C\text{-}F}$ = 272.2 Hz), 120.1, 51.3, 43.0, 41.9, 41.9, 25.2; IR (Neat Film NaCl) 3080, 2977, 2913, 1738, 1677, 1325, 1294, 1244, 1164, 1121, 1067, 859, 728, 701, 665 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{22}H_{21}NO_2F_3$ $[M+H]^+$: 388.1524, found 388.1525; $[\alpha]_D^{25}$ +78.3° (c 1.90, $CHCl_3$, 93% ee).



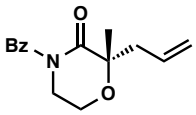
12

Benzoyl Lactam 12: Benzoyl lactam **12** was isolated by flash chromatography (SiO_2, 10 to 20% Et_2O in hexanes) as a white solid. 85.7% yield. R_f = 0.35 (35% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.63–7.58 (m, 2H), 7.58–7.52 (m, 1H), 7.49–7.40 (m, 2H), 5.87–5.73 (m, 1H), 5.32–5.20 (m, 2H), 4.00 (ddd, *J* = 11.5, 7.7, 6.5 Hz, 1H), 3.90–3.80 (m, 1H), 2.81–2.70 (m, 1H), 2.62–2.48 (m, 1H), 2.46–2.27 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 169.7 (d, $J_{C\text{-}F}$ = 23.1 Hz), 133.4, 132.4, 129.7 (d, $J_{C\text{-}F}$ = 7.1 Hz), 129.0, 127.9, 121.0, 97.0 (d, $J_{C\text{-}F}$ = 185.4 Hz), 42.0 (d, $J_{C\text{-}F}$ = 2.3 Hz), 38.4 (d, $J_{C\text{-}F}$ = 25.2 Hz), 28.5 (d, $J_{C\text{-}F}$ = 22.6 Hz); IR (Neat Film NaCl) 3076, 1760, 1676, 1365, 1314, 1253, 1132, 1058, 1008, 980, 920, 863, 791, 729 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{14}H_{15}NO_2F$ $[M+H]^+$: 248.1081, found 248.1092; $[\alpha]_D^{25}$ –120.5° (c 1.11, $CHCl_3$, 98% ee).



13

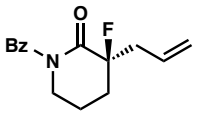
4-Methoxybenzoyl Lactam 13: Reaction performed in MTBE at 40 °C. 4-Methoxybenzoyl lactam **13** was isolated by flash chromatography (SiO_2, 8% Et_2O in hexanes) as a colorless oil. 83.2% yield. R_f = 0.48 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56–7.48 (m, 2H), 6.91–6.82 (m, 2H), 5.86–5.66 (m, 1H), 5.18–5.02 (m, 2H), 4.03 (ddd, *J* = 15.0, 8.0, 2.4 Hz, 1H), 3.88 (ddd, *J* = 15.1, 8.5, 2.1 Hz, 1H), 3.83 (s, 3H), 2.50 (ddt, *J* = 13.6, 7.0, 1.2 Hz, 1H), 2.35 (ddt, *J* = 13.7, 7.6, 1.1 Hz, 1H), 1.92–1.77 (m, 4H), 1.77–1.62 (m, 2H), 1.31 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.3, 174.7, 162.2, 133.9, 130.0, 128.9, 118.6, 113.5, 55.4, 47.7, 44.7, 43.0, 35.1, 28.2, 25.0, 23.4; IR (Neat Film NaCl) 3074, 2932, 1673, 1605, 1511, 1279, 1255, 1168, 1112, 1025, 837 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{24}NO_3$ $[M+H]^+$: 302.1751, found 302.1744; $[\alpha]_D^{25}$ –34.7° (c 0.75, $CHCl_3$, 93% ee).



14

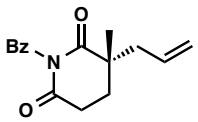
Benzoyl Lactam 14: Benzoyl lactam **14** was isolated by flash chromatography (SiO_2, 10 to 20% Et_2O in hexanes) as a colorless oil. 91.4% yield. R_f = 0.36 (35% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55–7.52 (m, 2H), 7.52–7.47 (m, 1H), 7.42–7.37 (m, 2H), 5.90 (ddt, *J* = 17.3, 10.3, 7.2 Hz, 1H), 5.26–5.10 (m, 2H), 4.12–3.95 (m, 3H), 3.94–3.81 (m, 1H), 2.71 (ddt, *J* = 14.1, 7.3, 1.2 Hz, 1H), 2.47 (ddt, *J* = 14.1, 7.0, 1.3 Hz, 1H), 1.48 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 173.1, 135.7, 132.1, 131.7, 128.1, 127.7, 119.3, 80.3, 59.4, 45.7, 43.1, 23.3; IR (Neat Film NaCl) 3075, 2978, 2894, 1685, 1448, 1373, 1283, 1227, 1111, 1092, 921, 726, 694 cm^{-1}; HRMS (FAB) *m/z* calc'd

for $C_{15}H_{18}NO_3$ $[M+H]^+$: 260.1287, found 260.1277; $[\alpha]_D^{25}$ –72.1° (c 0.97, $CHCl_3$, 99% ee).



15

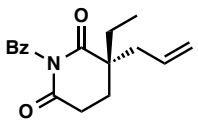
Benzoyl Lactam 15: Benzoyl lactam **15** was isolated by flash chromatography (SiO_2, 5 to 10% EtOAc in hexanes) as a colorless oil. 88.8% yield. R_f = 0.35 (35% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62–7.57 (m, 2H), 7.53–7.47 (m, 1H), 7.44–7.37 (m, 2H), 5.87–5.70 (m, 1H), 5.28–5.15 (m, 2H), 3.91 (dddd, J = 12.8, 6.0, 4.7, 1.4 Hz, 1H), 3.74 (dddd, J = 13.6, 9.2, 4.5, 2.4 Hz, 1H), 2.86–2.60 (m, 2H), 2.33–2.14 (m, 2H), 2.13–1.89 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5, 170.8 (d, $J_{C\text{-}F}$ = 23.5 Hz), 135.0, 132.0, 130.6 (d, $J_{C\text{-}F}$ = 6.5 Hz), 128.3, 128.0, 120.4, 93.9 (d, $J_{C\text{-}F}$ = 179.3 Hz), 46.4, 40.0 (d, $J_{C\text{-}F}$ = 23.6 Hz), 32.1 (d, $J_{C\text{-}F}$ = 22.5 Hz), 19.1 (d, $J_{C\text{-}F}$ = 4.6 Hz); IR (Neat Film NaCl) 3078, 2956, 1715, 1687, 1478, 1449, 1435, 1390, 1288, 1273, 1175, 1152, 1000, 930, 725, 694, 662 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{15}H_{16}NO_2F$ $[M+H]^+$: 262.1238, found 262.1244; $[\alpha]_D^{25}$ –120.6° (c 1.09, $CHCl_3$, 99% ee).



16

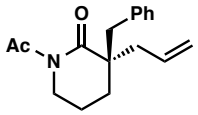
Benzoyl Glutarimide 16: Benzoyl glutarimide **16** was isolated by flash chromatography (SiO2, 17 to 25% EtOAc in hexanes) as a colorless oil. 81% yield. R_f = 0.21 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 8.29 Hz, 2H), 7.63 (t, J = 7.45

Hz, 1H), 7.48 (dd, *J* = 8.29, 7.45 Hz, 2H), 5.77 (dddd, *J* = 17.4, 10.2, 7.4, 7.0 Hz, 1H), 5.22–5.16 (m, 2H), 2.87–2.77 (m, 2H), 2.59 (ddt, *J* = 13.8, 7.0, 1.0 Hz, 1H), 2.40 (ddt, *J* = 13.8, 7.4, 1.0 Hz, 1H), 2.12 (ddd, *J* = 14.2, 7.73, 6.81 Hz, 1H), 1.85 (ddd, *J* = 14.2, 6.5, 6.1 Hz, 1H), 1.37 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.6, 171.6, 170.9, 134.8, 132.0, 131.9, 130.0, 129.1, 120.0, 41.9, 41.7, 29.2, 28.2, 22.8; IR (Neat Film NaCl) 3077, 2975, 2935, 1750, 1713, 1683, 1450, 1340, 1239, 1198, 981, 776 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{16}H_{18}NO_3[M+H]^+$: 272.1281, found 272.1281; $[\alpha]_D^{25}$ –31.3° (c 1.00, $CHCl_3$, 94% ee).



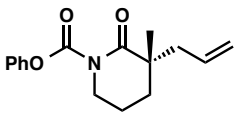
17

Benzoyl Glutarimide 17: Benzoyl glutarimide **17** was isolated by flash chromatography (SiO2, 17 to 25% EtOAc in hexanes) as a colorless oil. 86% yield. R_f = 0.24 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.38 Hz, 2H), 7.64 (t, *J* = 7.46 Hz, 1H), 7.48 (dd, *J* = 8.38, 7.46 Hz, 2H), 5.75 (dddd, *J* = 17.2, 10.2, 7.7, 7.0 Hz, 1H),5.20–5.15 (m, 2H), 2.86–2.76 (m, 2H), 2.60 (ddt, *J* = 14.0, 7.0, 1.1 Hz, 1H), 2.37 (ddt, *J* = 14.0, 7.7, 1.1 Hz, 1H), 2.05 (ddd, *J* = 14.3, 7.85, 6.81 Hz, 1H), 1.97 (ddd, *J* = 14.3, 6.56, 6.24 Hz, 1H), 1.87–1.75 (m, 2H), 0.97 (t, *J* = 7.46, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9, 171.6, 171.0, 134.8, 132.4, 131.9, 130.0, 129.0, 119.8, 45.4, 39.3, 29.0, 28.1, 25.4, 8.1; IR (Neat Film NaCl) 3076, 2974, 2940, 2882, 1750, 1713, 1683, 1450, 1340, 1239, 1195, 1001, 923, 778 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{17}H_{20}NO_3[M+H]^+$: 286.1438, found 286.1432; $[\alpha]_D^{25}$ –16.2° (c 1.00, $CHCl_3$, 96% ee).



18

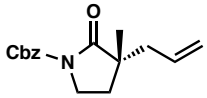
Acyl Lactam 18: Acyl lactam **18** was isolated by flash chromatography (SiO_2, 10 to 20% Et_2O in hexanes) as a colorless oil. 88.4% yield. R_f = 0.40 (35% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.17 (m, 3H), 7.17–7.09 (m, 2H), 5.77 (dddd, *J* = 17.0, 10.3, 7.9, 6.8 Hz, 1H), 5.19–5.05 (m, 2H), 3.60–3.48 (m, 1H), 3.44 (dddd, *J* = 13.0, 7.0, 4.6, 1.0 Hz, 1H), 3.27 (d, *J* = 13.3 Hz, 1H), 2.68 (d, *J* = 13.2 Hz, 1H), 2.66–2.62 (m, 1H), 2.51 (s, 3H), 2.23 (ddt, *J* = 13.5, 7.9, 1.1 Hz, 1H), 1.90–1.61 (m, 3H), 1.57–1.38 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.0, 174.2, 137.1, 133.2, 130.4, 128.3, 126.8, 119.2, 49.7, 45.1, 44.8, 44.5, 29.0, 27.6, 19.6; IR (Neat Film NaCl) 3028, 2941, 1691, 1367, 1291, 1247, 111178, 1131, 1031, 923 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{22}NO_2$ $[M+H]^+$: 272.1645, found 272.1646; $[\alpha]_D^{25}$ +11.4° (c 1.03, $CHCl_3$, 88% ee).



19

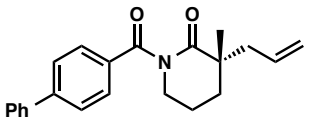
Phenyl Carbamate Lactam 19: Phenyl Carbamate lactam **19** was isolated by flash chromatography (SiO_2, 10 to 20% Et_2O in hexanes) as a colorless oil. 82.2% yield. R_f = 0.39 (35% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.35 (m, 2H), 7.25–7.21 (m, 1H), 7.20–7.15 (m, 2H), 5.79 (dddd, *J* = 16.7, 10.4, 7.8, 7.0 Hz, 1H), 5.18–5.08 (m, 2H), 3.89–3.82 (m, 1H), 3.78–3.70 (m, 1H), 2.55 (ddt, *J* = 13.6, 7.0, 1.2 Hz, 1H), 2.33 (ddt, *J* = 13.6, 7.8, 1.1 Hz, 1H), 2.00–1.85 (m, 3H), 1.70–1.59 (m, 1H), 1.30 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.3, 153.8, 150.8, 133.3, 129.3, 125.9, 121.5, 118.9,

48.2, 45.0, 44.1, 33.0, 25.3, 19.6; IR (Neat Film NaCl) 3074, 2939, 2870, 1783, 1733, 1718, 1494, 1299, 1265, 1203, 1153, 991, 920 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{20}NO_3$ $[M+H]^+$: 274.1438, found 274.1444; $[\alpha]_D^{25}$ –81.6° (c 1.11, $CHCl_3$, 94% ee).



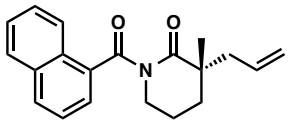
20

Benzyl Carbamate Lactam 20: Benzyl carbamate lactam **20** was isolated by flash chromatography (SiO_2, 10 to 30% Et_2O in hexanes) as a colorless oil. 85.9% yield. R_f = 0.41 (35% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.46–7.42 (m, 2H), 7.37 (ddd, *J* = 7.4, 6.3, 1.5 Hz, 2H), 7.35–7.30 (m, 1H), 5.74 (dddd, *J* = 15.9, 11.0, 7.9, 6.9 Hz, 1H), 5.28 (s, 2H), 5.18–5.06 (m, 2H), 3.77–3.63 (m, 2H), 2.33 (ddt, *J* = 13.8, 6.9, 1.2 Hz, 1H), 2.24 (ddt, *J* = 13.8, 7.9, 1.0 Hz, 1H), 2.03 (ddd, *J* = 12.9, 8.1, 6.9 Hz, 1H), 1.74 (ddd, *J* = 13.2, 7.7, 5.9 Hz, 1H), 1.19 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.0, 151.7, 135.3, 133.0, 128.6, 128.3, 128.1, 119.1, 68.0, 45.5, 42.9, 41.7, 29.5, 22.6; IR (Neat Film NaCl) 3066, 2973, 2930, 2903, 1789, 1750, 1719, 1456, 1380, 1363, 1301, 1217, 1001, 919, 776, 736 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{20}NO_3$ $[M+H]^+$: 274.1438, found 274.1438; $[\alpha]_D^{25}$ –41.4° (c 1.02, $CHCl_3$, 91% ee).



21

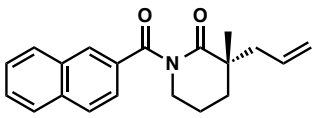
4-Phenylbenzoyl Lactam 21: 4-Phenylbenzoyl lactam **21** was isolated by flash chromatography (SiO_2, 10 to 15% Et_2O in pentane) as a colorless oil. 84.6% yield. R_f = 0.43 (35% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.64–7.57 (m, 6H), 7.45 (ddd, *J* = 7.8, 6.7, 1.1 Hz, 2H), 7.40–7.34 (m, 1H), 5.84–5.70 (m, 1H), 5.20–5.09 (m, 2H), 3.91–3.82 (m, 1H), 3.74 (ddd, *J* = 12.1, 7.4, 5.7 Hz, 1H), 2.59 (ddd, *J* = 13.7, 7.0, 1.3 Hz, 1H), 2.32 (ddt, *J* = 13.7, 7.7, 1.2 Hz, 1H), 2.10–1.91 (m, 3H), 1.77–1.64 (m, 1H), 1.34 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.1, 175.1, 144.2, 140.2, 135.1, 133.3, 128.8, 128.1, 127.8, 127.2, 126.9, 119.0, 47.2, 44.0, 43.3, 33.3, 25.2, 19.5; IR (Neat Film NaCl) 3073, 2938, 2869, 1677, 1607, 1478, 1383, 1295, 1279, 1145, 922, 849, 743, 698 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{22}H_{24}NO_2$ $[M+H]^+$: 334.1802, found 334.1812; $[\alpha]_D^{25}$ –82.6° (c 0.75, $CHCl_3$, 99% ee).



22

1-Naphthoyl Lactam 22: 1-Naphthoyl lactam **22** was isolated by flash chromatography (SiO_2, 10 to 20% Et_2O in hexanes) as a white solid. 86.3% yield. R_f = 0.42 (35% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.03–7.97 (m, 1H), 7.90–7.83 (m, 2H), 7.55–7.46 (m, 2H), 7.42 (dd, *J* = 8.1, 7.1 Hz, 1H), 7.37 (dd, *J* = 7.1, 1.3 Hz, 1H), 5.64 (dddd, *J* = 17.2, 10.2, 7.6, 7.1 Hz, 1H), 5.16–4.97 (m, 2H), 4.05 (dddd, *J* = 12.8, 6.3, 5.2, 1.3 Hz, 1H), 3.95–3.82 (m, 1H), 2.43 (ddt, *J* = 13.7, 7.1, 1.2 Hz, 1H), 2.19 (ddt, *J* = 13.7, 7.6, 1.1 Hz, 1H), 2.11–1.99 (m, 2H), 1.99–1.91 (m, 1H), 1.73–1.64 (m, 1H), 1.18 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.5, 174.3, 135.8, 133.6, 133.1, 130.0, 129.8, 128.4, 126.9, 126.2, 124.9, 124.5, 123.3, 118.9, 46.4, 44.1, 43.3, 33.2, 24.8, 19.5; IR (Neat Film NaCl)

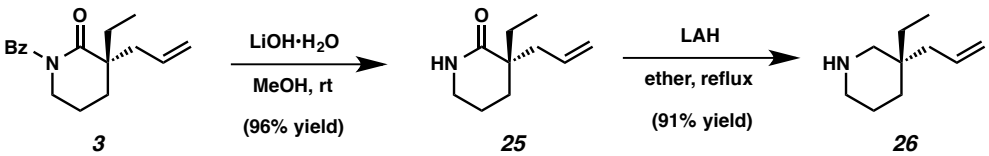
3062, 2937, 2869, 1702, 1677, 1381, 1295, 1251, 1147, 923, 781 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{20}H_{22}NO_2$ $[M+H]^+$: 308.1645, found 308.1648; $[\alpha]_D^{25}$ –102.3° (c 1.12, $CHCl_3$, 99% ee).



23

2-Naphthoyl Lactam 23: 2-Naphthoyl lactam **23** was isolated by flash chromatography (SiO_2, 10 to 20% Et_2O in hexames) as a colorless oil. 82.1% yield. R_f = 0.42 (35% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.93–7.76 (m, 3H), 7.63–7.43 (m, 3H), 5.87–5.67 (m, 1H), 5.21–5.06 (m, 2H), 3.95–3.84 (m, 1H), 3.84–3.72 (m, 1H), 2.58 (ddt, *J* = 13.8, 7.1, 1.2 Hz, 1H), 2.33 (ddt, *J* = 13.7, 7.6, 1.1 Hz, 1H), 2.12–1.89 (m, 3H), 1.71 (ddt, *J* = 10.9, 4.9, 4.3, 2.4 Hz, 1H), 1.34 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.0, 175.3, 134.6, 133.7, 133.3, 132.5, 128.9, 128.1, 127.7, 127.7, 127.5, 126.4, 124.1, 118.9, 47.2, 44.0, 43.3, 33.3, 25.1, 19.5; IR (Neat Film NaCl) 3059, 2938, 2869, 1677, 1467, 1383, 1293, 1234, 1165, 1139, 923, 862, 822, 780, 762 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{20}H_{22}NO_2$ $[M+H]^+$: 308.1650, found 308.1638; $[\alpha]_D^{25}$ –257.4° (c 0.92, $CHCl_3$, 97% ee).

*2.7.9 Procedures for the Derivatization of Lactam **3***



3 ***25*** ***26***

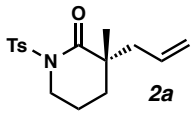
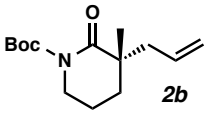
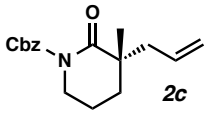
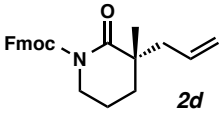
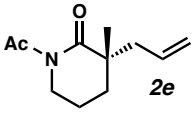
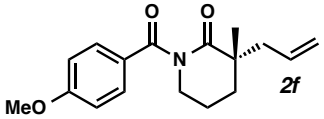
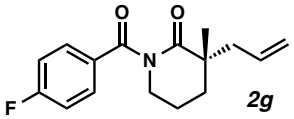
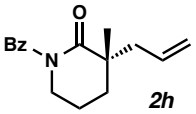
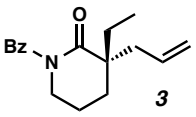
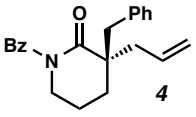
Piperidin-2-one 25: To a solution of lactam **3** (2.00 g, 7.37 mmol, 1.00 equiv) in MeOH (188 mL) was added a solution of $LiOH•H_2O$ (464 mg, 11.1 mmol, 1.50 equiv) in H_2O (75 mL). After 20 h, the reaction mixture was concentrated under reduced pressure and diluted with saturated aqueous $NaHCO_3$ (100 mL) and EtOAc (75 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (4 x 75 mL). The combined organic phases were washed with brine (2 x 30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (3 x 25 cm SiO_2, 40 to 60% EtOAc in hexanes) to afford known[30] lactam **25** as a colorless oil (1.18 g, 96% yield). R_f = 0.21 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 (br s, 1H), 5.88–5.66 (m, 1H), 5.12–4.95 (m, 2H), 3.25 (td, J = 5.8, 1.9 Hz, 2H), 2.48 (ddt, J = 13.6, 6.7, 1.3 Hz, 1H), 2.18 (ddt, J = 13.6, 8.1, 1.0 Hz, 1H), 1.87–1.62 (m, 5H), 1.49 (dq, J = 13.5, 7.4 Hz, 1H), 0.89 (t, J = 7.5 Hz, 3H); $[\alpha]_D^{25}$ – 13.7° (c 0.57, $CHCl_3$, 99% ee).

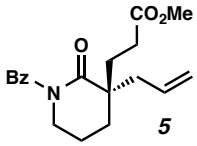
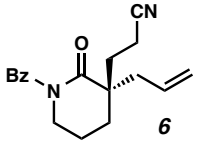
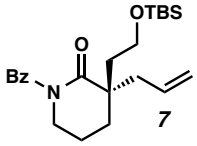
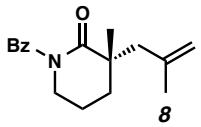
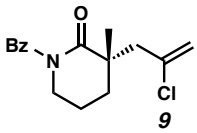
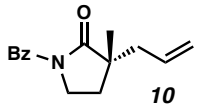
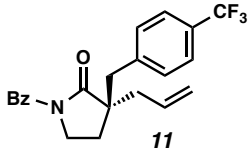
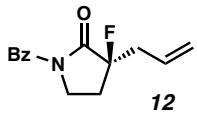
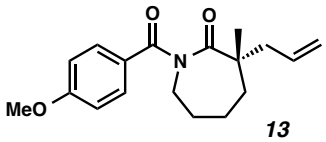
Piperidine 26: To a solution of piperidin-2-one **25** (250 mg, 1.49 mmol, 1.00 equiv) in ether (14.9 mL) was added lithium aluminum hydride (170 mg, 4.48 mmol, 3.0 equiv) (*Caution: Gas evolution and exotherm*). After stirring at ambient temperature for 5 min, the reaction mixture was heated to reflux for 36 h, cooled (0 °C), and quenched with saturated aqueous K_2CO_3 (20 mL, *Caution: Gas evolution and exotherm*). The phases were separated, and the aqueous phase was extracted with Et_2O (4 x 75 mL). The combined organic phases were washed with brine (2 x 30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide piperidine **26** (206 mg, 90% yield) as a colorless oil. R_f = 0.29 (20% MeOH in DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (ddt,

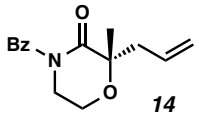
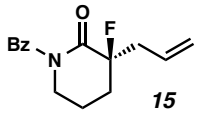
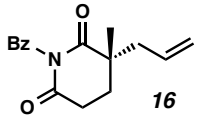
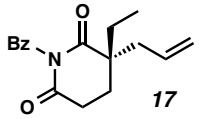
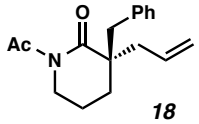
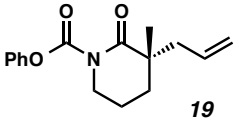
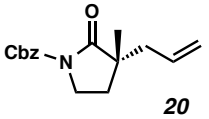
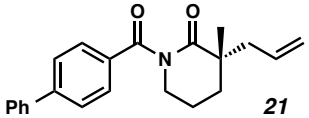
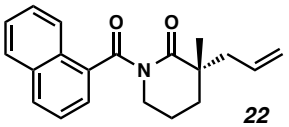
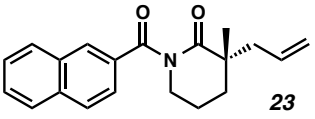
J = 16.4, 10.6, 7.5 Hz, 1H), 5.10–4.96 (m, 2H), 2.81–2.68 (m, 2H), 2.53 (dd, *J* = 13.0, 20.0 Hz, 2H), 2.06 (d, *J* = 7.5 Hz, 2H), 2.02 (br s, 1H), 1.55–1.42 (m, 2H), 1.40–1.30 (m, 2H), 1.32 (q, *J* = 7.5 Hz, 2H), 0.80 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.6, 116.9, 55.1, 47.0, 39.2, 34.9, 33.6, 27.7, 22.4, 7.1; IR (Neat Film NaCl) 3298, 3073, 2963, 2931, 2853, 2799, 1638, 1462, 1125, 996, 911 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{10}H_{20}N$ $[M+H]^+$: 154.1590, found 154.1590; $[\alpha]_D^{25}$ –7.5° (c 0.80, MeOH, 96% ee).

2.7.10 Methods for the Determination of Enantiomeric Excess

Table 2.5 Analytical HPLC and SFC assays and retention times

entry	product	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
1	 ***2a***	HPLC Chiralpak AD-H 5% EtOH in hexanes isocratic, 1.0 mL/min 254 nm	19.10	15.77	75
2	 ***2b***	HPLC Chiralcel OJ-H 0.1% IPA in hexanes isocratic, 1.0 mL/min 220 nm	15.22	18.10	81
3	 ***2c***	HPLC Chiralcel OJ-H 3% EtOH in hexanes isocratic, 1.0 mL/min 220 nm	18.68	17.60	86
4	 ***2d***	HPLC Chiralcel OD 3% EtOH in hexanes isocratic, 1.0 mL/min 254 nm	28.89	21.47	89
5	 ***2e***	HPLC Chiralcel OJ 1% IPA in hexanes isocratic, 1.0 mL/min 254 nm	10.15	9.71	91
6	 ***2f***	HPLC Chiralcel OD-H 3% IPA in hexanes isocratic, 1.0 mL/min 254 nm	15.73	18.12	99
7	 ***2g***	HPLC Chiralcel OJ-H 2% IPA in hexanes isocratic, 1.0 mL/min 254 nm	29.12	19.74	99
8	 ***2h***	HPLC Chiralcel OJ-H 5% IPA in hexanes isocratic, 1.0 mL/min 254 nm	32.97	31.16	99
9	 ***3***	SFC Chiralcel OJ-H 3% MeOH in CO_2 isocratic, 5.0 mL/min 254 nm	3.85	2.49	99
10	 ***4***	SFC Chiralcel OD-H 10% MeOH in CO_2 isocratic, 5.0 mL/min 254 nm	3.84	3.20	99

entry	product	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
11	 ***5***	HPLC Chiralpak AD-H 3% EtOH in hexane isocratic, 1.0 mL/min 254 nm	32.69	27.83	99
12	 ***6***	SFC Chiralpak IC 10% MeOH in CO_2 isocratic, 5.0 mL/min 254 nm	2.67	3.84	99
13	 ***7***	HPLC Chiralcel OJ-H 3% IPA in hexane isocratic, 1.0 mL/min 254 nm	7.75	5.95	96
14	 ***8***	HPLC Chiralcel OJ-H 8% IPA in hexane isocratic, 1.0 mL/min 254 nm	25.94	19.12	97
15	 ***9***	HPLC Chiralpak AD 2% IPA in hexane isocratic, 1.0 mL/min 254 nm	18.72	27.05	95
16	 ***10***	SFC Chiralcel OJ-H 10% MeOH in CO_2 isocratic, 5.0 mL/min 254 nm	2.93	1.84	98
17	 ***11***	SFC Chiralcel OJ-H 5% MeOH in CO_2 isocratic, 5.0 mL/min 254 nm	2.31	3.73	93
18	 ***12***	SFC Chiralpak AD-H 15% MeOH in CO_2 isocratic, 5.0 mL/min 254 nm	4.16	5.05	99
19	 ***13***	HPLC Chiralcel OJ-H 5% IPA in hexane isocratic, 1.0 mL/min 254 nm	29.16	24.82	93

entry	product	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
20	 ***14***	SFC Chiralpak AD-H 10% MeOH in CO_2 isocratic, 5.0 mL/min 254 nm	1.96	1.41	99
21	 ***15***	SFC Chiralcel OJ-H 5% MeOH in CO_2 isocratic, 5.0 mL/min 254 nm	2.55	2.25	99
22	 ***16***	SFC Chiralcel OJ-H 3% MeOH in CO_2 isocratic, 5.0 mL/min 254 nm	3.05	2.72	94
23	 ***17***	SFC Chiralcel OJ-H 3% MeOH in CO_2 isocratic, 5.0 mL/min 254 nm	3.28	2.87	96
24	 ***18***	SFC Chiralpak AD-H 3% MeOH in CO_2 isocratic, 3.0 mL/min 235 nm	4.03	4.69	88
25	 ***19***	SFC Chiralcel OB-H 10% MeOH in CO_2 isocratic, 5.0 mL/min 210 nm	2.65	2.39	94
26	 ***20***	SFC Chiralpak AD-H 15% MeOH in CO_2 isocratic, 5.0 mL/min 210 nm	4.23	2.51	91
27	 ***21***	SFC Chiralcel OJ-H 10% MeOH in CO_2 isocratic, 5.0 mL/min 254 nm	4.53	3.80	99
28	 ***22***	SFC Chiralcel OB-H 10% MeOH in CO_2 isocratic, 5.0 mL/min 210 nm	4.05	4.60	99
29	 ***23***	SFC Chiralpak AD-H 20% MeOH in CO_2 isocratic, 5.0 mL/min 254 nm	3.73	2.93	97

2.8 Notes and References

(1) Cordell, G. A., Ed. *The Alkaloids: Chemistry And Biology*. In *Alkaloids*; Elsevier: San Diego, 2010; Vol. 69, p. 609.

(2) Joule, J. A.; Mills, K. *Heterocycles in Medicine*. In *Heterocyclic Chemistry*, 5th Ed; Wiley: Chichester, 2010.

(3) Anton, A.; Baird, B. R. *Polyamides, fibers*. *Kirk-Othmer Encyclopedia of Chemical Technology* (5th Ed.) **2006**, *19*, 739–772.

(4) Schlack, P. *Pure Appl. Chem*. **1967**, *15*, 507–523.

(5) Kohan, M. I., Ed. *Nylon*. In *Plastics*; Interscience: New York, 1973.

(6) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843–9873.

(7) Enders, D.; Teschner, P.; Raabe, G.; Runsink, J. *Eur. J. Org. Chem*. **2001**, 4463–4477.

(8) Amat, M.; Lozano, O.; Escolano, C.; Molins, E.; Bosch, J. *J. Org. Chem*. **2007**, *72*, 4431–4439.

(9) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003–3025.

(10) Badillo, J. J.; Hanhan, N. V.; Franz, A. K. *Curr. Opin. Drug Disc. Dev*. **2010**, *13*, 758–776.

(11) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal*. **2010**, *352*, 1381–1407.

(12) Moss, T. A.; Alonso, B.; Fenwick, D. R.; Dixon, D. J. *Angew. Chem., Int. Ed*. **2010**, *49*, 568–571.

(13) Trost, B. M. *J. Org. Chem*. **2004**, *69*, 5813–5837.

(14) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed*. **2008**, *47*, 258–297.

(15) Mohr, J. T.; Stoltz, B. M. *Chem. Asian J*. **2007**, *2*, 1476–1491.

(16) Weaver, J. D.; Recio, A., III.; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846–1913.

(17) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045.

(18) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924–6927.

(19) Seto, M.; Roizen, J. L.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6873–6876.

(20) Streuff, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nature Chem.* **2010**, *2*, 192–196.

(21) McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738–7739.

(22) White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 810–811.

(23) Enquist, J. A., Jr.; Stoltz, B. M. *Nature* **2008**, *453*, 1228–1231.

(24) Day, J. J.; McFadden, R. M.; Virgil, S. C.; Kolding, H.; Alleva, J. L.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 6814–6818.

(25) McDougal, N. T.; Virgil, S. C.; Stoltz, B. M. *Synlett* **2010**, 1712–1716.

(26) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336–345.

(27) Tani, K.; Behenna, D. C.; McFadden, R. M.; Stoltz, B. M. *Org. Lett.* **2007**, *9*, 2529–2531.

(28) McDougal, N. T.; Streuff, J.; Mukherjee, H.; Virgil, S. C.; Stoltz, B. M. *Tetrahedron Lett.* **2010**, *51*, 5550–5554.

(29) Edler, M. C.; Yang, G.; Jung, M. K.; Bai, R.; Bornmann, W. G.; Hamel, E. *Arch. Biochem. Biophys.* **2009**, *487*, 98–104.

(30) Magnus, P.; Rainey, T. *Tetrahedron* **2001**, *57*, 8647–8651.

(31) Compound **27** can be prepared by methylation of diallyl malonate in a manner analogous to dimethyl 2-methylmalonate or by esterification of 2-methyl malonic acid, see: (a) Hosokawa, T.; Yamanaka, T.; Itotani, M.; Murahashi, S.-I. *J. Org. Chem.* **1995**, *60*, 6159–6167. (b) Imao, D.; Itoi, A.; Yamazaki, A.; Shirakura, M.; Ohtoshi, R.; Ogata, K.; Ohmori, Y.; Ohta, T.; Ito, Y. *J. Org. Chem.* **2007**, *72*, 1652–1658.

(32) Tsuzuki, Y.; Chiba, K.; Mizuno, K.; Tomita, K.; Suzuki, K. *Tetrahedron: Asymmetry* **2001**, *12*, 2989–2997.

(33) The palladium source was chosen solely to simply the chromatographic separation of the dba from the lactam product.