Enantioselective Synthesis of Cyclic Amides and Amines through Mo-Catalyzed Asymmetric Ring-Closing Metathesis (ARCM)

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General: All reactions were conducted in oven- (135 °C) or flame-dried glassware under an inert atmosphere of dry N₂. Infrared (IR) spectra were recorded on a Nicolet 210 spectrophotometer, νmax in cm⁻¹. Bands are characterized as broad (br), strong (s), medium (m) or weak (w). ¹H NMR spectra were recorded on a Varian Gemini 2000 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance resulting from incomplete deuteration as the internal standard (CDCl₃: δ 7.26, C₆D₆: δ 7.16, (CD₃)₂SO: δ 2.50). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), integration and assignment. ¹³C NMR spectra were recorded on a Varian Gemini 2000 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference (CDCl₃: δ 7.16, (CD₃)₂SO: δ 39.52). Enantiomer ratios were determined by chiral HPLC (Chiral Technologies chiralpak OD column (4.6 mm x 250 mm)) or by chiral GLC analysis (Alltech Associates Chiraldex GTA or BPH, or Supelco Betadex or Alphadex 120 column (30 m x 0.25 mm)) in comparison with authentic racemic materials. Elemental analyses were performed at Robertson Microlit Laboratories (Madison, NJ). High-resolution mass spectrometry was performed at the Mass Spectrometry Facility, Boston College. Optical rotation values were recorded on a Rudolph Research Analytical Autopol IV polarimeter.

Materials: Solvents were purged with argon and then purified under a positive pressure of dry argon by a modified Innovative Technologies purification system: Et₂O, CH₂Cl₂, and THF were passed through activated alumina columns; benzene, toluene, and pentane were passed successively through activated Cu and alumina columns. Unless otherwise stated, commercially available reagents were used as received. Mo complexes 1a, 1b, 1c, 3a, 3b, 3c, 2a, 2b, 2c, 4, 6, 5 and 35 were prepared according to published

(1) n-Pentane was stirred over concentrated H₂SO₄ for 5 days, washed with a saturated aqueous solution of NaHCO₃ followed by water, dried over MgSO₄, and filtered before use in the solvent purification system.
procedures. Mo complexes were handled under an inert atmosphere in a dry box. Olefin metathesis substrates were dried by repeated (three times) azeotropic distillation of water with benzene under high vacuum (except amines 30 and 32: distilled from metallic sodium under vacuum prior to use).

Silica gel column chromatography was driven with compressed N\textsubscript{2} or by gravity elution. For alkyl amines, Dragendorff’s reagent was used to visualize TLC spots. Chromatography solvent buffered with ammonia was prepared by washing the organic solvent components (usually a CH\textsubscript{2}Cl\textsubscript{2}:MeOH mixture) with 2% by volume concentrated NH\textsubscript{4}OH. The resulting organic solution was separated from the aqueous phase and used directly as solvent for elution.

\[ \text{NH}_3 \text{MeMeNH} \]

\[ \text{Me}_3\text{B} \]

2,2-Bis-(2-methyl-allyl)-pyrrolidine 14. Amine 14 was prepared through a reductive bisalkylation according to a literature procedure with slight modification (see below).\textsuperscript{9} The trimethallyl borane reagent was prepared (85% yield, 44 mmol) and purified according to a procedure reported by Brown and coworkers for the synthesis of triallyl borane (BF\textsubscript{3}OEt\textsubscript{2}, methallyl chloride, metallic Mg, Et\textsubscript{2}O).\textsuperscript{10} 2,5-dimethyl-hexa-1,5-diene, a byproduct formed during the preparation of trimethallyl borane, was removed through vacuum distillation (~2 mm) of the mixture. Further distillation under high vacuum (~2 mm) with mild heating (~50 °C) delivered the desired trimethallyl borane in 80-85% yield. This compound is air and moisture sensitive and may be stored for short periods under an inert atmosphere.

To a cold (0 °C) stirring solution of pyrrolidinone (2.16 mL, 28.5 mol, distilled before use) in 10 mL THF was added a solution of trimethallyl borane (6.51 g, 37.0 mmol in 3 mL THF) via cannula. THF (~2 mL) was used to complete the transfer. The reaction was heated at reflux for 1.5 h and then stirred for an additional 12 h at ambient temperature. At this time, 5 mL of MeOH was added. After 1 h, ~15 mL of an aqueous solution of NaOH (3 M) was added. Stirring was continued for an additional hour to ensure complete deboronation. The biphasic solution was then transferred to a separatory funnel with EtOAc. The aqueous layer was separated and washed 3x with 20 mL portions of EtOAc. The organic fractions were combined, dried over K\textsubscript{2}CO\textsubscript{3}, filtered and concentrated to give a clear oil (4.23 g, 23.6 mmol, 83%). Analysis by \textsuperscript{1}H NMR

(6) Unpublished results of Dr. A. F. Kiely, Boston College, Chestnut Hill, MA.
indicated that the product was \( >98\% \) pure. All spectral data were in accordance with that previously reported by Bubnov.

15. Amine 14 was combined with 1-bromo,3-butene (2 equiv) and K$_2$CO$_3$ (1 equiv) in DMF (0.1 M with respect to 14). The solution was then heated to 60 °C for 12 h. The mixture was then transferred to a separatory funnel and diluted with Et$_2$O and H$_2$O. The aqueous layer was washed three times with Et$_2$O. The combined organic fractions were dried with MgSO$_4$, filtered and concentrated to give a yellow oil. Analysis by $^1$H NMR indicated 30–40% conversion to 15 for several reactions ranging from 0.07 mmol to 3.00 mmol in scale. Purification of 15 was accomplished with silica gel chromatography (20:1 hexane:Et$_2$O washed with 1% v/v concentrated NH$_4$OH as the eluent). The substrate was obtained as a clear oil after Kugelrohr distillation over metallic Na. IR (neat): 3081 (m), 2956 (s), 2800 (m), 1650 (m), 1462 (m), 1381 (w), 900 (s) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 5.84 (ddt, $J = 16.8$, 9.9, 6.6 Hz, 1H, RC$_{\text{H}}=$CH$_2$), 5.05 (ddd, $J = 17.2$, 3.7, 1.5 Hz, 1H, RCH=CH$_2$A$\text{H}$), 4.98 (d(br), $J = 2.9$, 1.5 Hz, 2H, R(Me)C=CH$_2$A$\text{H}$), 4.65 (s(br), 2H, R(Me)C=CH$_2$B$\text{H}$), 2.76 (t, $J = 7.0$, 2H, NCH$_2$), 2.53 (t, $J = 7.7$ Hz, 2H, NCH$_2$), 2.49 (dd, $J = 15.7$, 7.0 Hz, 2H, H$_2$C=CHCH$_2$), 2.11 (ABq, $J = 13.6$ Hz, 4H, H$_2$C=CM$\text{e}$CH$_2$), 1.80 (s, 6H, CH$_3$), 1.76-1.65 (m, 4H, NCR$_2$CH$_2$CH$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 144.7, 138.1, 115.8, 114.9, 66.7, 50.8, 48.3, 42.2, 34.7, 32.2, 25.8, 21.7; HRMS Calcd for C$_{16}$H$_{27}$N (M+H): 234.2222, Found: 234.2219.

5,5-Bis-allyl-pyrrolidin-2-one 17a and 5,5-bis-(2-methyl-allyl)-pyrrolidin-2-one 17b. The procedure for the synthesis of 14 (see above) was adapted for the preparation of 17a,b.

17b. Succinimide (recrystallized from C$_6$H$_6$, 4.62 g, 46.6 mmol) was ground to a fine powder and diluted with 93 mL THF. After all solids had dissolved, the mixture was cooled to 0 °C in an ice bath. Trimethallyl borane (8.20 g, 46.6 mmol, 1 equiv.) was added over ~20 min via cannula to the stirring solution, causing it to change from colorless to yellow. The reaction was then stirred for 12 h at ambient temperature. MeOH, 5 mL, was added and stirring was continued for 0.5 h. Subsequently, ~5 mL of a 3 M aqueous solution of NaOH was added and the resulting orange mixture was stirred for an additional hour. At this time, the solution was diluted with ~30 mL Et$_2$O and 120 mL of a saturated aqueous solution of NaCl. The organic layer was separated and washed with an additional ~120 mL of a saturated aqueous solution of NaCl. The remaining
material was extracted from the combined aqueous layers with two 100 mL portions of CH₂Cl₂. The combined organic fractions were dried over MgSO₄, filtered, and concentrated in vacuo to afford an orange foam. This material was absorbed onto silica gel and loaded onto a silica column (~7 x 4 inches). The product was eluted with Et₂O washed with 1% v/v concentrated NH₄OH. A clean sample (by TLC analysis) of 17b (3.00 g) was obtained which could be recrystallized from hot Et₂O to give off-white needles. A second fraction (3.15 g) of 17b (~90% clean as judged by ¹H NMR analysis) was resubjected to the flash conditions for further purification (anisaldehyde for TLC visualization). Combined yield of 17b: 5.85 g (30.3 mmol, 65%). IR (neat): 3211 (w), 2974 (m), 1703 (s), 1652 (s), 1438 (m), 1313 (m), 1017 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 5.93 (s(br), 1H, N), 2.34 (t, J = 7.8 Hz, 2H, RCH=C(Me)C≡CH₂), 2.11 (t, J = 8.4 Hz, 2H), 1.75 (s, 6H, C₂H₄), 1.55 (s, 6H, C₂H₄); ¹³C NMR (100 MHz, CDCl₃): δ 177.9, 141.5, 115.9, 62.3, 48.6, 31.1, 29.6, 24.5; HRMS Calcd for C₁₂H₁₅NO (M+H): 194.1545, Found: 194.1543.

17a. An analogous procedure to that for the synthesis of 17b was followed with triallyl borane as the alkylating agent.¹⁰ The desired product was obtained in 39% yield (18 mmol) after purification by silica gel chromatography (1:1 Et₂O:EtOAc; CAM stain for TLC visualization of product, anisaldehyde stain for TLC visualization of impurities). IR (neat): 3225 (w), 2973 (w), 2936 (w), 1696 (s), 1446 (w), 1383 (w), 901 (m); ¹H NMR (400 MHz, CDCl₃): δ 5.70 (s(br), 1H, N), 2.08 (t, J = 7.8 Hz, 2H, RCH=C(Me)C≡CH₂), 2.27 (ABd, J = 13.9 Hz, 4H, H₂C=C(Me)CH₂R), 2.08 (t, J = 8.1 Hz, 2H, OCCH₂CH₂R), 1.80 (s, 6H, CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 177.9, 141.5, 115.9, 62.3, 48.6, 31.1, 29.6, 24.5; HRMS Calcd for C₁₂H₁₅NO (M+H): 166.1232, Found: 166.1226.

18a and 18b. The procedure for the N-alkylation of 17b (for the preparation of 19) was followed (see below) with allyl bromide as the electrophile. In both cases, ¹H NMR analysis of the unpurification reaction mixture indicated >98% conversion to the desired product.

18b. Silica gel chromatography (4:1 Et₂O:pentane) gave the desired triene 18b (5 mmol) in 95% yield as an off-white solid. IR (neat): 3087 (w), 2974 (m), 1703 (s), 1652 (w), 1457 (w), 1407 (m), 910 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 5.87 (ddt, J = 17.2, 10.3, 5.9 Hz, 1H, RCH=CH₂), 5.19 (dddt, J = 17.2, 1.5, 1.5 Hz, 1H, RCH=CH₂H₁), 5.12 (dddt, J = 10.3, 1.5, 1.5 Hz, 1H, RCH=CH₂H₂); 4.90 (tt, J = 1.5, 1.5 Hz, 2H, R(Me)C=CH₂), 4.75 (s(br), 2H, R(Me)C=CH₂H₁), 3.83 (dt, J = 5.5, 1.5 Hz, 2H, NCH₂); 2.35-2.23 (m, 6H), 2.11 (t, J = 8.4 Hz, 2H), 1.75 (s, 6H, CH₃); ¹³C NMR (100
MHz, CDCl$_3$): $\delta$ 175.3, 141.2, 134.7, 116.7, 116.3, 66.8, 46.8, 43.1, 30.4, 29.3, 24.7; HRMS Calcd for C$_{15}$H$_{23}$NO (M+Na): 256.1677, Found: 256.1681.

18a. Silica gel chromatography (2:1 Et$_2$O:hexane) gave the desired triene 18b (1.5 mmol) in 85% yield as an off-white solid. IR (neat): 3081 (w), 2981 (w), 2925 (w) 1693 (s), 1406 (m), 1000 (w), 919 (m) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.89 (ddt, $J$ = 17.2, 10.3, 6.2 Hz, 1H, NCH$_2$C$\equiv$CH$_2$), 5.73 - 5.63 (m, 2H, NCR(CH$_2$C$\equiv$CH$_2$)$_2$), 5.15 - 5.10 (m, 5H, CH=C$\equiv$CH$_2$), 3.84 (d(br), $J$ = 6.2 Hz, 2H, NCMeR), 2.38 (ddt, $J$ = 14.3, 6.2, 1.5 Hz, 2H, R(COH$_2$C$\equiv$CH$_2$)$_2$), 2.32 (t, $J$ = 8.4 Hz, 2H), 2.24 (ddt, $J$ = 13.9, 8.1, 1.0 Hz, 2H, R(CH$_2$C$\equiv$CH$_2$)$_2$), 1.91 (t, $J$ = 8.4 Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 175.4, 134.6, 132.7, 119.6, 117.1, 65.9, 43.7, 42.8, 29.9, 27.5; HRMS Calcd for C$_{13}$H$_{19}$NO (M+Na): 228.1364, Found: 228.1363.

19. In a N$_2$ filled glovebox, 17b (659 mg, 3.41 mmol) was dissolved in 17 mL THF and cooled to -30 °C. Benzyl potassium$^{11}$ (444 mg, 3.41 mmol) was added in portions. (If necessary, additional Benzyl potassium was added just until the orange color persists.) The mixture was sealed, removed from the glove box and cooled to 0 °C. The electrophile, 1,5 diiodo pentane (Aldrich, 1.32 mL, 10.2 mmol), was added drowise via syringe. The resulting white mixture was stirred for 12 h, at which time ~ 40 mL of a saturated aqueous solution of NaCl was added. The organic layer was separated and washed with two additional portions (~ 20 mL) of a saturated aqueous solution of NaCl. The combined aqueous layers were then washed with two 50 mL portions of CH$_2$Cl$_2$. The organic fractions were combined, dried over MgSO$_4$, and concentrated in vacuo. $^1$H NMR analysis of the crude reaction mixture indicated ~70% conversion to the desired product. Silica gel chromatography (4:1 pentane:Et$_2$O) of the mixture gave 520 mg of 1-(4-iodo-butyl)-5,5-bis-(2-methyl-allyl)-pyrrolidin-2-one (~40% yield) combined with ~5% 19. A solution of this material (346 mg) in 9 mL C$_6$H$_6$ was heated to reflux in the presence of 0.8 mL DBU (~6 equiv, distilled from CaH$_2$) for 1 h. At this time, white solids had precipitated from the reaction mixture and TLC analysis indicated complete consumption of starting material. Pentane (~20 mL) was added, causing further precipitation of the ammonium salts, and the resulting solution was filtered. Concentration of the filtrate gave an oil that was purified by silica gel chromatography (4:1 Et$_2$O:pentane) to give 59.4 mg of 19 (0.240 mmol, 26% yield). IR (neat): 3074 (w), 2974 (m), 2930 (m), 1697 (s), 1463 (m), 1406 (m), 1375 (w), 904 (m) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.82 (ddt, $J$ = 17.2, 10.3, 7.0 Hz, 1H, RCH=CH$_2$), 5.09 (ddd, $J$ = 17.2, 3.3, 1.8 Hz, 1H, RCH=CH$_2$), 5.04 (d(br), $J$ = 10.3 Hz, 1H, RCH=CH$_2$), 4.91 (t(br), $J$ = 1.5 Hz, 2H, R(Me)C=CH$_2$), 4.76 (s(br), 2H, R(OMe)C=CH$_2$), 3.19-3.15

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(m, 2H, NCH₂), 2.39-2.28 (m, 6H), 2.24 (t, J = 13.9 Hz, 2H), 2.09 (t, J = 8.0 Hz, 2H), 1.76 (s, 6H, CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 175.5, 141.2, 135.6, 116.7, 116.4, 66.6, 46.9, 40.4, 33.9, 30.5, 29.4, 24.7; HRMS Calcd for C₁₆H₂₅NO (M+Na): 270.1834, Found: 270.1835.

General procedure for Mo-catalyzed asymmetric ring-closing metathesis (ARCM) under inert (N₂) atmosphere: (Reactions performed entirely in an N₂ dry box). A one dram vial was charged with a solution of 51 (40 mg, 0.12 mmol) in 1.2 mL of C₆H₆. Mo catalyst 1b (4.4 mg, 5.9 µmol, 5 mol %) was added in one portion. The vial was sealed with a cap and the reaction was stirred at ambient temperature for 24 h. At this time, the vial was removed from the dry box, ~1 mL of wet (nondistilled) Et₂O was added to quench the catalyst and the resulting solution was concentrated in vacuo.

¹H NMR analysis of the unpurified reaction mixture indicated ~ 95% conversion to the desired product (52). Silica gel chromatography (3:1 hexanes:Et₂O) was used to purify 52 in 94% yield (35 mg, 0.11 mmol).

20. General procedure for ARCM was followed. Silica gel chromatography with 100% Et₂O was used for purification (84% yield, 0.083 mmol). IR (neat): 2967 (m), 2924 (m), 1701 (s), 1438 (m), 1413 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 5.62 (dd(br), J = 5.1, 5.1 Hz, 1H, R₂C=CH₂), 4.89 (dd, J = 1.8, 1.8 Hz, 1H, R₂C=CH₃), 4.73 (s(br), 1H, R₂C=CH₂), 4.05 (ddd, J = 13.6, 4.0, 4.0 Hz, 1H, NCH₂H₂R), 2.85 (ddd, J = 14.3, 12.1, 2.9 Hz, 1H, NCH₂H₂R), 2.61 (d, J = 14.3 Hz, 1H), 2.44 (d, J = 14.6 Hz, 1H), 2.41-2.09 (m, 6H), 2.04 (d, J = 13.9 Hz, 1H), 1.76 (s, 3H, CH₃), 1.75-1.72 (m, 1H), 1.71 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 174.5, 141.8, 135.2, 125.4, 115.9, 64.6, 47.0, 42.5, 37.7, 30.4, 30.1, 28.4, 27.3, 24.2; HRMS Calcd for C₁₄H₂₁NO (M+Na): 242.1521, Found: 242.1517; [α]D +14.9 (c = 0.5, CHCl₃).

21. The procedure for the N-alkylation of 17b (for the preparation of 19) was followed (see above) with 5-bromo-1-pentene as the electrophile. ¹H NMR analysis of the unpurified reaction mixture indicated ~60% conversion to the desired product. Silica gel chromatography (2:1 to 4:1 Et₂O:pentane) gave the desired triene 21 (4 mmol) in 57% yield as an off-white solid. IR (neat): 3087 (w), 2943 (m), 1690 (s), 1444 (m), 1407 (m), 1306 (w), 897 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 5.82 (ddt, J = 16.8, 10.3, 6.6 Hz, 1H, RCH=CH₂), 5.05 (ddt, J = 17.2, 1.8, 1.8 Hz, 1H, RCH=CH₂), 4.99 (ddt, J = 10.3, 2.6, 1.7 Hz, 1H, RCH=CH₂), 4.91 (tt, J = 2.9, 1.5 Hz, 2H, R(Me)C=CH₂), 4.76 (s(br), 2H, R(Me)C=CH₂), 3.13-3.08 (m, 2H, NCH₂), 2.33-2.21 (m, 6H), 2.13-2.07
(m, 4H), 1.76 (s, 6H, CH₃), 1.75-1.66 (m, 2H); HRMS Calcd for C₁₇H₂₇NO (M+Na): 284.1990, Found: 284.1990.

22. General procedure for ARCM was followed with some modification: toluene was used as a solvent and the vessel was loosely capped for the duration of the reaction. Silica gel chromatography with 100% Et₂O was used for purification (90% yield, 0.088 mmol). IR (neat): 2936 (m), 2861 (m), 1710 (s), 1457 (m), 1420 (m), 904 (w) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 5.56 (dd(br), J = 8.4, 8.4 Hz, 1H, R₂C=CHR), 4.91 (dd, J = 1.5, 1.5 Hz, 1H, R₂C=CHR₂), 4.72 (s(br), 1H, R₂C=CHR₂), 3.63 (d(br), J = 13.9 Hz, 1H, NCH₃H₃B), 2.82 (dd, J = 13.9, 13.9, 3.7 Hz, 1H, NCH₃H₃B), 2.48 (d, J = 14.3 Hz, 1H), 2.39-2.03 (m, 8H), 1.97-1.89 (m, 1H), 1.84 (s, 3H, CH₃), 1.85-1.79 (m, 1H), 1.68 (s, 3H, CH₃), 1.49-1.43 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 176.4, 141.9, 134.2, 128.7, 116.8, 68.0, 45.7 (br), 40.9, 30.4, 29.6, 27.7, 27.1, 26.3, 24.7; HRMS Calcd for C₁₃H₂₃NO (M+Na): 256.1677, Found: 256.1669; [α]₀D –27.2 (c = 1, CHCl₃).

23. General procedure for ARCM was followed. Silica gel chromatography with 1:1 EtOAc:Et₂O was used for purification (91% yield, 0.098 mmol). IR (neat): 2974 (m), 2943 (m), 2861 (m), 1710 (s), 1457 (m), 904 (w) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 5.38 (s(br), 1H, R₂C=CHR), 4.90 (s(br), 1H, R₂C=CHR₂), 4.72 (s(br), 1H, R₂C=CHR₂), 4.32 (d(br), J = 18.3 Hz, 1H, NCH₃H₃B), 3.43 (d(br), J = 17.6 Hz, 1H, NCH₃H₃B), 2.48-2.22 (m, 5H), 2.14-2.04 (m, 2H), 1.82-1.75 (m, 1H), 1.74 (s, 3H, CH₃), 1.69 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 173.8, 141.7, 131.5, 116.4, 116.0, 60.7, 43.7, 41.4, 38.6, 30.8, 30.0, 24.4, 23.6; HRMS Calcd for C₁₃H₁₉NO (M+H): 206.1545, Found: 206.1542. Anal. Calcd for C₁₃H₁₉NO: C, 76.06; H, 9.33; Found: C, 76.16; H, 9.60; [α]₀D +103.2 (c = 1, CHCl₃).

24. General procedure for ARCM was followed. Silica gel chromatography with 1:1 EtOAc:Et₂O was used for purification (92% yield, 0.122 mmol). IR (neat): 3075 (w), 3037 (w), 2925 (m), 2843 (m), 1693 (s), 1419 (m), 1212 (w), 925 (w) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 5.76-5.65 (m, 3H, RCH=CH₂, RCH=CHR), 5.14 (s(br), 1H, RCH=CH₂H₃B), 5.12-5.09 (m, 1H, RCH=CH₂H₃B), 4.36 (d(br), J = 19.0 Hz, 1H, NCH₃H₃B), 3.43 (d(br), J = 18.7 Hz, 1H, NCH₃H₃B), 2.47-2.31 (m, 3H), 2.26-2.12 (m, 4H), 1.76 (ddd, J = 12.8, 9.9, 6.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 173.8, 132.9,
123.8, 123.1, 119.5, 59.9, 40.8, 38.5, 36.3, 30.2, 29.8; HRMS Calcd for C_{11}H_{15}NO (M+Na): 200.1051, Found: 200.1054; [α]_D +57.7 (c = 1, CHCl_3).

30. Amine 30 was prepared in 84% yield (1.98 mmol) according to the procedure for the preparation of 15 with allyl bromide as the electrophile. IR (neat): 3075 (m), 2968 (s), 2804 (m), 1646 (m), 1451 (m), 922 (m), 878 (s) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 5.82 (dddd, \(J = 16.5, 10.3, 6.2, 6.2\) Hz, 1H, RCH=CH\(_2\)), 5.17 (dd, \(J = 3.3, 1.8\) Hz, 1H, RCH=CH\(_2\)), 5.13 (dd, \(J = 3.3, 1.5\) Hz, 1H, RCH=CH\(_2\)), 5.03 (m, 2H, R=CH\(_2\)), 5.00 (m, 2H, R=CH\(_2\)), 3.25 (ABq, \(J = 18.3\) Hz, 2H, NCH\(_2\)), 2.72 (dd, \(J = 7.0, 7.0\) Hz, 2H, NCH=CH\(_2\)), 2.12 (ABq, \(J = 13.6\) Hz, 4H, R(CH\(_2\)C(CH\(_3\))=CH\(_2\))), 1.81 (s, 6H, CH\(_3\)), 1.78-1.75 (m, 2H), 1.71-1.63 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 144.1, 137.8, 115.6, 114.4, 65.8, 51.2, 50.5, 41.8, 31.7, 25.3, 21.1; HRMS Calcd for C\(_{15}\)H\(_{25}\)N (M+H): 220.2065, Found: 220.2073.

31. General procedure for ARCM was followed. Silica gel chromatography with 15:1 CH\(_2\)Cl\(_2\):MeOH washed with 2% v/v concentrated NH\(_4\)OH was used for purification (56% yield, 0.053 mmol). \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 5.34 (s(br), 1H, RCH=CR\(_2\)), 4.82 (s(br), 1H, R=CH\(_2\)), 4.64 (s(br), 1H, R=CH\(_2\)), 3.25 (ABq, \(J = 18.3\) Hz, 2H, NCH\(_2\)), 2.87-2.75 (m, 2H, NCH\(_2\)), 2.26 (d, \(J = 13.2\) Hz, 1H), 1.95-1.77 (m, 6H), 1.77 (s, 3H, CH\(_3\)), 1.66 (s, 3H, CH\(_3\)), 1.58-1.51 (m, 1H). Enantiomeric excess was determined by GLC analysis of the derived amide (23). See below for details.

33. General procedure for ARCM was followed (pentane as solvent). Silica gel chromatography with 20:1 CH\(_2\)Cl\(_2\):MeOH washed with 1% v/v concentrated NH\(_4\)OH was used for purification (quantitative yield, 0.042 mmol). \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 5.50-5.45 (m, 1H, R=CHR), 4.83 (dd, \(J = 2.6, 1.5\) Hz, 1H, R=CH\(_2\)), 4.70 (s(br), 1H, R=CH\(_2\)), 2.97 (ddd, \(J = 13.2, 10.3, 2.6\) Hz, 1H, N=CH\(_2\)), 2.90-2.77 (m, 3H, NCH\(_2\)), 2.45 (d, \(J = 15.7\) Hz, 1H), 2.42-2.32 (m, 1H), 2.30 (d, \(J = 13.6\) Hz, 1H), 2.14 (d, \(J = 13.6\) Hz, 1H), 2.12-2.05 (m, 1H), 2.02 (d, \(J = 15.7\) Hz, 1H), 2.02-1.96 (m, 1H), 1.81 (s, 3H, CH\(_3\)), 1.75-1.68 (m, 2H), 1.70 (s, 3H, CH\(_3\)), 1.46 (ddd, \(J = 11.7, 9.5, 9.5\) Hz, 1H); LRMS Calcd for C\(_{14}\)H\(_{23}\)N (M+H): 206.19, Found: 206.19. Enantiomeric excess was determined by GLC analysis of the derived amide (20).
Enantiomeric excess determination of 31 and 33. Amines 31 and 33 was converted to the derived lactams (23 and 20 respectively) for ee analysis through an oxidation with iodosyl benzene (based on a literature procedure) as follows: 33 (12 mg, 0.06 mmol) was diluted with a 9:1 mixture of MeCN/H$_2$O (1.2 mL, 0.05M) and tetrabutylammonium iodide (4.5 mg, 0.01 mmol, 0.2 equiv) was added. Iodosyl benzene (prepared by hydrolysis of PhI(OAc)$_2$ according to a literature procedure, 29 mg, 0.13 mmol, 2.2 equiv) was then added in one portion. After stirring for ~3 h, the mixture changes to a homogeneous orange/brown solution. Stirring was continued for 20 h, and the mixture was then concentrated in vacuo. The resulting brown residue was dissolved in ~1 mL CHCl$_3$ and ~1 mL of a 5% aqueous solution of Na$_2$S$_2$O$_3$. The layers are separated, and the aqueous fraction was washed with two 1 mL portions of CHCl$_3$. The combined organic layers were washed with 3 mL H$_2$O, dried with Na$_2$SO$_3$, filtered, and concentrated with a N$_2$ purge. $^1$H NMR analysis of the unpurified mixture indicated a complex mixture of oxidation products (the majority of the material was unreacted 33). Nonetheless a minor amount (1-3%) of the desired amide 20 was present. Careful purification through a small plug of silica with Et$_2$O (anisaldehyde for TLC visualization) afforded ~0.5 mg of 20. GC analysis indicated 40% ee of the product in comparison with racemic material. An analogous procedure was followed for the oxidation of 31 to afford trace quantities of 23 sufficient for GC analysis.

34. Amine 14 (108 mg, 0.60 mmol) was stirred with K$_2$CO$_3$ and 3-butenoyl chloride (84 µL, 0.72 mmol, prepared by the addition of 1 equiv oxalyl chloride followed by 5 mol % DMF to a solution of vinyl acetic acid (0.1M in Et$_2$O)- after the gas evolution had ceased, the desired acid chloride was directly purified by simple distillation) in CH$_2$Cl$_2$ (3 mL) for 12 h. The mixture was then transferred to a separatory funnel and diluted with ~5 mL

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H₂O and 5 mL CH₂Cl₂. The aqueous layer was washed three times with 5 mL portions of CH₂Cl₂. The combined organic fractions were dried over MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography (5:1 pentane:EtOAc) gave 72 mg of 34 (48%). ¹H NMR (400 MHz, CDCl₃): δ 5.97 (ddt, J = 16.8, 10.3, 6.6 Hz, 1H, RCH=CH₂), 5.16 (d(br), J = 10.3 Hz, 1H, RCH=CH₃A), 5.11 (ddd, J = 17.2, 3.3, 1.8 Hz, 1H, RCH=CH₃B), 4.87-4.84 (m, 2H, R(Me)C=CH₂A), 4.69 (s(br), 2H, R(Me)C=CH₂B), 3.42 (t, J = 7.0 Hz, 2H, NCH₂₂R), 3.14 (d, J = 13.6 Hz, 2H, OCC₃H₃R), 3.02 (dt, J = 6.6, 1.5 Hz, 2H, H₂C=CMeCH₃A), 2.28 (d, J = 13.2 Hz, 2H, H₂C=CMeCH₃B), 1.97 (t, J = 7.3 Hz, 2H, NCR₂CH₂₂R), 1.76 (tt, J = 14.3, 7.0 Hz, 2H, NCH₂CH₂CH₂₂R), 1.72 (s, 6H, CH₃).

Reaction of 34. In a N₂ filled glove box, a threaded NMR tube was charged with 0.50 mL of a 0.1 M solution of 34 in C₆D₆. Mo catalyst 35 (1.92 mg, 2.5 µmol, 5 mol %) was added in one portion. A teflon cap was used to securely seal the tube and the reaction was monitored by ¹H NMR spectroscopy. None of the desired ring-closed product was observed and a new alkylidene resonance appeared (11.97 ppm, t, J = 4.5 Hz) that persisted for several hours.

Kinetic resolution of 37. Kinetic resolution substrate 37 was prepared according to published procedure.¹⁴ Kugelrohr distillation provided a clear oil for use in ARCM reactions. In a N₂ filled dry box, a solution of pyrrolidinone 37 (1.2 mL, 0.2 M in C₆H₆) was prepared in a 1 dram vial and sealed securely with a septum. A separate vial equipped with a stirbar was charged with a solution of Mo catalyst 1a (7.6 mg, 10 µmol in 1.0 mL C₆H₆, 0.01 M). This vial was also sealed completely with a septum and teflon tape. Both vials were then removed from the glove box. The vial containing the catalyst solution was connected to a full ethylene (99.99% anhydrous) balloon and purged for ~2 s through an exit needle. (The balloon apparatus consisted of a triple layered balloon connected to a short tube containing Ca₃SO₄, which was fitted with an 18 gauge needle. The entire apparatus was assembled in the glove box so as to exclude any air or moisture and then removed from the N₂ atmosphere and purged three times with anhydrous ethylene before filling.) The vial containing the starting material was then connected to a N₂ manifold and 1.0 mL of this solution (33 mg, 0.20 mmol) was transferred to the vial containing the catalyst solution via a gas-tight syringe that was first carefully purged with N₂. The reaction was stirred under an ethylene atmosphere for 6 h before 0.5 mL of wet Et₂O was added to quench the catalyst. The mixture was concentrated with a N₂ purge to give a brown residue. ¹H NMR analysis indicated 66% conversion to the ring-closed product, indolizidinone 38 with 34% unreacted starting material. Isolation of the optically-enriched starting material 37 (9.9 mg, 0.06 mmol, 30% yield) from the reaction mixture was accomplished with silica gel chromatography (EtOAc). GC analysis of 37 indicated 94% ee, corresponding to a kₑₐ value of 8. Lactam 37: ¹H NMR (400 MHz, CDCl₃).

CDCl$_3$): $\delta$ 5.74 (dddd, $J = 16.8$, 10.3, 6.6, 6.6 Hz, 1H, RCH$_2$CH=CH$_2$), 5.66, (ddd, $J = 17.2$, 10.3, 8.8 Hz, 1H, R$_2$CHCH=CH$_2$), 5.24 (d(br), $J = 15.7$ Hz, 1H, CH=CH$_2$H), 5.21 (d(br), $J = 9.2$ Hz, 1H, CH=CH$_2$H), 5.06 (d(br), $J = 17.6$ Hz, 1H, CH=CH$_2$H), 5.02 (d(br), $J = 11.4$ Hz, 1H, CH=CH$_2$H), 4.05 (ddd, $J = 8.1$, 8.1, 5.5 Hz, 1H, NCH), 3.60 (ddd, $J = 15.0$, 7.7, 7.7 Hz, 1H, NCH), 2.94 (ddd, $J = 13.6$, 8.1, 5.9 Hz, 1H, NCH), 2.45-2.16 (m, 5H), 1.73 (ddddd, $J = 12.8$, 9.5, 7.0, 5.5 Hz, 1H); [α]$_D^2$ +68.2 (c = 1, CHCl$_3$).

39. To a stirring solution of NaH (58.8 mg, 2.45 mmol, 1 equiv) in 40 mL THF was added 39 (440 mg, 2.45 mmol, 1 equiv, see below for preparation) by cannula transfer with a total of 10 mL THF. The mixture was stirred for 1 h at which time it was cooled to 0 °C and acetylchloride (174 µL, 2.45 mmol, 1 equiv) was added dropwise via syringe. The mixture was then stirred for 12 h. Water, 50 mL, was added to react with any remaining NaH and the aqueous layer was separated. Three 40 mL portions of Et$_2$O were used to extract the product from the aqueous layer. The combined organic fractions were dried over MgSO$_4$, filtered and concentrated in vacuo to give an oil. $^1$H NMR analysis indicated ~65% conversion to the desired product 39. This compound was purified by silica gel chromatography (20:1 CH$_2$Cl$_2$:Et$_2$O as the eluent) in 62% yield (336 mg, 1.52 mmol). IR (neat): 3069 (s), 2974 (s), 2917 (s), 1797 (w), 1652 (s), 1413 (s), 1250 (m), 1171 (s), 1036 (m), 885 (s) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, 25 °C), ~1:3 mixture of amide rotamers: $\delta$ 5.89 (ddtt, $J = 16.1$, 10.3, 5.9 Hz, 0.25H, RCH=CH$_2$), 5.78 (ddtt, $J = 15.7$, 10.6, 5.5 Hz, 0.75H, RCH=CH$_2$), 5.21-5.03 (m, 2.75H, RCH=CH$_2$, NCH$_2$), 4.85 (s,br), 0.5H, R$_2$C=CH$_2$H), 4.76 (s,br), 1.5H, R$_2$C=CH$_2$H), 4.73 (s,br), 0.5H, R$_2$C=CH$_2$H), 4.70 (s,br), 1.5H, R$_2$C=CH$_2$H), 4.02 (p, $J = 6.6$ Hz, 0.25H, NCH$_2$), 3.87 (d,br), $J = 5.9$ Hz, 0.5H, NCH$_2$), 3.75 (dt, $J = 5.1$, 1.5 Hz, 1.5H, NCH$_2$), 2.25-2.14 (m, 4H, NCH(CH$_2$R)$_2$), 2.13 (s, 0.75H, CH$_3$CO), 2.03 (s, 2.25H, CH$_3$CO), 1.75 (s, 6H, R$_2$CCCH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 172.0, 143.5, 142.1, 136.4, 136.0, 129.0, 117.1, 116.5, 114.6, 113.2, 56.2, 50.3 (br), 47.0 (br), 44.6 (br), 42.2, 23.1, 23.0, 22.9, 22.6; HRMS Calcd for C$_{14}$H$_{23}$NO (M+Na): 244.1677, Found: 244.1672.

40. General procedure for ARCM was followed. Silica gel chromatography with 1:1 EtOAc:hexanes was used for purification (90% yield, 0.22 mmol). IR (neat): 2962 (m), 2924 (m), 2855 (m), 1646 (s), 1426 (s), 1376 (w), 1237 (w), 891 (w) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, 25 °C), ~2:3 mixture of amide rotamers: $\delta$ 5.39 (s,br), 0.4H, R$_2$C=CHR), 5.33 (s,br), 0.6H, R$_2$C=CHR), 5.10 (ddd, $J = 14.6$, 7.3 Hz, 0.6H, NCH$_2$), 4.83 (s,br), 0.4H, R$_2$C=CH$_2$H), 4.73 (s,br), 0.6H, R$_2$C=CH$_2$H), 4.70 (s,br), 0.4H, R$_2$C=CH$_2$H), 4.65 (s,br), 0.6H, R$_2$C=CH$_2$H), 4.58 (d,br, $J = 19.0$ Hz, 0.4H, NCH$_2$H), 4.08 (dd, $J$
= 13.6, 6.6 Hz, 0.4H, NCHR₂), 3.91 (d(br), J = 17.6 Hz, 0.6H, NCH₃H₂R), 3.73 (d(br), J = 17.6 Hz, 0.4H, NCH₃H₂R), 3.39 (d(br), J = 19.0 Hz, 0.4H, NCH₃H₂R), 2.38-2.20 (m, 2.4H, NCHCH₂R), 2.11 (s, 1.2H, CH₃), 2.10-2.07 (m, 0.6H, NCHCH₂R), 2.04 (s, 1.8H, CH₃), 1.93-1.79 (m, 1H, NCHCH₂R), 1.78 (s, 1.8H, CH₃), 1.77 (s, 1.2H, CH₃), 1.71 (s(br), 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 170.1, 144.1, 142.5, 132.5, 130.1, 118.0, 116.5, 114.7, 113.3, 51.1, 44.4, 42.7, 41.0, 40.6, 39.2, 33.9, 33.2, 30.4; HRMS Calcd for C₁₂H₁₉NO (M+Na): 216.1364, Found: 216.1367.

**41.** To a solution of 43 (400 mg, 2.23 mmol, 1 equiv, see below for preparation), Et₃N (0.66 mL, 8.92 mmol, 4 equiv, distilled over CaH₂), and DMAP (55 mg, 0.45 mmol, 0.2 equiv) in DMSO (2.23 mL, distilled over CaH₂) was added CbzCl (carefully distilled to remove any BnCl resulting from decomposition, 0.64 mL, 4.46 mmol, 2 equiv) via syringe. The resulting mixture was heated to 50 °C and stirred for 12 h. The reaction was then allowed to cool to ambient temperature and ~10 mL H₂O followed by ~10 mL Et₂O was added. The aqueous phase was separated and washed three times with 10 mL portions of Et₂O. The combined organic fractions were washed with ~30 mL of a saturated aqueous solution of NaHCO₃, dried over MgSO₄, filtered, and concentrated in vacuo. ¹H NMR analysis of the unpurified reaction mixture in vacuo.

**42.** General procedure for ARCM was followed. Silica gel chromatography with CH₂Cl₂ was used for purification (98% yield, 0.24 mmol). IR (neat): 3069 (w), 3031 (w), 2974 (m), 2917 (m), 2836 (m), 1709 (s), 1432 (s), 1344 (s), 1294 (s), 1224 (s), 1105 (s), 1048 (m), 891 (m) cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆, 100 °C): δ 7.37-7.28 (m, 5H, ArH), 5.39 (s(br), 1H, R₂C=CHR), 5.07 (s, 2H, PhCH₂), 4.71 (s(br), 2H, R₂C=CHR), 4.65 (s(br), 1H, R₂C=CHR), 4.49 (dd, J = 13.6, 6.2 Hz, 1H, NCHR₁), 4.11 (d, J = 17.9 Hz, 1H, NCHR₂), 3.52 (d, J = 17.6 Hz, 1H, NCHR₂), 2.30 (d, J = 16.8 Hz, 1H,
NCH(CH$_2$)$_2$), 2.20 (dd, $J$ = 13.6, 8.4 Hz, 1H, NCH(CH$_2$)$_2$), 2.05 (dd, $J$ = 13.6, 7.0 Hz, 1H, NCH(CH$_2$)$_2$), 1.79 (d, $J$ = 17.2 Hz, NCH(CH$_2$)$_2$), 1.67 (s(br), 6H, CH$_3$); $^{13}$C NMR (100 MHz, DMSO-d$_6$, 100 ºC): δ 155.5, 143.2, 142.7, 137.1, 130.1, 128.5, 128.3, 128.0, 117.0, 116.5, 113.3, 113.0, 67.0, 47.2, 46.7, 40.1, 33.1, 32.6, 29.8, 23.6, 22.2; HRMS Calcd for C$_{18}$H$_{23}$NO$_2$ (M+Na): 308.1626, Found: 308.1622; [α]$_D$ –14.7 (c = 2, CHCl$_3$).

43. A reductive alkylation of allylformamide$^{15}$ with trimethallylborane was performed according to the procedure for the synthesis of 14 (see above). Secondary amine 43 is obtained in 71% yield (8.5 mmol) after silica gel chromatography (4:1 DCM:hexanes washed with 1% v/v concentrated NH$_4$OH, Dradendorff’s reagent for TLC visualization). The amine can be further purified by Kugelrohr distillation under vacuum to give a clear oil. IR (neat): 3087 (m), 2980 (m), 2936 (s), 1652 (m), 1457 (m), 1381 (m) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 5.85 (dddd, $J$ = 16.8, 10.3, 6.2, 6.2 Hz, 1H, RC=CH$_2$), 5.15 (ddd, $J$ = 17.2, 3.3, 1.5 Hz, 1H, RCH=C=CH$_2$), 5.08 (d(br), $J$ = 10.3 Hz, 1H, RCH=CH$_2$), 4.81 (s(br), 2H, R$_2$C=CH$_2$), 4.75 (s(br), 2H, R$_2$C=CH$_2$), 3.26 (d, $J$ = 5.9 Hz, 2H, NCH$_2$), 2.82 (dddd, $J$ = 6.6, 6.6, 6.6, 6.6 Hz, 1H, NCH$_2$), 2.15 (dd, $J$ = 13.9, 7.3 Hz, 2H, NCHCH$_2$), 2.07 (dd, $J$ = 13.9, 6.2 Hz, 2H, NCHCH$_2$), 1.72 (s, 6H, CH$_3$), 1.28 (s(br), 1H, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 143.5, 137.2, 116.0, 113.1, 52.0, 50.1, 43.4, 22.6; HRMS Calcd for C$_{12}$H$_{21}$N (M+H): 180.1752, Found: 180.1751.

Amine-borane complex 53. To a stirring solution of amine 43 (50.3 mg, 0.280 mmol) in Et$_2$O (2.8 mL) under an inert atmosphere was added 29.9 mL catechol borane (freshly distilled from CaH$_2$, 0.280 mmol). The resulting solution was stirred for 12 h. At this time, the solvent was removed by a stream of N$_2$ and then in vacuo. The complex was azeotroped with C$_6$H$_6$ (see materials section). $^1$H NMR analysis revealed that all starting material had been consumed, however, the signals for complex 53 were not well resolved.

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44. General procedure for ARCM was followed with a modified work-up: the unpurified reaction mixture was diluted with an equal volume of 1 M aqueous NaOH solution and stirred for 1 h. The aqueous phase was then separated and washed three times with CH₂Cl₂. The combined organic extracts were filtered with Na₂SO₄, concentrated almost to dryness (product is volatile). Silica gel chromatography with 20:1 CH₂Cl₂:MeOH washed with 2% v/v concentrated NH₄OH was used for purification (50% yield, 0.027 mmol). IR (neat): 3270 (w), 3075 (m), 2917 (s), 1659 (m), 1451 (s), 1381 (m), 897 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 5.41 (s(br), 1H RCH=CR₂), 4.83 (s(br), 1H, R₂C=CH₂H₂B), 3.78 (s(br), 2H, 2H, NCH₂R₂), 2.85 (dddd, J = 9.5, 7.7, 5.9, 4.4 Hz, 1H, NCHR₂), 2.17-2.13 (m, 2H, NCHCH₃R₂), 1.90-1.72 (m, 3H, NCHCH₃R₂, NH), 1.74 (s, 3H-CH₃), 1.67 (s, 3H-CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 142.9, 132.9, 120.1, 114.9, 50.4, 45.3, 37.3, 23.4, 22.5; HRMS Calcd for C₁₀H₁₇N (M+H): 152.1439, Found: 152.1436; [α]D +7.7 (c = 1). Enantiomeric excess was determined by GLC analysis of the derived acetamide (40).

45. Alkylation of allyl acetamide with trimethylallyl borane was performed according the procedure for the preparation of 2,2-bis-(2-methyl-allyl)-pyrrolidine 14 with the following modification: trimethylallyl borane was added to a −78 °C solution of allyl acetamide in THF. After the addition, the mixture was allowed to warm to ambient temperature and was subsequently stirred for 12 h before quench with MeOH and 3 M NaOH. Allyl-[1,3-dimethyl-1-(2-methyl-allyl)-but-3-etyl]-amine was obtained after purification by silica gel chromatography (15:1 pentane:Et₂O washed with 1% v/v concentrated NH₄OH) in 47% yield (7 mmol). This secondary amine was then converted to the acetamide under the conditions reported for the synthesis of 39. By this method, 45 was obtained in 44% yield after silica gel chromatography (20:1 CH₂Cl₂:Et₂O). IR (neat): 3087 (w), 2980 (m), 1671 (s), 1470 (m), 1401 (s), 1212 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 5.79 (ddt, J = 17.2, 11.0, 5.5 Hz, 1H, RCH=CH₂), 5.19-5.12 (m, 2H, RCH=CH₂), 4.87 (dq, J = 2.5, 1.1 Hz, 2H, R₂C=CH₂H₂B), 4.68-4.67 (m, 2H, R₂C=CH₂H₂B), 3.83 (dt, J = 5.5, 1.8 Hz, 2H, NCH₂R₂), 3.34 (d, J = 13.2 Hz, 2H, NC(Me)CH₂H₂R₂), 2.17 (d, J = 13.2 Hz, 2H, NCHCH₃R₂H₂R₂), 2.07 (s, 3H, CH₃CO), 1.73 (s, 6H, CR₂CH₃), 1.32 (s, 3H, NCR₂CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 172.3, 143.0, 136.2, 116.3, 115.4, 63.3, 49.8, 45.8, 25.5, 25.0, 24.6; HRMS Calcd for C₁₅H₂₅NO (M+H): 236.2014, Found: 236.2011.

46. General procedure for ARCM was followed. Silica gel chromatography with 15:1 CH₂Cl₂:Et₂O was used for purification (63% yield, 0.140 mmol). IR (neat): 3068 (m), 2968 (s), 2923 (s), 2861 (m), 1646 (s), 1694 (s), 1243 (m), 1168 (m), 897 (s) cm⁻¹; ¹H
NMR (400 MHz, CDCl₃): δ 5.53 (s(br), 1H, RCH=CR₂), 4.83 (s, 1H, R₂C=CH₂H₂B), 4.66 (s, 1H, R₂C=CH₂H₂B), 3.85 (dd, J = 15.7, 4.8 Hz, 1H, NCH₃H₂R), 3.68 (dd, J = 15.7, 1.5 Hz, 1H, NCH₃H₂R), 3.02 (d, J = 13.6 Hz, 1H, NCR₂CH₂H₂B), 2.34 (d, J = 14.6 Hz, 1H, NCR₂CH₂H₂B), 2.30 (d, J = 13.6 Hz, 1H, NCR₂CH₂H₂B), 2.06 (s, 3H, CH₃CO), 1.87 (d, J = 15.7 Hz, 1H, NCR₂CH₂H₂B), 1.74 (s, 3H, CH₃), 1.49 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 171.0, 143.3, 136.2, 117.6, 114.9, 58.7, 44.8, 42.5, 26.9, 25.5, 24.2, 23.0; HRMS Calcd for C₁₃H₂₁NO (M+H): 208.1701, Found: 208.1698.

47. Amine 47 was prepared according to the procedure for the synthesis of 49 (see below). ¹H NMR (400 MHz, CDCl₃): δ 7.46–7.43 (m, 2H), 7.32–7.27 (m, 2H), 7.21–7.16 (m, 1H), 6.01–5.92 (tdd, J = 16.0, 10.0, 5.6 Hz, 1H), 5.27–5.21 (ddd, J = 17.2, 2.0, 1.6 Hz, 1H), 5.10–5.06 (ddd, J = 10.4, 1.6, 1.2 Hz, 1H), 4.78–4.76 (td, J = 4, 1.6 Hz, 2H), 4.61 (s, 2H), 3.22–3.19 (td, J = 5.6, 1.2 Hz, 2H), 2.68–2.64 (d, J = 14 Hz, 2H), 2.54–2.50 (d, J = 14 Hz, 1H), 1.57 (s, 1H), 1.42 (s, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 145.9, 142.6, 137.4, 128.0, 127.0, 126.3, 115.2, 114.7, 61.1, 46.2, 45.1, 24.9.

48. General procedure for ARCM was followed. Silica gel chromatography with 2.5% MeOH in CH₂Cl₂ was used for purification (95% yield, 0.039 mmol). IR (neat): 3383 (br), 2961 (m), 2917 (s), 2848 (m), 2369 (w); ¹H NMR (400 MHz, CDCl₃): δ 7.38–7.28 (m, 4H), 7.23–7.18 (m, 1H), 5.30 (s, 1H), 4.77 (s, 1H), 4.60 (s, 1H), 3.32–3.24 (d, 20 Hz, 1H), 3.06–2.98 (d, 20 Hz, 1H), 2.55–2.24 (m, 4H), 1.75 (s, 3H), 1.25 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 146.0, 142.8, 131.4, 128.4, 127.3, 126.8, 121.5, 115.2, 57.5, 51.9, 42.6, 39.2, 24.9, 24.0; HRMS calcd for C₁₆H₂₇N: 228.1752 (M+H), Found 228.1747. Enantiomeric excess was determined by GLC analysis of the derived acetamide. Acetyl-protected 48: ¹H NMR (400 MHz, CDCl₃): δ 7.24–7.14 (m, 5H), 5.60 (s, 1H), 4.92 (s, 1H), 4.77 (s, 1H), 4.20–3.56 (m, 3H), 2.87–2.80 (t, J = 12 Hz, 2H), 2.20–2.16 (d, J = 16 Hz, 1H), 2.03 (s, 3H), 1.63 (s, 3H), 1.54 (s, 3H).

49. The primary amine required for the synthesis of 49 was prepared according to a modified literature procedure.¹⁶ A three-neck 500 mL round-bottom flask, with attached addition funnel and reflux condenser, was charged with cyclohexanecarbonitrile (3.30

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mL, 27.5 mmol), magnesium turnings (2.50 g, 103 mmol), and THF (200 mL). The resulting mixture was allowed to stir at ambient temperature. Methallyl chloride (6.80 mL, 68.7 mmol) and THF (68 mL) were transferred to the addition funnel. Then 10 mL of the methallyl chloride solution was slowly added to the mixture of cyclohexanecarbonitrile with heating (heat gun) to initiate the reaction (during initiation the solution became olive green and was exothermic). At this point the reaction mixture was no longer heated and the remainder of the methallyl chloride solution was added slowly over one hour. The reaction mixture was then refluxed. After 16 h the reaction mixture was cooled to 0 °C and quenched with a saturated aqueous solution of NH₄Cl (100 mL). The aqueous layer was separated and the organic layer was concentrated to remove the majority of the THF. The crude reaction mixture was diluted with Et₂O (100 mL), washed with H₂O (3 x 50 mL), dried (MgSO₄), filtered and concentrated in vacuo.

1-cyclohexyl-3-methyl-1-(2-methyl-allyl)-but-3-enylamine was purified by silica gel chromatography (20:1 CH₂Cl₂:MeOH) to give the primary amine 49 as a yellow oil (0.40 g, 68% yield). ^1H NMR (400 MHz, CDCl₃): δ 4.93–4.91 (dd, J = 2.4, 1.2 Hz, 2H), 4.73–4.71 (dd, J = 2.4, 1.2 Hz, 2H), 2.22–2.18 (d, J = 13.2 Hz, 2H), 2.07–2.04 (d, J = 13.2 Hz, 2H), 1.81 (s, 6H), 1.79–1.6 (m, 2H), 1.40–1.00 (m, 9H). A 50 mL round-bottom flask was charged with 1-cyclohexyl-3-methyl-1-(2-methyl-allyl)-but-3-enylamine (0.50 g, 2.3 mmol), potassium carbonate (0.31 g, 2.3 mmol), DMF (13 mL), and allyl bromide (0.20 mL, 2.3 mmol). The resulting solution was allowed to stir at ambient temperature for 16 h. The reaction mixture was then refluxed. After 16 h the reaction mixture was diluted with Et₂O (50 mL), washed with H₂O (6 x 25 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (20:1 CH₂Cl₂:MeOH) to give amine 50 as a yellow oil (0.40 g, 68% yield). ^1H NMR (400 MHz, CDCl₃): δ 5.96–5.86 (ddd, J = 18.0, 11.6, 6.0 Hz, 1H), 5.22–5.20 (ddd, J = 17.2, 3.6, 2.0 Hz, 1H), 5.17–5.15 (ddd, J = 17.2, 3.6, 2.0 Hz, 1H), 5.04–5.03 (dd, J = 3.6, 2.0 Hz, 1H), 5.02–5.00 (dd, J = 3.6, 2.0 Hz, 1H), 4.85–4.84 (dd, J = 2.4, 1.2 Hz, 2H), 4.75–4.74 (dd, J = 2.4, 1.2 Hz, 2H), 3.24–3.21 (m, 2H), 2.16 (s, 3H), 1.86 (s, 3H), 1.82–1.09 (m, 11H). ^13C NMR (100 MHz, CDCl₃): δ 144.4, 137.7, 114.6, 114.5, 60.6, 45.9, 42.9, 27.6, 27.5, 27.0, 25.5.

50. General procedure for ARCM was followed. Silica gel chromatography with 1:1 Et₂O:hexane was used for purification (56% yield, 0.076 mmol). IR (neat): 2924 (m), 2855 (m), 1734 (w), 1639 (w); ^1H NMR (400 MHz, CDCl₃): δ 5.38 (s, 1H), 4.92 (s, 1H), 4.72 (s, 1H), 3.40–3.21 (dd, J = 41.6, 16.8 Hz, 2H), 2.32–1.98 (m, 4H), 1.84 (s, 3H), 1.66 (s, 3H), 1.48–0.87 (m, 11H); ^13C NMR (100 MHz, CDCl₃): δ 131.3, 127.9, 120.0, 114.6, 42.8, 42.0, 40.7, 36.1, 27.5, 27.4, 27.3, 27.2, 25.5, 24.1; HRMS calcd for C₁₆H₂₇N: 234.2222 (M+H), Found 234.2224. Enantiomeric excess was determined by GLC analysis of the derived acetamide. Acetyl-protected 50: ^1H NMR (400 MHz, CDCl₃): δ 5.46 (s, 1H), 4.73 (s, 1H), 4.65 (s, 1H), 3.82–3.00 (m, 2H), 3.52–3.46 (m, 1H), 2.75–2.65 (m, 1H), 2.20–2.10 (m, 1H), 2.10 (s, 3H), 2.10–2.00 (m, 1H), 1.78 (s, 3H), 1.62 (s, 3H), 1.45–0.82 (m, 11H).
51. Alklylation of ethyl formimidate·HCl was performed according the procedure for the preparation of 2,2-bis-(2-methyl-allyl)-pyrrolidine 14 with the following modification: after the addition of trimethyl borane, 1.2 equiv of Et₃N (distilled from CaH₂) was added (with respect to substrate). The desired primary amine was obtained in 57% yield (6 mmol) after purification with silica gel chromatography (30:1 CH₂Cl₂:MeOH washed with 4% v/v concentrated NH₄OH). IR (neat): 3075 (m), 2936 (s), 1646 (m), 1448 (m), 1130 (w), 904 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.82 (s(br), 2H, R₂C=CH₁H₈), 4.77 (s(br), 2H, R₂C=CH₁H₈), 3.08 (ddd, J = 8.8, 8.8, 4.4, 4.4 Hz, 1H, NCHR₂), 2.13 (dd, J = 13.6, 4.4 Hz, 2H, RCH₂CH₃R), 1.95 (dd, J = 14.3, 9.5 Hz, 2H, RCH₂CH₃R), 1.74 (s, 6H, CH₃), 1.18 (s(br), 2H, NH₂); ¹³C NMR (100 MHz, CDCl₃): δ 143.4, 112.8, 46.8, 46.0, 22.4; HRMS Calcd for C₉H₁₇N (M+H): 140.1439, Found: 140.1436. 3-Methyl-1-(2-methyl-allyl)-but-3-enyl]-amine (500 mg, 3.59 mmol, 1 equiv) was diluted with 36 mL DMF (dried over 4 Å molecular sieves). Potassium carbonate (546 mg, 3.95 mmol, 1.1 equiv) was added followed by 5-bromo-1-pentene (0.47 mL, 3.95 mmol, 1.1 equiv, distilled from CaH₂). The reaction was sealed and stirred at 60 °C for 3 days. At this time, the mixture was diluted with ~40 mL H₂O and an equal portion of CH₂Cl₂. The aqueous layer was separated and washed with three additional portions of CH₂Cl₂. The organic fractions were combined, washed with three 200 mL portions of a saturated aqueous solution of NaCl, dried over Na₂SO₄, filtered and concentrated to an oil. Purification with silica gel chromatography delivered the desired secondary amine [3-methyl-1-(2-methyl-allyl)-but-3-enyl]-pent-4-enyl-amine in 74% yield (549 mg, 2.64 mmol). IR (neat): 3075 (m), 2930 (s), 1652 (m), 1451 (w), 904 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 5.80 (ddt, J = 17.1, 10.1, 6.7 Hz, 1H, RCH=CH₂), 5.01 (ddd, J = 17.1, 3.6, 1.5 Hz, 1H, RCH=CH₂H₈), 4.95 (d(br), J = 10.4 Hz, 1H, RCH=CH₂H₈), 4.82 (s(br), 2H, R₂C=CH₁H₈), 4.75 (s(br), 2H, R₂C=CH₁H₈), 2.75 (p, J = 6.4 Hz, 1H, NCHR₂), 2.61 (t, J = 7.0 Hz, 2H, NCHR₂), 2.17-2.04 (m, 6H), 1.72 (s, 6H, CH₃), 1.56 (p, J = 7.3 Hz, 2H), 1.24 (s(br), 1H, NH); ¹³C NMR (100 MHz, CDCl₃): δ 143.5, 138.5, 114.8, 112.9, 53.1, 47.0, 43.5, 31.6, 29.5, 22.6; HRMS Calcd for C₁₄H₂₃N (M+H): 208.2065, Found: 208.2069. This material was protected under standard conditions (2 equiv CbzCl, 2.2 equiv K₂CO₃, THF, 0 °C to ambient temperature, 1 h) to give 51 in 92% yield. IR (neat): 3087 (w), 2974 (m), 2930 (m), 1690 (s), 1658 (w), 1413 (m), 1274 (m), 1224 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃, 25 C), ~2:3 mixture of amide rotamers: δ 7.37-7.27 (m, 5H, ArH), 5.82 (ddt, J = 16.8, 10.3, 6.6 Hz, 0.4H, RCH=CH₂), 5.75 (ddt, J = 16.8, 10.3, 6.6 Hz, 0.6H, RCH=CH₂), 5.13 (s, 2H, PhCH₂), 5.06-4.94 (m, 2H, RCH=CH₂), 4.76 (s(br), 2H, R₂C=CH₂), 4.71 (s, 1H, R₂C=CH₂), 4.67 (s, 1H, R₂C=CH₂), 4.45 (s(br), 0.6H, NCHR₂), 4.33 (s(br), 0.4H, NCHR₂), 3.12-3.02 (m, 2H, NCHR₂), 2.30-1.97 (m, 7H), 1.75 (s, 3H, CH₃), 1.72-1.59 (m, 1H), 1.65 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 156.4 (br), 142.8, 142.4, 138.2, 138.0, 137.3, 137.0, 128.5 (br), 128.3, 128.1, 127.9, 127.7, 115.1, 115.0, 113.2, 112.9, 67.1, 66.8, 53.3 (br), 43.4 (br), 41.8, 41.5, 31.6 (br), 28.8, 29.3, 28.4, 22.4; HRMS Calcd for C₂₂H₃₁NO₂ (M+H): 342.2433, Found: 342.2434.
52. General procedure for ARCM was followed. Silica gel chromatography with 10:1 hexane:Et$_2$O was used for purification (95% yield, 0.95 mmol). IR (neat): 3062 (w), 3031 (w), 2974 (m), 2930 (m), 1703 (s), 1627 (m), 1501 (m), 1269 (m), 1168 (s), 998 (m) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, 25 °C), ~2:3 mixture of amide rotamers: δ 7.37-7.27 (m, 5H, ArH), 5.54 (dd, $J = 7.3$, 7.3 Hz, 0.4H, R$_2$C=CHR), 5.48 (dd, $J = 8.1$, 8.1 Hz, 0.6H, R$_3$C=CHR), 5.12 (s, 1.2H, PhCH$_2$), 5.09 (ABq, $J = 12.5$ Hz, 0.8H, PhCH$_2$), 4.73-4.64 (m, 2.6H, R$_2$C=CH$_2$, NCHR$_2$), 4.52-4.44 (m, 0.4H, NCHR$_2$), 3.64 (dd, $J = 14.3$, 2.9, 2.9 Hz, 0.4H, NCH$_2$H$_3$R), 3.55 (ddd, $J = 15.0$, 3.3, 3.3 Hz, 0.6H, NCH$_2$H$_3$R), 2.88-2.76 (m, 1H, NCH$_2$H$_3$R), 2.36-2.22 (m, 2H), 2.13 (dd, $J = 13.9$, 5.9 Hz, 1H), 2.08-1.91 (m, 3H), 1.87-1.79 (m, 1H), 1.77 (s, 3H, CH$_3$), 1.66 (s, 1.8H, CH$_3$), 1.63 (s, 1.2H, CH$_3$), 1.53-1.44 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 156.9, 156.2, 142.9, 142.3, 137.5, 137.2, 135.5, 134.9, 128.5, 127.9, 127.8, 127.6, 126.3, 113.3, 112.8, 66.83, 66.81, 52.7, 52.6, 43.3, 42.35, 42.26, 42.1, 36.7, 36.5, 29.9, 29.1, 27.9, 26.9, 26.5, 24.3, 23.8, 22.30, 22.27; HRMS Calcd for C$_{20}$H$_{25}$NO$_2$ (M+Na): 336.1939, Found: 336.1927. Enantiomeric excess was determined by GLC analysis of the derived trifluoroacetamide, obtained by acylation of 54. See below for details.

54. A 15 mL two-necked flask containing a teflon stirbar was charged with ~11 mg metallic Na (0.6 mmol, 6 equiv., washed with hexanes). The flask was then fitted with a Dewar condenser and purged with N$_2$. After cooling the flask and condenser to −78 °C, ~4 mL of NH$_3$ (0.03 M) was condensed onto the metallic Na with stirring to produce a deep blue solution. A solution of Cbz-protected azocine 52 (33.1 mg, 0.106 mmol) and 60 µL of t-BuOH in ~1 mL of Et$_2$O was rapidly added to the stirring solution via cannula. An additional 1 mL of Et$_2$O was used for complete transfer. The resulting mixture should remain deep blue. On occasion, the color changed to white or pale yellow and a second portion of metallic Na was added to again produce a deep blue solution. The reaction was allowed to stir for 5 min at −78 °C. At this time, solid NH$_4$Cl was added in small portions until the blue color dissipated. The mixture was then allowed to gradually warm to ambient temp (without stirring). After bubbling (of NH$_3$) had ceased, the mixture was transferred to a separatory funnel with ~15 mL CH$_2$Cl$_2$ and ~10 mL H$_2$O. The aqueous layer was washed 2x with 10 mL portions of CH$_2$Cl$_2$. The combined organic extracts were dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Analysis by $^1$H NMR indicated >90% conversion of starting material. Purification by silica gel chromatography in 30:1 CH$_2$Cl$_2$:MeOH washed with 2% v/v concentrated NH$_3$OH (Dragendorff’s reagent for TLC visualization) afforded 17.5 mg (0.098 mmol, 88%) of pure azocine 54. IR (neat): 3367 (w), 3075 (w), 2920 (s), 2851 (m), 1648 (w), 1443 (m), 1375 (w), 1133 (m), 903 (m) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 5.43 (dd, $J = 8.1$, 8.1
Enantiomeric excess determination of 52. Deprotection of 52 was performed as reported above. Standard conditions (pyridine, TFAA, CH₂Cl₂) were then employed for the synthesis of trifluoroacetamide-protected 54, obtained in 84% yield after silica gel chromatography (9:1 hexanes:EtOAc). TFA-protected 54: ¹H NMR (400 MHz, CDCl₃, 25 °C), 1:4 mixture of amide rotamers: δ 5.58 (dd, J = 8.4, 8.4 Hz, 0.8H, R₂C=CHR), 5.54 (dd, J = 7.7, 7.7 Hz, 0.2H, R₂C=CHR), 5.05 (s(br), 0.2H, NCHR₂), 4.87 (s(br), 0.8H, R₂C=CH₃H₃), 4.77 (s(br), 1H, R₂C=CH₃H₃), 4.66 (s(br), 0.2H, R₂C=CH₃H₃), 4.12 (s(br), 0.8H, NCHR₂), 3.87 (d(br), J = 13.9 Hz, 0.8H, NCHR₂H₂), 3.71 (d(br), J = 16.5 Hz, 0.2H, NCHR₂H₂), 3.12 (m, 0.2H, NCHR₂H₂), 3.04 (dd, J = 12.8, 12.8 Hz, 0.8H, NCHR₂H₂), 2.42 (dd, 1H), 2.36-1.58 (m, 7H), 1.76 (s, 3H, CH₃), 1.69 (s, 3H, CH₃).

55. A round-bottomed flask was charged with 36.6 mg (0.117 mmol) of 52 in 1.2 mL CH₂Cl₂. The resulting mixture was cooled to 0 °C in an ice bath. mCPBA, 21.1 mg (0.123 mmol, commercial reagent washed with pH 7 buffer and dried in vacuo) was added in one portion to the stirring solution and the reaction was then allowed to warm to ambient temperature. After 1 h, TLC analysis indicated that most of the starting material had been consumed. The reaction was then diluted with CH₂Cl₂, ~5 mL, and transferred to a separatory funnel. The solution was washed with ~5 mL of a 20% wt/wt aqueous solution of NaHSO₃ followed by ~5 mL of a 10% wt/wt aqueous solution of NaHCO₃. The organic phase was separated, dried over Na₂SO₄, filtered and concentrated in vacuo to a colorless oil. ¹H NMR analysis of the unpurified reaction mixture indicated ~95% conversion of the starting material. The product was purified by silica gel chromatography with 2:1 hexane:Et₂O as the eluent. Cbz-protected azocine oxirane 55 was thus obtained in 82% yield (31.7 mg, 0.096 mmol). IR (neat): 2932(m), 1698 (s), 1480 (m), 1424 (m), 1338 (m), 1269 (m), 1126 (m), 1058 (w) cm⁻¹; ¹H NMR (400 MHz, CDCl₃, 25 °C), 2:3 mixture of amide rotamers: δ 7.37-7.28 (m, 5H, ArH), 5.16 (ABq, J = 12.5 Hz, 1.2H, PhCH₂O), 5.11 (s, 0.8H, PhCH₂O), 4.79-4.72 (m, 0.6H, NCHR₂), 4.72 (s(br), 1H, R₂C=CH₃H₃), 4.62 (d, J = 8.1 Hz, 1H, R₂C=CH₃H₃), 4.47 (ddd, J = 17.9,
9.5, 4.8 Hz, 0.4H, NCHR$_2$), 3.74 (d(br), $J = 14.3$ Hz, 0.4H, NCH$_A$H$_B$R), 3.63 (d (br), $J = 15.0$ Hz, 0.6H, NCH$_B$H$_A$R), 2.74-2.58 (m, 2H), 2.34-1.17 (m, ~8H), 1.76 (s, 1.8H, CH$_3$), 1.61 (s, 1.2H, CH$_3$), 1.33 (s, 1.2 H, CH$_3$), 1.23 (s, 1.2H, CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 156.6, 156.0, 142.4, 141.7, 137.2, 136.6, 128.6, 128.54, 128.48, 128.3, 128.0, 127.9, 113.9, 113.4, 67.4, 67.1, 62.4, 62.2, 59.5, 59.2, 51.0, 50.7, 43.7, 42.9, 42.2. 42.0, 37.3, 37.0, 30.1, 29.9, 23.8, 22.8, 22.24, 22.21, 22.19, 21.95; HRMS Calcd for C$_{20}$H$_{27}$NO$_3$ (M+Na): 352.1889, Found: 352.1879.

56. Deprotection of 55 was performed according to the procedure for the preparation of 54. The derived unprotected azocine oxirane was obtained in 77% yield after silica gel chromatography in 30:1 CH$_2$Cl$_2$ washed with 2% v/v concentrated NH$_2$OH (Dragendorff’s reagent for TLC visualization). IR (neat): 3364 (w), 3081 (w), 2924 (s), 2855 (m), 1646 (w), 1470 (m), 1382 (m), 1143 (m), 897 (m) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.85 (s(br), 1H, R$_2$C=CH$_A$H$_B$), 4.75 (s(br), 1H, R$_2$C=CH$_A$H$_B$), 3.04 (ddd, $J = 14.6$, 3.7, 3.3 Hz, 1H, NCH), 2.91-2.85 (m, 1H, NCH), 2.72 (dd, $J = 9.9$, 3.7 Hz, 1H, ROCHR), 2.47 (dddd, $J = 11.4$, 11.4, 2.6, 2.6 Hz, 1H, NCH), 2.16-2.00 (m, 3H), 1.86 (d, $J = 13.9$ Hz, 1H), 1.73 (s, 3H, CH$_3$), 1.66-1.43 (m, 5H), 1.38 (s, 3H, CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 142.9, 113.7, 63.4, 59.3, 54.0, 45.4, 42.4, 27.2, 25.7, 25.7, 22.7, 22.2; HRMS Calcd for C$_{12}$H$_{21}$NO (M+H): 196.1701, Found: 196.1701. The secondary amine was subjected to transannular ring-closure according to the following method: A 1-dram vial was charged with 8.4 mg (43 µmol) of the unprotected azocine oxirane and 0.5 mL EtOH (distilled from CaH$_2$). The vial was sealed and the reaction was stirred for 6 h at 75 ºC. After cooling to ambient temperature, the solution was concentrated in vacuo. $^1$H NMR analysis of the unpurified mixture indicated ~90% conversion to the desired bicycle. Subsequent purification through a short plug of silica gel with 4:1 CH$_2$Cl$_2$:MeOH washed with 2% v/v concentrated NH$_4$OH as an eluent (Dragendorff’s reagent for TLC visualization) delivered 8.1 mg (41 µmol, 72% yield) of 56 as a white solid. Crystals sufficient for x-ray analysis were obtained from heptane. See below for data. IR (neat): 3364 (s), 3087 (m), 2968 (s), 1652 (w), 1464 (m), 1388 (m), 1281 (w), 1149 (m), 897 (m) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.76 (s(br), 1H, R$_2$C=CH$_A$H$_B$), 4.73 (s(br), 1H, R$_2$C=CH$_A$H$_B$), 2.96 (ddd, $J = 8.4$, 8.4, 5.1 Hz, 1H, NCH$_A$H$_B$R), 2.79 (s(br), 1H, NCH(CH$_2$C(Me)=CH$_2$)R), 2.62 (s(br), 1H, NCH(C(Me)(R)OH)R), 2.39 (dd, $J = 13.9$, 5.5 Hz, 1H, RCH$_A$H$_B$C(Me)=CH$_2$), 2.29 (s(br), 1H, NCH$_A$H$_B$R), 2.17 (dd, $J = 13.6$, 8.1 Hz, 1H, NCH(R)C=CH$_A$H$_B$R), 2.09 (dd, $J = 14.6$, 8.8 Hz, 1H, RCH$_A$H$_B$C(Me)=CH$_2$), 2.04-1.92 (m, 1H), 1.85 (dd, $J = 13.9$, 7.3 Hz, 1H, NCH(R)C=CH$_A$H$_B$R), 1.74 (s, 3H, R$_2$CCCH$_3$), 1.68-1.57 (m, 1H), 1.26 (s, 3H, R$_2$C(OH)CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 143.6, 112.1, 77.3, 74.8, 57.2, 50.5, 47.0, 43.1, 27.2, 25.0, 23.0, 20.8; HRMS Calcd for C$_{12}$H$_{21}$NO (M+H): 196.1701, Found: 196.1704; [α]$_D$ +25.8 (c = 0.25, CHCl$_3$).
Trifluoroacetamide 57 was prepared according to a modified sequence reported by Blechert and coworkers for a related unsaturated amine.17

i. Oxidation of 2-butyne-1-ol was accomplished according to published procedure18 with some modification. To a rapidly stirring solution of 2-butyne-1-ol (1.15 mL, 16.0 mmol) in 32 mL of CH₂Cl₂ and 32 mL of an aqueous solution of NaHCO₃ (0.5 M) and K₂CO₃ (0.05 M) was added TBACl (443 mg, 1.60 mmol) followed by TEMPO (250 mg, 1.60 mmol). To the resulting light orange mixture was added NCS (3.43 g, 25.6 mmol, recrystallized from toluene) in one portion. The mixture was then stirred for 6 h. At this time, the aqueous layer was separated and washed with two 30 mL portions of CH₂Cl₂. The combined organic fractions were washed with a saturated aqueous solution of NaCl (150 mL), dried over MgSO₄ and filtered. A small aliquot (~3 mL) of this solution was carefully concentrated under reduced pressure. Analysis by ¹H NMR spectroscopy revealed >98% conversion of the alcohol to the desired product. ¹H NMR (400 MHz, CDCl₃): δ 9.15 (s(br), 1H, RCH=O), 2.07 (s(br), 3H, CH₃). The unpurified solution of aldehyde was directly subjected to imine formation: MgSO₄ was added followed by 1 equiv. of allyl amine (assuming quantitative yield for the oxidation, 1.20 mL, 16.0 mmol). The resulting mixture was stirred for 6 h, filtered, and concentrated in vacuo. ¹H NMR analysis of the unpurified reaction indicated complete consumption of the aldehyde. Kugelrohr distillation of the reaction mixture (high vacuum, ~60-80 °C) delivered 0.97 g of the imine i as a pale orange oil. ¹H NMR (400 MHz, CDCl₃), ~1:1 mixture of cis and trans isomers: δ 7.49-7.46 (m, 1H, N=CHR), 6.06-5.91 (m, 1H, RCH=CH₂), 5.23-5.10 (m, 2H, RCH=CH₂), 4.24 (m, 1H, NCH₂), 4.11 (m, 1H, NCH₂), 2.04 (d(br), J = 1.8 Hz, 1.5H, CH₃), 1.99 (d(br), J = 1.8 Hz, 1.5H, CH₃).

ii. A modified procedure for the alkylation of imine i with the requisite propargyl lithium was adapted from the literature.19 Propyne (~2 mL) was condensed into 5 mL of THF in a graduated 2-neck tube at −78 °C. The solution was made homogeneous by gentle shaking of the tube. The resulting mixture was then transferred via cannula to a 100 mL round-bottom flask containing 30 mL of THF at −78 °C. A solution of nBuLi (1.59 M in hexanes, 8.50 mL, 13.5 mmol) was then added. The resulting milky solution was stirred at −78 °C for 30 min. A solution of imine i (725 mg, 6.77 mmol) in ~3 mL of THF was added via cannula (~2 mL of THF to complete the transfer). Subsequently, BF₃OEt₂ (1.71 mL, 13.5 mmol, distilled from CaH₂) was added dropwise via syringe.

The resulting mixture, while stirring for an additional 30 min at −78 °C, turned pale yellow. It was then allowed to warm to ambient temperature (~30 min). ~10 mL of a 10% wt/wt aqueous solution of NaOH was then added and the resulting mixture was stirred rapidly for ~15 min. The now orange solution was poured into a separatory funnel and diluted with H2O. The aqueous phase was washed 3x with 30 mL portions of Et2O. The combined organic fractions were washed with a saturated aqueous solution of NaCl, dried over Na2SO4, filtered and concentrated. Purification with silica gel chromatography (30:1 CH2Cl2 washed with 2% v/v concentrated NH4OH) gave 571 mg (3.87 mmol) of the desired amine ii in 67% yield. 1H NMR (400 MHz, CDCl3): δ 5.91 (ddt, J = 16.1, 10.3, 5.9 Hz, 1H, RCH=CH2), 5.23 (ddd, J = 17.2, 3.3, 1.5 Hz, 1H, RCH=CH2H), 5.11 (ddd, J = 10.3, 2.9, 1.1 Hz, 1H, RCH=CH2H), 4.27 (p, J = 2.2 Hz, 1H, NCHR2), 3.36 (dt, J = 5.9, 1.5 Hz, 2H, NCH2R), 1.85 (d, J = 2.2 Hz, 6H, CH3), 1.43 (s(br), 1H, NH).

iii. Metallic Na (~140 mg, 8.1 mmol, 6 equiv., washed with hexanes) was placed in a 50 mL two-necked flask containing a teflon stirbar. The flask was then fitted with a Dewar condenser and purged with N2. After cooling the flask and condenser to −78 °C, ~45 mL of NH3 (0.03 M with respect to amine ii) was condensed onto the metallic Na with stirring to produce a deep blue solution. A solution of amine ii (198 mg, 1.34 mmol) and 772 μL of t-BuOH in ~4 mL of Et2O was rapidly added to the stirring solution via cannula. An additional 1 mL of Et2O was used for complete transfer. The resulting mixture should remain deep blue. If the color dissipates to white or pale yellow, a second portion of metallic Na was added. The reaction was stirred for 45 min at −55 °C. At this time, the blue color disappears (or solid NH4Cl was added in small portions until the blue color dissipates). The mixture was diluted with CH2Cl2 (~15 mL) and then allowed to gradually warm to ambient temp (without stirring). After bubbling of (NH3) had ceased, the mixture was transferred into a separatory funnel with ~5 mL CH2Cl2 and ~20 mL H2O. The aqueous layer was washed 3x with 20 mL portions of CH2Cl2. The combined organic extracts were dried over Na2SO4, filtered and concentrated under reduced pressure to give an orange oil. 1H NMR analysis indicated that the unpurified product was contaminated with ~20 % of the over-reduced propyl amine. Purification by silica gel chromatography (4:1 CH2Cl2:Et2O washed with 2% v/v concentrated NH4OH, Dragendorff’s reagent for TLC visualization) gave 99.4 mg (0.657 mmol) of the desired unsaturated amine iii (50% yield). 1H NMR (400 MHz, CDCl3): δ 5.90 (ddt, J = 16.1, 10.3, 5.9 Hz, 1H, RCH=CH2), 5.57 (ddd, J = 15.0, 12.8, 6.2 Hz, 2H, RCH=CHR), 5.37 (ddq, J = 15.4, 7.7, 1.5 Hz, 2H, RCH=CHR), 5.14 (ddd, J = 17.2, 3.3, 1.5 Hz, 1H, RCH=CH2H), 5.06 (ddd, J = 10.3, 2.9, 1.1 Hz, 1H, RCH=CH2H), 3.54 (t, J = 7.7 Hz, 1H, NCHR2), 3.18 (dt, J = 5.9, 1.5 Hz, 2H, NCH2R), 1.68 (dd, J = 6.6, 1.5 Hz, 6H, CH3), 1.13 (s(br), 1H, NH).

57. To a −15 °C 0.1 M solution of amine iii (97 mg, 0.64 mmol) in pyridine:CH2Cl2 (1:3 v/v) was slowly added trifluoroacetic anhydride (0.18 mL, 1.3 mmol) dropwise. The reaction was stirred at ambient temperature for 2 h, at which time TLC analysis indicated that no starting material remained. The solution was then concentrated in vacuo, and the resulting oil was redissolved in CH2Cl2 (~2 mL). Silica gel was then added until a thick slurry formed. A purge of N2, followed by reduced pressure lead to the removal of solvent. The mixture, now absorbed onto silica gel, was transferred to the top of a silica gel column packed with 15:1 hexanes:EtOAc. The desired product, TFA-protected amine 57 was obtained in 65% yield (101 mg, 0.41 mmol) after eluting
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with 15:1 hexanes:EtOAc (anisaldehyde stain for TLC visualization). \(^1\)H NMR (400 MHz, CDCl\(_3\), 25 °C), ~1:1 mixture of amide rotamers: \(\delta\) 5.83-5.72 (m, 1H, RCH=CH\(_2\)), 5.71-5.58 (m, 3H, RCH=CHR), 5.49 (dd, J = 15.4, 5.5 Hz, 1H, RCH=CHR), 5.22-5.11 (m, 2H, RCH=CH\(_2\)), 5.00-4.95 (m, 1H, NCH\(_2\)R), 3.99 (d, J = 5.1Hz, 1H, NCH\(_2\)R), 3.89 (d, J = 5.5 Hz, 1H, NCH\(_2\)R), 1.74-1.70 (m, 3H, CH\(_3\)) ; HRMS Calcd for C\(_{12}\)H\(_{16}\)F\(_3\)NO (M+Na): 270.1082, Found: 270.1082.

\[\text{TFA} \quad \text{5 mol \% 2a} \quad \text{C}_6\text{H}_6, 22 °C, 24 h \quad \text{TFA} \]

**58.** General procedure for ARCM was followed. Silica gel chromatography with 9:1 hexane:Et\(_2\)O was used for purification (70% yield, 0.045 mmol). IR (neat): 2924 (w), 2879 (w), 1714 (s), 1463 (m), 1230 (s), 1213 (s), 1146 (s), 962 (w) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\), 25 °C), ~1:4 mixture of amide rotamers: \(\delta\) 5.87-5.64 (m, 3H), 5.41 (dddd, J = 15.4, 7.3, 3.3, 1.5 Hz, 0.8H), 5.37-5.30 (m, 0.2H), 5.25 (s(br), 1H, NC\(_H\)R\(_2\)), 4.43 (ABq, J = 15.0 Hz, 1.6H, NCH\(_2\)R), 4.34 (ABq, J = 17.6 Hz, 0.4H, NCH\(_2\)R), 1.70 (dd, J = 6.6, 1.8 Hz, 3H, CH\(_3\)), 5.49 (dd, J = 15.4, 5.5 Hz, 1H, RCH=CHR), 5.22-5.11 (m, 2H, RCH=CH\(_2\)), 5.00-4.95 (m, 1H, NCH\(_2\)R), 3.99 (d, J = 5.1Hz, 1H, NCH\(_2\)R), 3.89 (d, J = 5.5 Hz, 1H, NCH\(_2\)R), 1.74-1.70 (m, 3H, CH\(_3\)) ; \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 155.3 (q, J = 36.4 Hz), 130.0, 129.8, 129.2, 128.94, 128.91, 128.6, 127.3, 124.13, 124.11, 123.6, 116.3 (q, J = 287 Hz), 67.3, 66.45, 66.42, 54.8, 52.9 (q, J = 3.8 Hz), 31.7, 28.1, 22.8, 22.6, 17.8, 17.7, 14.2; HRMS Calcd for C\(_9\)H\(_{10}\)F\(_3\)NO (M+Na): 228.0612, Found: 228.0608; \([\alpha]_D^{20} = -86.8 (c = 0.5, \text{CHCl}_3)\).

\[\text{TFA} \quad \text{K}_2\text{CO}_3, \text{THF/MeOH} \quad \text{TFA} \]

**59.** Trifluoroacetamide 58 (13.6 mg, 0.066 mmol) was combined with 2 mL of a K\(_2\)CO\(_3\) solution (10% in 5:2 MeOH:H\(_2\)O). The mixture was allowed to stir for 15 h and then transferred to a separatory funnel with CH\(_2\)Cl\(_2\) and H\(_2\)O. The aqueous layer was washed three times with 2 mL portions of CH\(_2\)Cl\(_2\). The combined organic fractions were dried over Na\(_2\)SO\(_4\), filtered, and carefully concentrated with a stream of N\(_2\) to give amine 59 (3.7 mg, 0.032 mmol, 50% yield) as an oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 5.87 (d(br), J = 4.8 Hz, 1H, RCH=CHR), 5.71 (s(br), 1H, RCH=CHR), 5.60 (ddd, J = 14.3, 12.8, 6.2 Hz, 1H, RCH=CHR), 5.40 (ddd, J = 15.0, 7.7, 1.5 Hz, 1H, RCH=CHR), 4.43 (s(br), 1H, NCH), 3.81 (s(br), 1H, NCH), 3.73 (s(br), 1H, NCH), 1.77 (s(br), 1H, NH), 1.68 (dd, J = 6.2, 1.1 Hz, 3H, RCH\(_3\)).
60. The synthesis of 60 was accomplished in a sequence related to that for the preparation of 57.

iv. The procedure for the preparation of i was followed (see above) with the following modifications: for the oxidation of 2-butyn-1-ol, 2.5 mol % of TEMPO and 5 mol % TBACl was used. $^1$H NMR (400 MHz, CDCl$_3$), δ 1:1 mixture of cis and trans isomers: δ 7.55 (s(br), 1H, N=CHR), 7.33-7.21 (m, 5H, ArH), 4.81 (s(br), 1H, NCH$_2$Ph), 4.66 (s(br), 1H, NCH$_2$Ph), 2.07 (s(br), 1.5H, CH$_3$), 1.99 (s(br), 1.5H, CH$_3$).

v. The procedure for the preparation of ii was followed (see above). Imine iv was directly subjected to alkylation without purification. Benzyl amine v was obtained in 40% yield over three steps after purification with silica gel chromatography (2:1 hexane:Et$_2$O washed with 2% v/v concentrated NH$_4$OH as an eluent). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.37-7.21 (m, 5H, ArH), 4.24 (dq, J = 4.4, 2.2 Hz, 1H, NCHR$_2$), 3.90 (s(br), 2H, PhCH$_2$), 1.85 (t(br), J = 2.2 Hz, 6H, CH$_3$).

vi. The HCl salt of v was prepared as follows: through a solution of v (2.0 g) in ~50 mL dry Et$_2$O was bubbled HCl gas for ~1 min. A gooey solid immediately precipitated. The solvent was then removed in vacuo to give 2.07 g of an orange foam (88% yield). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.52-25 (m, 5H, ArH), 4.43 (s(br), 1H, NCHR$_2$), 4.07 (s, 2H, PhCH$_2$), 1.85 (s(br), 6H, CH$_3$). This material was then transferred to a round-bottom flask and diluted with 1:1 mixture of MeOH:CHCl$_3$ to make a 0.5 M solution. A 37% aqueous solution of formaldehyde (0.73 mL) was added, followed by 2.86 mL of allyl tributyl stannane. The reaction was sealed and stirred for 14 h. The mixture was then poured into a separatory funnel and diluted with ~20 mL of a 1 M aqueous HCl solution. The organic layer was separated, washed with a saturated aqueous solution of NaHCO$_3$, dried with Na$_2$SO$_4$, filtered and concentrated. Silica gel chromatography (15:1 hexanes:Et$_2$O) gave 1.58 g of vi as a clear oil (72% yield). Note: for more polar amines, the workup described in the literature$^{20}$ is convenient for the facile removal of the stannane byproducts (before chromatography). In this case, unexpectedly, the HCl salt of vi is not water soluble.

vi. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.37-7.20 (m, 5H, ArH), 5.80 (ddd, J = 16.8, 9.9, 6.6, 6.6 Hz, 1H, RCH=CH$_2$), 5.03 (d(br), J = 17.2 Hz, 1H, RCH=CH$_2$H$_3$), 4.97 (d(br), J = 10.3 Hz, 1H, RCH=CH$_2$H$_3$), 4.32 (p, J = 2.2 Hz, 1H, NCHR$_2$), 3.67 (s, 2H, PhCH$_2$), 2.66 (t, J = 7.32 Hz, 2H, NCH$_2$R), 2.25 (dd, J = 14.6, 6.6 Hz, 2H, NCH$_2$CH$_2$R), 1.85 (d, J = 2.2 Hz, 6H, CH$_3$).

60. Into a two-neck round-bottomed flask, equipped with a Dewar condenser (at –78 °C), was condensed ~50 mL of NH$_3$ at –60 °C. Through the side arm, 555 mg of

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metallic Na (32.6 mmol) was added in one portion. To the stirring deep blue solution was then added a solution of amine vi (410 mg, 1.63 mmol, in two portions of 2 mL THF) via cannula. The blue color did not dissipate as the reaction was stirred for 1 h at ~60 °C. At this time, solid NH₄Cl was added until the mixture became colorless. Et₂O, ~5 mL, was added, and the mixture was allowed to warm to ambient temperature. The solution was poured into a separatory funnel and diluted with ~10 mL Et₂O and 15 mL H₂O. The aqueous layer was washed two times with 15 mL portions of Et₂O. The combined organic fractions were washed with two 30 mL portions of a saturated aqueous solution of NaCl, dried over Na₂SO₄, filtered and concentrated in vacuo. The desired product, 60, was obtained in 92% yield (381 mg) after silica gel chromatography (30:1 hexanes:EtoAc) for purification (83% yield, 0.174 mmol). ¹H NMR (400 MHz, CDCl₃): δ 7.35-7.19 (m, 5H, ArH), 5.76 (ddt, J = 17.2, 10.3, 7.0 Hz, 1H, RCH=CH₂), 5.54-5.43 (m, 2H, RCH=CHR), 5.48 (dd, J = 5.1, 5.1 Hz, 2H, RCH=CHR), 4.99-4.91 (m, 2H, RCH=CH₂), 3.57-3.55 (m, 1H, NCHR₂), 3.58 (s, 2H, PhCH₂), 2.50 (t, J = 7.5 Hz, 2H, NCH₂R), 2.15 (dd(br), J = 13.9, 7.0 Hz, 2H, NCH₂CH₂R), 1.7 (dd, J = 4.8, 0.7 Hz, 6H, CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 141.2, 137.5, 131.5, 128.7, 128.2, 127.7, 126.6, 115.2, 64.2, 54.5, 49.6, 32.6, 18.1; HRMS Calcd for C₁₃H₂₅N (M+H): 256.2065, Found: 256.2065.

61. General procedure for ARCM was followed. ¹H NMR analysis of the unpurified reaction mixture indicated complete conversion of the starting material to the desired product (90%) and ~10% conversion to unidentified byproducts. Silica gel chromatography with 15:1 hexane:EtoAc was used for purification (83% yield, 0.174 mmol). ¹H NMR (400 MHz, CDCl₃): δ 7.34-7.19 (m, 5H, ArH), 5.75 (ddd, J = 9.9, 4.8, 2.4, 2.4 Hz, 1H, RCH=CHR), 5.62 (ddd, J = 15.7, 12.8, 7.0 Hz, 1H, RCH=CHR), 5.49-5.39 (m, 2H, RCH=CHR), 3.98 (d, J = 13.6 Hz, 1H, PhCH₃H₃B), 3.37 (ddd, J = 8.4, 2.6, 2.6 Hz, 1H, NCHR₂), 3.24 (d, J = 13.6 Hz, 1H, PhCH₃H₃B), 2.81 (ddd, J = 11.4, 4.4, 4.4 Hz, 1H, NCH₂H₃R), 2.25 (ddd, J = 11.4, 8.4, 4.4 Hz, 1H, NCH₂H₃R), 2.18-2.08 (m, 1H, NCH₂CH₂H₃R), 2.02-1.93 (m, 1H, NCH₂CH₂H₃R), 1.71 (dd, J = 6.2, 1.5 Hz, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 139.7, 132.8, 129.8, 129.1, 128.26, 128.23, 126.8, 125.3, 63.4, 58.8, 46.7, 26.0, 18.0; Anal. Calcd. for C₁₅H₁₀N: C, 84.46; H, 8.98; Found: C, 84.59; H, 9.27; [α]D = 180.9 (c = 1, CHCl₃).

(R)-Conine. A test tube containing a teflon stirbar was charged with a solution of amine 61 (105 mg, 0.491 mmol) in 2.46 mL C₆H₆ and Wilkinson’s catalyst (45.4 mg, 0.049 mmol, 10 mol %, prepared according to literature procedure) under an inert atmosphere.

The container was then placed inside high pressure apparatus, which was subsequently sealed and pressurized to 400 psi H\(_2\). After stirring for 48 h, the reaction vessel was removed from the bomb and the solution was concentrated in vacuo. Analysis by \(^1\)H NMR indicated that the starting material had been consumed. Benzyl protected coniine was purified by silica gel chromatography in 10:1 hexane:EtOAc washed with 2% v/v concentrated NH\(_4\)OH (90.9 mg, 0.419 mmol, 85% yield of a pale yellow oil). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.34-7.20 (m, 5H, Ar\(\text{H}\)), 3.97 (d, \(J = 13.6\) Hz, 1H, PhCH\(_{A}\)H\(_{B}\)), 3.22 (d, \(J = 13.6\) Hz, 1H, PhCH\(_{A}\)H\(_{B}\)), 2.73 (ddd, \(J = 11.7, 3.7, 3.7\) Hz, 1H, NCH\(_{2}\)), 2.31-2.25 (m, 1H, NCH\(_{2}\)), 2.05-1.99 (m, 1H, NCH\(_{2}\)), 1.69-1.26 (m, 10H), 0.91 (dd, \(J = 7.3, 7.3\) Hz, 3H, CH\(_3\))\(^3\); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 140.2, 129.1, 128.2, 126.7, 60.8, 57.7, 51.8, 34.3, 30.4, 25.3, 23.9, 24.8; HRMS Calcd for C\(_{15}\)H\(_{23}\)N (M+H): 218.1909, Found: 218.1905; \([\alpha]_D^\circ\) –65.7 (c = 1, CHCl\(_3\)). Benzyl deprotection was accomplished through hydrogenolysis as follows: A test-tube equipped with a teflon stirbar was charged with 55.4 mg (0.255 mmol) of benzyl-protected coniine and 11.1 mg of Pd(OH)\(_2\) on carbon (20% by wt) in 1.6 mL EtOH (distilled from CaH\(_2\)). The container was placed inside high pressure apparatus, which was subsequently sealed and pressurized to 400 psi H\(_2\). After stirring for 48 h (TLC analysis after 24 h indicated that starting material remained), the reaction vessel was removed from the bomb and the solution was filtered through celite (MeOH used to complete the transfer). After concentration to ~ 100 \(\mu\)L with a gentle purge of N\(_2\), the mixture was purified by silica gel chromatography in 10:1 CH\(_2\)Cl\(_2\):MeOH washed with 2% v/v concentrated NH\(_4\)OH to give coniine (27.5 mg, 0.216 mmol) in 84% yield. IR (neat): 3277 (w), 2937 (s), 2851 (m), 1443 (m), 1332 (m), 1128 (m), 751 (m) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 3.06 (dddd, \(J = 11.7, 4.0, 2.2, 1.8\) Hz, 1H, NCH\(_{A}\)H\(_{B}\)), 2.61 (ddd, \(J = 11.7, 11.7, 2.6\) Hz, 1H, NCH\(_{A}\)H\(_{B}\)), 2.47-2.41 (m, 1H, NCHR\(_2\)), 1.78-1.01 (m, 11H), 0.90 (dd, \(J = 7.0, 7.0\) Hz, 3H, CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 56.8, 47.4, 39.8, 33.1, 26.8, 25.1, 19.2, 14.4; HRMS Calcd for C\(_8\)H\(_{17}\)N (M+H): 128.1439, Found: 128.1434; \([\alpha]_D^\circ\) –5.5 (c = 1, CHCl\(_3\)), literature\(^{22}\) \([\alpha]_D^{20}\) –8.1 (c = 2, CHCl\(_3\)).