Multifaceted Interception of 2-chloro-2-oxoacetic Anhydrides: A Direct Asymmetric Synthesis of β-lactams

Li Huang, Wenjun Zhao, Richard J. Staples and William D. Wulff
Department of Chemistry, Michigan State University, East Lansing, MI 48824

Supporting Information_I

Table of Contents

I. General experimental

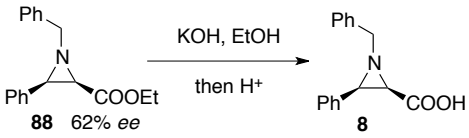
General information: Dichloromethane was distilled from calcium hydride under nitrogen. Toluene and benzene were distilled from sodium under nitrogen. Hexanes and ethyl acetate were ACS grade and used as purchased. Other reagents were used as purchased from Aldrich. VANOL and VAPOL were prepared according to a literature procedure and were determined to be at least 99% optical purity.[1] Preparation of aziridine esters **9**[2], **82**[3], **88**[4], **89**[2], **91**[2], **93-98**[4], **99**[9], **101**[2], **103**[3], **110**[2], **118**[2], **122**[5], **124**[5] have been previously reported.

Melting points were determined on a Thomas Hoover capillary melting point apparatus and were uncorrected. IR spectra were taken on a Galaxy series FTIR-3000 spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on a Varian Inova-300 MHz, Varian UnityPlus-500 MHz or Varian Inova-600 MHz instrument in $CDCl_3$ unless otherwise noted. $CDCl_3$ was used as the internal standard for both ^{1}H NMR (δ = 7.24) and ^{13}C NMR (δ = 77.0). HR-MS was performed in the department of Biochemistry at Michigan State University. Analytical thin-layer chromatography (TLC) was performed on silica gel plates with F-254 indicator. Visualization was by short wave (254 nm) and long wave (365 nm) ultraviolet light, or by staining with phosphomolybdic acid in ethanol. Column chromatography was performed with silica gel 60 (230 – 450 mesh). HPLC analyses were carried out using a Varian Prostar 210 Solvent Delivery Module with a Prostar 330 PDA Detector and a Prostar Workstation. Optical rotations were obtained on a Perkin-Elmer 341 polarimeter at a wavelength of 589 nm (sodium D line) using a 1.0-decimeter cell with a total volume of 1.0 mL. Specific rotations are reported in degrees per decimeter at 20 °C.

Although we have not experienced any problems with the use of ethyl diazoacetate herein, we note that diazo compounds in general are heat sensitive and potentially explosive and should be handled with due care.

II. Preparation of acids

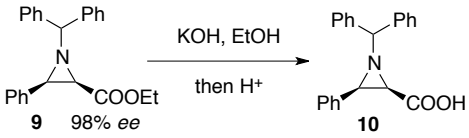
*Preparation of acid **8**:*



88 62% *ee* **8**

To a suspension of ester **88**[4] (62% *ee*, 170 mg, 0.600 mmol, 1.00 equiv) in ethanol (1 mL) was added a solution of KOH (170 mg, 3.00 mmol, 5.00 equiv) in H_2O (2 mL). The resulting mixture was refluxed for 1 h. After it was cooled to rt, *aq* citric acid (2N, 2 mL) was added. The white precipitate was collected by filtration. The product was obtained as a white solid (150 mg, 0.593 mmol) in 99% yield; mp 123-125 °C; R_f = 0.10 (hexane:EtOAc 4:1). Spectral data for **8**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.74 (d, 1H, *J* = 6.0 Hz), 3.18 (d, 1H, *J* = 6.5 Hz), 3.60 (d, 1H, *J* = 14.0 Hz), 3.81 (d, 1H, *J* = 14.0 Hz), 7.12-7.48 (m, 10H), 12.20 (brs, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 46.22, 46.74, 62.06, 126.90, 127.03, 127.63, 127.69, 128.23, 135.98, 138.73, 168.78 (One sp^2 C not located); IR (thin film) 1718(s) 1224(s) cm^{-1}; HRMS calcd for $C_{16}H_{16}NO_2$ (M+H, ESI^+) *m/z* 254.1181, meas 254.1163; $[\alpha]^{20}_D$ 18.2° (*c* 1.0, CH_2Cl_2) on 62% *ee* material.

*Preparation of acid **10**:*

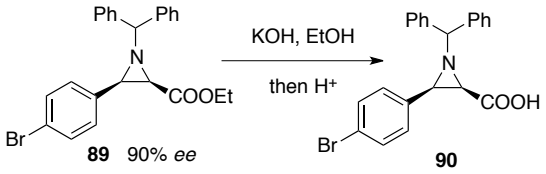


9 98% *ee* **10**

To a 50 mL round bottom flask containing ester **9**[2] (98% *ee*, 1.07 g, 3.00 mmol, 1.00 equiv) and ethanol (5 mL) was added an aqueous solution of KOH (840 mg, 15.0 mmol, 5.00 equiv) in H_2O (5 mL). The resulting suspension was refluxed for 1 h during which time it became a homogeneous solution. After it was cooled to rt, ethanol was removed by rotary evaporation. To the remaining aqueous solution was added *aq* citric acid (2N, 10 mL). The resulting white precipitate was collected by filtration and washed with H_2O and hexane to obtain the pure acid **10** (976 mg, 2.98 mmol, 99%) as a white solid; mp 143-145 °C; R_f = 0.10 (hexane:EtOAc 4:1). Spectral data for acid **10**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.78 (d, 1H, *J* = 7.2 Hz), 3.40 (d, 1H, *J* = 6.6 Hz), 4.04 (s, 1H), 7.20-7.30 (m, 8H), 7.32 (q, 4H, *J* = 7.2 Hz), 7.47 (t, 4H, *J* = 8.4 Hz); ^{1}H NMR

(600 MHz, DMSO-d_6) δ 2.77 (d, 1H, *J* = 7.2 Hz), 3.32 (d, 1H, *J* = 6.6 Hz), 4.17 (s, 1H), 7.14-7.30 (m, 7H), 7.34 (t, 2H, *J* = 7.8 Hz), 7.41 (d, 2H, *J* = 7.8 Hz), 7.49 (d, 2H, *J* = 8.4 Hz), 7.61 (d, 2H, *J* = 7.8 Hz), 12.22 (brs, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 46.39, 47.14, 75.34, 126.94, 126.99, 127.05, 127.08, 127.25, 127.59, 127.63, 128.31, 128.34, 135.70, 143.07, 143.20, 168.58; IR (thin film) 1705(s), 1244(m) cm^{-1}; HRMS calcd for $C_{22}H_{20}NO_2$ (M+H, ESI$^+$) *m/z* 330.1494, meas 330.1506; $[\alpha]^{20}_D$ 19.6° (*c* 0.5, CH_2Cl_2) on 98% *ee* material.

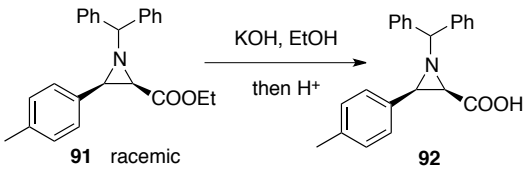
*Preparation of acid **90**:*



89 90% *ee* **90**

To a suspension of ester **89**[2] (90% *ee*, 872 mg, 2.00 mmol, 1.00 equiv) in ethanol (5 mL) was added a solution of KOH (560 mg, 10.00 mmol, 5.00 equiv) in H_2O (5 mL). The resulting mixture was refluxed for 1 h. After it was cooled to rt, *aq* citric acid (2N, 5 mL) was added. The white precipitate was collected by filtration and washed with H_2O and hexanes. The solid was dissolved in Et_2O (25 mL), dried (Na_2SO_4) and filtered. The filtrate was concentrated to afford the product **90** as a white solid (810 mg, 1.985 mmol) in 99% yield; mp 140-142 °C; R_f = 0.20 (hexane:EtOAc 4:1). Spectral data for acid **90**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.79 (d, 1H, *J* = 7.0 Hz), 3.32 (d, 1H, *J* = 7.0 Hz), 4.03 (s, 1H), 7.17 (d, 2H, *J* = 8.5 Hz), 7.22-7.60 (m, 13H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 45.45, 48.15, 77.23, 122.04, 126.98, 127.40, 127.77, 127.88, 128.75, 128.84, 129.30, 131.45, 133.02, 141.14, 141.55, 169.82; IR (thin film) 1711(s), 1265(m) cm^{-1}; HRMS calcd for $C_{22}H_{19}NO_2{}^{79}Br$ (M+H, ESI$^+$) *m/z* 408.0599, meas 408.0576; $[\alpha]^{20}_D$ 3.5° (*c* 1.0, CH_2Cl_2) on 90% *ee* material.

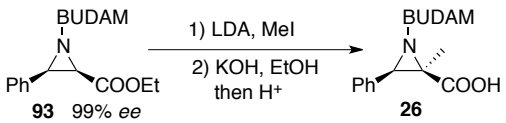
*Preparation of acid **92**:*



91 racemic **92**

To a 50 mL round bottom flask containing ester **91**[2] (racemic, 250 mg, 0.674 mmol, 1.00 equiv), ethanol (2 mL) and THF (1 mL) was added an aqueous solution of KOH (189 mg, 3.37 mmol, 5.00 equiv) in H_2O (2 mL). The resulting suspension was refluxed for 2 h during which time it became a homogeneous solution. After it was cooled to rt, *aq* citric acid (2N, 5 mL) was added. The resulting white precipitate was collected by filtration and washed with H_2O and hexane to obtain the pure acid **92** (230 mg, 0.670 mmol, 99%) as a white solid; mp 147-149 °C; R_f = 0.10 (hexane:EtOAc 4:1). Spectral data for acid **92**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.23 (s, 3H), 2.72 (d, 1H, *J* = 6.5 Hz), 3.26 (d, 1H, *J* = 6.5 Hz), 4.14 (s, 1H), 7.00-7.40 (m, 10H), 7.46 (d, 2H, *J* = 7.5 Hz), 7.58 (d, 2H, *J* = 7.5 Hz), 12.16 (brs, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 20.67, 46.33, 47.03, 75.32, 126.92, 127.00, 127.20, 127.48, 128.24, 128.31, 132.64, 136.19, 143.09, 143.21, 168.58 (Two sp^2 carbon not located); IR (thin film) 1705(s), 1244(m) cm^{-1}; HRMS calcd for $C_{23}H_{22}NO_2$ (M+H, ESI$^+$) *m/z* 344.1651, meas 344.1679.

*Preparation of acid **26**:*

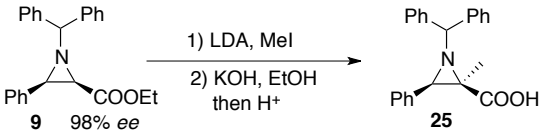


*Alkylation: General procedure for alkylation, illustrated for the acid **26:*** To a flame-dried 50 mL round bottom flask filled with N_2 was charged with dry *i*-Pr_2NH (0.050 mL, 0.33 mmol, 2.1 equiv) and dry THF (3 mL). The vacuum adapter was quickly replaced with a septum to which a N_2 balloon was attached *via* a needle. The flask was cooled in a dry ice-acetone bath (–78 °C). *n*-BuLi (2.3M, 0.14 mL, 0.32 mmol, 2.0 equiv) was added dropwise *via* syringe. After it was stirred at –78 °C for 5 min, the solution was stirred at 0 °C for 15 min. After the flask was cooled to –78 °C again, a solution of ester **93**[4] (99% *ee*, 100 mg, 0.160 mmol, 1.00 equiv) in dry THF (2 mL) was added dropwise. The resulting yellow solution was stirred at –78 °C for 30 min. Then CH_3I (0.030 mL, 0.48 mmol, 3.0 equiv) was added *via* syringe. The resulting mixture was stirred at –78 °C for 1 h, and then dry ice-acetone bath was removed. And the reaction mixture was allowed to warm up to rt slowly over a period of 1 h. Then *aq* sat $NaHCO_3$ (2 mL) and ether (10 mL) were added. The aqueous layer was separated and extracted with ether (2 × 5 mL). The combined

organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated to afford the methylated ester **18** used directly in the next step.

Hydrolysis: To the mixture of the methylated ester in THF (1 mL) and ethanol (1 mL) was added an aqueous solution of KOH (45 mg, 0.80 mmol, 5.0 equiv) in H_2O (1 mL). The resulting mixture was refluxed overnight (~17 h). After it was cooled to rt, the volatiles were evaporated and *aq* citric acid (2N, 2 mL) was added. The mixture was extracted with ether (10 mL + 2 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1). The product **26** was obtained as a white solid (85 mg, 0.14 mmol) in 87% yield over 2 steps; mp 72-74 °C; R_f = 0.30 (hexane:EtOAc 4:1). Spectral data for **26**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36, 1.38 (2s, 36H), 1.63 (s, 3H), 3.24 (s, 1H), 3.638, 3.642 (2s, 6H), 4.31 (s, 1H), 6.96-7.00 (m, 2H), 7.14-7.18 (m, 3H), 7.24 (s, 2H), 7.29 (s, 2H), 10.00 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.14, 32.01, 32.09, 35.80, 35.82, 49.48, 53.65, 64.19, 64.24, 71.06, 125.00, 126.08, 127.28, 128.03, 128.36, 134.54, 135.49, 135.85, 143.83, 143.90, 158.72, 159.15, 170.50; IR (thin film) 2963(s), 1768(m), 1414(m) cm^{-1}; HRMS calcd for $C_{41}H_{58}NO_4$ (M+H, ESI$^+$) *m/z* 628.4366, meas 628.4321; $[\alpha]^{20}_D$ 23.6 °(*c* 1.0, Et_2O) on 99% *ee* material.

*Preparation of acid **25**:*



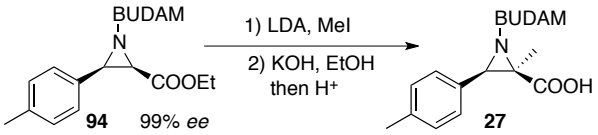
9 98% *ee* **25**

Alkylation: The general procedure for the alkylation described for acid **26** was followed with ester **9**[2] (98% *ee*, 357 mg, 1.00 mmol, 1.00 equiv), *i*-Pr_2NH (0.30 mL, 2.1 mmol, 2.1 equiv), *n*-BuLi (2.3M, 0.87 mL, 2.0 mmol, 2.0 equiv) and CH_3I (0.20 mL, 3.0 mmmol, 3.0 equiv). After workup, the crude product was obtained which was used directly in the next step.

Hydrolysis: To the mixture of the above methylated ester in ethanol (2 mL) was added an aqueous solution of KOH (280 mg, 5.00 mmol, 5.00 equiv) in H_2O (5 mL). The resulting mixture was refluxed overnight (~12 h). After it was cooled to rt, *aq* citric acid (2N, 5 mL) was added. The resulting precipitate was collected by filtration. The product was obtained as a slightly brown solid

(250 mg, 0.730 mmol) in 73% yield over 2 steps; mp 155-156 °C; R_f = 0.10 (hexane:EtOAc 4:1). Spectral data for acid **25**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.45 (s, 3H), 3.15 (s, 1H), 4.68 (s, 1H), 7.08-7.44 (m, 11H), 7.56 (d, 2H, *J* = 7.5 Hz), 7.71 (d, 2H, *J* = 7.5 Hz), 12.0 (brs, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.22, 50.26, 51.56, 68.86, 126.58, 126.63, 126.77, 126.96, 127.17, 127.54, 127.68, 128.19, 128.27, 136.63, 143.92, 144.20, 170.84; IR (thin film) 1720(s), 1265(m) cm^{-1}; HRMS calcd for $C_{23}H_{22}NO_2$ (M+H, ESI$^+$) *m/z* 344.1651, meas 344.1626; $[\alpha]^{20}_D$ 110.3° (*c* 0.67, CH_2Cl_2) on 98% *ee* material.

*Preparation of acid **27**:*

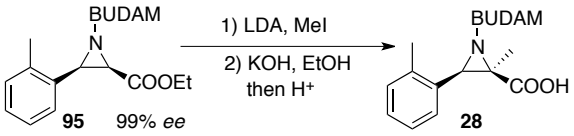


Alkylation: The general procedure for the alkylation described for acid **26** was followed with ester **94**[4] (99% *ee*, 656 mg, 1.00 mmol, 1.00 equiv), *i*-Pr_2NH (0.30 mL, 2.1 mmol, 2.1 equiv), *n*-BuLi (2.5M, 0.84 mL, 2.1 mmol, 2.1 equiv) and CH_3I (0.19 mL, 3.0 mmmol, 3.0 equiv). After workup, the crude product was obtained which was used directly in the next step.

Hydrolysis: To the mixture of the crude product in THF (2.5 mL) and ethanol (2.5 mL) was added an aqueous solution of KOH (280 mg, 5.00 mmol, 5.00 equiv) in H_2O (2.5 mL). The resulting mixture was refluxed for 42 h. After it was cooled to rt, the volatiles were evaporated and *aq* HCl (6N) was added to pH ~2. The mixture was extracted with ether (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 25 × 200 mm, hexane:acetone 9:1). The product was obtained as a white solid (602 mg, 0.937 mmol) in 94% yield over 2 steps; mp 82-85 °C; R_f = 0.50 (hexane:EtOAc 4:1). Spectral data for acid **27**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40, 1.41 (2s, 36H), 1.65 (s, 3H), 2.26 (s, 3H), 3.24 (s, 1H), 3.67, 3.68 (2s, 6H), 4.32 (s, 1H), 6.89 (d, 2H, *J* = 8.0 Hz), 6.99 (d, 2H, *J* = 8.0 Hz), 7.28 (s, 2H), 7.34 (s, 2H), 9.50 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.07, 21.07, 32.02, 32.08, 35.79, 35.80, 49.33, 53.48, 64.17, 64.24, 71.08, 124.99, 126.09, 127.17, 129.02, 131.59, 135.60, 135.92, 137.73, 143.78, 143.85, 158.68, 159.12, 170.66;

IR (thin film) 2961(s), 1718(s), 1224(s) cm^{-1}; HRMS calcd for $C_{42}H_{60}NO_4$ (M+H, ESI^+) *m/z* 642.4522, meas 642.4482; $[\alpha]^{20}_D$ 9.3° (*c* 2.0, CH_2Cl_2) on 99% *ee* material.

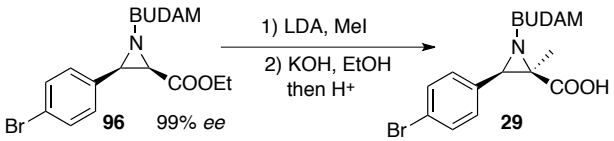
*Preparation of acid **28**:*



Alkylation: The general procedure for the alkylation described for acid **26** was followed with ester **95**[4] (96% *ee*, 656 mg, 1.00 mmol, 1.00 equiv), *i*-Pr_2NH (0.30 mL, 2.1 mmol, 2.1 equiv), *n*-BuLi (2.5M, 0.84 mL, 2.1 mmol, 2.1 equiv) and CH_3I (0.19 mL, 3.0 mmmol, 3.0 equiv). After workup, the methlylated ester was obtained which was used directly in the next step.

Hydrolysis: To the mixture of the methylated ester in THF (2.5 mL) and ethanol (2.5 mL) was added an aqueous solution of KOH (280 mg, 5.00 mmol, 5.00 equiv) in H_2O (5 mL). The resulting mixture was refluxed for 22 h. After it was cooled to rt, the volatiles were evaporated and *aq* HCl (6N, 5 mL) was added to pH ~2. The mixture was extracted with ether (20 mL + 2 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 25 × 180 mm, hexane:acetone 9:1). The product **28** was obtained as a white solid (507 mg, 0.780 mmol) in 78% yield over 2 steps; mp 76-78 °C; R_f = 0.50 (hexane:acetone 4:1). Spectral data for acid **28**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.43, 1.46 (2s, 36H), 1.71 (s, 3H), 2.30 (s, 3H), 3.23 (s, 1H), 3.68, 3.71 (2s, 6H), 4.40 (s, 1H), 7.00-7.20 (m, 4H), 7.34 (s, 2H), 7.39 (s, 2H), 9.80 (brs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.91, 18.86, 31.98, 32.08, 35.74, 35.78, 49.09, 53.75, 64.13, 64.15, 71.32, 124.92, 125.49, 126.00, 127.04, 127.93, 129.94, 132.96, 135.56, 135.83, 136.55, 143.72, 143.86, 158.66, 159.07, 170.32; IR (thin film) 2961(s), 1767(s), 1414(m) cm^{-1}; HRMS calcd for $C_{42}H_{60}NO_4$ (M+H, ESI^+) *m/z* 642.4522, meas 642.4491; $[\alpha]^{20}_D$ 31.3° (*c* 1.0, CH_2Cl_2) on 99% *ee* material.

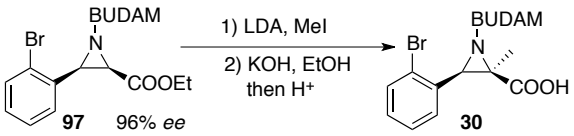
*Preparation of acid **29**:*



Alkylation: The general procedure for the alkylation described for acid **26** was followed with ester **96**[4] (99% *ee*, 720 mg, 1.00 mmol, 1.00 equiv), *i*-Pr_2NH (0.30 mL, 2.1 mmol, 2.1 equiv), *n*-BuLi (2.5M, 0.84 mL, 2.1 mmol, 2.1 equiv) and CH_3I (0.19 mL, 3.0 mmmol, 3.0 equiv). After workup, the methylated ester was obtained which was used directly in the next step.

Hydrolysis: To the mixture of the methylated ester in ethanol (2.5 mL) was added an aqueous solution of KOH (280 mg, 5.00 mmol, 5.00 equiv) in H_2O (2.5 mL). The resulting mixture was refluxed for 3 h. After it was cooled to rt, CH_2Cl_2 (5 mL) was added and the mixture was refluxed for 66 hours until it became a homogeneous solution. After it was cooled to rt, the volatiles were removed by rotary evaporation and *aq* HCl (6N) was added to pH ~2. The mixture was extracted with ether (20 mL + 2 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 25 × 250 mm, hexane:acetone 9:1). The product **29** was obtained as a white solid (383 mg, 0.54 mmol) in 54% yield over 2 steps; mp 78-80 °C; R_f = 0.30 (hexane:acetone 9:1). Spectral data for acid **29**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45, 1.47 (2s, 36H), 1.71 (s, 3H), 3.26 (s, 1H), 3.73 (s, 6H), 4.40 (s, 1H), 6.94 (d, 2H, *J* = 8.4 Hz), 7.30-7.40 (m, 6H), 9.60 (brs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 12.11, 32.01, 32.07, 35.78, 35.80, 49.63, 52.83, 64.17, 64.26, 70.91, 122.08, 124.96, 126.01, 129.04, 131.45, 133.75, 135.29, 135.75, 143.90, 143.92, 158.73, 159.17, 170.34; IR (thin film) 2961(s), 1769(m), 1414(m) cm^{-1}; HRMS calcd for $C_{41}H_{57}NO_4{}^{79}Br$ (M+H, ESI^+) *m/z* 706.3471, meas 706.3450; $[\alpha]^{20}_D$ 18.6° (*c* 1.0, CH_2Cl_2) on 99% *ee* material.

*Preparation of acid **30**:*

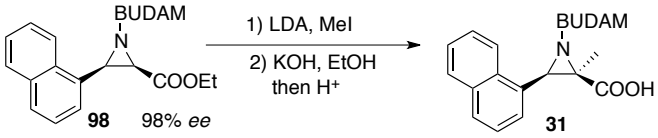


97 96% *ee* **30**

Alkylation: The general procedure for the alkylation was followed with ester **97**[4] (96% *ee*, 432 mg, 0.600 mmol, 1.00 equiv), *i*-Pr_2NH (0.18 mL, 1.3 mmol, 2.1 equiv), *n*-BuLi (2.3M, 0.51 mL, 1.3 mmol, 2.0 equiv) and CH_3I (0.12 mL, 1.8 mmmol, 3.0 equiv). After workup, the methlylated ester was obtained which was used directly in the next step.

Hydrolysis: To the mixture of the methylated ester in THF (2 mL) and ethanol (2 mL) was added an aqueous solution of KOH (168 mg, 3.00 mmol, 5.00 equiv) in H_2O (2 mL). The resulting mixture was refluxed for 12 h. And another portion of KOH (168 mg, 3.00 mmol, 5.00 equiv) in H_2O (2 mL) was added. The resulting mixture was refluxed for 48 h. After it was cooled to rt, the volatiles were removed by rotary evaporation and *aq* citric acid (2N, 5 mL) was added. The mixture was extracted with ether (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 25 × 200 mm, hexane:acetone 5:1). The product was obtained as a white solid (240 mg, 0.340 mmol) in 57% yield over 2 steps; mp 76-80 °C; R_f = 0.50 (hexane:acetone 5:1). Spectral data for acid **30**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37, 1.40 (2s, 36H), 1.71 (s, 3H), 3.27 (s, 1H), 3.63, 3.67 (2s, 6H), 4.38 (s, 1H), 7.00-7.16 (m, 3H), 7.27, 7.30 (2s, 4H), 7.44-7.50 (dd, 1H, *J* = 7.5, 1.5 Hz), 9.80 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.12, 32.00, 32.10, 35.79, 35.83, 49.88, 55.31, 64.19, 64.21, 71.03, 123.73, 124.98, 125.95, 126.95, 128.91, 129.55, 132.47, 134.44, 135.21, 135.71, 143.86, 143.95, 158.77, 159.12, 169.57; IR (thin film) 2961(s), 1773(m), 1414(m) cm^{-1}; HRMS calcd for $C_{41}H_{57}NO_4{}^{79}Br$ (M+H, ESI$^+$) *m/z* 706.3471, meas 706.3497; $[\alpha]^{20}_D$ 12.0° (*c* 1.0, CH_2Cl_2) on 96% *ee* material.

*Preparation of acid **31**:*

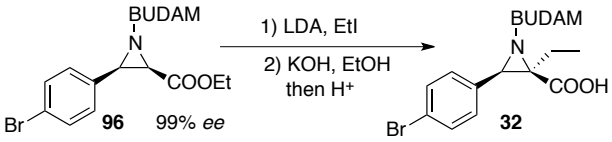


Alkylation: The general procedure for the alkylation described for acid **26** was followed with ester **98**[4] (98% *ee*, 691 mg, 1.00 mmol, 1.00 equiv), *i*-Pr_2NH (0.30 mL, 2.1 mmol, 2.1 equiv), *n*-BuLi (2.5M, 0.84 mL, 2.1 mmol, 2.1 equiv) and CH_3I (0.19 mL, 3.0 mmol, 3.0 equiv). After workup, the methylated ester was obtained which was used directly in the next step.

Hydrolysis: To the mixture of the methylated ester in ethanol (2.5 mL) was added an aqueous solution of KOH (280 mg, 5.00 mmol, 5.00 equiv) in H_2O (2.5 mL). The resulting mixture was refluxed for 6 h. After it was cooled to rt, the volatiles were removed by rotary evaporation and *aq* HCl (6N) was added to pH ~2. The mixture was extracted with ether (3 × 10 mL). The

combined organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 25 × 200 mm, hexane:EtOAc 9:1). The product **31** was obtained as a white solid (380 mg, 0.560 mmol) in 56% yield over 2 steps; mp 88-91 °C; R_f = 0.45 (hexane:EtOAc 4:1). Spectral data for **31**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 18H), 1.41 (s, 18H), 1.83 (s, 3H), 3.27 (s, 1H), 3.65 (s, 3H), 3.67 (s, 3H), 4.46 (s, 1H), 7.12 (d, 1H, *J* = 7.0 Hz), 7.20-7.26 (m, 1H), 7.32, 7.35 (2s, 4H), 7.44-7.54 (m, 2H), 7.70 (d, 1H, *J* = 8.5 Hz), 7.80 (d, 1H, *J* = 7.5 Hz), 7.85 (d, 1H, *J* = 7.5 Hz), 9.80 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.13, 32.02, 32.13, 32.23, 35.81, 35.85, 49.32, 53.18, 64.23, 71.47, 123.18, 124.86, 125.06, 125.15, 126.14, 126.17, 126.72, 128.62, 128.68, 130.76, 131.24, 133.38, 135.40, 135.81, 143.87, 143.98, 158.79, 159.20, 170.14; IR (thin film) 2963(s), 1770(m), 1414(m) cm^{-1}; HRMS calcd for $C_{45}H_{60}NO_4$ (M+H, ESI$^+$) *m/z* 678.4522, meas 678.4510; $[\alpha]^{20}_D$ 9.0° (*c* 1.0, CH_2Cl_2) on 98% *ee* material.

*Preparation of acid **32**:*

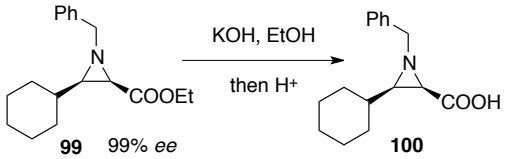


Alkylation: The general procedure for the alkylation described for acid **26** was followed with ester **96**[4] (99% *ee*, 720 mg, 1.00 mmol, 1.00 equiv), *i*-Pr_2NH (0.30 mL, 2.1 mmol, 2.1 equiv), *n*-BuLi (2.5M, 0.84 mL, 2.1 mmol, 2.1 equiv) and ethyl iodide (0.24 mL, 3.0 mmmol, 3.0 equiv). After workup, the ethylated ester was obtained which was used directly in the next step.

Hydrolysis: To the mixture of the ethylated ester in THF (2.5 mL) and ethanol (2.5 mL) was added an aqueous solution of KOH (280 mg, 5.00 mmol, 5.00 equiv) in H_2O (2.5 mL). The resulting mixture was refluxed for 16 h. After it was cooled to rt, additional THF (2.5 mL) was added and the mixture was refluxed for 48 h. After it was cooled to rt, the volatiles were removed by rotary evaporation and *aq* HCl (6N) was added to pH ~2. The mixture was extracted with ether (20 mL + 2 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 25 × 200 mm, hexane:acetone 9:1). The product **32** was obtained as a white solid (382 mg, 0.530 mmol) in 53%

yield over 2 steps; mp 83-87 °C; R_f = 0.50 (hexane:EtOAc 4:1). Spectral data for **32**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (t, 3H, *J* = 7.0 Hz), 1.38, 1.40 (2s, 36H), 1.74 (dq, 1H, *J* = 7.5, 7.5 Hz), 2.31 (dq, 1H, *J* = 7.5, 7.5 Hz), 3.14 (s, 1H), 3.64 (s, 3H), 3.67 (s, 3H), 4.35 (s, 1H), 6.79 (d, 2H, *J* = 8.0 Hz), 7.28 (d, 2H, *J* = 8.0 Hz), 7.30 (s, 4H), 9.00 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.27, 20.09, 31.99, 32.07, 35.78, 35.79, 51.42, 54.64, 64.26, 64.30, 70.62, 122.03, 124.97, 126.01, 128.98, 131.44, 133.74, 135.17, 135.79, 143.95, 144.00, 158.83, 159.23, 169.38; IR (thin film) 2961(s), 1710(s), 1224(s) cm^{-1}; HRMS calcd for $C_{42}H_{59}NO_4{}^{79}Br$ (M+H, ESI$^+$) *m/z* 720.3627, meas 720.3578; $[\alpha]^{20}_D$ 6.4° (*c* 1.0, CH_2Cl_2) on 99% *ee* material.

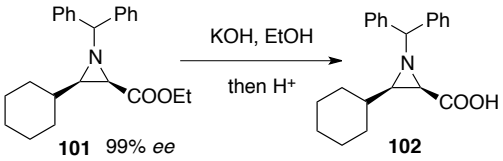
*Preparation of acid **100**:*



99 99% *ee* **100**

To a solution of ester **99**[9] (99% *ee*, 287 mg, 1.00 mmol, 1.00 equiv) in ethanol (2 mL) was added a solution of KOH (280 mg, 5.00 mmol, 5.00 equiv) in H_2O (2 mL). The resulting mixture was refluxed for 2 h. After cooling to rt, *aq* citric acid (2N, 5 mL) was added. The resulting white precipitate was collected by filtration. The product **100** was obtained as a white solid (217 mg, 0.838 mmol, 84%); mp 195-196 °C; R_f = 0.05 (hexane:EtOAc 4:1). Spectral data for acid **100**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84-1.24 (m, 6H), 1.50-1.70 (m, 5H), 1.84 (t, 1H, *J* = 8.0 Hz), 2.45 (d, 1H, *J* = 7.0 Hz), 3.48 (d, 1H, *J* = 13.0 Hz), 3.69 (d, 1H, *J* = 13.0 Hz), 7.10-7.40 (m, 5H), 7.70 (brs, 1H); ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.80-1.28 (m, 6H), 1.50-1.70 (m, 5H), 1.70-1.80 (m, 1H), 2.24 (d, 1H, *J* = 7.2 Hz), 3.32 (d, 1H, *J* = 13.2 Hz), 3.54 (d, 1H, *J* = 13.2 Hz), 7.20-7.40 (m, 5H), 11.80 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 25.11, 25.19, 25.76, 29.50, 30.74, 35.68, 41.88, 50.76, 62.91, 126.97, 128.08, 128.28, 138.76, 170.91; IR (thin film) 2924(w), 1755(s) cm^{-1}; HRMS calcd for $C_{16}H_{22}NO_2$ (M+H, ESI$^+$) *m/z* 260.1651, meas 260.1667; $[\alpha]^{20}_D$ 52° (*c* 0.5, DMSO) on 99% *ee* material.

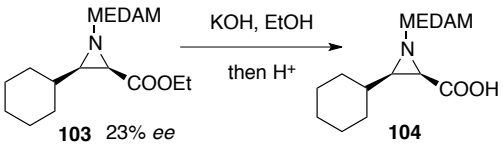
*Preparation of acid **102**:*



101 99% *ee* **102**

To a suspension of ester **101**[2] (99% *ee*, 363 mg, 1.00 mmol, 1.00 equiv) in ethanol (3 mL) was added a solution of KOH (280 mg, 5.00 mmol, 5.00 equiv) in H_2O (3 mL). The resulting mixture was refluxed for 1 h. After it was cooled to rt, the volatiles were removed by rotary evaporation. Then *aq* citric acid (2N, 5 mL) was added. The resulting precipitate was collected by filtration and washed with H_2O, affording the product **102** as a white solid (306 mg, 0.913 mmol) in 93% yield; mp 151-152 °C; R_f = 0.25 (hexane:EtOAc 4:1). Spectral data for acid **102**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.46 (q, 1H, *J* = 10.5 Hz), 0.90-1.10 (m, 5H), 1.16-1.28 (m, 1H), 1.30-1.70 (m, 4H), 1.89 (t, 1H, *J* = 7.0 Hz), 2.22 (d, 1H, *J* = 7.0 Hz), 3.80 (s, 1H), 7.16-7.40 (m, 8H), 7.45 (d, 2H, *J* = 7.5 Hz), 12.40 (brs, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 24.92, 25.09, 25.63, 29.44, 30.26, 35.60, 42.27, 51.07, 75.77, 126.67, 126.71, 127.20, 127.96, 128.13, 128.19, 143.08, 143.28, 170.79; IR (thin film) 2926(s), 1705(m), 1450(m) cm^{-1}; HRMS calcd for $C_{22}H_{26}NO_2$ (M+H, ESI^+) *m/z* 336.1964, meas 336.1950; $[\alpha]^{20}_D$ 75.2° (*c* 0.5, CH_2Cl_2) on 99% *ee* material.

*Preparation of acid **104**:*

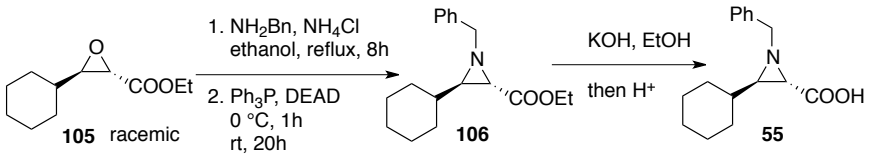


103 23% *ee* **104**

To a solution of ester **103**[3] (23% *ee*, 200 mg, 0.420 mmol, 1.00 equiv) in ethanol (2 mL) was added a solution of KOH (117 mg, 2.09 mmol, 5.00 equiv) in H_2O (2 mL). The resulting mixture was refluxed for 1 h. After cooling to rt, *aq* citric acid (2N, 2 mL) and ether (10 mL) were added. The aqueous layer was separated and extracted with ether (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 28 × 280 mm, hexane:acetone 4:1 to 3:1) to afford the product **104** (180 mg, 0.400 mmol) as a white solid in 96% yield; mp 85-90 °C; R_f = 0.30 (hexane:acetone 4:1). Spectral data for **104**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.50-0.70 (m, 1H), 0.90-1.70 (m, 10H),

1.88 (dd, 1H, *J* = 9.3, 6.9 Hz), 2.22, 2.23 (2s, 12H), 2.37 (d, 1H, *J* = 6.9 Hz), 3.48 (s, 1H), 3.66, 3.67 (2s, 6H), 6.97 (s, 4H), 9.00 (brs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.11, 16.22, 25.28, 25.34, 25.95, 29.87, 30.97, 37.26, 43.16, 53.15, 59.58, 59.67, 76.72, 127.15, 127.98, 130.70, 131.06, 136.56, 137.12, 156.24, 156.41, 170.75; IR (thin film) 2928(s), 1710(w) cm^{-1}; HRMS calcd for $C_{28}H_{38}NO_4$ (M+H, ESI^+) *m/z* 452.2801, meas 452.2791; $[\alpha]^{20}_D$ 10.6° (*c* 0.5, CH_2Cl_2) on 23% *ee* material.

*Preparation of acid **55**:*

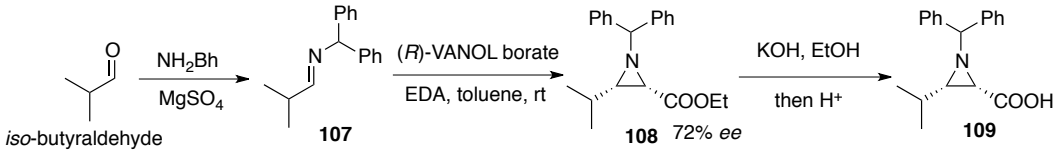


trans-ester formation[6,7]: A mixture of *trans*-epoxide **105**[6] (racemic, 500 mg, 2.50 mmol, 1.00 equiv), NH_4Cl (400 mg, 7.50 mmol, 3.00 equiv) and benzylamine (1.35 mL, 12.5 mmol, 5.00 equiv) in absolute ethanol (5 mL) was refluxed for 8 h. After cooling, the solvent was evaporated and H_2O (10 mL) was added. And the mixture was extracted with ether (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 28 × 280 mm, hexane: EtOAc 4:1) to give the ring-opening product (404 mg, 1.32 mmol, 53%). To a solution of the ring-opening product and triphenylphosphine (694 mg, 2.65 mmol, 2.00 equiv) in THF (5 mL) at 0 °C was added diethylazodicarboxylate (DEAD, 0.420 mL, 2.65 mmol, 2.00 equiv) dropwise under N_2. After it was stirred at 0 °C for 1 h, the resulting mixture was stirred at rt for 20 h. The reaction mixture was concentrated and purified by column chromatography (1st column, silica gel, 28 × 280 mm, hexane:EtOAc 9:1; 2nd column, silica gel, 18 × 180 mm, hexane:EtOAc 15:1) afforded the *trans*-aziridine **106** (100 mg, 0.348 mmol) as a colorless oil in 14% over 2 steps; R_f = 0.60 (hexane:EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86-1.30 (m, 9H), 1.50-1.80 (m, 5H), 2.07 (dd, 1H, *J* = 7.0 , 2.5 Hz), 2.50 (d, 1H, *J* = 3.0 Hz), 3.87 (d, 1H, *J* = 13.5 Hz), 3.92 (d, 1H, *J* = 13.5 Hz), 4.10 (q, 2H, *J* = 7.5 Hz), 7.20-7.4 (m, 1H), 7.26-7.38 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.12, 25.62, 25.74, 26.22, 29.93, 30.71, 39.70, 40.71, 52.70, 55.64, 60.89, 126.94, 128.24,

128.54, 139.32, 169.77; IR (thin film) 2926(s), 1728(s) cm^{-1}; HRMS calcd for $C_{18}H_{26}NO_2$ (M+H, ESI^+) *m/z* 288.1964, meas 288.1972.

Hydrolysis: To solution of ester **106** (100 mg, 0.348 mmol, 1.00 equiv) in ethanol (1 mL) was added a solution of KOH (97 mg, 1.7 mmol, 5.0 equiv) in H_2O (2 mL). The resulting mixture was refluxed for 30 min. After cooling, *aq* citric acid (2N, 2 mL) was added. The resulting white precipitate was collected by filtration. Then the white solid was dissolved in ether (20 mL), dried (Na_2SO_4) and filtered. The filtrate was concentrated to give the product *trans*-aziridine acid **55** (85 mg, 0.33 mmol, 94%) as a white solid; mp 135-136 °C (decomposition); R_f = 0.05 (hexane:EtOAc 4:1); ^1H NMR (500 MHz, DMSO-d_6) δ 0.80-1.30 (m, 11H), 1.98 (d, 1H, *J* = 2.5 Hz), 2.37 (d, 1H, *J* = 2.5 Hz), 3.81 (d, 1H, *J* = 13.5 Hz), 3.86 (d, 1H, *J* = 13.0 Hz), 7.20-7.40 (m, 5H), 12.52 (brs, 1H); ^{13}C NMR (125 MHz, DCMSO-d_6) δ 25.14, 25.24, 25.78, 29.36, 30.03, 38.82, 39.77, 51.63, 54.69, 126.79, 128.12, 128.33, 139.60, 170.74; IR (thin film) 2924(s), 1722(s) cm^{-1}; HRMS calcd for $C_{16}H_{22}NO_2$ (M+H, ES^+) *m/z* 260.1651, meas 260.1660.

*Preparation of **109**:*



iso-butyraldehyde **107** **108** 72% *ee* **109**

Imine formation: The mixture of *iso*-butyraldehyde (173 mg, 0.220 mL, 2.40 mmol, 1.20 equiv), benzhydryl amine (378 mg, 2.00 mmol, 1.00 equiv), $MgSO_4$ (960 mg, 8.00 mmol, 4.00 equiv) and dry CH_2Cl_2 (10 mL) was stirred under N_2 for 2 h. After the reaction was filtered over a Celite pad on a sintered glass funnel, the filtrate was concentrated to give the product **107** (450 mg, 1.90 mmol, 95%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (d, 6H, *J* = 6.9 Hz), 2.40-2.54 (m, 1H), 5.24 (s, 1H), 7.08-7.30 (m, 10H), 7.64 (d, 1H, *J* = 5.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.34, 34.18, 77.74, 126.79, 127.54, 128.32, 143.95, 169.83.

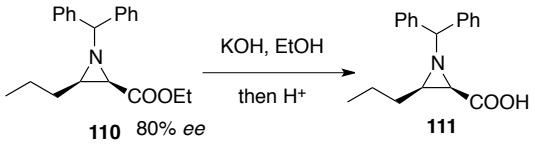
Aziridination: A 25 mL pear-shaped single neck flask which had its 14/20 joint replaced by a threaded high vacuum Teflon valve was flame dried (with a stir bar in it), cooled to rt under N_2 and charged with 5 mol% (*R*)-VANOL (22 mg, 0.050 mmol, 0.050 equiv), 20 mol% triphenyl borate (58 mg, 0.20 mmol, 0.20 equiv), H_2O (9 μL) and dry toluene (1 mL). The Teflon valve was

closed and the flask was heated at 80 °C for 1 hour. After the flask was cooled to rt, the toluene was carefully removed by exposing to high vacuum (0.1 mmHg) by slightly cracking the Teflon value. After the solvent was removed, the Teflon valve was completely opened and the flask was heated at 80 °C under high vacuum for 30 min. The flask was then allowed to cool to rt. The solution of imine **107** (237 mg, 1.00 mmol, 1.00 equiv) in toluene (2 mL) was added. And then EDA (0.25 mL, 2.4 mmol, 2.4 equiv) was added *via* syringe in one portion. The solution was stirred at rt for 17 h. The reaction was quenched with hexane (5 mL) and concentrated. After column chromatography (silica gel, 28 × 280 mm, hexane:EtOAc 15:1), ester **108** was obtained as a white solid (230 mg, 0.712 mmol) in 71% yield. The optical purity was determined to be 72% *ee* by HPLC analysis (Chiralcel OD-H column, 99:1 hexane/2-propanol at 222 nm, flow-rate 1.0 mL/min); Retention times: R_t = 3.24 min (major enantiomer) and R_t = 5.98 min (minor enantiomer); mp 102-104 °C; R_f = 0.40 (hexane:EtOAc 4;1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.56 (d, 3H, *J* = 6.0 Hz), 0.85 (d, 3H, *J* = 7.0 Hz), 1.29 (t, 3H, *J* = 7.0 Hz), 1.60-1.70 (m, 1H), 1.81 (dd, 1H, *J* = 9.5, 7.0 Hz), 2.32 (d, 1H, *J* = 7.0 Hz), 3.68 (s, 1H), 4.14-4.32 (m, 2H), 7.20-7.26 (m, 2H), 7.28-7.36 (m, 4H), 7.38-7.44 (m, 2H), 7.55 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.18, 19.53, 20.32, 27.25, 43.58, 53.52, 60.59, 78.01, 126.83, 126.97, 127.43, 128.21, 128.25, 128.29, 142.29, 142.75, 169.48; IR (thin film) 961(m), 1734(s) cm^{-1}; HRMS calcd for $C_{21}H_{26}NO_2$ (M+H, ESI^+) *m/z* 324.1964, meas 324.1964; $[\alpha]^{20}_D$ –123.5° (*c* 0.5, CH_2Cl_2) on 72% *ee* material.

Hydrolysis: To the mixture of ester **108** (100 mg, 0.310 mmol, 1.00 equiv) in ethanol (0.5 mL) was added a solution of KOH (87 mg, 1.6 mmol, 5.0 equiv) in H_2O (1 mL). The resulting mixture was refluxed for 30 min. After cooling to rt, *aq* citric acid (2N, 2 mL) and ether (10 mL) were added. The aqueous layer was separated and extracted with ether (2 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated to give the crude product as a white solid. CH_2Cl_2 (10 mL) was added to the solid and this mixture was filtered and washed well with CH_2Cl_2. The filtrate was concentrated to give the product **109** as a white foamy solid (80 mg, 0.27 mmol, 88%); mp 84-86 °C; R_f = 0.005 (hexane:EtOAc 4:1). Spectral data for acid **109**: ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.41 (d, 3H, *J* = 6.6 Hz), 0.75 (d, 3H, *J* = 7.2 Hz), 1.44-1.56 (m, 1H), 1.84 (dd, 1H, *J* = 9.0, 6.0 Hz), 2.22 (d, 1H, *J* = 6.6 Hz), 3.82 (s,

1H), 7.14-7.54 (m, 10H), 12.40 (brs, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 19.30, 20.25, 26.67, 42.59, 52.70, 75.71, 126.70, 127.18, 127.97, 128.12, 128.18, 143.06, 143.32, 170.75 (One sp^2 carbon not located); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.52, 20.50, 28.15, 43.47, 54.55, 77.48, 126.83, 127.55, 127.84, 127.93, 128.52, 128.74, 141.25, 141.82, 171.03; IR (thin film) 2963(m), 1720(s) cm^{-1}; HRMS calcd for $C_{19}H_{22}NO_2$ (M+H, ESI$^+$) *m/z* 296.1651, meas 296.1640; $[\alpha]^{20}_D$ – 51.1° (*c* 0.5, CH_2Cl_2) on 72% *ee* material.

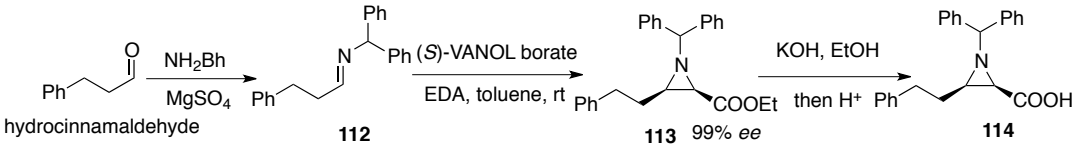
*Preparation of acid **111**:*



110 80% *ee* **111**

To a solution of ester **110**[2] (80% *ee*, 70 mg, 0.22 mmol, 1.0 equiv) in ethanol (1 mL) was added a solution of KOH (60 mg, 1.54 mmol, 5.00 equiv) in H_2O (1 mL). After the mixture was refluxed for 30 min, THF (1 mL) was added. And the resulting mixture was refluxed for another 30 min. After it was cooled to rt, the volatiles were removed by rotary evaporation and ether (5 mL) was added. The aqueous layer was separated and extracted with ether (2 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 18 × 180 mm, hexane:CH_2Cl_2:EtOAc 2:2:1 to 1:1:1) to obtain the product **111** (45 mg, 0.15 mmol) as a white foamy solid in 71% yield; mp 50-52 °C; R_f = 0.20 (hexane:CH_2Cl_2:EtOAc 2:2:1). Spectral data for acid **111**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.77 (t, 3H, *J* = 7.0 Hz), 1.10-1.28 (m, 2H), 1.38-1.48 (m, 1H), 1.56-1.64 (m, 1H), 2.19 (q, 1H, *J* = 7.0 Hz), 2.48 (d, 1H, *J* = 7.0 Hz), 3.80 (s, 1H), 7.00-8.00 (m, 11H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.57, 20.18, 31.45, 43.22, 47.71, 77.02, 127.05, 127.37, 127.65, 127.70, 128.56, 128.81, 141.35, 141.74, 170.61; IR (thin film) 1720(s) cm^{-1}; HRMS calcd for $C_{19}H_{22}NO_2$ (M+H, ESI$^+$) *m/z* 296.1651, meas 296.1626; $[\alpha]^{20}_D$ 8.9° (*c* 1.0, CH_2Cl_2) on 80% *ee* material.

*Preparation of acid **114**:*



hydrocinnamaldehyde **112** **113** 99% *ee* **114**

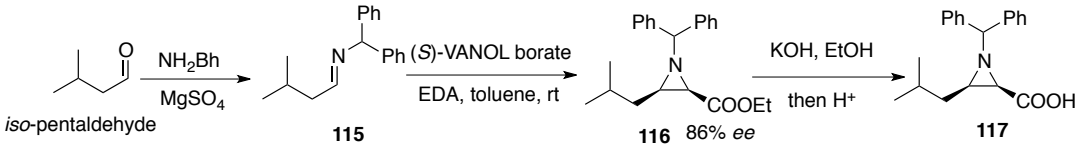
Imine formation: The mixture of hydrocinnamaldehyde (90% by weight, 328 mg, 2.20 mmol, 1.10 equiv), $BhNH_2$ (378 mg, 2.00 mmol, 1.00 equiv) and $MgSO_4$ (960 mg, 8.00 mmol, 4.00 equiv) in CH_2Cl_2 (10 mL) was stirred at rt for 1.5 h. After it was filtered over a Celite pad on a sintered glass funnel, the filtrate was concentrated to give the imine **112** as a colorless oil which was put on the vacuum for 10 sec prior to use.

Aziridination: A 25 mL pear-shaped single neck flask which had its 14/20 joint replaced by a threaded high vacuum Teflon valve was flame dried (with a stir bar in it), cooled to rt under N_2 and charged with 5 mol% (*S*)-VANOL (22 mg, 0.050 mmol, 0.050 equiv), 20 mol% triphenyl borate (58 mg, 0.20 mmol, 0.20 equiv), H_2O (9 μL) and dry toluene (1 mL). The Teflon valve was closed and the flask was heated at 80 ^oC for 1 hour. After the flask was cooled to rt, the toluene was carefully removed by exposing to high vacuum (0.1 mmHg) by slightly cracking the Teflon value. After the solvent was removed, the Teflon valve was completely opened and the flask was heated at 80 ^oC under high vacuum for 30 min. The flask was then allowed to cool to rt. The solution of imine **112** (306 mg, 1.00 mmol, 1.00 equiv) in toluene (2 mL) was added. And then EDA (311 μL, 3.00 mmol, 3.00 equiv) was added *via* syringe in one portion. The solution was stirred at rt for 22 h. The reaction was quenched with n-hexane (5 mL) and concentrated by removing all volatiles. After column chromatography (1^{st} column, silica gel, 28 × 280 mm, hexane:EtOAc 9:1; 2^{nd} column, silica gel, 28 × 280 mm, benzene:EtOAc 50:1), ester **113** was obtained as a white solid (262 mg, 0.680 mmol) in 68% yield. The optical purity was determined to be 78% ee by HPLC analysis (Chiralcel OD-H column, 99:1 hexane/2-propanol at 222 nm, flow-rate 1.0 mL/min); Retention times: R_t = 5.06 min (minor enantiomer) and R_t = 10.16 min (major enantiomer). A single recrystallization of 78% ee material afforded the product (141 mg, 0.366 mmol) with 37% recovery and 99.1% *ee*; mp 114-115 °C; R_f = 0.50 (hexane:EtOAc 4:1); ^1H NMR (500 MHz, $CDCl_3$) δ 1.27 (t, 3H, *J* = 7.5 Hz), 1.82-2.00 (m, 2H), 2.08 (q, 1H, *J* = 6.5 Hz), 2.28-2.40 (m, 2H), 2.44-2.54 (m, 1H), 3.71 (s, 1H), 4.14-4.26 (m, 2H), 6.98 (d, 2H, *J* = 7.5 Hz), 7.14-7.40 (m, 9H), 7.49 (d, 2H, *J* = 8.0 Hz), 7.53 (d, 2H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.22, 29.58, 33.22, 43.19, 46.07, 60.72, 77.79, 125.70, 126.98, 127.02, 127.44, 127.83, 128.16, 128.31, 128.33, 128.39, 141.28, 142.40, 142.88, 169.33; IR (thin film) 2918(m), 1734(s)

cm^{-1}; Anal calcd for $C_{26}H_{27}NO_2$: C, 81.01; H, 7.06; N, 3.63. Found: C, 80.86; H, 7.06; N, 3.63; $[\alpha]^{20}_D$ 86.2° (*c* 0.5, CH_2Cl_2) based on 99.1% *ee* material.

Hydrolysis: To a suspension of ester **113** (100 mg, 0.260 mmol, 1.00 equiv) in ethanol (1 mL) was added a solution of KOH (73 mg, 1.3 mmol, 5.0 equiv) in H_2O (2 mL). The resulting mixture was refluxed for 45 min. After cooling to rt, *aq* citric acid (2N, 2 mL) was added. The resulting precipitate was collected by filtration. The product **114** was obtained as a white solid (91 mg, 0.26 mmol, 98%); mp 70-72 °C; R_f = 0.13 (hexane:EtOAc 4:1). Spectral data for **114**: ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.72-1.90 (m, 2H), 2.15-2.24 (m, 1H), 2.28-2.38 (m, 1H), 2.38-2.50 (m, 2H), 3.97 (s, 1H), 6.98-7.04 (m, 2H), 7.20-7.60 (m, 13H), 12.50 (brs, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 29.52, 32.71, 42.23, 45.23, 75.42, 125.69, 126.78, 127.14, 127.52, 128.01, 128.02, 128.19, 128.21, 128.30, 128.45, 141.20, 143.49, 170.61; IR (thin film) 1734(s) cm^{-1}; HRMS calcd for $C_{24}H_{24}NO_2$ (M+H, ESI^+) *m/z* 358.1807, meas 358.1834; $[\alpha]^{20}_D$ 30.5° (*c* 0.5, CH_2Cl_2) on 99% *ee* material.

*Preparation of acid **41**:*



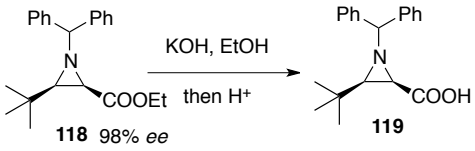
Imine formation: The mixture of *iso*-pentaldehyde (189 mg, 2.20 mmol, 1.10 equiv), $BhNH_2$ (378 mg, 2.00 mmol, 1.00 equiv) and $MgSO_4$ (960 mg, 8.00 mmol, 4.00 equiv) in CH_2Cl_2 (10 mL) was stirred at rt for 2 h. After it was filtered over a Celite pad on a sintered glass funnel, the filtrate was concentrated to give the imine **115** as a colorless oil which was put on the vacuum for 10 sec prior to use.

Aziridination: A 25 mL pear-shaped single neck flask which had its 14/20 joint replaced by a threaded high vacuum Teflon valve was flame dried (with a stir bar in it), cooled to rt under N_2 and charged with 5 mol% (*S*)-VANOL (22 mg, 0.050 mmol, 0.050 equiv), 20 mol% triphenyl borate (58 mg, 0.20 mmol, 0.20 equiv), H_2O (9 μL) and dry toluene (1 mL). The Teflon valve was closed and the flask was heated at 80 ^{o}C for 1 hour. After the flask was cooled to rt, the toluene was carefully removed by exposing to high vacuum (0.1 mmHg) by slightly cracking the Teflon

value. After the solvent was removed, the Teflon valve was completely opened and the flask was heated at 80 ^{o}C under high vacuum for 30 min. The flask was then allowed to cool to rt. The solution of imine **115** (251 mg, 1.00 mmol, 1.00 equiv) in toluene (2 mL) was added. Then EDA (375 μL, 3.60 mmol, 3.60 equiv) was added via syringe in one portion. The solution was stirred at rt for 19 h. The reaction was quenched with n-hexane (5 mL) and concentrated by removing all volatiles. After column chromatography (silica gel, 28 × 280 mm, hexane:acetone 9:1), ester **116** was obtained as a white solid (205 mg, 0.608 mmol) in 61% yield. The optical purity was determined to be 86% ee by HPLC analysis (Chiralcel OD-H column, 99:1 hexane/2-propanol at 222 nm, flow-rate 1.0 mL/min); Retention times: R_t = 3.26 min (minor enantiomer) and R_t = 6.01 min (major enantiomer); mp 105-106 °C; R_f = 0.48 (hexane:acetone 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.65 (d, 3H, *J* = 6.5 Hz), 0.76 (d, 3H, *J* = 7.0 Hz), 1.23 (t, 3H, *J* = 7.0 Hz), 1.26-1.44 (m, 2H), 1.48-1.56 (m, 1H), 2.06 (q, 1H, *J* = 6.5 Hz), 2.27 (d, 1H, *J* = 7.0 Hz), 3.36 (s, 1H), 4.10-4.22 (m, 2H), 7.16-7.30 (m, 6H), 7.36-7.42 (m, 2H), 7.44-7.48 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.26, 21.63, 22.93, 26.66, 36.49, 43.43, 45.71, 60.70, 78.06, 126.99, 127.12, 127.36, 127.82, 128.36, 142.51, 142.79, 169.56 (One sp^2 carbon not located); IR (thin film) 1784(s) cm^{-1}; HRMS calcd for $C_{22}H_{28}NO_2$ (M+H, ESI$^+$) *m/z* 338.2120, meas 338.2141; $[\alpha]^{20}_D$ 94.7° (*c* 1.0, CH_2Cl_2) on 86% *ee* material.

Hydrolysis: To a mixture of ester **116** (60 mg, 0.18 mmol, 1.0 equiv) in ethanol (1 mL) was added a solution of KOH (50 mg, 0.90 mmol, 5.0 equiv) in H_2O (1 mL). The resulting mixture was refluxed for 30 min. After the reaction mixture was cooled to rt, *aq* citric acid (2N, 2 mL) was added. And the mixture was extracted with ether (3 × 10 mL). The organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated to give a white viscous foamy solid (50 mg, 0.16 mmol, 91%); mp 124-125 °C; R_f = 0.50 (hexane:acetone 2:1). Spectral data for acid **117**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.71 (d, 3H, *J* = 6.6 Hz), 0.80 (d, 3H, *J* = 6.6 Hz), 1.16-1.70 (m, 3H), 2.23 (q, 1H, *J* = 6.7 Hz), 2.49 (d, 1H, *J* = 7.2 Hz), 3.83 (s, 1H), 7.00-8.00 (m, 11H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.79, 22.76, 26.67, 37.25, 43.32, 46.88, 127.05, 127.24, 127.71, 127.83, 128.62, 128.89, 141.25, 141.59, 169.86; IR (thin film) 1734(s) cm^{-1}; HRMS calcd for $C_{20}H_{24}NO_2$ (M+H, ESI$^+$) *m/z* 310.1807, meas 310.1811; $[\alpha]^{20}_D$ 26.7° (*c* 1.0, Et_2O) on 86% *ee* material.

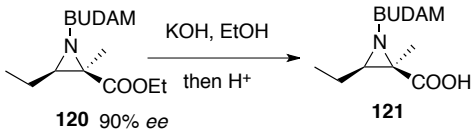
*Preparation of acid **119**:*



118 98% *ee* **119**

To the mixture of ester **118**[2] (98% *ee*, 270 mg, 0.800 mmol, 1.00 equiv) in ethanol (4 mL) was added a solution of KOH (224 mg, 4.00 mmol, 5.00 equiv) in H_2O (4 mL). After the mixture was refluxed for 1.5 h, THF (1 mL) was added. The resulting mixture was refluxed for another 1.5 h. After it was cooled to rt, *aq* citric acid (2N, 5 mL) was added. The resulting white precipitate was collected by filtration. The solid was then dissolved in ether (30 mL) and washed with H_2O (3 × 5 mL). The organic layer was dried (Na_2SO_4) and concentrated to obtain the product **119** (234 mg, 0.757 mmol, 95%) as a white solid; mp 164-166 °C; R_f = 0.25 (hexane:EtOAc 4:1). Spectral data for acid **119**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (s, 9H), 2.00 (d, 1H, *J* = 7.5 Hz), 2.36 (d, 1H, *J* = 8.0 Hz), 3.69 (s, 1H), 7.22-7.28 (m, 3H), 7.30-7.34 (m, 4H), 7.40-7.46 (m, 4H); ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.66 (s, 9H), 1.81 (d, 1H, *J* = 7.2 Hz), 2.20 (d, 1H, *J* = 7.8 Hz), 3.78 (s, 1H), 7.18-7.22 (m, 2H), 7.26-7.30 (m, 4H), 7.38 (dd, 2H, *J* = 8.4, 1.2 Hz), 7.60 (dd, 2H, *J* = 8.4, 1.2 Hz), 12.40 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.57, 31.61, 42.98, 59.16, 78.86, 127.03, 127.60, 127.80, 127.86, 128.55, 128.97, 141.33, 141.81 (The carbonyl peak not located); ^{13}C NMR (150 MHz, DMSO-d_6) δ 27.34, 31.29, 42.58, 54.89, 76.94, 126.92, 127.04, 127.98, 128.08, 128.24, 143.14, 143.87, 170.86 (One sp^2 carbon not located); IR (thin film) 2961(s), 1705(s) cm^{-1}; HRMS calcd for $C_{20}H_{24}NO_2$ (M+H, ESI^+) *m/z* 310.1807, meas 310.1781; $[\alpha]^{20}_D$ 30.6° (*c* 0.5, CH_2Cl_2) on 98% *ee* material.

*Preparation of acid **121**:*

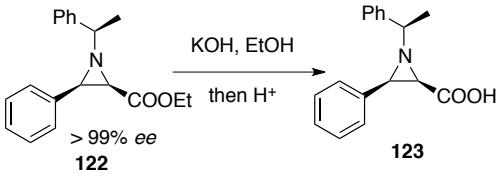


120 90% *ee* **121**

To the mixture of ester **120** (90% *ee*, 800 mg, 1.30 mmol, 1.00 equiv) in THF (2.5 mL) and ethanol (2.5 mL) was added a solution of KOH (364 mg, 6.50 mmol, 5.00 equiv). The resulting mixture was refluxed for 24 h. After cooling to rt, *aq* HCl (6N) was added to pH ~2. The mixture

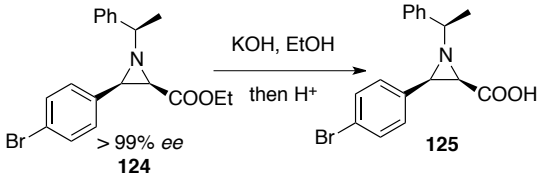
was extracted with ether (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 25 × 200 mm, hexane:acetone 5:1) to give the product **121** (565 mg, 0.976 mmol, 75%) as a white foamy solid; mp 73-76 °C; R_f = 0.25 (hexane:EtOAc 4:1). Spectral data for **121**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.65 (t, 3H, *J* = 7.5 Hz), 1.30-1.52 (m, 38H), 1.54 (s, 3H), 1.96 (t, 1H, *J* = 7.0 Hz), 3.67 (s, 6H), 4.14 (s, 1H), 7.20 (s, 2H), 7.22 (s, 2H), 9.60 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.68, 11.91, 21.97, 31.80, 35.52, 35.54, 48.00, 53.60, 63.89, 63.97, 70.24, 124.78, 125.61, 135.57, 135.67, 143.32, 143.51, 158.37, 158.73, 171.17 (One sp^3 carbon not located); IR (thin film) 2964(s), 1774(m) cm^{-1}; HRMS calcd for $C_{37}H_{58}NO_4$ (M+H, ES$^+$) *m/z* 580.4366, meas 580.4296; $[\alpha]^{20}_D$ 33.1° (*c* 1.0, CH_2Cl_2) on 90% *ee* material.

*Preparation of acid **123**:*



To a suspension of ester **122**[5] (> 99% *ee*, 150 mg, 0.500 mmol, 1.00 equiv) in EtOH (1 mL) was added an aqueous solution KOH (140 mg, 2.50 mmol, 5.00 equiv) in H_2O (1 mL). The resulting mixture was refluxed for 30 min. After it was cooled to rt, *aq* citric acid (2N, 2 mL) and ether (10 mL) were added. The aqueous layer was separated and extracted with ether (2 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated to give the product **123** a white foamy solid 130 mg (0.487 mmol, 94%). mp 48-50 °C; R_f = 0.10 (hexane:EtOAc 4:1). Spectral data for acid **123**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.61 (d, 3H, *J* = 7.0 Hz), 2.80 (d, 1H, *J* = 7.0 Hz), 3.07 (q, 1H, *J* = 6.5 Hz), 3.28 (d, 1H, *J* = 7.0 Hz), 7.20-7.80 (m, 11H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.60, 44.88, 47.71, 68.44, 126.95, 127.41, 127.78, 127.92, 128.33, 128.69, 133.96, 142.16, 175.51; IR (thin film) 3400(m), 1775(s) cm^{-1}; HRMS calcd for $C_{17}H_{18}NO_2$ (M+H, ESI$^+$) *m/z* 268.1338, meas 268.1331; $[\alpha]^{20}_D$ 16.6° (*c* 1.0, CH_2Cl_2) on > 99% *ee* material.

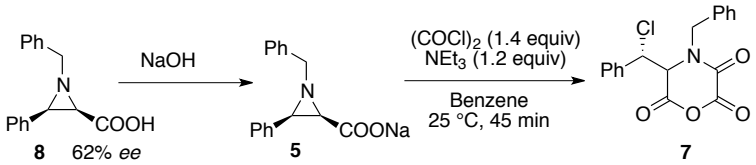
*Preparation of acid **125**:*



To a suspension of ester **124**[5] (> 99% *ee*, 187 mg, 0.500 mmol, 1.00 equiv) in EtOH (1 mL) was added an aqueous solution KOH (140 mg, 2.50 mmol, 5.00 equiv) in H_2O (2 mL). The resulting mixture was refluxed for 30 min. After it was cooled to rt, *aq* citric acid (2N, 2 mL) was added, followed by the addition of ether (10 mL). The aqueous layer was separated and extracted with ether (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated to give a white foamy solid 175 mg (0.505 mmol, 101%); mp 80-82 °C; R_f = 0.10 (hexane:EtOAc 4:1). Spectral data for acid **125**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55 (d, 3H, *J* = 6.5 Hz), 2.74 (d, 1H, *J* = 7.0 Hz), 2.98 (q, 1H, *J* = 6.5 Hz), 3.12 (d, 1H, *J* = 7.0 Hz), 7.00-7.40 (m, 10H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 22.91, 45.71, 46.16, 67.62, 120.13, 126.58, 127.02, 128.30, 129.75, 130.49, 135.51, 143.97, 168.78; IR (thin film) 3408(m), 1770(s) cm^{-1}; HRMS calcd for $C_{17}H_{17}NO_2{}^{79}Br$ (M+H, ESI$^+$) *m/z* 346.0443, meas 346.0435; $[\alpha]^{20}_D$ –19.4° (*c* 1.0, CH_2Cl_2) on > 99% *ee* material.

III. Formation of morpholine-2,3,5-triones (Scheme 3 and 4)

*The formation of morpholine-2,3,5-trione **7**:*

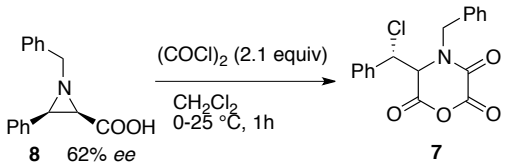


*Formation of **5**:* To a solution of acid **8** (62% *ee*, 38 mg, 0.15 mmol, 1.0 equiv) in acetone (0.5 mL) was added a NaOH solution (6.0 mg in 0.3 mL of H_2O, 0.15 mmol, 1.0 equiv). The resulting solution was stirred at rt for 2 h. Then the volatiles were removed by evaporation (acetone was added and evaporated several times) until a white solid was obtained.

*Reaction of **5** with oxalyl chloride and NEt_3 (Scheme 3):* To a solution of NEt_3 (12 mg, 0.12 mmol, 1.2 equiv) in benzene (1 mL) under N_2 was added $(COCl)_2$ (0.012 mL, 0.14 mmol, 1.4

equiv). Upon the addition of $(COCl)_2$, the solution turned from colorless to dark orange. Then 28 mg (0.10 mmol, 1.0 equiv) of the above sodium salt was added to the mixture of Et_3N and $(COCl)_2$ all at once. After it was stirred at rt for 45 min under N_2, CH_2Cl_2 (10 mL) and HCl (2N, 2 mL) were added carefully. The organic layer was separated, washed with $NaHCO_3$ (2 mL) and H_2O (2 mL), dried (Na_2SO_4) and filtered. The filtrate was concentrated to give the crude mixture whose ^1H NMR spectrum showed the major product was compound **7** in a yield of 34% as determined with the aid of an internal standard (Ph_3CH). Absorptions for the lactam **6** were not observed in the ^1H NMR spectrum of the crude mixture.

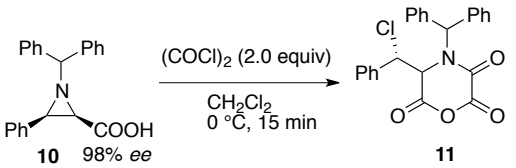
*Reaction of **8** with oxalyl chloride in CH_2Cl_2 (Scheme 3):*



8 62% *ee* **7**

To a flame-dried 25 mL round bottom flask filled with N_2 was added acid **8** (28 mg, 0.11 mmol, 1.0 equiv) and CH_2Cl_2 (1 mL). The vacuum adapter was replaced with a septum to which a N_2 balloon was attached *via* a needle. The flask was cooled in an ice bath. And $(COCl)_2$ (0.020 mL, 0.23 mmol, 2.1 equiv) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 5 min and the ice bath was removed. After the mixture was stirred at rt for 1 h, the volatiles were removed by rotary evaporation to give a foamy solid. Hexane was then added and the solid was collected by filtration and washed with a mixture of CH_2Cl_2 and hexane (v/v 1:10, 2 mL). The product **7** was obtained as a yellow solid (31 mg, 82%). The yield of this yellow solid was checked by NMR and found to be 91% with the aid of triphenylmethane as an internal standard. Spectral data for **7**: ^1H NMR (500 MHz, $CDCl_3$) δ 3.21 (d, 1H, J = 15.0 Hz), 4.77 (d, 1H, J = 3.0 Hz), 5.18 (d, 1H, J = 15.0 Hz), 5.39 (d, 1H, J = 2.5 Hz), 6.80-7.60 (m, 10H); IR (thin film) 1830(s), 1780(s), 1701(s) cm^{-1}. Unfortunately, the product as obtained was contaminated with some impurities. Thus, a clean ^{13}C NMR could not be obtained.

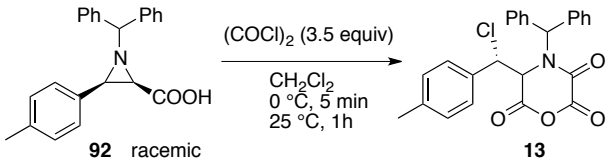
*The formation of morpholine-2,3,5-trione **11**:*



10 98% *ee* **11**

*General procedure for the formation of morpholine-2,3,5-trione: Illustrated for the formation of **11***: To a flame-dried 25 mL round bottom flask filled with N_2 was added acid **10** (98% ee, 33 mg, 0.10 mmol, 1.00 equiv) and CH_2Cl_2 (1 mL). The vacuum adapter was replaced with a septum to which a N_2 balloon was attached *via* a needle. The flask was cooled in an ice bath and then $(COCl)_2$ (25.1 mg, 0.017 mL, 0.20 mmol, 2.0 equiv) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 15 min and concentrated by rotary evaporator to afford a foamy solid. The amount of **11** present in this yellow solid was checked by the 1H NMR spectrum and found to be 92% yield with the aid of triphenylmethane as an internal standard. Hexane was then added and the solid was collected by filtration and washed with a mixture of CH_2Cl_2 and hexane (v/v 1:10). This gave the product **11** as a pale yellow solid (31 mg, 0.074 mmol, 74%); mp 129-131 °C. Spectral data for **11**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77 (d, 1H, *J* = 3.9 Hz), 5.02 (d, 1H, *J* = 3.9 Hz), 6.98-7.10 (m, 4H), 7.15 (s, 1H), 7.28-7.46 (m, 6H), 7.40-7.62 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 58.35, 62.30, 64.51, 126.39, 128.40, 128.82, 129.26, 129.70, 130.08, 130.38, 130.47, 131.01, 131.05, 135.73, 136.27, 148.33, 151.23, 157.65; IR (thin film) 1832(m), 1782(s), 1705(s) cm^{-1}; HRMS calcd for $C_{24}H_{19}NO_4{}^{35}Cl$ (M+H, ESI$^+$) *m/z* 420.1003, meas 420.0970; $[\alpha]^{20}_D$ – 164.5° (*c* 0.5, CH_2Cl_2) on 98% ee material. Recrystallization from CH_2Cl_2 and hexane gave X-ray quality crystals. The crystallographic data for **11** has been deposited at the Cambridge Crystallographic Data Center (CCDC 884446).

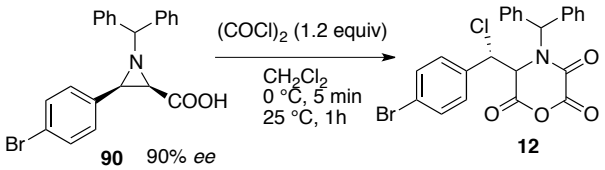
*The formation of morpholine-2,3,5-trione **13**:*



92 racemic **13**

The general procedure for the formation of morpholine-2,3,5-trione **11** was followed with acid **92** (racemic, 35 mg, 0.10 mmol, 0.10 equiv), $(COCl)_2$ (0.030 mL, 0.35 mmol, 3.5 equiv) and CH_2Cl_2 (1 mL). The product **13** was obtained as a yellow solid. The NMR yield was 82% as determined on this yellow solid with the aid of PH_3CH as an internal standard. Spectral data for **13**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.34 (s, 3H), 3.73 (d, 1H, *J* = 4.0 Hz), 5.00 (d, 1H, *J* = 3.5 Hz), 6.90 (d, 2H, *J* = 7.8 Hz), 7.03 (d, 2H, *J* =7.5 Hz), 7.10-7.60 (m, 11H); IR (thin film) 1832(s), 1782(s), 1703(s) cm^{-1}. Unfortunately, this product was contaminated with some impurities and a clean ^{13}C NMR spectrum was not obtained.

*The formation of morpholine-2,3,5-trione **12**:*

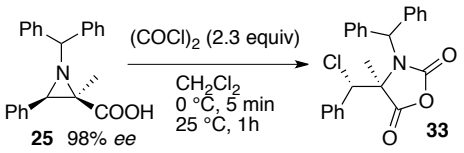


90 90% *ee* **12**

The general procedure for the formation of morpholine-2,3,5-trione **11** was followed with acid **90** (90% *ee*, 40.8 mg, 0.10 mmol, 1.0 equiv), $(COCl)_2$ (0.010 mL, 0.12 mmol, 1.2 equiv) and CH_2Cl_2 (1 mL). The product **12** was obtained as a yellow solid (42.3 mg, 0.085 mmol, 85%). The NMR yield was determined to be 95% with the aid of PH_3CH as an internal standard. This procedure was repeated to give **12** in 75% isolated yield; mp 120-122 °C. Spectral data for **12**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (d, 1H, *J* = 4 Hz), 5.00 (d, 1H, *J* = 4 Hz), 6.89 (d, 2H, *J* = 8.5 Hz), 7.02 (d, 2H, *J* =7 Hz), 7.13 (s, 1H), 7.32-7.42 (m, 4H), 7.46-7.60 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 57.81, 62.47, 64.38, 125.65, 126.41, 128.48, 129.30, 130.12, 130.17, 130.25, 130.37, 130.45, 132.91, 135.53, 136.24, 148.60, 151.13, 157.38; IR (thin film) 1832(m), 1784(s), 1708(s) cm^{-1}; HRMS calcd for $C_{24}H_{18}NO_4{}^{79}Br^{35}Cl$ (M+H, ESI$^+$) *m/z* 498.0108, meas 498.0150; $[\alpha]^{20}_D$ –90.3° (*c* 0.5, CH_2Cl_2).

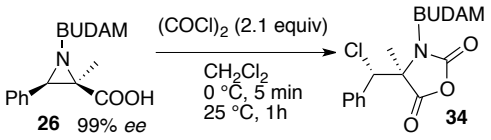
IV. Formation of *N*-carboxy anhydrides (NCAs) (Table 1)

*The formation of NCA **33**:*



General procedure for N-carboxyanhydride (NCA) formation: Illustrated for the formation of NCA **33**. A flame-dried 25 mL round bottom flask filled with N_2 was charged with the acid **25** (98% ee, 69 mg, 0.20 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N_2 balloon was attached via a needle. Dry CH_2Cl_2 (2.0 mL) was added via syringe. The flask was cooled to 0 °C and $(COCl)_2$ (0.040 mL, 0.46 mmol, 2.3 equiv) was added dropwise at 0 °C. After the mixture was stirred at 0 °C for 5 min and at rt for 1 h, the volatiles were removed. The product was purified from the crude mixture by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1) to give the product **33** as a white foamy solid (44 mg, 0.11 mmol) in 54% yield; mp 49-50 °C; R_f = 0.30 (hexane:EtOAc 4:1). Spectral data for NCA **33**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 (s, 3H), 5.13 (s, 1H), 5.30 (s, 1H), 7.10-7.16 (m, 2H), 7.22-7.48 (m, 13H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.02, 62.73, 65.45, 71.33, 127.63, 127.94, 128.33, 128.44, 128.49, 128.64, 128.76, 129.33, 129.73, 133.11, 137.89, 139.16, 150.23, 170.09; IR (thin film) 1848(s), 1780(s) cm^{-1}; HRMS calcd for $C_{24}H_{21}NO_3{}^{35}Cl$ (M+H, ESI$^+$) *m/z* 406.1210, meas 406.1235; $[\alpha]^{20}_D$ 21.3° (*c* 1.0, CH_2Cl_2) on 98% *ee* material.

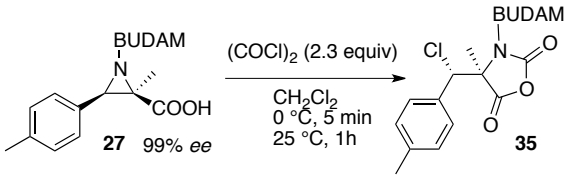
*The formation of NCA **34**:*



The general procedure for NCA formation was followed with acid **26** (99% *ee*, 70 mg, 0.11 mmol, 1.0 equiv), $(COCl)_2$ (0.020 mL, 0.23 mmol, 2.1 equiv) and CH_2Cl_2 (2 mL). After purification by column chromatography (1st column, silica gel, 18 × 180 mm, hexane:EtOAc 15:1; 2nd column, silica gel, 18 × 180 mm, benzene:EtOAc 100:1), the product **34** was obtained as a white solid (54 mg, 0.078 mmol) in 69% yield; mp 41-42 °C; R_f = 0.50 (hexane:EtOAc 4:1). Spectral data for **34**:

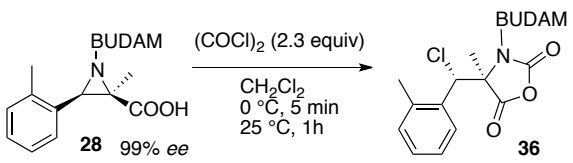
^{1}H NMR (600 MHz, $CDCl_3$) δ 1.31 (s, 18H), 1.42 (s, 18H), 1.68 (s, 3H), 3.64 (s, 3H), 3.75 (s, 3H), 5.06 (s, 1H), 5.27 (s, 1H), 6.89 (s, 2H), 7.18-7.26 (m, 6H), 7.35 (t, 1H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.00, 31.93, 32.10, 35.70, 35.89, 62.61, 64.20, 64.33, 65.21, 71.33, 126.79, 127.34, 128.38, 128.82, 129.48, 132.17, 132.96, 133.44, 143.24, 143.43, 149.70, 158.78, 159.07, 170.39; IR (thin film) 2960(m), 1847(m), 1785(s) cm^{-1}; HRMS calcd for $C_{42}H_{57}NO_5{}^{35}Cl$ (M, ESI$^+$) *m/z* 690.3925, meas 690.3954; $[\alpha]^{20}_D$ 5.8° (*c* 0.5, CH_2Cl_2) on 99% *ee* material. Recrystallization of **34** gave X-ray quality single crystals. The crystallographic data for **34** has been deposited at the Cambridge Crystallographic Data Center (CCDC 884444).

*The formation of NCA **35**:*



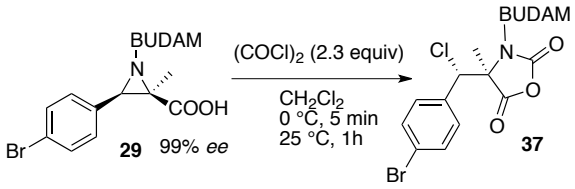
The general procedure for NCA formation was followed with acid **27** (99% *ee*, 129 mg, 0.200 mmol, 1.00 equiv), $(COCl)_2$ (0.040 mL, 0.46 mmol, 2.3 equiv) and CH_2Cl_2 (2 mL). After column chromatography (silica gel, 18 × 180 mm, benzene:EtOAc 100:1), the product **35** was obtained as a white foamy solid (106 mg, 0.0150 mmol) in 75% yield; mp 71-78 °C; R_f = 0.60 (benzene:EtOAc 100:1). Spectral data for NCA **35**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (s, 18H), 1.39 (s, 18H), 1.63 (s, 3H), 2.31 (s, 3H), 3.61 (s, 3H), 3.72 (s, 3H), 5.08 (s, 1H), 5.21 (s, 1H), 6.86 (s, 2H), 7.01 (d, 2H, *J* = 8.0 Hz), 7.04 (d, 2H, *J* = 8.5 Hz), 7.21 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.79, 21.82, 31.66, 31.84, 35.43, 35.62, 62.20, 63.95, 64.07, 64.85, 71.08, 126.58, 127.05, 128.43, 128.78, 130.18, 131.96, 132.69, 139.23, 142.94, 143.14, 149.44, 158.50, 158.79, 170.19; IR (thin film) 2961(m), 1846(m), 1784(s) cm^{-1}; HRMS calcd for $C_{43}H_{59}NO_5{}^{35}Cl$ (M+H, ESI$^+$) *m/z* 704.4082, meas 704.4030; $[\alpha]^{20}_D$ 3.2° (*c* 1.0, CH_2Cl_2) on 99% *ee* material.

*The formation of NCA **36**:*



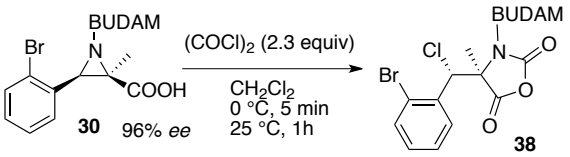
The general procedure for NCA formation was followed with acid **28** (129 mg, 0.200 mmol, 1.00 equiv), $(COCl)_2$ (0.040 mL, 0.46 mmol, 2.3 equiv) and CH_2Cl_2 (2 mL). After purification by column chromatography (silica gel, 18 × 180 mm, benzene:EtOAc 100:1), the product **36** was obtained as a white foamy solid (100 mg, 0.0142 mmol) in 71% yield; mp 72-78 °C; R_f = 0.60 (benzene:EtOAc 100:1). Spectral data for **36**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.29 (s, 18H), 1.38 (s, 18H), 1.62 (s, 3H), 2.35 (s, 3H), 3.62 (s, 3H), 3.70 (s, 3H), 5.33 (s, 1H), 5.59 (s, 1H), 6.94-7.00 (m, 3H), 7.15 (d, 1H, *J* = 7.2 Hz), 7.20-7.24 (m, 3H), 7.42 (d, 1H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.15, 20.79, 32.16, 32.30, 35.93, 36.07, 62.39, 63.25, 64.40, 64.50, 71.63, 126.55, 126.70, 128.13, 129.40, 129.62, 131.02, 132.37, 132.98, 133.55, 136.33, 143.21, 143.45, 150.13, 158.74, 159.25, 170.81; IR (thin film) 2961(m), 1846(m), 1784(s) cm^{-1}; HRMS calcd for $C_{43}H_{59}NO_5{}^{35}Cl$ (M+H, ES$^+$) *m/z* 704.4082, meas 704.4040; $[\alpha]^{20}_D$ –9.0° (*c* 1.0, CH_2Cl_2) on 99% *ee* material.

*The formation of NCA **37**:*



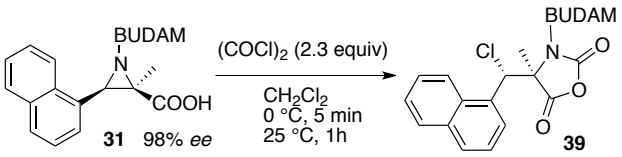
The general procedure for NCA formation was followed with acid **29** (141 mg, 0.200 mmol, 1.00 equiv), $(COCl)_2$ (0.040 mL, 0.46 mmol, 2.3 equiv) and CH_2Cl_2 (2 mL). After purification by column chromatography (silica gel, 18 × 180 mm, benzene:EtOAc 100:1), the product **37** was obtained as a white foamy solid (120 mg, 0.0156 mmol) in 78% yield; mp 78-80 °C; R_f = 0.60 (benzene:EtOAc 100:1). Spectral data for **37**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (s, 18H), 1.40 (s, 18H), 1.73 (s, 3H), 3.62 (s, 3H), 3.73 (s, 3H), 4.99 (s, 1H), 5.15 (s, 1H), 6.88 (s, 2H), 6.94 (d, 2H, *J* = 8.4 Hz), 7.22 (s, 2H), 7.29 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.74, 31.91, 32.09, 35.71, 35.91, 62.67, 64.18, 64.39, 64.41, 71.24, 123.72, 126.85, 127.35, 130.38, 131.51, 132.20, 132.40, 132.48, 143.37, 143.57, 149.55, 158.97, 159.09, 169.95; IR (thin film) 2963(m), 1848(m), 1784(s) cm^{-1}; HRMS calcd for $C_{42}H_{56}NO_5{}^{79}Br^{35}Cl$ (M+H, ESI$^+$) *m/z* 768.3030, meas 768.2977; $[\alpha]^{20}_D$ –11.3° (*c* 2.0, CH_2Cl_2) on 99% *ee* material.

*The formation of NCA **38**:*



The general procedure for NCA formation was followed with acid **30** (96% *ee*, 71 mg, 0.10 mmol, 1.0 equiv), $(COCl)_2$ (0.020 mL, 0.23 mmol, 2.3 equiv) and CH_2Cl_2 (1 mL). After column chromatography (silica gel, 18 × 180 mm, benzene:EtOAc 100:1), the product **38** was obtained as a white foamy solid (56 mg, 0.073 mmol) in 73% yield; mp 75-80 °C; R_f = 0.75 (benzene:EtOAc 100:1). Spectral data for **38**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 18H), 1.43 (s, 18H), 1.80 (s, 3H), 3.67 (s, 3H), 3.74 (s, 3H), 5.39 (s, 1H), 5.96 (s, 1H), 7.03 (s, 2H), 7.12-7.18 (m, 1H), 7.22-7.32 (m, 3H), 7.49 (d, 1H, *J* = 8.0 Hz), 7.61 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.23, 31.96, 32.11, 35.74, 35.88, 62.89, 64.20, 64.32, 64.57, 71.17, 124.56, 126.39, 127.80, 127.86, 130.97, 131.07, 132.14, 133.02, 133.06, 134.15, 143.15, 143.22, 149.78, 158.64, 159.04, 169.72; IR (thin film) 2961(m), 1848(m), 1784(s) cm^{-1}; HRMS calcd for $C_{42}H_{56}NO_5{}^{79}Br^{35}Cl$ (M+H, ESI$^+$) *m/z* 768.3030, meas 768.3070; $[\alpha]^{20}_D$ –6.4° (*c* 0.5, CH_2Cl_2) on 96% *ee* material.

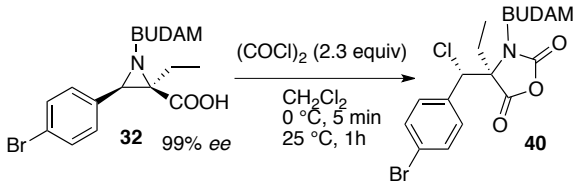
*The formation of NCA **39**:*



The general procedure for NCA formation was followed with acid **31** (98% *ee*, 136 mg, 0.200 mmol, 1.00 equiv), $(COCl)_2$ (0.040 mL, 0.46 mmol, 2.3 equiv) and CH_2Cl_2 (2 mL). After purification by column chromatography (silica gel, 18 × 180 mm, benzene:EtOAc 100:1), the product **39** was obtained as a white foamy solid (118 mg, 0.016 mmol) in 80% yield; mp 89-91 °C; R_f = 0.65 (benzene:EtOAc 50:1). Spectral data for **39**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (s, 18H), 1.41 (s, 18H), 1.52 (s, 3H), 3.56 (s, 3H), 3.71 (s, 3H), 5.12 (s, 1H), 6.31 (s, 1H), 6.82 (s, 2H), 7.12 (t, 1H, *J* = 8.0 Hz), 7.26 (s, 2H), 7.52 (t, 1H, *J* = 7.0 Hz), 7.60 (t, 2H, *J* = 8.5 Hz), 7.83 (d, 1H, *J* =8.0 Hz), 7.89 (d, 1H, *J* = 8.5 Hz), 8.03 (d, 1H, *J* = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$)

δ 21.94, 31.88, 32.14, 35.65, 35.91, 61.12, 63.08, 64.13, 64.37, 72.10, 122.34, 124.98, 126.13, 126.44, 127.31, 127.99, 128.73, 129.39, 129.69, 130.27, 131.23, 132.34, 133.16, 133.38, 143.04, 143.06, 150.09, 158.54, 158.94, 171.10; IR (thin film) 2963(m), 1848(m), 1784(s) cm^{-1}; HRMS calcd for $C_{46}H_{59}NO_5{}^{35}Cl$ (M+H, ES^+) *m/z* 740.4082, meas 740.4075; $[\alpha]^{20}_D$ –10.3° (*c* 1.0, CH_2Cl_2) on 98% *ee* material.

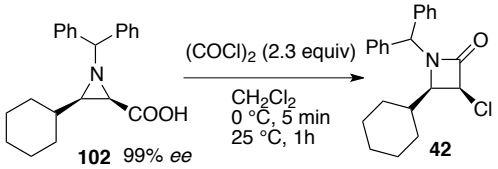
*The formation of NCA **40**:*



The general procedure for NCA formation was followed with acid **32** (99% *ee*, 144 mg, 0.200 mmol, 1.00 equiv), $(COCl)_2$ (0.040 mL, 0.46 mmol, 2.3 equiv) and CH_2Cl_2 (2 mL). After column chromatography (1^{st} silica gel, 18 × 180 mm, benzene:EtOAc 100:1; 2^{nd} silica gel, 18 × 180 mm, benzene:EtOAc 100:1), the product **40** was obtained as a white foamy solid (30 mg, 0.038 mmol) in 20% yield; mp 60-61 °C; R_f = 0.725 (benzene:EtOAc 100:1). Spectral data for **40**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.42 (t, 3H, *J* = 7.5 Hz), 1.28 (s, 18H), 1.36 (s, 18H), 1.74 (dq, 1H, *J* = 7.5, 7.5 Hz), 2.02 (dq, 1H, *J* = 7.5, 7.5 Hz), 3.58 (s, 3H), 3.70 (s, 3H), 4.94 (s, 1H), 5.35 (s, 1H), 6.93 (s, 2H), 7.18 (s, 2H), 7.23 (d, 2H, *J* = 8.5 Hz), 7.40 (d, 2H, *J* = 8.5 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 7.73, 27.97, 31.90, 32.11, 35.67, 35.91, 62.87, 64.25, 64.32, 64.72, 76.19, 123.86, 126.19, 128.29, 130.41, 131.55, 131.71, 132.75, 133.12, 143.07, 143.64, 150.01, 158.54, 159.42, 169.60; IR (thin film) 2963(m), 1846(m), 1782(s) cm^{-1}; HRMS calcd for $C_{43}H_{58}NO_5{}^{35}Cl^{79}Br$ (M+H, ES^+) *m/z* 782.3187, meas 782.3253; $[\alpha]^{20}_D$ 9.8° (*c* 1.0, CH_2Cl_2) on 99% *ee* material.

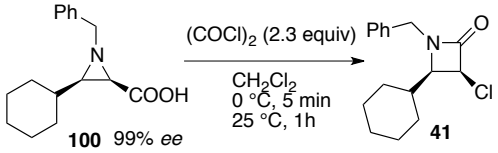
V. Formation of *β*-lactams with $(COCl)_2$ (Table 2)

*The formation of β-lactam **42**:*



The general procedure for β-lactam formation with $(COCl)_2$ illustrated for ***42***: A flame-dried 25 mL round bottom flask filled with N_2 was charged with acid **102** (99% *ee*, 67 mg, 0.20 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N_2 balloon was attached *via* a needle. Dry CH_2Cl_2 (2 mL) was added *via* syringe. The flask was cooled to 0 °C and $(COCl)_2$ (0.040 mL, 0.46 mmol, 2.3 equiv) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 5 min and 1 h at rt. After the volatiles were removed, the crude mixture was placed under high vacuum (0.1 mmHg) to give the product **42** (70 mg, 0.198 mmol, 99%) as a white foamy solid; The optical purity was determined to be >99% ee by HPLC analysis (Chiralpak AS column, 90:10 hexane/2-propanol at 222 nm, flow-rate 1.0 mL/min); Retention times: R_t = 9.57 min ((3S, 4R)-**42**, major enantiomer) and R_t = 32.35 min ((3R, 4S)-**42**, minor enantiomer); mp 113-114 °C; R_f = 0.50 (hexane:EtOAc 4:1). Spectral data for **42**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84-0.98 (m, 1H), 1.02-1.36 (m, 4H), 1.62-1.94 (m, 6H), 3.57 (dd, 1H, *J* = 8.5, 5.0 Hz), 4.80 (d, 1H, *J* = 5.0 Hz), 5.62 (s, 1H), 7.26-7.46 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.55, 25.80, 26.23, 29.94, 30.01, 38.96, 58.69, 62.94, 64.88, 127.92, 128.21, 128.39, 128.55, 128.70, 128.88, 138.28, 139.25, 165.08; IR (thin film) 2927(m), 1764(s) cm^{-1}; HRMS calcd for $C_{22}H_{25}NO^{35}Cl$ (M+H, ESI$^+$) *m/z* 354.1625, meas 354.1638; $[\alpha]^{20}_D$ –96.6° (*c* 1.0, CH_2Cl_2) on 99% *ee* material.

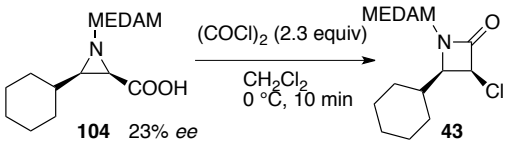
The formation of β-lactam ***41****:*



The general procedure for β-lactam formation with $(COCl)_2$ was followed with acid **100** (99% *ee*, 52 mg, 0.20 mmol, 1.0 equiv), $(COCl)_2$ (0.040 mL, 0.46 mmol, 2.3 equiv) and CH_2Cl_2 (2 mL). The ratio of *cis:trans* was determined to be ≥ 50:1 from the ^{1}H NMR spectrum of the crude reaction mixture with the aid of an authentic sample of the *trans*-isomer **56.** The product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1). The product **41** was obtained as a white crystalline solid (46 mg, 0.17 mmol) in 83% yield; mp 118-119 °C from hexane and benzene; R_f = 0.40 (hexane:EtOAc 4:1). Spectral data for **41**: ^{1}H NMR (500 MHz,

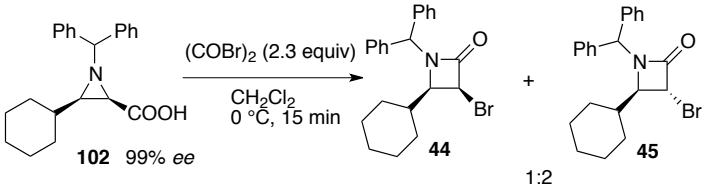
$CDCl_3$) δ 0.80 (qd, 1H, *J* = 11.0, 3.5 Hz), 0.98 (qd, 1H, *J* = 12.0, 3.5 Hz), 1.10 (qt, 1H, *J* = 13.0, 3.5 Hz), 1.18-1.32 (m, 2H), 1.62-1.80 (m, 6H), 3.33 (dd, 1H, *J* = 9.0, 5.0 Hz), 4.08 (d, 1H, *J* =15.0 Hz), 4.81 (d, 1H, *J* = 5.0 Hz), 4.86 (d, 1H, *J* = 15.0 Hz), 7.18-7.22 (m, 2H), 7.26-7.36 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.29, 25.54, 25.95, 29.78, 29.80, 38.63, 47.06, 58.93, 61.18, 127.95, 128.20, 128.90, 135.06, 165.44; IR (thin film) 2924(m), 1755(s) cm^{-1}; HRMS calcd for $C_{16}H_{21}NO^{35}Cl$ (M+H, ESI^+) *m/z* 278.1312, meas 278.1313; $[\alpha]^{20}_D$ –20.3° (*c* 0.5, CH_2Cl_2) on 99% *ee* material. Recrystallization of **41** gave X-ray quality single crystals. The crystallographic data for **41** has been deposited at the Cambridge Crystallographic Data Center (CCDC 884445).

*The formation of β-lactam **43**:*



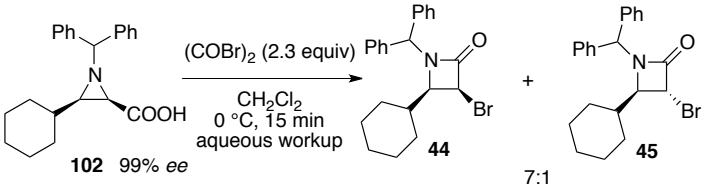
A flame-dried 25 mL round bottom flask filled with N_2 was charged with acid **104** (23% *ee*, 45 mg, 0.10 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N_2 balloon was attached *via* a needle. Dry CH_2Cl_2 (1 mL) was added *via* syringe. The flask was cooled to 0 °C and $(COCl)_2$ (0.020 mL, 0.23 mmol, 2.3 equiv) was added dropwise at 0 °C. After the mixture was stirred at 0 °C for 10 min, the reaction mixture was concentrated on a rotary evaporator to dryness. The product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1) to afford the β-lactam **43** as a white solid (42 mg, 0.090 mmol) in 89% yield; mp 58-60 °C; R_f = 0.30 (hexane:EtOAc 4:1). Spectral data for **43**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (qd, 1H, *J* = 12.0, 2.0 Hz), 1.00-1.30 (m, 4H), 1.60-1.90 (m, 6H), 2.23, 2.24 (2s, 12H), 3.52 (dd, 1H, *J* = 8.5, 5.5 Hz), 3.69, 3.70 (2s, 6H), 4.78 (d, 1H, *J* = 5.5 Hz), 5.37 (s, 1H), 6.87, 6.88 (2s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.24, 16.29, 25.41, 25.70, 26.06, 29.68, 29.71, 38.79, 58.34, 59.62, 62.40, 63.85, 128.45, 128.64, 130.73, 130.99, 133.42, 134.48, 156.30, 156.53, 164.85 (One sp^3 carbon not located); IR (thin film) 2928(s), 1765(w) cm^{-1}; HRMS calcd for $C_{28}H_{37}NO_3{}^{35}Cl$ (M+H, ESI^+) *m/z* 470.2462, meas 470.2459; $[\alpha]^{20}_D$ 10.6° (*c* 0.5, CH_2Cl_2) on 23% *ee* material.

*The formation of β-lactam **44** and **45**:*



102 99% *ee* **44** **45** 1:2

A flame-dried 25 mL round bottom flask filled with N_2 was charged with acid **102** (99% *ee*, 67 mg, 0.20 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N_2 balloon was attached *via* a needle. Dry CH_2Cl_2 (2 mL) was added *via* syringe. The flask was cooled to 0 °C and $(COBr)_2$ (0.040 mL, 0.46 mmol, 2.3 equiv) was added dropwise at 0 °C. After the mixture was stirred at 0 °C for 15 min, the reaction mixture was concentrated on a rotary evaporator to dryness. The ^{1}H NMR spectrum of the crude reaction mixture showed a 2:1 *trans*:*cis* ratio of **45:44**. Purification by column chromatography (1st column, silica gel, 18 × 180 mm, hexane:EtOAc 5:1; 2nd column, silica gel, 18 × 180 mm, hexane:EtOAc 15:1) gave the major product **45** (22 mg, 0.055 mmol) in a pure form as a colorless oil in 28% yield and a mixture of **44** and **45** in 66% yield. The overall yield for *cis* and *trans*-isomers was 94%. Extended reaction times or increased temperatures do not enhance the trans/cis ratio past 2:1. Spectral data for **45**: R_f = 0.35 (hexane:EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.60-1.80 (m, 11H), 3.72 (dd, 1H, *J* = 5.0, 2.0 Hz), 4.51 (d, 1H, *J* = 2.0 Hz), 5.78 (s, 1H), 7.20-7.60 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.36, 25.76, 26.03, 26.47, 29.31, 38.86, 43.53, 62.25, 69.23, 127.81, 128.02, 128.05, 128.36, 128.59, 128.69, 138.09, 138.17, 163.76; IR (thin film) 1765(s), 1265(m) cm^{-1}; HRMS calcd for $C_{22}H_{25}NO^{79}Br$ (M+H, ESI$^+$) *m/z* 398.1120, meas 398.1117; $[\alpha]^{20}_D$ –8.3° (*c* 1.0, CH_2Cl_2) on 99% *ee* material.

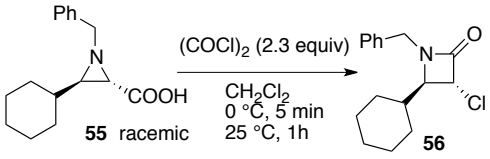


102 99% *ee* **44** **45** 7:1

A flame-dried 25 mL round bottom flask filled with N_2 was charged with acid **102** (99% *ee*, 34 mg, 0.10 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N_2

balloon was attached *via* a needle. Dry CH_2Cl_2 (1 mL) was added *via* syringe. The flask was cooled to 0 °C and $(COBr)_2$ (0.020 mL, 0.23 mmol, 2.3 equiv) was added dropwise at 0 °C. After the reaction mixture was stirred at 0 °C for 15 min, *aq* sat $NaHCO_3$ (1 mL) was added at 0 °C *via* syringe along with CH_2Cl_2 (10 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated and the ^{1}H NMR spectrum of this crude reaction mixture showed a 7:1 *cis*:*trans* ratio of **44:45**. The major product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 9:1). The pure *cis*-isomer **44** (100:1 *cis:trans* ratio by ^{1}H NMR, 33 mg, 0.083 mmol) was obtained as a colorless oil in 83% yield and a mixture of *cis*- and *trans*-isomers was obtained in 12% yield. The overall yield for the *cis* and *trans*-isomers was 95%. Spectral data for **44**: solidified in the refrigerator, mp 83-85 °C; R_f = 0.35 (hexane:EtOAc 4:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.86 (qd, 1H, *J* = 11.4, 3.0 Hz), 1.02-1.32 (m, 4H), 1.62-1.74 (m, 3H), 1.78-1.90 (m, 3H), 3.48 (dd, 1H, *J* = 9.0, 5.4 Hz), 4.86 (d, 1H, *J* = 5.4 Hz), 5.61 (s, 1H), 7.20-7.40 (m, 10H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.21, 25.52, 25.98, 29.84, 30.01, 40.02, 47.94, 61.30, 64.78, 127.70, 127.99, 128.17, 128.36, 128.48, 128.66, 138.04, 139.04, 165.00; IR (thin film) 1765(s) cm^{-1}; HRMS calcd for $C_{22}H_{25}NO^{79}Br$ (M+H, ESI^+) *m/z* 398.1120, meas 398.1125; $[\alpha]^{20}_D$ –33.9° (*c* 0.5, CH_2Cl_2) on 99% *ee* material.

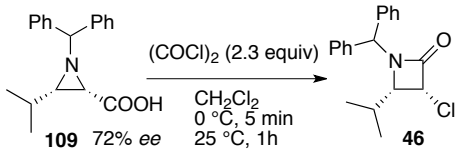
*The formation of β-lactam **56**:*



The general procedure for β-lactam formation with $(COCl)_2$ was followed with *trans*-acid **55** (racemic, 50 mg, 0.193 mmol, 1.0 equiv), $(COCl)_2$ (0.04 mL, 0.46 mmol, 2.3 equiv) and CH_2Cl_2 (2 mL). The ratio of *trans:cis* was determined to be ≥ 100:1 from the ^{1}H NMR spectrum of the crude reaction mixture with the aid of an authentic sample of the *cis*-isomer **41.** The product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1). The product *trans*-**56** was obtained as a colorless oil (45 mg, 0.162 mmol) in 85% yield; R_f = 0.33

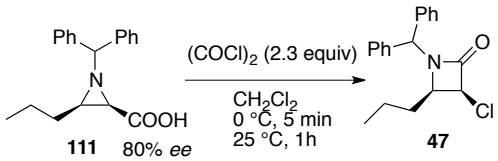
(hexane:EtOAc 4:1). Spectral data for *trans*-**56**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88-1.26 (m, 5H), 1.48-1.78 (m, 6H), 3.33 (dd, 1H, *J* = 6.0, 2.0 Hz), 4.06 (d, 1H, *J* =15.5 Hz), 4.48 (d, 1H, *J* = 2.0 Hz), 4.80 (d, 1H, *J* = 15.0 Hz), 7.20-7.40 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.46, 25.55, 25.96, 27.52, 29.45, 39.17, 45.82, 57.22, 67.73, 127.95, 128.10, 128.89, 134.86, 164.15; IR (thin film) 2928(m), 1770(s) cm^{-1}; HRMS calcd for $C_{16}H_{21}NO^{35}Cl$ (M+H, ESI^+) *m/z* 278.1312, meas 278.1316.

The formation of β-lactam ***46****:*



The general procedure for β-lactam formation with $(COCl)_2$ was followed with acid **109** (72% *ee*, 30 mg, 0.10 mmol, 1.0 equiv), $(COCl)_2$ (0.020 mL, 0.23 mmol, 2.3 equiv) and CH_2Cl_2 (1 mL). The crude product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1). The product **46** was obtained as a white solid (30 mg, 0.096 mmol) in 96% yield; mp 110-112 °C; R_f = 0.35 (hexane:EtOAc 4:1). Spectral data for **46**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.95 (d, 3H, *J* = 6.6 Hz), 0.99 (d, 3H, *J* = 7.2 Hz), 2.08-2.18 (m, 1H), 3.56 (dd, 1H, *J* = 9.0, 5.4 Hz), 4.82 (d, 1H, *J* = 5.4 Hz), 5.62 (s, 1H), 7.24-7.40 (m, 10H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.55, 19.71, 29.36, 58.49, 64.25, 64.31, 127.78, 128.00, 128.23, 128.29, 128.55, 128.66, 138.09, 138.89, 164.69; IR (thin film) 1759(s) cm^{-1}; HRMS calcd for $C_{19}H_{21}NO^{35}Cl$ (M+H, ESI^+) *m/z* 314.1312, meas 314.1299; $[\alpha]^{20}_D$ 66.9° (*c* 0.5, CH_2Cl_2) on 72% *ee* material.

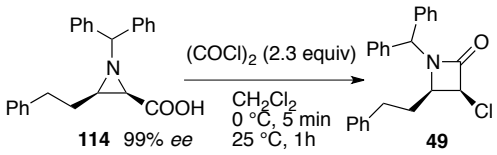
The formation of β-lactam ***47****:*



The general procedure for β-lactam formation with $(COCl)_2$ was followed with acid **111** (80% *ee*, 30 mg, 0.10 mmol, 1.0 equiv), $(COCl)_2$ (0.020 mL, 0.23 mmol, 2.3 equiv) and CH_2Cl_2 (1 mL). The product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc

5:1). The β-lactam **47** was obtained as a colorless oil (25 mg, 0.080 mmol) in 81% yield; R_f = 0.30 (hexane:EtOAc 4:1). Spectral data for **47**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (t, 3H, *J* = 7.0 Hz), 1.04-1.18 (m, 1H), 1.26-1.40 (m, 1H), 1.44-1.54 (m, 1H), 1.70-1.82 (m, 1H), 3.64-3.74 (m, 1H), 4.88 (d, 1H, *J* = 5.0 Hz), 5.96 (s, 1H), 7.18-7.42 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.69, 18.98, 31.57, 57.71, 59.15, 61.04, 127.83, 127.85, 128.13, 128.58, 128.69, 128.77, 137.60, 138.57, 164.07; IR (thin film) 1765(s) cm^{-1}; HRMS calcd for $C_{19}H_{21}NO^{35}Cl$ (M+H, ESI$^+$) *m/z* 314.1312, meas 314.1313; $[\alpha]^{20}_D$ –28.5° (*c* 1.0, CH_2Cl_2) on 80% *ee* material.

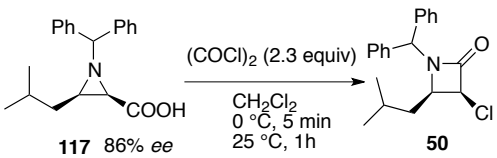
*The formation of β-lactam **49**:*



114 99% *ee* **49**

The general procedure for β-lactam formation with $(COCl)_2$ was followed with acid **114** (99% *ee*, 36 mg, 0.10 mmol, 1.0 equiv), $(COCl)_2$ (0.020 mL, 0.23 mmol, 2.3 equiv) and CH_2Cl_2 (1 mL). The crude product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1). The product **49** was obtained as a white solid (27 mg, 0.072 mmol) in 72% yield; mp 93-94 °C; R_f = 0.13 (hexane:EtOAc 4:1). Spectral data for **49**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72-1.88 (m, 1H), 2.00-2.16 (m, 1H), 2.28-2.44 (m, 1H), 2.58-2.72 (m, 1H), 3.64-3.76 (m, 1H), 4.90 (d, 1H, *J* = 5.1 Hz), 5.94 (s, 1H), 6.94-7.02 (m, 2H), 7.20-7.40 (m, 13H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.12, 31.72, 57.03, 58.96, 60.92, 126.20, 127.78, 127.87, 128.18, 128.23, 128.50, 128.64, 128.66, 128.81, 137.33, 138.39, 140.31, 163.94; IR (thin film) 1765(s) cm^{-1}; HRMS calcd for $C_{24}H_{23}NO^{35}Cl$ (M+H, ESI$^+$) *m/z* 376.1468, meas 376.1441; $[\alpha]^{20}_D$ –50.8° (*c* 1.0, CH_2Cl_2) on 99% *ee* material.

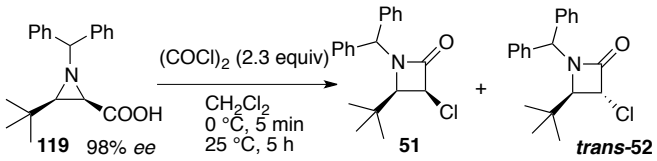
*The formation of β-lactam **50**:*



117 86% *ee* **50**

The general procedure for β-lactam formation with $(COCl)_2$ was followed with acid **117** (86% *ee*, 31 mg, 0.10 mmol, 1.0 equiv), $(COCl)_2$ (0.02 mL, 0.23 mmol, 2.3 equiv) and CH_2Cl_2 (1 mL) with a reaction time to be 30 min at rt. The product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1). The product **50** was obtained as a pale yellow solid (24 mg, 0.074 mmol) in 75% yield; solidified in the refrigerator, mp 72-73 °C; R_f = 0.25 (hexane:EtOAc 4:1). Spectral data for **50**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.68 (d, 3H, *J* = 6.3 Hz), 0.81 (d, 3H, *J* = 6.6 Hz), 1.22-1.34 (m, 1H), 1.40-1.56 (m, 1H), 1.72-1.82 (m, 1H), 3.66-3.76 (m, 1H), 4.86 (d, 1H, *J* = 4.8 Hz), 5.96 (s, 1H), 7.14-7.20 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.64, 23.04, 25.06, 37.97, 56.27, 59.40, 60.90, 127.77, 127.81, 128.21, 128.60, 128.77, 128.85, 137.50, 138.55, 164.19; IR (thin film) 1767(s) cm^{-1}; HRMS calcd for $C_{20}H_{23}NO^{35}Cl$ (M+H, ESI$^+$) *m/z* 328.1468, meas 328.1475; $[\alpha]^{20}_D$ –10.4° (*c* 1.0, CH_2Cl_2) on 86% *ee* material.

*The formation of β-lactam **51**:*

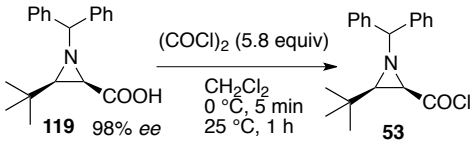


A flame-dried 25 mL round bottom flask filled with N_2 was charged with acid **119** (98% *ee*, 62 mg, 0.20 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N_2 balloon was attached *via* a needle. Dry CH_2Cl_2 (2 mL) was added *via* syringe. The flask was cooled to 0 °C and $(COCl)_2$ (0.040 mL, 0.46 mmol, 2.3 equiv) was added dropwise at 0 °C. After the mixture was stirred at 0 °C for 5 min and rt for 5 h, it was concentrated and kept at rt for 3 months. The products were purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 9:1). The pure *cis*-**51** (40 mg, 0.12 mmol) was obtained as a white solid in 62% yield and the pure *trans*-**52** (10 mg, 0.031 mmol) was obtained as a white solid in 15% yield. If this reaction was repeated for 24 h at 25 °C and then quenched with aq $NaHCO_3$ before concentration, a 38% yield of **51** was isolated. The 1H NMR spectrum of the crude reaction mixture indicated the presence of a 4% yield of the *trans*-isomer **52** along with a 46% yield of the acid chloride **53**.

Spectral data for *cis*-**51**: mp 136-138 °C; R_f = 0.33 (hexane:EtOAc 4:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.12 (s, 9H), 3.74 (d, 1H, *J* = 6.0 Hz), 4.82 (d, 1H, *J* = 5.4 Hz), 5.48 (s, 1H), 7.18-7.44 (m, 10H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.84, 34.10, 57.58, 65.60, 67.63, 127.73, 128.03, 128.15, 128.41, 128.53, 128.72, 138.24, 138.87, 164.69; IR (thin film) 1763(s) cm^{-1}; HRMS calcd for $C_{20}H_{23}NO^{35}Cl$ (M+H, ESI^+) *m/z* 328.1468, meas 328.1476; $[\alpha]^{20}_D$ –89.5° (*c* 0.5, CH_2Cl_2) on 98% *ee* material;

Spectral data for *trans*-**52**: mp 101-103 °C; R_f = 0.40 (hexane:EtOAc 4:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.98 (s, 9H), 3.51 (d, 1H, *J* = 2.4 Hz), 4.41 (d, 1H, *J* = 2.4 Hz), 5.44 (s, 1H), 7.24-7.38 (m, 10H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.08, 33.11, 56.30, 65.44, 73.80, 127.86, 127.91, 127.98, 128.54, 128.59, 128.79, 138.29, 138.41, 163.77; IR (thin film) 2963(m), 1768 (s) cm^{-1}; HRMS calcd for $C_{20}H_{23}NO^{35}Cl$ (M+H, ESI^+) *m/z* 328.1468, meas 328.1453; $[\alpha]^{20}_D$ –15.4° (*c* 1.0, CH_2Cl_2) on 98% *ee* material.

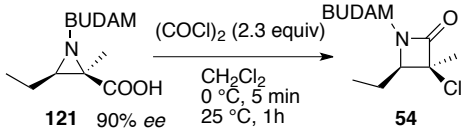
*The formation of acid chloride **53**:*



A flame-dried 25 mL round bottom flask filled with N_2 was charged with acid **119** (98% *ee,* 93 mg, 0.30 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N_2 balloon was attached *via* a needle. Dry CH_2Cl_2 (3 mL) was added *via* syringe. The flask was cooled to 0 °C and $(COCl)_2$ (0.15 mL, 1.75 mmol, 5.8 equiv) was added dropwise at 0 °C. After the mixture was stirred at 0 °C for 5 min and rt for 1 h, it was concentrated by rotary evaporator. The product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 9:1) to give the acid chloride **53** (20 mg, 0.033 mmol) as a white solid in 22% yield; mp 85-86 °C; R_f = 0.70 (hexane:EtOAc 4:1). Spectral data for **53**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.78 (s, 9H), 2.07 (d, 1H, *J* = 7.0 Hz), 2.67 (d, 1H, *J* = 7.0 Hz), 3.66 (s, 1H), 7.20-7.42 (m, 8H), 7.57 (d, 2H, *J* = 7.5 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 27.77, 32.83, 52.33, 60.27, 79.18, 127.20, 127.55, 127.98, 128.25, 128.72, 128.81, 141.93, 142.66, 170.36; IR (thin film) 1790(s) cm^{-1}; Anal calcd for $C_{20}H_{22}NOCl$:

C, 73.27; H, 6.76; N, 4.27. Found: C, 72.84; H, 6.71; N, 4.18. $[\alpha]^{20}_{D}$ 139.2° (*c* 0.5, CH_2Cl_2) on 98% *ee* material.

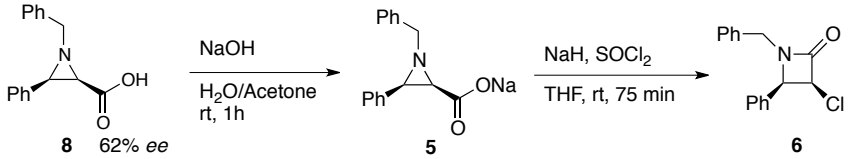
*The formation of β-lactam **54**:*



The general procedure for β-lactam formation with $(COCl)_2$ was followed with acid **121** (90% *ee,* 58 mg, 0.10 mmol, 1.0 equiv), $(COCl)_2$ (0.020 mL, 0.23 mmol, 2.3 equiv) and CH_2Cl_2 (1 mL). The product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 15:1). The β-lactam **54** was obtained as a white foamy solid (23 mg, 0.39 mmol) in 39% yield; mp 73-76 °C; R_f = 0.30 (hexane:EtOAc 4:1). Spectral data for **54**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.74 (t, 3H, *J* = 7.2 Hz), 1.26-1.50 (m, 37H), 1.64-1.80 (m, 4H), 3.10 (dd, 1H, *J* = 10.2, 3.3 Hz), 3.65, 3.66 (2s, 6H), 5.94 (s, 1H), 7.00 (s, 2H), 7.06 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.35, 24.13, 24.41, 32.05, 32.08, 35.79, 35.85, 59.59, 64.26, 64.28, 67.11, 71.60, 125.98, 127.23, 131.51, 132.41, 143.34, 143.74, 158.79, 158.94, 166.94; IR (thin film) 2964(s), 1770(s) cm^{-1}; HRMS calcd for $C_{37}H_{57}NO_3{}^{35}Cl$ (M+H, ESI^+) *m/z* 598.4027, meas 598.4039; $[\alpha]^{20}_{D}$ –7.1° (*c* 0.5, CH_2Cl_2) on 90% *ee* material.

VI. Formation of *β*-lactams with $SOCl_2$ (Scheme 3 and Table 2)

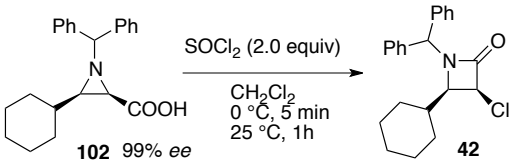
*The formation of β-lactam **6**:*



*Formation of **5**:* To a solution of acid **8** (62% *ee*, 222 mg, 0.88 mmol, 1.0 equiv) in acetone (3 mL) was added a NaOH solution (35.1 mg in 2.4 mL of H_2O, 0.88 mmol, 1.0 equiv). The resulting solution was stirred at rt for 1 h. Then the volatiles were removed by evaporation (acetone was added and evaporated several times) until a white solid was obtained.

*Reaction of **5** with thionyl chloride and NaH (Scheme 3):* To a flame-dried 5 mL round bottom flask was added NaH (2 mg, 60% dispersion in mineral oil, 0.05 mmol, 0.29 equiv) which was washed three times with hexane (0.5 ml × 3) (hexane was added to the flask and the top clear solution was carefully removed by a syringe). The remaining volatiles were removed by vacuum and the flask was filled with N_2. To the flask containing dry NaH was added THF (freshly distilled, 0.5 ml) to form a slurry. Then 46.8 mg of the above sodium salt **5** (0.17 mmol, 1 equiv) was added to the slurry followed by the dropwise addition of thionyl chloride (19 μL, 0.25 mmol, 1.5 equiv) to form an orange reaction mixture. After the mixture was stirred at rt for 75 min under N_2, the solvent was removed by rotary evaporation and EtOAc (3 mL) was added followed by the careful addition of water (0.7 mL). The organic layer was separated, washed with H_2O (1 mL), dried with Na_2SO_4 and filtered. The filtrate was concentrated to give the crude mixture whose ^1H NMR spectrum showed that the major product was compound **6** in a yield of 56% as determined with the aid of an internal standard (Ph_3CH).

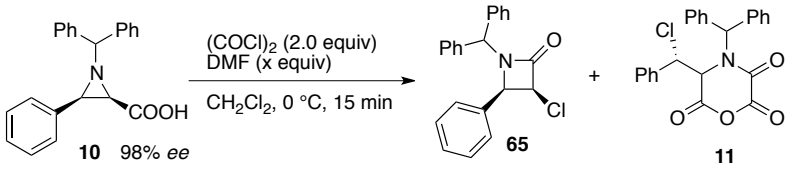
*The formation of β-lactam **42:***



102 99% *ee* **42**

To a 10 mL flame-dried round bottom flask equipped with a stir bar and filled with N_2 was added acid **102** (99% *ee*, 34 mg, 0.1 mmol, 1.0 equiv). The vacuum adapter was replaced by a septum to which a N_2 balloon was attached *via* a needle. Then dry CH_2Cl_2 (1mL) was added *via* a syringe. After the solution was cooled to 0 °C, $SOCl_2$ (15 μL, 0.2 mmol, 2.0 equiv) was added to the reaction flask in a dropwise manner. The reaction mixture was stirred at 0 °C for 5 min and then at room temperature for 1h. Then it was concentrated on a rotary evaporator to dryness. The product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1) to afford the β-lactam **42** (22 mg, 0.062 mmol, 62%) as a off-white solid.

VII. Reaction of 3-phenylaziridine 10 with $(COCl)_2$ in the presence of DMF (Table 3)

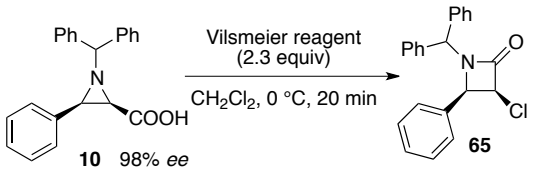


*The general procedure for the reaction of 3-phenylaziridine **10** with $(COCl)_2$ in the presence of DMF illustrated for **entry 3** in Table 3:* To a 10 mL flame-dried round bottom flask equipped with a stir bar and filled with N_2 was added acid **10** (98% *ee*, 33 mg, 0.1 mmol, 1.0 equiv) and dry CH_2Cl_2 (1ml) followed by the addition of dry DMF (7.8 μL, 0.1 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N_2 balloon was attached *via* a needle. The mixture was cooled to 0 °C. Then $(COCl)_2$ (17 μL, 0.2 mmol, 2.0 equiv) was added to the reaction flask in a dropwise manner. The reaction mixture was stirred at 0 °C for 15 min and then concentrated on a rotary evaporator to dryness. The NMR yields for **65** and **11** were 7% and 28%, respectively, determined from the ^1H NMR spectrum of the crude reaction mixture with the aid of Ph_3CH as internal standard in $CDCl_3$.

VIII. Formation of *β*-lactam and acid chloride with Vilsmeier reagent (Table 3 and Table 4)

Procedure A** for β-lactam formation with Vilsmeier reagent illustrated for β-lactam **65:

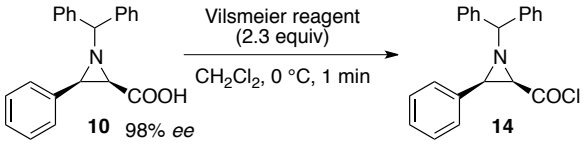
*The formation of β-lactam **65***:



Vilsmeier reagent preparation: To a flame-dried 10 mL round bottom flask filled with N_2 was added dry DMF (22.5 μL, 0.29 mmol, 2.9 equiv) and dry CH_2Cl_2 (0.2 mL) *via* syringe. The vacuum adapter was replaced with a septum to which a N_2 balloon was attached *via* a needle. Then $(COCl)_2$ (20 μL, 0.23 mmol, 2.3 equiv) was added in a dropwise manner at rt with stirring to form Vilsmeier reagent which precipitated as a white solid. Stirring was continued at rt for 20 min. Then the preformed Vilsmeier reagent was cooled to 0°C prior to use.

Lactam formation: To an oven-dried 5 mL round bottom flask filled with N_2 was added acid **10** (98% *ee*, 33 mg, 0.10 mmol, 1.0 equiv) and dry CH_2Cl_2 (0.6 mL) at rt. The resulting solution was transferred to the preformed Vilsmeier reagent in a dropwise manner *via* syringe at 0 °C. The 5 mL flask was rinsed with another two portions of dry CH_2Cl_2 (0.2 mL, 0.1 mL) which were also transferred to the reaction flask containing the Vilsmeier reagent. The reaction mixture was stirred at 0 °C for 20 min and concentrated by rotovap. The NMR yield of **65** was 82% as determined from the ^{1}H NMR spectrum of the crude reaction mixture with the aid of Ph_3CH as internal standard in $CDCl_3$. The product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1) to afford the β-lactam **65** (28.7 mg, 0.083 mmol, 83%) as a white solid; mp 107-108 °C; R_f = 0.20 (hexane:EtOAc 4:1). Spectral data for **65**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.95 (d, 1H, *J* = 5.0 Hz), 5.13 (d, 1H, *J* = 5.0 Hz), 5.65 (s, 1H), 7.20-7.46 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 60.28, 61.86, 62.89, 127.92, 127.96, 128.17, 128.26, 128.41, 128.56, 128.61, 128.64, 128.91, 133.14, 137.52, 138.22, 164.31; IR (thin film) 1767(s) cm^{-1}; HRMS calcd for $C_{22}H_{19}NO^{35}Cl$ (M+H, ES$^+$) *m/z* 348.1155, meas 348.1161; $[\alpha]^{20}_D$ –59.2° (*c* 1.0, CH_2Cl_2) on 98% *ee* material.

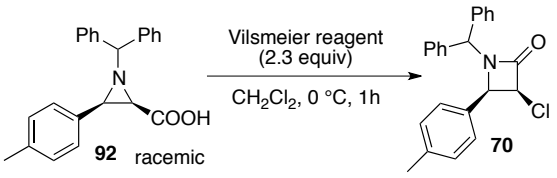
*The formation of acid chloride **14**:*



Procedure A for β-lactam formation with Vilsmeier reagent was followed with acid **10** (98% *ee*, 164.7 mg, 0.50 mmol, 1.0 equiv), Vilsmeier reagent (1.16 mmol, 2.3 equiv) in 2.2 mL dry CH_2Cl_2 (0.6 mL for making Vilsmeier reagent and 1.6 ml for transferring the starting material aziridine acid **10** to Vilsmeier reagent **61**) with a reaction time of 1 min at 0 °C. Then the reaction mixture was quickly loaded onto a chromatography column without concentration (silica gel 20 × 180 mm, hexane:EtOAc 7:1). Elution afforded the acid chloride **14** (99.6 mg, 0.286 mmol, 57%) as a white solid; mp 103-105 °C; R_f = 0.31 (hexane:EtOAc 7:1). Spectral data for **14**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.17 (d, 1H, *J* = 7.0 Hz), 3.50 (d, 1H, *J* = 6.5 Hz), 4.00 (s, 1H), 7.15-7.19 (m, 1H), 7.22-7.30 (m, 6H), 7.32-7.36 (m, 2H), 7.37-7.40 (m, 2H), 7.41-7.45 (m, 2H), 7.51-7.55 (m,

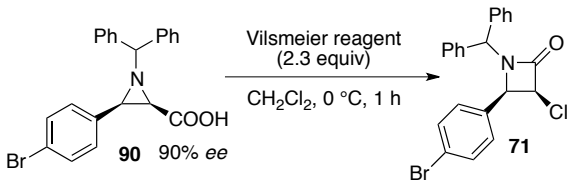
2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 51.34, 54.40, 77.34, 127.04, 127.33, 127.64, 127.71, 127.75, 128.21, 128.22, 128.66, 128.77, 133.03, 141.53, 141.63, 167.95; IR (thin film) 1799(s), 1028 (s), 698(s) cm^{-1}; HRMS calcd for $C_{22}H_{19}NO^{35}Cl$ (M+H, ES$^+$) *m/z* 348.1155, meas 348.1147; $[\alpha]^{20}_D$ +72.8° (*c* 1.0, CH_2Cl_2) on 98% *ee* material.

*The formation of β-lactam **70**:*



Procedure A for β-lactam formation with Vilsmeier reagent was followed with acid **92** (racemic, 34.4 mg, 0.10 mmol, 1.0 equiv), Vilsmeier reagent (0.23 mmmol, 2.3 equiv) with a reaction time of 1 h at 0 °C. After the column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1), the product was obtained as white foamy solid (21.7 mg, 0.06 mmol, 60%); mp 117-118 °C; R_f = 0.30 (hexane:EtOAc 4:1). Spectral data for **70**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.30 (s, 3H), 4.89 (d, 1H, *J* = 5.4 Hz), 5.08 (d, 1H, *J* = 5.0 Hz), 5.58 (s, 1H), 7.05 (d, 2H, *J* = 8.4 Hz), 7.10 (d, 2H, *J* =7.8 Hz), 7.20-7.46 (m, 10H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.22, 60.40, 61.76, 62.96, 127.36, 127.87, 127.95, 128.19, 128.54, 128.62, 128.65, 128.94, 130.05, 137.55, 138.45, 138.88, 164.34; IR (thin film) 1767(s) cm^{-1}; HRMS calcd for $C_{23}H_{21}NO^{35}Cl$ (M+H, ESI$^+$) m/z 362.1312, meas 362.1303.

*The formation of β-lactam **71**:*

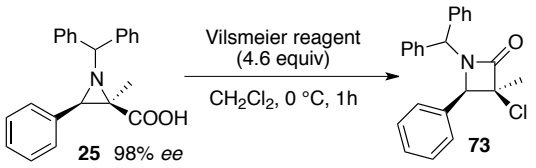


Procedure A for β-lactam formation with Vilsmeier reagent was followed with acid **90** (90% *ee*, 41 mg, 0.10 mmol, 1.0 equiv) and Vilsmeier reagent (0.23 mmmol, 2.3 equiv) with a reaction time of 1h. The product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1) to afford the β-lactam **71** (36.1 mg, 0.085 mmol, 85%) as a white foamy solid;

mp 48-50 °C; R_f = 0.30 (hexane:EtOAc 4:1). Spectral data for **71**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.89 (d, 1H, *J* = 5.4 Hz), 5.12 (d, 1H, *J* = 4.8 Hz), 5.68 (s, 1H), 6.96-7.01 (m, 2H), 7.14-7.18 (m, 2H), 7.20-7.26 (m, 5H), 7.28-7.34 (m, 3H), 7.36-7.40 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 60.06, 61.41, 62.78, 123.04, 128.04, 128.10, 128.31, 128.34, 128.67, 130.25, 131.35, 132.37, 137.33, 137.95, 164.12 (One sp^2 carbon not located); IR (thin film) 1767(s) cm^{-1}; HRMS calcd for $C_{22}H_{18}NO^{35}Cl^{79}Br$ (M+H, ESI$^+$) *m/z* 426.0260, meas 426.0274; $[\alpha]^{20}_D$ –85.0° (*c* 1.0, CH_2Cl_2) on 90% *ee* material.

Procedure B *for β-lactam formation with Vilsmeier reagent illustrated for β-lactam* ***73****:*

The formation of β-lactam ***73***:

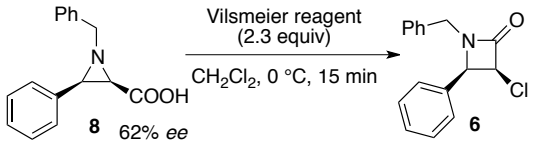


Vilsmeier reagent preparation: To a flame-dried 50 mL round bottom flask filled with N_2 was added dry DMF (0.10 mL, 1.2 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N_2 balloon was attached *via* a needle. Dry CH_2Cl_2 (5 mL) was added *via* syringe. Then $(COCl)_2$ (0.10 mL, 1.2 mmol, 1.0 equiv) was added dropwise at rt. The resulting solution was stirred at rt for at least 5 min prior to use. The concentration of Vilsmeier reagent is 0.23 M in CH_2Cl_2.

Lactam formation: To a flame-dried 25 mL round bottom flask filled with N_2 was added acid **25** (98% *ee*, 34 mg, 0.10 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N_2 balloon was attached *via* a needle. The flask was cooled to 0 °C and the Vilsmeier reagent (0.23M, 2 mL, 0.46 mmol, 4.6 equiv) was added to the flask *via* syringe all at once at 0 °C. After the reaction mixture was stirred at 0 °C for 1 h, it was concentrated by rotary evaporator. The product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1) to afford the β-lactam **73** (8 mg, 0.022 mmol, 22%) as a white solid; mp 130-132 °C; R_f = 0.50 (hexane:EtOAc 4:1). Spectral data for **73**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.84 (s, 3H), 4.57 (s, 1H), 5.53 (s, 1H), 7.15-7.40 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.38, 62.80, 69.72, 72.91,

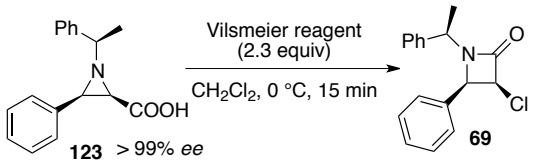
127.93, 127.94, 128.17, 128.25, 128.30, 128.50, 128.55, 128.72, 128.88, 134.19, 137.64, 138.63, 167.28; IR (thin film) 1767(s) cm^{-1}; HRMS calcd for $C_{23}H_{21}NO^{35}Cl$ (M+H, ESI^+) *m/z* 362.1312, meas 362.1299; $[\alpha]^{20}_D$ –9.6° (*c* 1.0, CH_2Cl_2) on 98% *ee* material.

The formation of β-lactam ***6****:*



Procedure B for β-lactam formation with Vilsmeier reagent was followed with acid **8** (62% *ee*, 26 mg, 0.10 mmol, 1.0 equiv), Vilsmeier reagent (0.23 M, 1.0 mL, 0.23 mmmol, 1.0 equiv) with a reaction time of 15 min at 0 °C. The crude product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1), affording the product **6** (20 mg, 0.074 mmol, 74%) as a viscous oil; R_f = 0.35 (hexane:EtOAc 4:1). Spectral data for **6**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 (d, 1H, *J* = 14.5 Hz), 4.78 (d, 1H, *J* = 5.0 Hz), 4.90 (d, 1H, *J* = 14.5 Hz), 5.07 (d, 1H, *J* = 5.0 Hz), 7.10-7.42 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.96, 60.26, 61.15, 128.13, 128.25, 128.55, 128.62, 128.93, 129.14, 132.69, 134.34, 163.99; IR (thin film) 2922(m), 1770(s) cm^{-1}; $[\alpha]^{20}_D$ –56.0° (*c* 1.0, CH_2Cl_2) on 62% *ee* material. Spectral data match those previously reported data.[8]

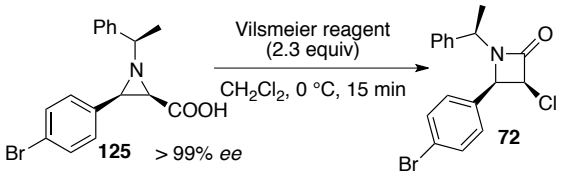
The formation of β-lactam ***69****:*



Procedure B for β-lactam formation with Vilsmeier reagent was followed with acid **123** (> 99% *ee*, 27 mg, 0.10 mmol, 1.0 equiv) and Vilsmeier reagent (0.23M, 1.0 mL, 0.23 mmmol, 2.3 equiv). The product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1), to afford the β-lactam **69** (22 mg, 0.077 mmol, 77%) as a white foamy solid; mp 95-96 °C; R_f = 0.30 (hexane:EtOAc 4:1). Spectral data for **69**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (d, 3H, *J* = 7.0 Hz), 4.69 (d, 1H, *J* = 5.0 Hz), 4.98 (d, 1H, *J* = 5.0 Hz), 5.07 (q, 1H, *J* = 7.0

Hz), 7.20-7.40 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.08, 53.04, 60.29, 60.42, 127.28, 128.15, 128.72, 128.81, 129.08, 134.21, 138.99, 164.22 (One sp^2 carbon not located); IR (thin film) 1761(s) cm^{-1}; HRMS calcd for $C_{17}H_{17}NO^{35}Cl$ (M+H, ESI^+) *m/z* 286.0999, meas 286.0975; $[\alpha]^{20}_D$ –84.5° (*c* 1.0, CH_2Cl_2) on > 99% *ee* material.

The formation of β-lactam ***72****:*

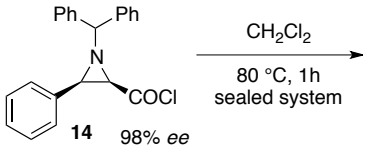


Procedure B for β-lactam formation with Vilsmeier reagent was followed with acid **125** (> 99% *ee,* 35 mg, 0.10 mmol, 1.0 equiv) and Vilsmeier reagent (0.23M, 1.0 mL, 0.23 mmmol, 2.3 equiv). The crude product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1), affording the product **72** (25 mg, 0.069 mmol, 69%) as a white foamy solid; mp 102-103 °C; R_f = 0.20 (hexane:EtOAc 4:1). Spectral data for **72**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (d, 3H, *J* = 7.5 Hz), 4.60 (d, 1H, *J* = 5.0 Hz), 4.94 (d, 1H, *J* = 5.0 Hz), 5.01 (q, 1H, *J* = 7.0 Hz), 7.08-7.14 (m, 2H), 7.16-7.20 (m, 2H), 7.28-7.34 (m, 3H), 7.46-7.50 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.08, 53.18, 59.86, 60.10, 123.22, 127.25, 128.27, 128.88, 130.31, 131.40, 133.36, 138.77, 164.00; IR (thin film) 1767(s) cm^{-1}; HRMS calcd for $C_{17}H_{16}NO^{35}Cl^{79}Br$ (M+H, ESI^+) *m/z* 364.0104, meas 364.0078; $[\alpha]^{20}_D$ –116.3° (*c* 1.0, CH_2Cl_2) on > 99% *ee* material.

IX. Conversion of acid chloride 14 to *β*-lactam 65

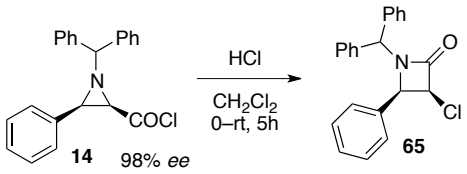
i. Thermolysis of acid chloride **14**:

The acid chloride **14** was relatively stable in CD_2Cl_2 solution at room temperature. Acid chloride **14** (0.1 mmol) was dissolved in dry CD_2Cl_2 (0.7 mL) and the ^{1}H NMR spectrum was taken at certain intervals with quantitation aided by an internal standard (Ph_3CH). After 23 hours at room temperature, there was 72% acid chloride **14** remaining, only a 5% yield of the lactam **65** and 23% conversion to other compounds.



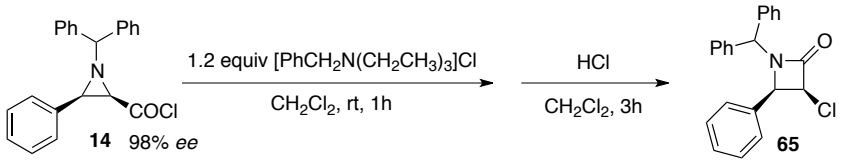
To a flame-dried 5 mL Schlenk flask was added the acid chloride **14** (98% *ee,* 34.8 mg, 0.1 mmol) and dry CH_2Cl_2 (1 mL). The flask was sealed and heated at 80 °C for an hour. Then the mixture was allowed to cool to room temperature and a small amount of the mixture was taken out and dissolved in $CDCl_3$. The ^1H NMR spectrum of the crude reaction revealed that a mixture of the acid chloride **14** and lactam **65** in a ratio of 1: 0.13 was obtained along with other unknown side products.

ii. The conversion of acid chloride **14** to β-lactam **65** with HCl:



To a flame-dried 10 mL round bottom flask filled with N_2 was added the acid chloride **14** (98% *ee,* 48 mg, 0.14 mmol, 1.0 equiv) and dry CH_2Cl_2 (1.5 mL). Then dry HCl was passed through the reaction flask for 5 min. More CH_2Cl_2 was added to replenish the solvent loss during passing through dry HCl. The reaction mixture was stirred at 0 °C for 1h and then warmed up to rt. The reaction mixture was stirred for another 4h at rt and then concentrated by rotary evaporator. The ^1H NMR spectrum of the crude reaction was taken which revealed that the lactam **65** was formed in 18% yield and only 16% of the acid chloride **14** was unreacted by comparing the integrations of the methine and aromatic protons.

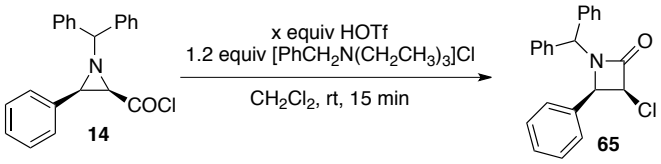
iii. The conversion of acid chloride **14** to β-lactam **65** with HCl in the presence of a chloride source:



To a flame-dried 10 mL round bottom flask filled with N_2 was added benzyltriethylammonium chloride (22 mg, 0.096 mmol, 1.2 equiv), the acid chloride **14** (98% *ee,*

27.7mg, 0.080 mmol, 1.0 equiv) and dry CH_2Cl_2 (1.5 mL). The reaction mixture was stirred at rt for 1h. Then dry HCl was passed through the reaction flask until the acidity of the vapor inside the flask was pH ~1. More CH_2Cl_2 was added to replenish the solvent loss during the purge with dry HCl. The mixture was stirred at rt for another 3h and then concentrated by rotary evaporator. After the addition of Ph_3CH as an internal standard, the ^1H NMR spectrum of the crude reaction was taken which revealed that the lactam **65** was formed in 20% yield and only 9% of the acid chloride **14** was unreacted.

iv. The conversion of acid chloride **14** to β-lactam **65** with HOTf in the presence of a chloride source:

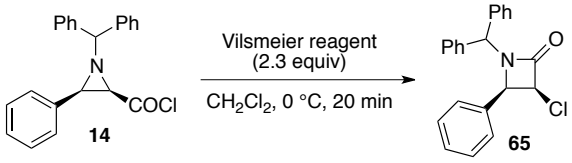


To a flame-dried 10 mL round bottom flask filled with N_2 was added benzyltriethylammonium chloride (28 mg, 0.12 mmol, 1.2 equiv), a 1 M solution of the acid chloride **14** (34.8mg, 0.10 mmol, 1.0 equiv) in dry CH_2Cl_2 and a certain amount of TfOH from the stock solution. The reaction mixture was stirred at rt for 15 min and then concentrated by rotary evaporator. Then NMR yield of the β-lactam **65** and the amount of leftover acid chloride **14** and were determined from the ^1H NMR spectrum of the crude reaction mixture in $CDCl_3$ with the aid of Ph_3CH as an internal standard. The results are listed in **Table 5**.

Table 5. The conversion of acid chloride **14** to β-lactam **65** with HOTf and a chloride source

Entry	TfOH (equiv)	Yield of lactam(%)	Acid Chloride (%)
1	0	5.6	70
2	0.08	11	64
3	0.5	19	67
4	1.2	14	52

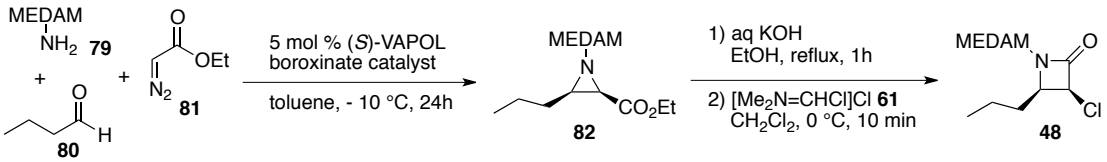
v. The conversion of acid chloride **14** to β-lactam **65** with Vilsmeier reagent **61**:



Vilsmeier reagent preparation: To a flame-dried 10 mL round bottom flask filled with N_2 was added dry DMF (22.5 μL, 0.29 mmol, 2.9 equiv) and dry CH_2Cl_2 (0.2 mL) *via* syringe. The vacuum adapter was replaced with a septum to which a N_2 balloon was attached *via* a needle. Then $(COCl)_2$ (20 μL, 0.23 mmol, 2.3 equiv) was added in a dropwise manner at rt with stirring to form Vilsmeier reagent which precipitated as a white solid. Stirring was continued at rt for 20 min. Then the preformed Vilsmeier reagent was cooled to 0°C prior to use.

Lactam formation: To an oven-dried 5 mL round bottom flask filled with N_2 was added the acid chloride **14** (98% *ee*, 34.7 mg, 0.10 mmol, 1.0 equiv) and dry CH_2Cl_2 (0.6 mL) at rt. The resulting solution was transferred to the preformed Vilsmeier reagent in a dropwise manner *via* syringe at 0 °C. The 5 mL flask was rinsed with another two portions of dry CH_2Cl_2 (0.2 mL, 0.1 mL) which were also transferred to the reaction flask containing the Vilsmeier reagent. The reaction mixture was stirred at 0 °C for 20 min and concentrated by rotary evaporator. The product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1) to afford the β-lactam **65** (23.6 mg, 0.068 mmol) in 68% isolated yield.

X. Sequential multi-component catalytic asymmetric aziridination and ring expansion to β-lactam 48 (Scheme 9)



Multi-component catalytic asymmetric aziridination[3]: To a 25 mL flame-dried Schlenck flask equipped with a stir bar and filled with N_2 was added (*S*)-VAPOL (13.7 mg, 0.025 mmol), $B(OPh)_3$ (21.8 mg, 0.075 mmol) and amine **79** (149.7 mg, 0.5 mmol). Dry toluene (1 mL) was added under

an N_2 atmosphere to dissolve the reagents. The reaction mixture was stirred at room temperature for 1 h. Then 4Å Molecular Sieves (150 mg, freshly flame-dried) were added. After the reaction mixture was cooled to – 10 °C, the aldehyde **80** (47.0 µL, 0.522 mmoL, 1.04 equiv) was added followed by the addition of ethyl diazoacetate (EDA) **81** (125 µL, 1.0 mmoL, 2.0 equiv). The resulting mixture was stirred for 24 h at – 10 °C. The reaction was dilluted by addition of hexane (6 mL). The reaction mixture was then filtered through a Celite pad to a 100 mL round bottom flask. The reaction flask was rinsed with EtOAc (3 mL × 3) and the rinse was filtered through the same Celite pad. The resulting solution was then concentrated in vacuo followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude aziridine **82** as a viscous yellow oil.

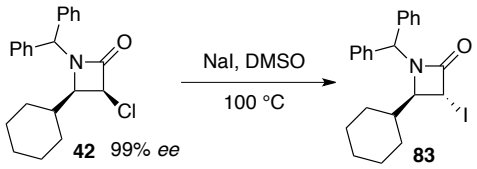
Hydrolysis: To the solution of the crude aziridine **82** in ethanol (2 mL) was added a solution of KOH (140.3 mg, 2.5 mmol, 5.00 equiv) in H_2O (2 mL). The resulting mixture was refluxed for 1 h and then cooled to rt. Then *aq* citric acid (2N, 2.5 mL) and ether (10 mL) were added. The organic layer was separated and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated to afford the crude aziridine acid as a yellow foamy solid.

Ring-expansion: To a flame-dried round bottom flask equipped with a stir bar and filled with N_2 was added dry DMF (147.5 µL, 1.9 mmol, 3.8 equiv) and dry CH_2Cl_2 (1 mL). The flask was fitted with a rubber septum and a nitrogen balloon. Then $(COCl)_2$ (131 µL, 1.53 mmol, 3.06 equiv) was added dropwise to the reaction flask with stirring and the Vilsmeier salt precipitated out as a white solid. The mixture was stirred for 20 min at room temperature and cooled to 0 °C. A solution of the crude aziridine acid in dry CH_2Cl_2 (5 mL) was added dropwise to the reaction flask containing the Vilsmeier salt (1.53 mmol, 3.06 equiv) over 5 min. The reaction mixture was stirred for 10 min at 0 °C and concentrated to afford a foamy crude product. The yield of lactam **48** was 59% (over three steps) as determined from the with ^{1}H NMR spectrum of the crude reaction mixture in $CDCl_3$ with the aid of Ph_3CH as an internal standard. The product was purified by column chromatography (silica gel, 25 × 210 mm, hexane: CH_2Cl_2: ethyl acetate 8:8:1) to afford β-lactam **48** (124 mg, 0.29 mmol) as a colorless semi-solid in 58% isolated yield (over three steps); The optical purity was determined to be 96% *ee* by HPLC analysis (Chiralcel OD-H

column, 98:2 hexane/2-propanol at 222 nm, flow-rate 1.0 mL/min); Retention times: R_t = 7.06 min (major enantiomer, **48**) and R_t = 11.73 min (minor enantiomer, *ent*-**48**). R_f = 0.25 (hexane: CH_2Cl_2: ethyl acetate 8:8:1). Spectral data for **48**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (t, 3H, *J* = 7.2 Hz), 1.04-1.16 (m, 1H), 1.24-1.36 (m, 1H), 1.42-1.50 (m, 1H), 1.68-1.76 (m, 1H), 2.241 (s, 6H), 2.242 (s, 6H), 3.63-3.68 (m, 1H), 3.70 (s, 3H), 3.71 (s, 3H), 4.83 (d, *J* = 5.5 Hz, 1H), 5.70 (s, 1H), 6.82 (s, 2H), 6.85 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.65, 16.19, 16.20, 18.90, 31.43, 57.39, 59.01, 59.62, 59.63, 60.19, 128.13, 128.95, 130.84, 131.06, 132.92, 133.82, 156.44, 156.60, 163.99; IR (thin film) 2934(w), 1767(s), 1485(w), 1221(w) cm^{-1}; HRMS calcd for $C_{25}H_{33}NO_3Cl$ (M+H, ESI$^+$) *m/z* 430.2149, meas 430.2141; $[\alpha]^{20}_D$ – 13.7° (*c* 1.0, CH_2Cl_2) on 96% ee material.

XI. Transformations of *β*-lactam 42 (Scheme 10)

*Substitution of β-lactam **42** with sodium iodide:*

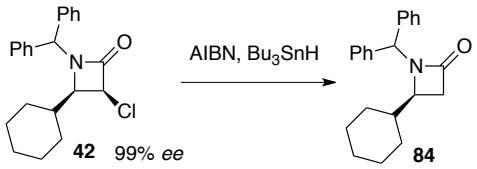


42 99% *ee* **83**

To a flame-dried test tube sized Schlenck flask filled with N_2 were added the lactam **42** (99% *ee*, 36 mg, 0.10 mmol, 1.0 equiv), NaI (150 mg, 1.00 mmol, 10.0 equiv) and DMSO-d_6 (0.40 mL). The resulting mixture was stirred at 100 °C for 66 h. After cooling to rt, H_2O (2 mL) and ether (10 mL) were added. The aqueous layer was separated and extracted with ether (2 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated and the product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1) to afford the β-lactam **83** (34 mg, 0.076 mmol) as a viscous oil in 76% yield; R_f = 0.50 (hexane:EtOAc 4:1). Spectral data for **83**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78-1.30 (m, 6H), 1.42-1.70 (m, 5H), 3.78 (dd, 1H, *J* = 5.1, 2.1 Hz), 4.60 (d, 1H, *J* = 1.8 Hz), 5.75 (s, 1H), 7.20-7.40 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.65, 25.33, 25.80, 26.07, 26.32, 29.34, 39.82, 62.22, 70.05, 127.76, 128.02, 128.19, 128.36, 128.55, 128.64, 138.21, 138.36, 164.89; IR (thin film)

2926(m), 1759(s) 1265(s) cm^{-1}; HRMS calcd for $C_{22}H_{25}NOI$ (M+H, ESI^+) *m/z* 446.0981, meas 446.0948; $[\alpha]^{20}_D$ –12.8° (*c* 1.0, CH_2Cl_2) on 99% *ee* material.

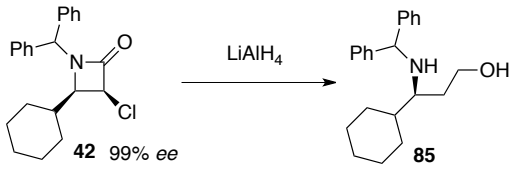
*Reduction of β-lactam **42** with Bu_3SnH:*



42 99% *ee* **84**

To a flame-dried Schlenk flask filled with N_2 was added 3-chlorolactam **42** (99% *ee*, 36 mg, 0.10 mmol, 1.0 equiv), AIBN (10 mg), and dry benzene (1 mL), then tri-butyltin hydride (119 mg, 0.100 mL, 0.400 mmol, 4.00 equiv) was quickly added under a N_2 stream. Then the Schlenk flask was sealed and the reaction was stirred at 80 °C for 19 h. After it was cooled to rt, *aq* sat KF (3 mL) and CH_2Cl_2 (10 mL) were added. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated and the product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1) to give the β-lactam **84** as a white solid (31 mg, 0.097 mmol, 97%). mp 74-76 °C; R_f = 0.50 (hexane:EtOAc 4:1). Spectral data for **84**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.78-1.12 (m, 5H), 1.22-1.32 (m, 1H), 1.46-1.68 (m, 5H), 2.69 (dd, 1H, *J* = 2.5, 15.0 Hz), 2.85 (dd, 1H, *J* = 5.5, 15.0 Hz), 3.55 (td, 1H, *J* = 5.5, 2.5 Hz), 5.78 (s, 1H), 7.22-7.38 (m, 10H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.52, 25.90, 26.23, 26.37, 29.76, 38.21, 39.34, 57.07, 62.19, 127.47, 127.65, 128.17, 128.43, 128.49, 139.01, 139.30, 167.72 (One sp^2 C not located); IR (thin film) 2924(m), 1749(s) cm^{-1}; HRMS calcd for $C_{22}H_{26}NO$ (M+H, ESI^+) *m/z* 320.2014, meas 320.2007; $[\alpha]^{20}_D$ –82.8° (*c* 1.0, CH_2Cl_2) on 99% *ee* material.

*Reductive ring opening of β-lactam **42** with $LiAlH_4$:*

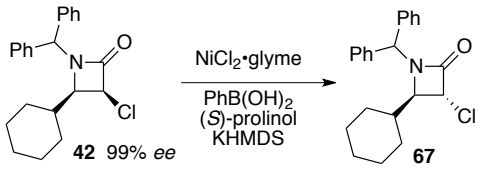


42 99% *ee* **85**

To a flame-dried 25 mL round bottom flask filled with N_2 was added $LiAlH_4$ (20 mg, 0.50 mmol, 5.0 equiv). The vacuum adapter was quickly replaced with a septum to which a N_2 balloon

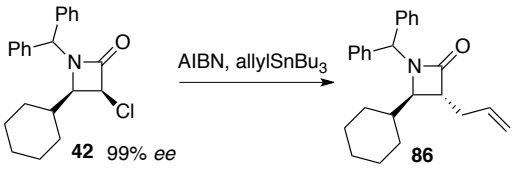
was attached *via* a needle. Dry THF (0.5 mL) was added and the resulting solution was cooled to 0 °C. A solution of 3-chlorolactam **42** (99% ee, 36 mg, 0.10 mmol, 1.0 equiv) in THF (0.5 mL) was added dropwise *via* syringe. After the mixture was stirred at 0 °C for 5 min, the ice bath was removed. After the reaction mixture was stirred at rt for 2 h, H_2O (0.1 mL) was added carefully at 0 °C. The mixture was stirred at 0 °C for 15 min, and then filtered through Na_2SO_4 on a Celite pad on a sintered glass funnel. The filtrate was concentrated and the product was purified by column chromagraphy (silica gel, 18 × 180 mm, hexane:EtOAc 3:1) to give the amino alcohol **85** as a white solid (29 mg, 0.090 mmol, 90%). mp 92-94 °C; R_f = 0.30 (hexane:EtOAc 3:1). Spectral data for **85**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.44-0.54 (m, 1H), 0.90-1.20 (m, 5H), 1.28 (d, 1H, *J* =12.6 Hz), 1.42-1.64 (m, 6H), 1.79 (q, 1H, *J* = 6.0 Hz), 3.52-3.60 (m+s, 2H), 3.67-3.74 (m, 1H), 7.16-7.30 (m, 6H), 7.37 (d, 2H, *J* = 7.2 Hz), 7.43 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.62, 25.74, 26.19, 30.92, 31.42, 36.93, 44.68, 50.58, 60.66, 78.90, 127.07, 127.17, 127.25, 127.95, 128.23, 128.59, 143.15, 143.55; IR (thin film) 3400(m), 2926(s) cm^{-1}; HRMS calcd for $C_{22}H_{30}NO$ (M+H, ESI^+) *m/z* 324.2327, meas 324.2303; $[\alpha]^{20}_D$ 4.0° (*c* 1.0, CH_2Cl_2) on 99% ee material.

*Trans-Chloro β-lactam **67** under Suzuki coupling conditions:*



To a flame-dried test-tube size Schlenk flask filled with N_2 was added (*S*)-prolinol (5 mg, 0.048 mmol, 0.48 equiv), $NiCl_2$•glyme (5 mg, 0.024 mmol, 0.24 equiv), phenylboronic acid (24 mg, 0.20 mmol, 2.0 equiv), KHMDS (40 mg, 0.20 mmol, 2.0 equiv) and *i*-PrOH (0.5 mL). Then the mixture was stirred at rt for 5 min. The starting material **42** (99% ee, 36 mg, 0.10 mmol, 1.0 equiv) was added. Then the Teflon valve was closed and the flask was heated at 80 °C for 24 h. ^{1}H NMR spectrum of the crude reaction mixture indicated a 95% conversion of the *cis*-chloro β-lactam **42** to the *trans*-chloro β-lactam **67**. The *trans*-chloro-lactam **67** was tentatively identified in the ^{1}H NMR spectrum of the crude reaction mixture by the following absorptions: 3.60 (dd, 1H, *J* = 5.0, 2.0 Hz), 4.49 (d, 1H, *J* =1.5 Hz), 5.77 (s, 1H).

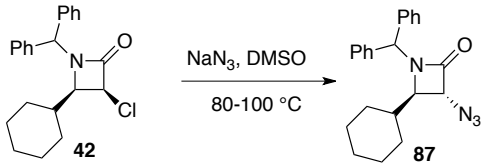
*The transformation of β-lactam **42** with allyltributyltin:*



42 99% *ee* **86**

To a flame-dried test-tube size Schlenk flask filled with N_2 was added 3-chlorolactam **42** (99% ee, 36 mg, 0.10 mmol, 1.0 equiv), AIBN (10 mg) and dry benzene (0.5 mL). Allyl tri-butyltin (134 mg, 0.130 mL, 0.400 mmol, 4.00 equiv) was added under a N_2 stream. Then the Teflon valve was closed the reaction mixture was heated at 80 °C for 17 h. After the mixture was cooled to rt, it was concentrated and the product was purified by column chromatography (silica gel, 18 × 18 mm, hexane:EtOAc 5:1) to give the β-lactam **86** (32 mg, 0.089 mmol, 89%) as a colorless oil which solidified during storage; mp 62-64 °C; R_f = 0.50 (hexane:EtOAc 4:1). Spectral data for **86**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.78-1.12 (m, 5H), 1.26-1.34 (m, 1H), 1.46-1.70 (m, 5H), 2.26-2.34 (m, 1H), 2.42-2.50 (m, 1H), 2.88-2.94 (m, 1H), 3.24 (dd, 1H, *J* = 2.5, 5.5 Hz), 5.01 (dd, 1H, *J* = 10.0, 2.0 Hz), 5.07 (dt, 1H, *J* = 17.0, 1.5 Hz), 5.68-5.78 (m+s, 2H), 7.20-7.50 (m, 10H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.67, 25.99, 26.23, 27.27, 30.24, 33.27, 39.37, 50.49, 62.11, 63.41, 117.23, 127.44, 127.60, 128.27, 128.36, 128.42, 128.43, 134.91, 139.06, 139.36, 170.01; IR (thin film) 2926(m), 1747(s) cm^{-1}; HRMS calcd for $C_{25}H_{30}NO$ (M+H, ESI$^+$) *m/z* 360.2327, meas 360.2334; $[\alpha]^{20}_D$ –42.7° (*c* 1.0, CH_2Cl_2) on 99% ee material.

*Substitution of β-lactam **42** with NaN_3:*



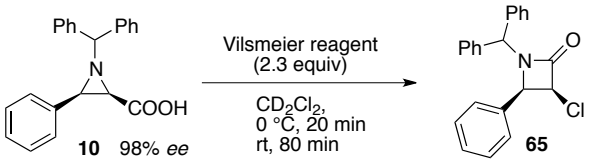
42 **87**

To a flame-dried test tube sized Schlenk flask filled with N_2 were added the lactam **42** (99% ee, 36 mg, 0.10 mmol, 1.0 equiv), NaN_3 (66 mg, 1.0 mmol, 10 equiv) and DMSO-d_6 (0.20 mL). The resulting mixture was stirred at 80 °C for 48 h and 100 °C for 12 h. H_2O (2 mL) was added

and the mixture was extracted with ether (3 × 5 mL). The combined organic extracts were washed with H_2O (2 × 1 mL), dried (Na_2SO_4) and filtered. The filtrate was concentrated and the product as purified by column chromatography (silica gel, 18 × 150 mm, hexane:EtOAc 5:1) to afford the azido-β-lactam **87** (31 mg, 0.086 mmol) as a white solid in 86% yield; mp 105-107 °C; R_f = 0.50 (hexane:EtOAc 4:1). Spectral data for **87**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78-1.40 (m, 6H), 1.46-1.76 (m, 5H), 3.42 (dd, 1H, *J* = 5.4, 2.4 Hz), 4.31 (d, 1H, *J* = 2.1 Hz), 5.73 (s, 1H), 7.20-7.40 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.48, 25.77, 26.06, 26.89, 29.53, 37.91, 62.36, 64.80, 65.39, 127.84, 128.04, 128.16, 128.33, 128.59, 128.72, 138.08, 138.24, 164.36; IR (thin film) 2928(m), 2106(s) 1765(s) cm^{-1}; HRMS calcd for $C_{22}H_{25}N_4O$ (M+H, ESI$^+$) *m/z* 361.2028, meas 361.2041; $[\alpha]^{20}_D$ 74.4° (*c* 0.5, CH_2Cl_2) on 99% ee material.

XII. NMR studies on lactam formation with Vilsmeier reagent or with $(COCl)_2$

i. Formation of *β*-lactam **65** from acid **10** and Vilsmeier reagent **61.**



Vilsmeier reagent preparation: To a flame-dried 10 mL round bottom flask filled with N_2 was added dry DMF (22.5 μL, 0.29 mmol, 2.9 equiv) and dry CD_2Cl_2 (0.2 mL) *via* syringe. The vacuum adapter was replaced with a septum to which a N_2 balloon was attached *via* a needle. Then $(COCl)_2$ (20 μL, 0.23 mmol, 2.3 equiv) was added in a dropwise manner at rt with stirring to form Vilsmeier reagent which precipitated as a white solid. Stirring was continued at rt for 20 min. Then the preformed Vilsmeier reagent was cooled to 0°C prior to use. Ph_3CH was added as an internal standard.

Lactam formation: To an oven-dried 5 mL round bottom flask filled with N_2 was added acid **10** (98% *ee*, 33 mg, 0.10 mmol, 1.0 equiv) and dry CD_2Cl_2 (0.6 mL) at rt. The resulting solution was transferred to the preformed Vilsmeier reagent in a dropwise manner *via* syringe at 0 °C. The 5 mL flask was rinsed with another two portions of dry CD_2Cl_2 (0.2 mL, 0.1 mL) which were also

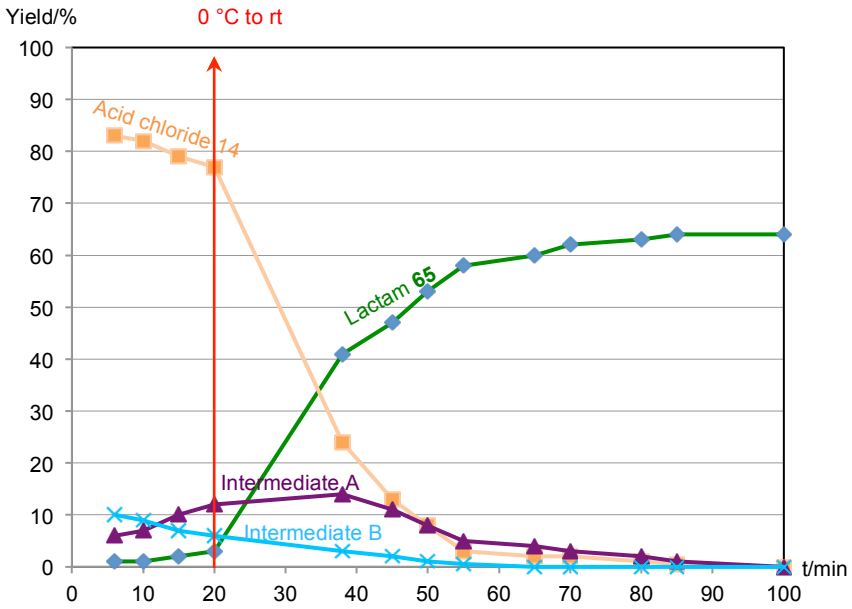
transferred to the reaction flask containing the Vilsmeier reagent. After the acid **10** was completely transferred to the Vilsmeier reagent over ~2 min at 0 °C, the reaction mixture was transferred to a cold dry NMR tube filled with N_2 and pre-cooled to 0 °C. The ^{1}H NMR spectrum was taken at certain intervals at 0 °C in the first 20 min. Subsequentially the NMR tube was warmed to rt and the collection of NMR data continued for 80 min. The results are shown in **Table 6** and **Chart 1**.

The first data point at 6 minutes reveals that there is rapid conversion of the acid **10** to the acid chloride **14** (83% yield). In the first 20 minutes at 0 °C there is very little β-lactam **65** formed (3%) and it is not until the temperature is raised to 25 °C that substantial amount of the acid chloride **14** is consumed with concomitant β-lactam formation. In addition, two intermediates are observed to grow in then completely disappear after 100 minutes, but neither accumulates in any significant amount. These intermediates were not identified. The following ^{1}H NMR absorptions were observed: intermediate A: ^{1}H NMR (500 MHz, CD_2Cl_2) δ 4.52 (d, *J* = 10 Hz, 1H), 5.22 (s, 1H), 6.58 (d, *J* = 10.5 Hz, 1H); intermediate B ^{1}H NMR (500 MHz, CD_2Cl_2) δ 3.92 (d, *J* = 3.5 Hz, 1H), 4.93 (s, 1H), 5.75 (d, *J* = 3.5 Hz, 1H).

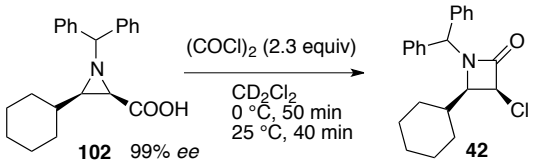
Table 6. Time course of the reaction of **10** with Vilsmeier reagent **61**

Time (min)	**14** (%)	**65** (%)	Intermediate A (%)	Intermediate B (%)
6	83	1	6	10
10	82	1	7	9
15	79	2	10	7
20	77	3	12	6
38	24	41	14	3
45	13	47	11	2
50	8	53	8	1
55	3	58	5	0.5
65	2	60	4	0
70	2	62	3	0
80	1	63	2	0
85	0.5	64	1	0
100	0	64	0	0

Chart 1. Time course of the reaction of **10** with Vilsmeier reagent **61**



ii. Formation of β-lactam **42** from acid **102** and $(COCl)_2$



A flame-dried 25 mL round bottom flask filled with N_2 was charged with acid **102** (99% *ee*, 33.5 mg, 0.10 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N_2 balloon was attached *via* a needle. Dry CD_2Cl_2 (1 mL) was added *via* syringe. The flask was cooled to 0 °C and $(COCl)_2$ (0.020 mL, 0.23 mmol, 2.3 equiv) was added dropwise at 0 °C. The reaction mixture was immediately transferred to a NMR tube filled with N_2 and pre-cooled to 0 °C. The ^1H NMR spectrum was taken at certain intervals at 0 °C in the first 50 min. Subsequently the NMR tube was warmed to rt and the collection of NMR data was continued. The results are shown in **Table 7** and **Chart 2**.

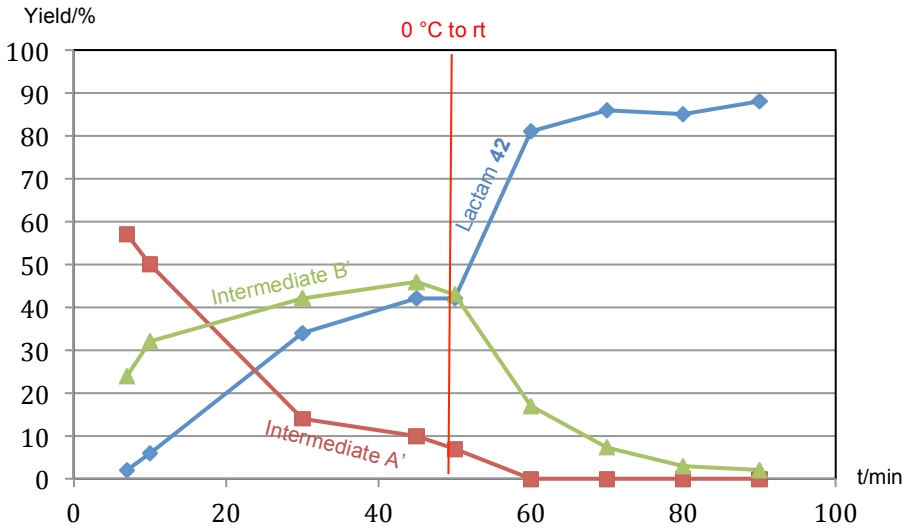
In contrast to the phenyl substituted aziridine carboxylic acid **10**, the cyclohexyl substituted aziridine carboxylic acid **102** is converted to corresponding β-lactam **42** at a much faster rate at 0

°C. After the temperature is raised to 25 °C, β-lactam formation is complete within 40 minutes (90 min in total) (88% yield). Two intermediates are observed to grow in but both are consumed as β-lactam formation proceeds. These intermediates have not been identified but neither are considered to be the acid chloride **126** (See below, Part iii). The following ^{1}H NMR absorptions were observed for intermediates A' and B': intermediate A': ^{1}H NMR (500 MHz, CD_2Cl_2) δ 2.35 (br, 1H), 3.10 (br, 1H), 3.94 (br, 1H); intermediate B': ^{1}H NMR (500 MHz, CD_2Cl_2) δ 2.61 (br, t, *J* = 12 Hz, 1H), 3.82 (br, t, *J* = 3.8 Hz, 1H).

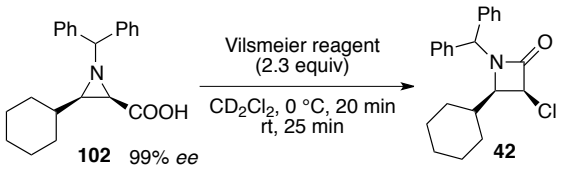
Table 7. Time course of the reaction of **102** with $(COCl)_2$

Time (min)	**42** (%)	Intermediate A' (%)	Intermediate B' (%)
7	2	57	24
10	6	50	32
30	34	14	42
45	42	10	46
50	42	7	43
60	81	0	17
70	86	0	7.3
80	85	0	3
90	88	0	2

Chart 2. Time course of the reaction of **102** with $(COCl)_2$



iii. Formation of β-lactam **42** from acid **102** and Vilsmeier reagent **61**



Vilsmeier reagent preparation: To a flame-dried 10 mL round bottom flask filled with N_2 was added dry DMF (22.5 μL, 0.29 mmol, 2.9 equiv) and dry CD_2Cl_2 (0.2 mL) *via* syringe. The vacuum adapter was replaced with a septum to which a N_2 balloon was attached *via* a needle. Then $(COCl)_2$ (20 μL, 0.23 mmol, 2.3 equiv) was added in a dropwise manner at rt with stirring to form Vilsmeier reagent which precipitated as a white solid. Stirring was continued at rt for 20 min. Then the preformed Vilsmeier reagent was cooled to 0°C prior to use. Ph_3CH was added as an internal standard.

Lactam formation: To an oven-dried 5 mL round bottom flask filled with N_2 was added acid **102** (99% *ee*, 33.5 mg, 0.10 mmol, 1.0 equiv) and dry CD_2Cl_2 (0.6 mL) at rt. The resulting solution was transferred to the preformed Vilsmeier reagent in a dropwise manner *via* syringe at 0 °C. The 5 mL flask was rinsed with another two portions of dry CD_2Cl_2 (0.2 mL, 0.1 mL) which were also transferred to the reaction flask containing the Vilsmeier reagent. After the acid **102** was completely transferred to the Vilsmeier reagent over ~2 min at 0 °C, the reaction mixture was transferred to a cold dry NMR tube filled with N_2 and pre-cooled to 0 °C. The ^1H NMR spectrum was taken at certain intervals at 0 °C in the first 20 min. Subsequently the NMR tube was warmed to rt and the collection of NMR data continued for 25 min. The results are shown in **Table 8** and **Chart 3**.

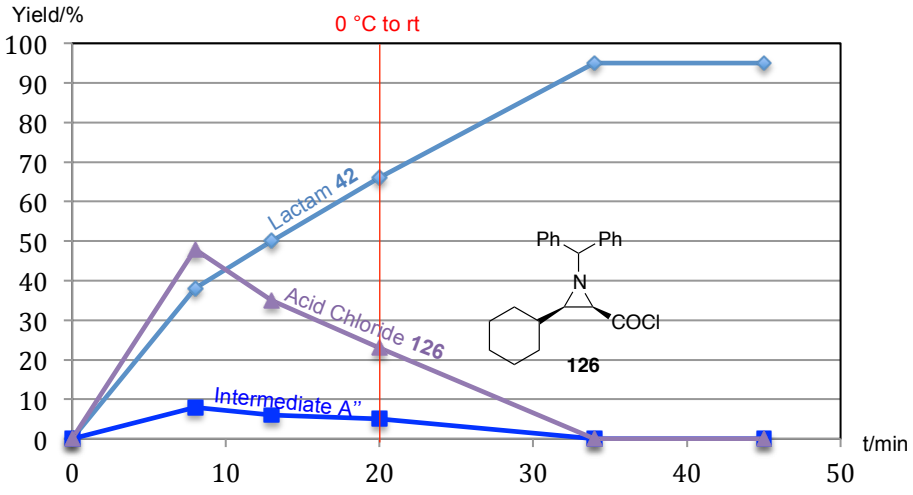
Compared to the phenyl substituted aziridine carboxylic acid **10**, the cyclohexyl substituted aziridine carboxylic acid **102** is converted to corresponding β-lactam **42** at a much faster rate at 0 °C by Vilsmeier reagent. After the temperature is raised to 25 °C, β-lactam formation is complete within 14 minutes (45 min in total) (95% yield). Acid Chloride **126** and intermediate A'' are observed to grow in but both are consumed as β-lactam formation proceeds. The following ^1H

NMR absorptions were observed for acid chloride **126** and intermediates A'': acid chloride **126:** ^{1}H NMR (500 MHz, CD_2Cl_2) δ 2.22 (dd, 1H, *J* = 9.3, 6.5 Hz), 2.97 (d, 1H, *J* = 7 Hz), 3.81 (s, 1H); intermediate A'' ^{1}H NMR (500 MHz, CD_2Cl_2) δ 5.84 (s, 1H), 5.98 (d, 1H, *J* = 8 Hz). The assignment of the major intermediate in this reaction as the acid chloride **126** was made on the basis of the close similarities of the absorptions observed for this intermediate with those of the isolated and characterized acid chlorides **14** and **53**.

Table 8. Time course of the reaction of **102** with Vilsmeier reagent **61**

Time (min)	**42** (%)	Intermediate A'' (%)	Acid Chloride (%)
8	38	8	48
13	50	6	35
20	66	5	23
34	95	0	0
45	95	0	0

Chart 3. Time course of the reaction of **102** with Vilsmeier reagent **61**



The cyclohexyl substituted aziridine carboxylic acid **102** can be converted to the β-lactam **42** with both $(COCl)_2$ and Vilsmeier reagent but via different intermediates. The ^1H NMR spectra of the reaction mixture in the early stages of each reaction are shown in Figures 1 and 2. The intermediate in the reaction with the Vilsmeier reagent is assigned as the acid chloride **126** and this intermediate does not appear to be present in the reaction mixture with oxalyl chloride.

Figure 1. ^1H NMR spectrum of reaction between acid **102** and $(COCl)_2$ at 10 min at 0 °C

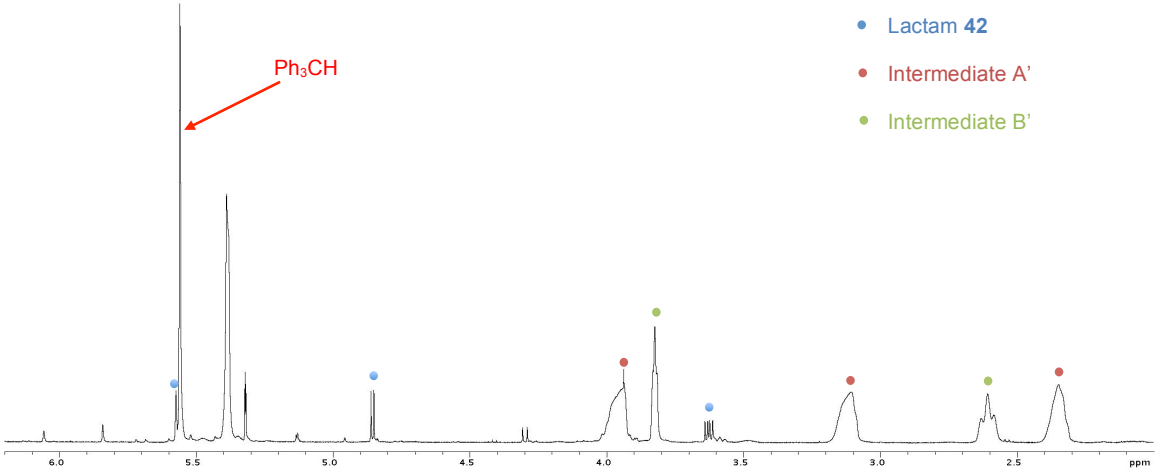
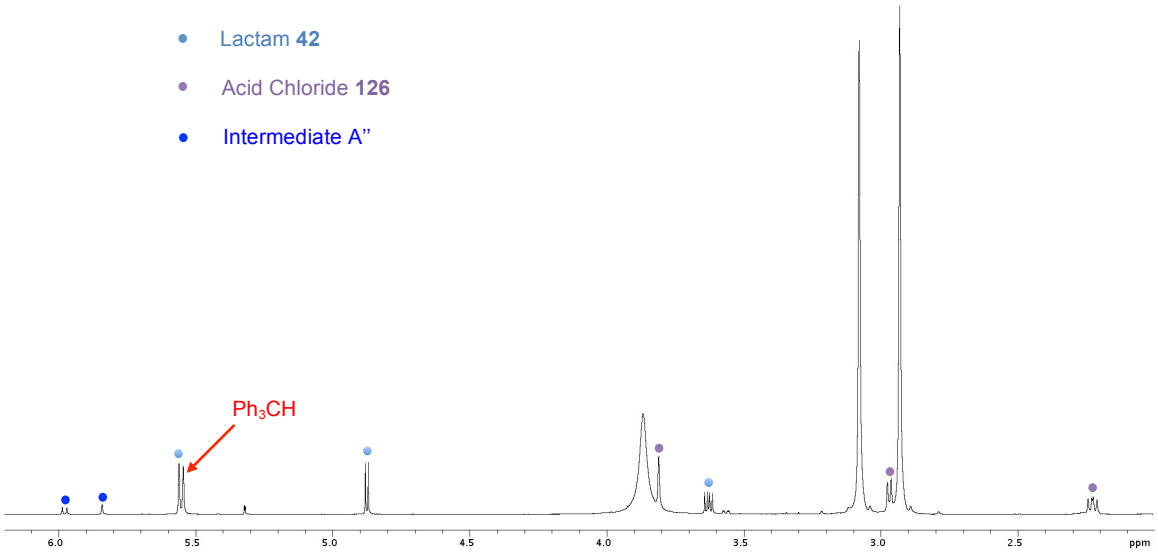


Figure 2. ^1H NMR spectrum of the reaction between acid **102** and Vilsmeier reagent at 8 min at 0 °C



XIII. References:

1. A. Ding, W. E. G. Osminski, H. Ren, W. D. Wulff, *Org. Process. Res. Dev.* **2011**,*15*,1089–1107.

2. Y. Zhang, A. Desai, Z. Lu, G. Hu, Z. Ding, W. D. Wulff, *Chem. Eur. J.* **2008**, *14*, 3785–3803.

3. A. K. Gupta, M. Mukherjee, W. D. Wulff, *Org. Lett.* **2011**, *13*, 5866–5869.

4. Y. Zhang, Z. Lu, A. Desai, W. D. Wulff, *Org. Lett.* **2008**, *8*, 5429–5432.

5. L. Huang, Y. Zhang, R. D. Staples, W. D. Wulff, *Chem. Eur. J.* **2012**,*18*, 5302–5313.

6. L. Thijs, J. J. M. Porskamp, A. A. W. M. van Loon, M. P. W. Derks, R. W. Feenstra, J. Legters, B. Zwanenburg, *Tetrahedron* **1990**, *46*, 2611-2614.

7. S. Wattanasin, F. G. Kathawala, *Synth. Commun.* **1992**, *22*, 1487–1490.

8. Y. Dejaegher, B. Denolf, C. V. Stevens, N. D. Kimpe, *Synthesis*, **2005**, *2*, 193–198.

9. A. P. Patwardhan, V. R. Pulgam, Y. Zhang, W. D. Wulff, *Angew. Chem. Int. Ed*. **2005**, *44*, 6169–6172.