Supporting Information for:

Stereocontrolled Synthesis of Vicinally Functionalized Piperidines by Nucleophilic
β-Addition of Alkylolithiums to α-Aryl Substituted Piperidine Enecarbamates

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Contents:
General Remarks .................................................................................................................. S-2
General Procedures .............................................................................................................. S-2
Carbolithiation/Substitution of Enecarbamates ................................................................... S-4
Full Reaction Coordinate of the Carbolithiation Process .................................................. S-46
Computational Details ........................................................................................................ S-46
References .......................................................................................................................... S-48
**General Remarks**

All experiments involving organolithium reagents were carried out under an inert atmosphere of argon or nitrogen using freshly distilled solvents. Et₂O and THF were distilled either from sodium benzophenone ketyl or predried by degassing with argon for 60 min and passed through activated alumina columns. All electrophile reagents that were not newly purchased from commercial suppliers were distilled immediately before use. TMEDA was purified by short path distillation over CaH₂. Column chromatography was performed on silica gel (60Å, 230-400 mesh). Thin-layer chromatography (TLC) was performed using Silicycle SiliaplateTM glass backed plates (250 μm thickness, 60 Å porosity, F-254 indicator) and visualized using UV (254 nm) or KMnO₄ stain. Unless otherwise indicated, ¹H, ¹³C, and DEPT-135 NMR, COSY 45, HMQC, and NOESY spectra were acquired using C₆D₆ as solvent at room temperature. Chemical shifts are quoted in parts per million (ppm).

IR spectra were recorded on a Bruker Alpha FT-IR spectrophotometer using a diamond ATR accessory and are reported in frequency of absorption (cm⁻¹). HRMS-EI⁺ data were obtained using either electrospray ionization (ESI) or electron impact (EI) techniques. High-resolution ESI was obtained on an LTQ-FT (ion trap; analyzed using Excalibur). High resolution EI was obtained on an Autospec (magnetic sector; analyzed using MassLynx). Melting points were measured with MEL-TEMP II (LABORATORY DEVICE INC.) and are reported in degree Celsius (°C).

**Synthesis of Starting materials**

N-Boc-piperidine was prepared according to a literature procedure reported by O’Brien.¹ It is also commercially available.

N-Boc-2-methylpiperidine was synthesized as previously reported.²

All α-aryl enecarbamates were synthesized using the method of Occhiato.³

The substituted lactam precursors used in the synthesis of α-aryl enecarbamates were synthesized by Ru-catalyzed α-oxidation of the saturated piperidine.⁴

The Boc-protected cis-2,4-dimethylpiperidine precursor to cis-7m was prepared using the method of Baudoin.⁵

**General Procedures**

**General Procedure A: Carbolithiation followed by direct trapping with the electrophile**

To an oven-dried, septum-capped, round-bottomed flask equipped with a stir bar was added a solution of the 2-substituted enecarbamate (1.0 equiv) in THF or Et₂O (5 mL) under argon or nitrogen, in the presence or absence of TMEDA[note1]. The mixture was cooled to −78 °C and the organolithium (2 – 3 equiv) was added slowly. After 5 min at this temperature, the solution was transferred to a bath at 0 °C
and stirred for 10 to 30 min. After complete consumption of the starting material (as judged by LCMS and TLC monitoring), the solution was cooled to $-78 \, ^\circ C$[note 2] and quenched with the desired electrophile ($\sim 1.2$ to 3 equiv). After 2–16 h, MeOH was added and the solution was stirred for 5 min. The mixture was warmed to room temperature and sat. NH$_4$Cl was added. The layers were separated and the aqueous layer was extracted with Et$_2$O. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and evaporated to obtain the crude product, which was purified by flash chromatography on silica (pretreated with 1% Et$_3$N; especially important to isolate the enamide byproduct) eluting with Hexane/AcOEt (1:0 to 30:1) or with CH$_2$Cl$_2$/petroleum ether.

**Note 1**: Early experiments were conducted in the presence of TMEDA in Et$_2$O. We later found that the use of THF obviates the need for TMEDA. However, organolithiums such as sec-BuLi can lithiate THF at high temperatures. Furthermore, the sec-BuLi/TMEDA combination can induce competing $\alpha'$-lithiation. Thus, specific conditions for each entry depend on the organolithium that is being utilized.

**Note 2**: Trapping of the intermediate organolithium with MeOH or MeOD can be done at 0 °C without affecting the efficiency and stereoselectivity of the transformation. However, trapping with other electrophiles such as dimethyl sulfate requires cooling to $-78 \, ^\circ C$ in order to maximize the yield of the reaction. For consistency, all quenches were performed at $-78 \, ^\circ C$.

**General Procedure B: Removal of Boc group**

To the $N$-Boc-compound (1.0 equiv) dissolved in freshly distilled CH$_2$Cl$_2$, was added CF$_3$CO$_2$H under argon at 0 °C. The resulting solution was stirred for 5 h at this temperature and concentrated in vacuo to obtain the salt. The salt was basified to pH 10–12 with 20% NaOH$_{aq}$. The aqueous layer was extracted with AcOEt (two times) and the combined organic layers were washed with brine, dried over K$_2$CO$_3$ and concentrated under reduced pressure to give a residue. The residue was purified by flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with Hexane/AcOEt (30:1) +1% Et$_3$N.

**General Procedure C: p-Nitrobenzoylation**

To the secondary amine (1.0 equiv) dissolved in freshly distilled THF (0.1 M), was added Et$_3$N (2.0 equiv) and $p$-nitrobenzoylchloride (1.5 equiv) under nitrogen at 0 °C. The reaction mixture was stirred for 6 h at room temperature and sat. NH$_4$Cl was added. The layers were separated and the aqueous layer was extracted with Et$_2$O. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure to give the crude product material. The crude product was purified by flash chromatography on silica eluting with Hexane/AcOEt (50:1 to 10:1).
Carbolithiation/Substitution of Enecarbamates

**Compound 9aA:** Prepared from 7a (50 mg, 0.193 mmol), \textit{n}-BuLi (0.26 mL, 2.2 M in hexanes, 3.0 equiv), and MeOH (0.5 mL) using **General Procedure A.** Purification: Flash chromatography on silica (pretreated with 1% Et\textsubscript{3}N) eluting with Hexane/AcOEt (1:0 to 30:1). Yield = 25 mg; 41% (colorless oil).

\textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.41–7.25 (m, 5H), 5.26 (br s, 1H), 4.13–4.09 (m, 1H), 2.79 (dt, \(J = 3.1,\) 13.6 Hz, 1H), 2.34–2.33 (m, 1H), 1.77–1.31 (m, 19H), 0.98 (t, \(J = 8.0\) Hz, 3H).

\textbf{\textsuperscript{13}C NMR} (101 MHz, CDCl\textsubscript{3}) \(\delta\) 156.1, 140.7, 128.5, 126.6, 126.3, 79.4, 57.0, 39.6, 35.2, 31.2, 30.1, 28.4, 23.9, 22.9, 20.1, 14.1.

\textbf{IR} (ATR, cm\textsuperscript{-1}): 2930, 2859, 1696, 1413, 1364, 1271, 1170, 1137, 872.

\textbf{HRMS-\textsuperscript{EI} (m/z):} Calcd. for C\textsubscript{20}H\textsubscript{31}NO\textsubscript{2} [M\textsuperscript{+}] 317.2355; found, 317.2347.
**Compound 10**: Isolated in 44% yield as a byproduct of carbolithiation of 7a with $n$-BuLi. $^1$H NMR (400 MHz, $C_6D_6$) $\delta$ 7.46–6.99 (m, 5H), 5.16 (t, $J = 4.0$ Hz, 1H), 3.76 (br s, 2H), 1.92 (t, $J = 4.0$ Hz, 2H), 1.84–1.80 (m, 2H), 1.59–1.47 (m, 4H), 1.07 (m, $J = 8.0$ Hz, 2H), 0.67 (t, $J = 8.0$ Hz, 3H). $^{13}$C NMR (101 MHz, $C_6D_6$) $\delta$ 173.2, 141.5, 140.7, 128.9, 127.8, 125.7, 118.2, 43.4, 36.4, 27.8, 24.3, 23.9, 22.6, 13.9. IR (ATR, cm$^{-1}$): 2930, 1658, 1632, 1447, 1368, 1209, 1068, 994, 758, 698. HRMS-EI$^+$ ($m/z$): Calcd. for $C_{16}H_{21}NO$ [M]$^+$ 243.1623; found, 243.1627.
**Compound 9bA**: Prepared from 7b (0.25 mmol), n-BuLi (2 equiv), and MeOH (0.5 mL) using **General Procedure A**. Purification: Flash chromatography on silica eluting with hexane:EtOAc (80:20). Yield = 84.4 mg; 92%.

**1H NMR** (400 MHz, C₆D₆) δ 7.80–7.17 (m, 7H), 5.57 (br s, 1H), 4.29 (br d, J = 16.0 Hz, 1H), 2.78 (dt, J = 4.0, 12.0 Hz, 1H), 2.25–2.20 (m, 1H), 1.75–0.90 (m, 22H).

**13C NMR** (101 MHz, C₆D₆) δ 155.7, 138.5, 133.7, 132.5, 128.3, 127.7, 127.5, 125.9, 125.5, 125.4, 125.1, 78.8, 57.1, 39.7, 35.3, 31.3, 30.1, 28.1, 23.8, 23.0, 20.1, 14.0. **IR** (ATR, cm⁻¹): 2929, 2859, 1685, 1454, 1412, 1364, 1270, 1171, 1137, 1096, 759. **HRMS-El⁺ (m/z)**: Calcd. for C₂₄H₃₃NO₂ [M]⁺ 367.2511; found, 367.2510.
Compound 9aB: Prepared from 7a (90 mg, 0.347 mmol), sec-BuLi (0.5 mL, 1.4 M in cyclohexane, 2 equiv), and MeOH (0.5 mL) using General Procedure A, *in the absence of* TMEDA. Purification: Flash chromatography on silica eluting with hexane:EtOAc (80:20). Yield = 99 mg; 90%. $^1$H NMR (400 MHz, C$_6$D$_6$) δ 7.43–7.15 (m, 5H), 5.60 (br s, 0.5H), 5.53 (br s, 0.5H), 4.23–4.18 (m, 1H), 2.81–2.72 (m, 1H), 1.83–1.61 (m, 3H), 1.49–0.65 (m, 20H). $^{13}$C NMR (101 MHz, C$_6$D$_6$) δ 155.6, 155.6, 141.3, 141.3, 128.6, 127.0, 126.5, 126.5, 126.2, 126.2, 78.8, 78.7, 55.5, 55.5, 40.7, 39.9, 39.4, 39.3, 32.6, 32.1, 28.1, 27.8, 25.4, 20.6, 20.4, 20.3, 17.5, 15.6, 11.1, 10.2. **IR** (ATR, cm$^{-1}$): 2962, 2931, 2871, 1686, 1448, 1364, 1269, 1171, 1141, 1094, 701. **HRMS-El** ($m/z$): Calcd. for C$_{20}$H$_{31}$NO$_2$ [M]$^+$ 317.2355; found, 317.2352.
Compound 9cB: Prepared from 7c (80 mg, 0.276 mmol), sec-BuLi (0.5 mL, 1.4 M in cyclohexane, 2 equiv), and MeOH (0.5 mL) using General Procedure A, in the absence of TMEDA. Purification: Flash chromatography on silica eluting with hexane:EtOAc (40:60). Yield = 68 mg; 71%. $^1$H NMR (400 MHz, C$_6$D$_6$) $\delta$ 7.17–7.05 (m, 2H), 6.93–6.92 (m, 1H), 6.70–6.67 (m, 1H), 5.68 (br s, 0.5H), 5.62 (br s, 0.5H), 4.29–4.25 (m, 1H), 3.37 (s, 3H), 2.89–2.81 (m, 1H), 1.89–1.61 (m, 3H), 1.46–0.78 (m, 20H). $^{13}$C NMR (101 MHz, C$_6$D$_6$) $\delta$ 160.4, 155.6, 155.5, 143.3, 143.2, 129.6, 129.5, 119.6, 118.8, 118.8, 113.1, 112.9, 112.9, 111.2, 78.7, 78.7, 55.5, 54.4, 54.3, 40.7, 40.0, 39.5, 39.4, 32.7, 32.1, 28.1, 27.7, 25.5, 25.4, 20.8, 20.4, 20.3, 17.4, 15.6, 11.0, 10.3. IR (ATR, cm$^{-1}$): 2960, 2931, 1687, 1600, 1583, 1413, 1364, 1251, 1141, 1094, 757. HRMS-ESI$^+$ (m/z): Calcd. for C$_{21}$H$_{33}$NO$_3$ [M]$^+$ 347.2460; found, 347.2453.
$^1^3$C NMR (101 MHz, C$_6$D$_6$): 160.40, 155.63, 155.53, 143.30, 143.23, 129.68, 129.51, 119.66, 118.82, 118.80, 113.11, 112.97, 112.93, 111.20, 78.75, 76.70, 55.50, 54.42, 54.36, 40.75, 40.04, 39.59, 39.48, 32.71, 32.18, 28.11, 27.79, 25.51, 25.43, 20.80, 20.40, 20.36, 17.49, 15.64, 11.09, 10.30.
**Compound 9aC:** Prepared from 7a (73 mg, 0.281 mmol), *tert*-BuLi (0.41 mL, 1.7 M in pentane, 2.5 equiv), and MeOH (0.5 mL) using **General Procedure A** in the absence of TMEDA. Purification: Flash chromatography on silica eluting with hexane:EtOAc (100:0 to 80:20). Yield = 83 mg; 93%. 

**1H NMR** (400 MHz, C₆D₆) δ 7.32 (d, J = 8.0 Hz, 2H), 7.18 (t, J = 8.0 Hz, 2H), 7.05 (t, J = 8.0 Hz, 1H), 5.65 (br s, 1H), 3.82 (br s, 1H), 3.19–3.13 (m, 1H), 1.94 (m, 1H), 1.46–1.10 (m, 13H), 0.95 (s, 9H). 

**13C NMR** (101 MHz, C₆D₆) δ 155.7, 144.7, 128.8, 126.64, 126.56, 79.1, 53.8, 47.73, 41.1, 34.2, 28.6, 28.1, 21.8, 21.1. 

**IR (ATR, cm⁻¹):** 2953, 2870, 1686, 1475, 1396, 1364, 1161, 1104, 1049, 875, 697. **HRMS-EI⁺ (m/z):** Calcd. for C₂₀H₃₁NO₂ [M⁺] 317.2355; found, 317.2354.
Compound 9dC: Prepared from 7d (73.5 mg, 0.25 mmol), tert-BuLi (1.7 M in pentane, 2 equiv), and MeOH (0.5 mL) using General Procedure A in the absence of TMEDA. Purification: Flash chromatography on silica eluting with hexane:EtOAc (90:10). Yield = 77.2 mg; 88%. $^1$H NMR (400 MHz, C$_6$D$_6$) δ 7.47 (br s, 1H), 7.09 (m, 1H), 7.04 (m, 1H), 6.88 (t, $J$ = 7.8 Hz, 1H), 5.57 (br s, 1H), 3.71 (br s, 1H), 3.08–3.04 (m, 1H), 1.78 (br s, 1H), 1.44–1.29 (m, 11H), 1.15–1.10 (m, 1H), 1.02–0.98 (m, 1H), 0.89 (s, 9H). $^{13}$C NMR (101 MHz, C$_6$D$_6$) δ 155.6, 147.3, 135.0, 130.1, 127.0, 126.8, 124.8, 79.4, 53.5, 48.1, 41.0, 34.2, 28.5, 28.0, 21.7, 21.0. IR (ATR, cm$^{-1}$): 2957, 2869, 1688, 1636, 1392, 1363, 1248, 1106, 861, 770. HRMS-EI$^+$ (m/z): Calcd. for C$_{20}$H$_{30}$NO$_2$Cl [M]$^+$ 351.1965; found, 351.1957.
**Compound 9bD**: Prepared from 7b (102 mg, 0.329 mmol), MeLi•LiBr (1.5 M in Et₂O, 3.0 equiv), and MeOH (0.5 mL) using General Procedure A. Purification: Flash chromatography on silica eluting with hexane:EtOAc (80:20). Yield = 74 mg; 59% as a colorless oil. 

**¹H NMR** (400 MHz, CDCl₃) δ 7.83–7.79 (m, 3H), 7.68 (s, 1H), 7.48–7.38 (m, 3H), 5.17 (s, 1H), 4.13–4.09 (m, 1H), 2.85 (dt, J = 4.0, 12.0 Hz, 1H), 2.75–2.63 (m, 1H), 1.88–1.70 (m, 2H), 1.46–1.34 (m, 11H), 1.22 (d, J = 8.0 Hz, 3H). 

**¹³C NMR** (101 MHz, CDCl₃) δ 156.34, 138.49, 132.70, 132.30, 126.40, 126.05, 125.77, 125.67, 125.30, 125.16, 79.61, 59.78, 39.83, 30.18, 28.52, 25.67, 20.00, 18.33. 

**IR** (ATR, cm⁻¹): 2965, 2861, 1685, 1412, 1364, 1270, 1254, 1173, 1140, 855, 818. 

**HRMS-El⁺** (m/z): Calcd. for C₂₁H₂₇NO₂ [M]⁺ 325.2042; found, 325.2041.
Compound 9bC: Prepared from 7b (140 mg, 0.452 mmol), tert-BuLi (1.7 M in pentane, 2 equiv), and MeOH (0.5 mL) using General Procedure A in the absence of TMEDA. Purification: Flash chromatography on silica eluting with hexane:EtOAc (80:20). Yield = 145 mg; 87%. $^1$H NMR (400 MHz, C6D6) δ 7.83 (s, 1H), 7.67–7.52 (m, 4H), 7.28–7.23 (m, 2H), 5.85 (br s, 1H), 3.90 (br s, 1H), 3.27–3.21 (m, 1H), 2.12 (m, 1H), 1.50–1.44 (m, 11H), 1.33–1.17 (m, 2H), 1.02 (s, 9H). $^{13}$C NMR (101 MHz, CDCl3) δ 155.8, 142.2, 134.1, 132.9, 128.7, 128.4, 127.9, 126.3, 125.9, 125.6, 125.1, 79.2, 54.0, 47.8, 41.1, 34.3, 28.6, 28.2, 21.8, 21.2. IR (ATR, cm$^{-1}$): 2952, 2869, 1684, 1474, 1396, 1364, 1159, 1102, 1051, 855, 739. HRMS-EL$^+$ (m/z): Calcd. for C24H33NO2 [M]$^+$ 367.2511; found, 367.2515.
**Compound 11:** Piperidine 9bC (130 mg, 0.354 mmol) was subjected to TFA-mediated Boc-cleavage using **General Procedure B** to give a crude oil. *p*-Nitrobenzoylation of the oil using **General Procedure C** afforded 11 (108 mg, 74%) as a white powder, which was recrystallized from Et₂O/Hexane (1/1) + one drop of DCM. **¹H NMR** (600 MHz, Acetone-d₆) δ 8.32–7.52 (m, 11H), 6.22 (s, 1H), 3.37 (m, 2H), 2.49 (s, 1H), 1.88 (m, 2H), 1.69–1.56 (m, 2H), 1.09 (s, 9H). **¹³C NMR** (151 MHz, Acetone-d₆) δ 169.4, 149.1, 144.6, 140.3, 134.5, 133.5, 129.3, 129.0, 128.6, 128.3, 127.0, 126.8, 126.7, 126.4, 124.6, 53.2, 46.6, 43.5, 34.8, 28.7, 22.5, 21.8. **MP:** 120–123 °C, **IR** (ATR, cm⁻¹): 2944, 2863, 1624, 1602, 1523, 1430, 1347, 1271, 1083, 846, 812, 750. **HRMS-ESI⁺** (m/z): Calcd. for C₂₆H₂₉N₂O₃ [M+H]⁺ 417.2173; found, 417.2172.
Compound 10g: Obtained as a byproduct from 7g (0.25 mmol), n-BuLi (3 equiv), and MeOH (0.5 mL) using General Procedure A. Purification: Flash chromatography on silica eluting with hexane:EtOAc (90:10). Yield = 66 mg; 90%. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.02–8.00 (m, 1H), 7.86–7.83 (m, 1H), 7.79–7.77 (m, 1H), 7.48–7.43 (m, 4H), 5.51 (m, 1H), 4.01 (s, 2H), 2.41–2.37 (m, 2H), 2.01–1.95 (m, 2H), 1.69 (br s, 2H), 1.19 (br s, 2H), 0.87 (br s, 2H), 0.56 (br s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 172.7, 138.9, 137.7, 133.9, 130.8, 128.7, 128.3, 126.5, 126.0, 125.8, 125.5, 124.9, 120.6, 43.2, 35.9, 27.3, 24.1, 24.1, 22.2, 13.6. IR (ATR, cm$^{-1}$): 2954, 2928, 1654, 1628, 1448, 1364, 1175, 1140, 1066, 774. HRMS-EL$^+$ (m/z): Calcd. for C$_{20}$H$_{23}$NO [M]$^+$ 293.1780; found, 293.1785.
**Compound 9iC**: Prepared from 7i (138 mg, 0.505 mmol), 1.7 M t-BuLi in pentane (2.5 equiv), and MeOD (0.5 mL) using **General Procedure A** to give the carbolithiated product. Acidic removal of Boc group using **General Procedure B** afforded 9iC as a pale yellow oil in 78% yield (over 2 steps). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.43–7.21 (m, 5H), 3.17–3.00 (m, 2H), 2.10–2.02 (m, 1H), 1.95–1.86 (m, 1H), 1.72–1.71 (m, 1H), 1.48–1.41 (m, 1H), 1.32 (d, $J$ = 7.2 Hz, 3H), 0.89 (s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 147.7, 128.2, 127.5, 126.3, 57.0 (1:1:1 triplet split by C-D coupling, $J$ = 80.4 Hz), 54.6, 39.7, 34.8, 29.2, 27.9, 27.6, 24.7. IR (ATR, cm$^{-1}$): 2948, 2867, 1475, 1448, 1365, 1134, 762, 699, 649. HRMS-El$^+$ (m/z): Calcd. for C$_{16}$H$_{24}$ND [M]$^+$ 232.2050; found, 232.2051.
**Compound 9jC**: Prepared from 7j (115 mg, 0.356 mmol), 1.7 M t-BuLi in pentane (2.5 equiv), and MeOH (0.5 mL) using **General Procedure A** to give the carbolithiated product, which was deprotected using **General Procedure B** to afford 9jC as a pale yellow oil in 79% yield (over 2 steps). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.86–7.78 (m, 4H), 7.66–7.57 (m, 1H), 7.51–7.30 (m, 2H), 4.10 (d, \(J = 7.2\) Hz, 1H), 3.22–3.05 (m, 2H), 2.13–1.84 (m, 3H), 1.51–1.44 (m, 1H), 1.25 (d, \(J = 7.2\) Hz, 3H), 0.93 (s, 9H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 133.6, 132.4, 127.9, 127.8, 127.6, 126.3, 126.0, 125.8, 125.3, 57.6, 54.6, 39.8, 34.9, 29.2, 27.9, 27.7, 24.7. IR (ATR, cm\(^{-1}\)): 2922, 2860, 1368, 1340, 1298, 1130, 1074, 906, 864, 810, 758. HRMS-\(\text{EI}^+\) (\(m/z\)): Calcd. for C\(_{20}\)H\(_{27}\)N [M]\(^+\) 281.2144; found, 281.2142.
Compound 12: Prepared from 9jC (64 mg, 0.227 mmol) using General Procedure C to give 12 (83 mg, 85%) as a white powder, which was recrystallized from Et₂O/Hexane (1/1) + three drops of DCM. **MP**: 151–154 °C, **IR** (ATR, cm⁻¹): 2923, 1623, 1601, 1520, 1410, 1342, 1270, 846, 815. **HRMS-EI⁺ (m/z)**: Calcd. for C₂₇H₃₀N₂O₃ [M]+ 430.2256; found, 430.2260. This compound was fully characterized by X-ray crystallographic analysis. CYLview (some hydrogens removed) and ORTEP representations are provided below. See CIF file for details.

Compound 9kC: Prepared from 7k (250 mg, 0.91 mmol), 1.7 M t-BuLi in pentane (2.5 equiv), and MeOH (0.5 mL) using General Procedure A to give the carbolithiated product, which was deprotected using General Procedure B to afford 9jC as a colorless oil in 80% yield (over 2 steps). **¹H NMR** (400 MHz, CDCl₃) δ 7.54–7.24 (m, 5H), 3.58 (d, J = 9.6 Hz, 1H), 2.79–2.71 (m, 1H), 2.08–2.02 (m, 1H), 1.79–1.74 (m, 1H), 1.64–1.57 (m, 1H), 1.41–1.23 (m, 3H), 1.09 (d, J = 6.0 Hz, 3H), 0.68 (s, 9H). **¹³C NMR** (101 MHz, CDCl₃) δ 146.09, 128.56, 128.21, 127.13, 66.05, 52.95, 50.04, 35.00, 33.05, 29.28, 27.27, 22.75. **IR** (ATR, cm⁻¹): 2955, 2923, 1464, 1363, 1280, 1115, 1050, 978, 761, 730, 698. **HRMS-EI⁺ (m/z)**: Calcd. for C₁₆H₂₅N [M]+ 231.1987; found, 231.1984.
Compound 9kA: Prepared from 7k (68.3 mg, 0.25 mmol), n-BuLi (2.5 equiv), and MeOH (0.5 mL) using General Procedure A. Purification: Flash chromatography on silica eluting with hexane:EtOAc (90:10). Yield = 58 mg; 70%. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.50 to 7.30 (m, 5H), 5.25 (br s, 1H), 4.43 to 4.39 (m, 1H), 2.43 to 2.35 (m, 1H), 2.17 to 1.83 (m, 2H), 1.68 to 1.21 (m, 17H), 1.00 to 0.80 (m, 6H verlapping doublet and triplet). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 156.4 (C=O), 143.7 (C), 128.0 (CH), 127.0 (CH), 126.3 (CH), 79.4 (C), 55.9 (CH), 46.9 (CH), 33.9 (CH), 32.8 (CH$_2$), 29.8 (CH$_2$), 28.5 (3 x CH$_3$), 23.4 (CH$_2$), 22.9 (CH$_3$), 21.2 (CH$_2$), 21.2 (CH$_2$), 14.2 (CH$_3$). IR (ATR, cm$^{-1}$): 2951, 2870, 1680, 1449, 1391, 1364, 1323, 1170, 1082, 880, 702. HRMS-El$^+$ (m/z): Calcd. for C$_{21}$H$_{33}$NO$_2$ [M]$^+$ 331.2511; found, 331.2505.
Compound 9iA: Prepared from 9i (0.25 mmol), n-BuLi (2.5 equiv), and MeOH (0.5 mL) using General Procedure A, then B. Yield = 68 mg; 86% (over 2 steps). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.26 (br s, 1H), 8.68 (br s, 1H), 7.42 to 6.77 (m, 4H), 3.84 (s, 3H), 3.60 to 3.54 (t, 1H), 3.11 to 2.95 (m, 1H), 2.10 to 1.94 (m, 1H) 1.84 to 1.55 (m, 2H), 1.36 to 0.69 (m, 14H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 159.9, 142.6, 136.4, 129.7, 119.7, 112.9, 112.8, 66.3, 55.3, 54.4, 37.7, 31.3, 30.4, 28.9, 27.8, 22.5, 17.9, 13.8.
Compound A was prepared using the method of Baudoin.\textsuperscript{5}

It was oxidized to the lactam using Zhang's procedure.\textsuperscript{4}

Triflation and arylation were effected using the method of Occhiato.\textsuperscript{3}

\textbf{H NMR} (400 MHz, CDCl\textsubscript{3}) $\delta$ 7.34–7.27 (m, 5H), 5.52 (d, $J$ = 2.8 Hz, 1H), 4.57 (sext, $J$ = 6.4 Hz, 1H), 2.39–2.27 (m, 2H), 1.37–1.32 (m, 4H), 1.09 (d, $J$ = 6.8 Hz, 3H), 1.05 (s, 9H). \textbf{C NMR} (101 MHz, CDCl\textsubscript{3}) $\delta$ 153.8, 140.9, 137.5, 128.1, 127.0, 125.1, 124.1, 80.1, 48.6, 40.6, 27.9, 27.5, 21.7, 20.3. \textbf{MP}: 64–67 °C, \textbf{IR} (ATR, cm\textsuperscript{-1}): 2974, 2916, 1686, 1637, 1346, 1302, 1176, 1100, 1052, 997, 766. \textbf{HRMS-EI\textsuperscript{+} (m/z):} Calcd. for C\textsubscript{18}H\textsubscript{25}NO\textsubscript{2} [M]\textsuperscript{+} 287.1885; found, 287.1886.
Compound 9mC: Prepared from 7m (140 mg, 0.487 mmol), 1.7 M t-BuLi in pentane (2.5 equiv), and MeOH (0.5 mL) using General Procedure A to give the carbolithiated product (149 mg, 89%). Acidic removal of Boc group using General Procedure B afforded 9mC (94%) as a colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.39–7.18 (m, 5H), 3.74 (d, \(J = 8.8\) Hz, 1H), 2.97 (sext, \(J = 6.4\) Hz, 1H), 1.94–1.84 (m, 2H), 1.72–1.69 (m, 1H), 1.29 (d, \(J = 6.8\) Hz, 3H), 1.20–1.13 (m, 1H), 1.09 (d, \(J = 6.4\) Hz, 3H), 0.81 (s, 9H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 148.5, 128.3, 128.2, 126.5, 62.3, 54.1, 49.6, 39.1, 34.8, 29.7, 29.7, 27.8, 24.4. IR (ATR, cm\(^{-1}\))): 2951, 2866, 1559, 1457, 1364, 1171, 1115, 978, 881, 774, 699, 667. HRMS-EI\(^+\) (m/z): Calcd. for C\(_{17}\)H\(_{27}\)N [M]+ 245.2144; found, 245.2136.
$^{1}H$ & $^{13}C$ NMR spectra of 9mC in acetone-d6
**Compound 21**: Prepared from 7i (69 mg, 0.25 mmol), n-BuLi (2 equiv), and Me₂SO₄ (3 equiv) using General Procedure A. Purification: Flash chromatography on silica eluting with hexane:EtOAc (95:5). Yield = 66 mg; 76%. 

**¹H NMR** (400 MHz, CDCl₃) δ 7.34 to 7.15 (m, 5H), 3.83 to 3.64 (m, 2H), 2.04 to 1.96 (m, 1H), 1.70 to 0.84 (m, 24H), 0.61 to 0.58 (t, 3H). 

**¹³C NMR** (101 MHz, CDCl₃) δ 155.9 (C=O), 149.3 (C), 127.4 (CH), 125.7 (CH), 125.4 (CH), 79.3 (C), 63.3 (C), 53.3 (CH), 40.6 (CH₂), 33.1 (CH₂), 32.5 (CH₂), 31.7 (CH), 30.0 (CH₂), 27.9 (3 x CH₃), 22.6 (CH₂), 21.3 (CH), 16.5 (CH₃), 13.6 (CH₃).
S-45
Computational Details

Computations presented in the manuscript as well as those for the full reaction coordinate were performed using Gaussian09 revision D01. Optimized gas phase geometries were obtained with the DFT/B3LYP/6-311+G(d,p) method. At these geometries, single point energies (DFT/B3LYP/6-311+G(d,p)) in diethyl ether as the solvent (scrf, pcm) at 273.15 K were computed. Geometry optimization for structures A were
obtained by applying the same solvation model as stated above to the geometry optimization process. In addition, the parameters opt=tight and int=ultrafine were applied when necessary. All data reported include zero-point energy correction. Minima were confirmed by frequency analysis and transition states further by IRC calculation, both at the same level as stated above. Graphical visualization was done using CYLview. 

Additional computations (presented in tables below) were performed using Gaussian09 revision C01. Geometries were optimized in the gas phase at the DFT/B3LYP/6-31G level and do not include zero-point energy correction. Minima were confirmed by the absence of imaginary frequencies using analytical second derivatives. Graphical visualization was done using Mercury.

Additionally Investigated Structures:

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<th>Structure</th>
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<th>rel. E (syn vs. anti) in kcal/mol</th>
<th>C-Li distance in Å</th>
<th>O-Li distance in Å</th>
<th>C-C-Li bond angle in Å</th>
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Color code: C (black), N (blue), O (red), Cl (green), Li (violet). Hydrogen atoms are omitted for clarity.

**Summary of Bond Angle Correlation to Yield:**

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<th>GC Yield (%)</th>
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**References**

6. Gaussian 09, Revision C.01 and D.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.;
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   Tomasi, J.; Cossi, M.; Rega, N.; Millam, M. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.;
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