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Photocatalytic α-alkylation of carbamates with vinyl azaarenes

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Dedicated to the memory of Alan and Linde Katritzky

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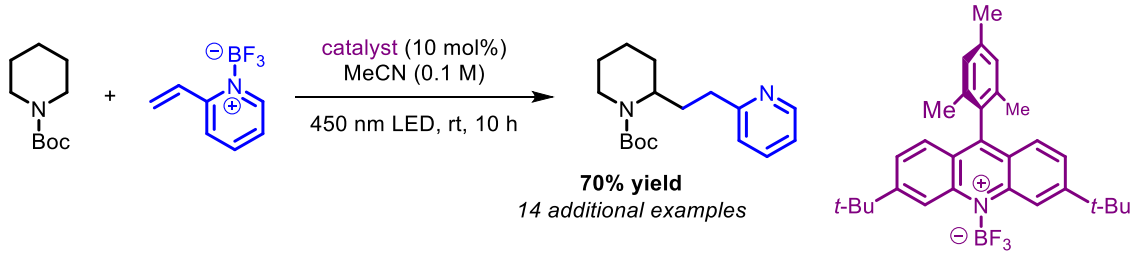
Abstract

An acridine-BF_3 complex is a competent photocatalyst for the α-C–H bond functionalization of *N*-Boc amines. Upon the photoinduced formation of the corresponding α-carbamyl radicals, these species undergo Giese-type additions to BF_3-activated vinyl azaarenes. Reactions tolerate a range of different azacycles and show good functional group compatibility.

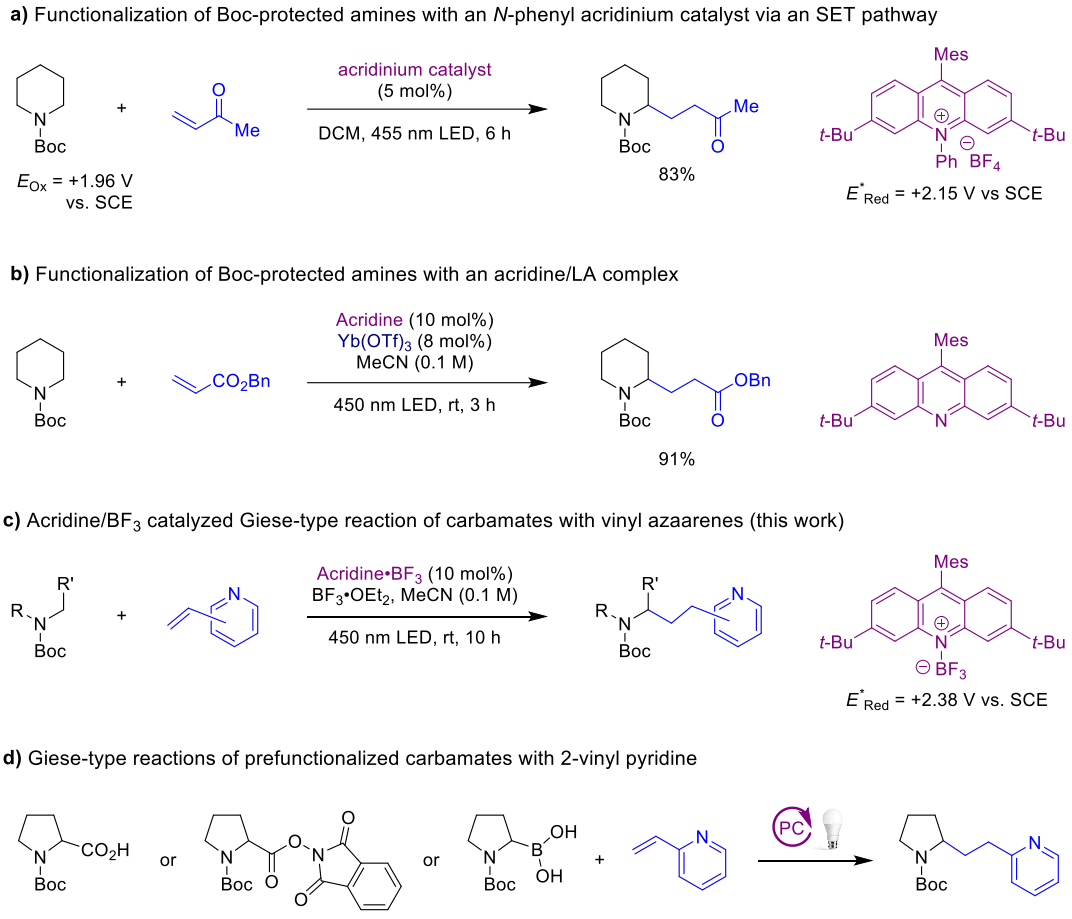


Keywords: Photocatalysis, C–H functionalization, acridine, azacycles, pyridine, azaarenes

Introduction

Functionalized azacycles represent highly important core structures of many bioactive substances.[1,2] Pyridine- and piperidine-containing materials are of particular interest as they are currently the two most frequently encountered nitrogen heterocycles in FDA-approved drugs.[3] Given the privileged status of these motifs, efforts continue to prepare more complex azacycles through diversification of simple azacycles via C–H bond functionalization, utilizing a variety of mechanistically distinct approaches.[4,5] Photochemical transformations are especially attractive, given that they tend to operate under mild reaction conditions while typically exhibiting excellent functional group tolerance.[6,7] While earlier photochemical approaches are often limited to readily oxidizable *N*-alkyl and *N*-aryl amines,[8-11] more recent methods have expanded the scope to more favorable *N*-carbamoyl amines, specifically *N*-Boc (*tert*-butoxy carbonyl) protected amines, due to the ease of deprotection. Typically, photochemical approaches to the α-C–H bond functionalization of *N*-Boc amine substrates involve α-carbamyl radical intermediates that are generated via hydrogen atom transfer (HAT), a process that is facile due to the relatively low bond dissociation energies (BDEs) of the α-C–H bond.[12-20] In contrast, α-C–H bond functionalizations of *N*-Boc amine substrates that operate via a single electron transfer (SET) oxidation/deprotonation sequence remain challenging due to the high oxidation potentials of these substrates, which are outside the reach of most common photocatalysts. In pioneering work, Nicewicz and coworkers achieved the α-C–H bond functionalization of *N*-Boc piperidine and related substrates with an *N*-phenyl acridinium catalyst possessing a large excited state reduction potential.[21,22] α-Carbamyl radicals generated via a SET pathway were shown to undergo Giese reactions[23] with a range of acceptors (Scheme 1a). While acridinium-type photocatalyst are wildly popular,[24-26] acridine photocatalysts are gaining popularity.[27-40] We recently reported a strategy that expands the scope of these Giese reactions to more challenging amine substrates and less electrophilic conjugate acceptors such as simple acrylates (Scheme 1b).[41] This method involves the use of a photoactive complex formed in situ from an acridine and a Lewis acid,[42,43] a modular approach that allows for dialing in the excited state reduction potential (+2.07–2.38 V vs. SCE) of the catalyst. Here we report an extension of this concept by employing vinyl azaarenes as conjugate acceptors (Scheme 1c). These reactions are attractive in that they generate products that contain two common azacyclic pharmacophores.

Vinyl azaarenes such as vinyl pyridines have been utilized in a range of photochemical Giese-type reactions, engaging with a variety of different alkyl radicals.[44-52] Previous photocatalytic methods for the addition of α-carbamyl radicals to vinyl azaarenes are limited to prefunctionalized carbamate substrates (Scheme 1d).[53-57] For instance, Sparling and co-workers developed a photoinduced decarboxylation of *N*-Boc proline to generate the corresponding α-carbamyl radical which was then trapped with 2-vinylpyridine.[53] The König group employed a decarboxylation strategy involving redox active esters.[54] A similar approach was later utilized by Lin and coworkers.[55] Sharma and co-workers exploited α-boronic acids as carbamyl radical precursors.[56] Overall, the existing photochemical methods exhibit limited substrate scope with respect to the carbamyl radical precursors.

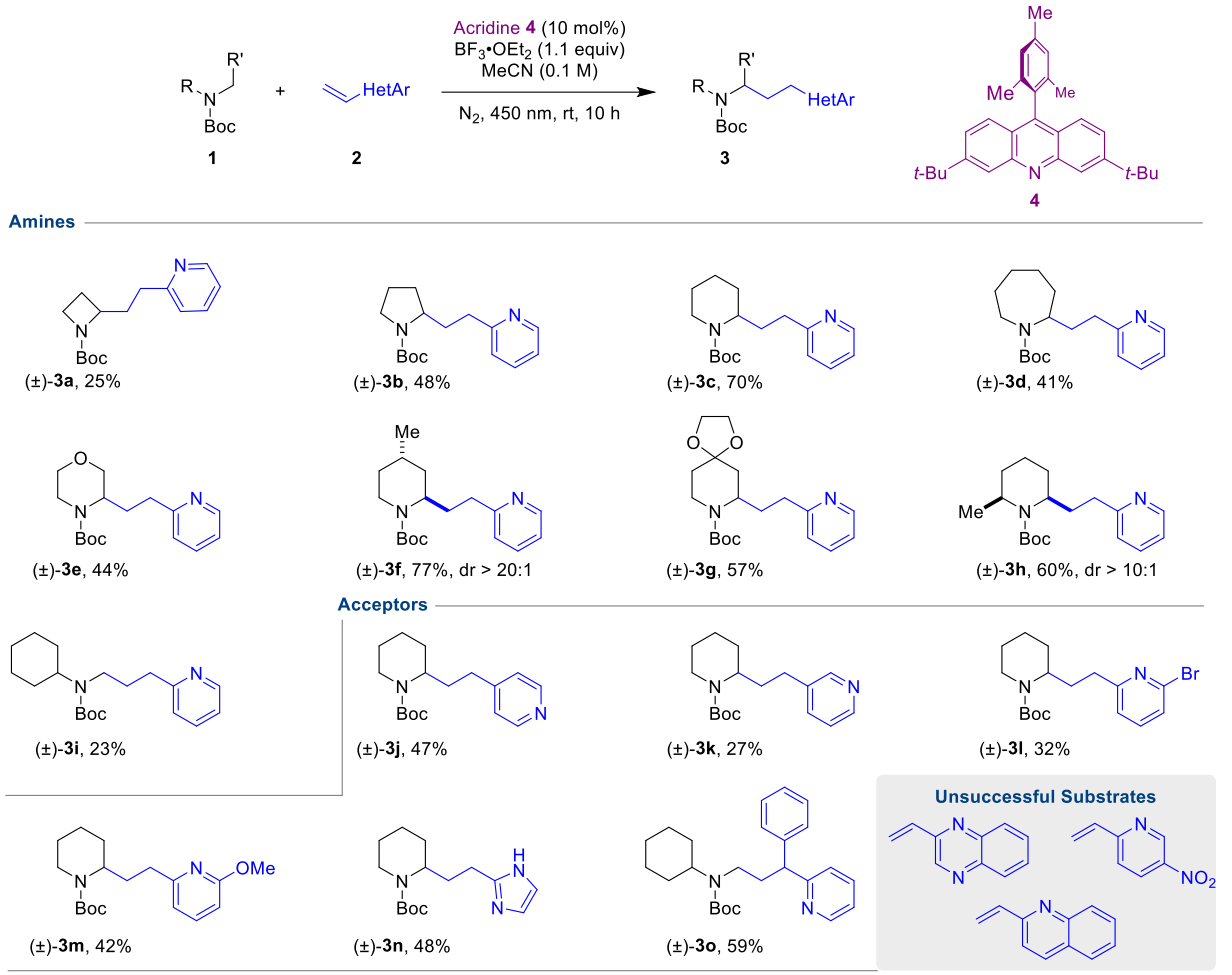


Scheme 1. Relevant precedent and current work.

Results and Discussion

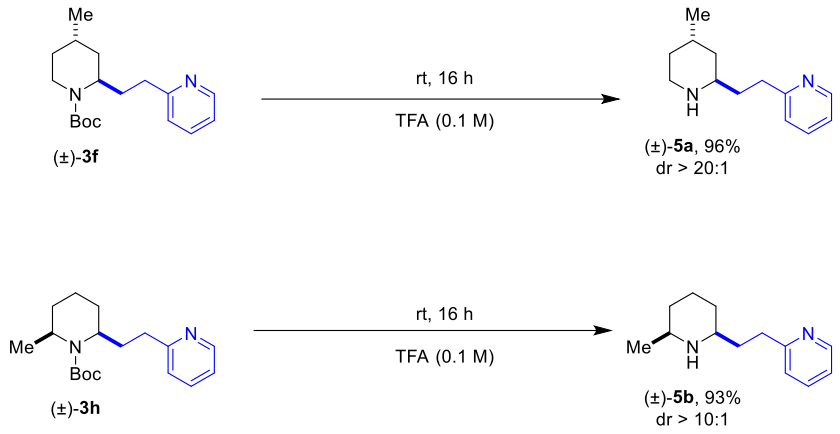
Our previous study on the acridine/Lewis acid catalyzed α-C–H bond functionalization of carbamates focused on Giese reactions of photochemically generated carbamyl radicals with α,β-unsaturated esters.[41] In an extension of this concept, we also reported a single example of a Giese-type reaction of *tert*-butyl 4-benzylpiperidine-1-carboxylate with 2-vinylpyridine. In this case, it proved essential to employ an excess of boron trifluoride etherate as an additive, the role of which is twofold: 1) generate the active photocatalyst, and 2) activate 2-vinylpyridine toward addition. To explore the scope and limitations of this transformation, we evaluated a range of carbamate donors **1** and vinyl azaarene acceptors **2** (Scheme 2). A variety of *N*-Boc amines engaged 2-vinylpyridine upon irradiation with 450 nm LED light in presence of acridine **4** and excess boron trifluoride etherate. While the yields are variable, a range of different ring sizes were tolerated (products **3a**–**d**). *N*-Boc morpholine also underwent the title reaction to provide product **3e**. Piperidine rings containing substituents at the C4- and C6-positions furnished products **3f** and **3h** in good yields and excellent diastereoselectivities. These reactions presumably proceed via a Fürst-Plattner-type transition state, highly favoring one diastereomer as seen in related reactions (not shown).[21,41] An acid-labile ketal functionality (product **3g**) and linear amines (product **3i**) were also tolerated. Next, we explored azaarene acceptors. 4-Vinylpyridine performed well (product **3j**). Interestingly, 3-vinylpyridine also furnished the corresponding product **3k**, albeit in low yield. *N*-Boc piperidine engaged differently substituted vinyl pyridines to provide

halogen-substituted product **3l** and methoxy-substituted product **3m**. Regarding different types of acceptors, 2-vinylimidazole was identified as a viable substrate (product **3n**). As an example of a 1,1-disubstituted acceptor, 2-(1-phenylvinyl)pyridine readily underwent the title reaction (product **3o**). Current substrate limitations include fused heterocycles such as vinyl quinoxaline and vinyl quinoline. While the reasons for the failure of these substrates to undergo the title reaction remain unclear, it appears that, at least in some cases, polymerization of the acceptors represents one of the potential decomposition pathways. Product deprotection was readily accomplished as illustrated in two representative examples (Scheme 3).



Reactions were performed with 0.60 mmol of **1** and 0.20 mmol of **2**. All yields correspond to isolated yields of chromatographically purified products.

Scheme 2. Scope of the reaction.



Scheme 3. Deprotection of selected products.

Conclusions

In summary, a photoactive acridine-BF_3 complex was shown to catalyze the addition of various *N*-Boc amines to vinyl azaarenes, achieving α-C–H bond functionalization under mild conditions. This approach allows for the facile synthesis of small molecules containing multiple nitrogen heterocycles. These materials are likely of interest to medicinal chemistry programs.

Experimental Section

General: Starting materials and reagents were purchased from commercial sources and used as received unless stated otherwise. Anhydrous acetonitrile (MeCN) was dried using a mBraun solvent system. Purification of reaction products was carried out by flash column chromatography using Sorbent Technologies Standard Grade silica gel (60 Å, 230–400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F_{254} plates. Visualization was accomplished with UV light, potassium permanganate, and Dragendorff-Munier stains followed by heating. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker Avance HD II spectrometer operating at 400 MHz or a Bruker Avance HD II operating at 600 MHz instrument and chemical shifts are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, qt = quintet, dd = doublet of doublets, td = triplet of doublets, m = multiplet; coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C NMR) spectra were recorded on a Bruker Avance HD II spectrometer operating at 400 MHz or Bruker Avance HD II operating at 600 MHz instrument and chemical shifts are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 77.16 ppm). Some NMR signals are broad (br) due to the time scale of the rotation about the N–CO bond. Most compounds are a mixture of rotamers. High resolution mass spectra (HRMS) were obtained from the Mass Spectrometry Core Laboratory of the University of Florida (Agilent 6230 ESI-TOF instrument). Photochemical reactions were carried out using a PennPhD Photoreactor M2 with a 450 nm LED. The light source was operated at an intensity level of 85% and a stir rate of 350 rpm was applied. Boc-protected substrates were purchased from commercial sources or prepared according to literature procedures.[41] The following substrates were prepared according to literature

procedures and characterization data matched our own in all regards: 3-vinylpyridine,[58] 2-bromo-6-vinylpyridine,[59] 2-methoxy-6-vinylpyridine,[60] 2-(1-phenylvinyl)pyridine,[60] and 2-vinyl-1*H*-imidazole.[61] 3,6-di-*tert*-butyl-9-mesitylacridine (**4**) was prepared according to our previous reports.[38,41]

General Procedure A (Reactions with 2-Vinylpyridine): To a flame dried vial was added a stir bar, 3,6-di-*tert*-butyl-9-mesitylacridine (8.2 mg, 0.02 mmol, 0.1 equiv), and Boc-amine (0.6 mmol, 3 equiv). Anhydrous MeCN (2 mL) was added, and the vial was sealed with a rubber septum. Nitrogen gas was bubbled through the reaction mixture for 5 minutes. After purging with nitrogen, 2-vinyl pyridine (21.5 µL, 0.2 mmol, 1 equiv) was added followed by $BF_3{\cdot}OEt_2$ (27.0 µL,0.22 mmol, 1.1 equiv) resulting in a bright yellow solution. The septum was wrapped in parafilm. The reaction vial was irradiated with 450 nm light (85% intensity) at room temperature for 10 hours. Following irradiation, 1 M NaOH (2 mL) was added, and the reaction was vigorously stirred for 30 minutes and then extracted with DCM (3 × 3 mL). The combined organic layers were dried over Na_2SO_4. The dried organic layer was filtered, and the solvent was removed under reduced pressure. The resulting residue was purified using silica gel chromatography.

General Procedure B (Liquid Vinyl Azaarenes): To a flame dried vial was added a stir bar, 3,6-di-*tert*-butyl-9-mesitylacridine (8.2 mg, 0.02 mmol, 0.1 equiv), and Boc-amine (0.6 mmol, 3equiv). Anhydrous MeCN (2 mL) was added, and the vial was sealed with a rubber septum. Nitrogen gas was bubbled through the reaction mixture for 5 minutes. After purging with nitrogen, radical acceptor (0.2 mmol, 1 equiv) was added followed by $BF_3{\cdot}OEt_2$ (27.0 µL,0.22 mmol, 1.1 equiv) resulting in a bright yellow solution. The septum was wrapped in parafilm. The reaction vial was irradiated with 450 nm light (85% intensity) at room temperature for 10 hours. Following irradiation 1 M NaOH (2 mL) was added, and the reaction was vigorously stirred for 30 minutes and then extracted with DCM (3 × 3 mL). The combined organic layers were dried over Na_2SO_4. The dried organic layer was filtered, and the solvent was removed under reduced pressure. The resulting residue was purified using silica gel chromatography.

General Procedure C (Solid Vinyl Azaarenes): To a flame dried vial was added a stir bar, 3,6-di-*tert*-butyl-9-mesitylacridine (8.2 mg, 0.02 mmol, 0.1 equiv), Boc-amine (0.6 mmol, 3equiv), and radical acceptor (0.2 mmol, 1 equiv). Anhydrous MeCN (2 mL) was added, and the vial was sealed with a rubber septum. Nitrogen gas was bubbled through the reaction mixture for 5 minutes. After purging with nitrogen, $BF_3{\cdot}OEt_2$ (27.0 µL, 0.22 mmol, 1.1 equiv) was added resulting in a bright yellow solution. The septum was wrapped in parafilm. The reaction vial was irradiated with 450 nm light (85% intensity) at room temperature for 10 hours. Following irradiation 1 M NaOH (2 mL) was added, and the reaction was vigorously stirred for 30 minutes and then extracted with DCM (3 × 3 mL). The combined organic layers were dried over Na_2SO_4. The dried organic layer was filtered, and the solvent was removed under reduced pressure. The resulting residue was purified using silica gel chromatography.

***tert*-Butyl 2-[2-(pyridin-2-yl)ethyl]azetidine-1-carboxylate (3a)**: Following general procedure A, compound (±)-**3a** was obtained from *tert*-butyl azetidine-1-carboxylate (94.3 mg, 0.6 mmol, 3 equiv) and 2-vinylpyridine (21.5 µL, 0.2 mmol, 1 equiv) as a light yellow oil in 25% yield (13.1 mg). Hexane containing ethyl acetate (25–80%) was used as the eluent for silica gel chromatography. R_f = 0.34 in EtOAc/Hexanes 80:20 v/v. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 8.52–8.49 (m, 1H), 7.58 (app td, *J* = 7.7, 1.9 Hz, 1H), 7.17 (app d, *J* = 7.7 Hz, 1H), 7.11–7.07 (m, 1H), 4.30–4.21 (m, 1H), 3.86–3.76 (m, 2H), 2.88–2.79 (m, 2H), 2.34–2.20 (m, 2H), 2.09–1.99 (m, 1H), 1.89–1.80 (m, 1H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 161.7, 156.8, 149.3, 136.5, 122.8, 121.2, 79.3, 62.6, 46.6, 35.7, 33.9, 28.6, 22.0. HRMS (ESI-TOF): Calculated for $C_{15}H_{23}N_2O_2$ $[M + H]^+$: 263.1754, found: 263.1766.

***tert*-Butyl 2-[2-(pyridin-2-yl)ethyl]pyrrolidine-1-carboxylate (3b):** Following general procedure A, compound (±)-**3b** was obtained from *tert*-butyl pyrrolidine-1-carboxylate (102.7 mg, 0.6 mmol, 3 equiv) and 2-vinylpyridine (21.5 µL, 0.2 mmol, 1 equiv) as a colorless oil in 48% yield (26.5 mg). Hexane containing ethyl acetate (25–50%) was used as the eluent for silica gel chromatography. Compound (±)-**3b** is known and the published characterization data matched our own in all respects.[53] R_f = 0.22 in EtOAc/Hexanes 50:50 v/v. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 8.52–8.46 (m, 1H), 7.61–7.53 (m, 1H), 7.21–7.04 (m 2H), 3.95–3.72 (m, 1H), 3.45–3.23 (m, 2H), 3.88–2.68 (m, 2H), 2.24–2.01 (m, 1H), 1.98–1.66 (m, 5H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 162.0, 154.8, 149.4, 136.5, 122.7, 121.1, 79.1, 57.0, 47.9, 46.2, 35.9, 34.9, 34.3, 30.8, 30.1, 28.7, 23.9, 23.2. HRMS (ESI-TOF): Calculated for $C_{16}H_{25}N_2O_2$ $[M + H]^+$: 277.1911, found: 277.1923.

***tert*-Butyl 2-[2-(pyridin-2-yl)ethyl]piperidine-1-carboxylate (3c)**: Following general procedure A, compound (±)-**3c** was obtained from *tert*-butyl piperidine-1-carboxylate (111.2 mg, 0.6 mmol, 3 equiv) and 2-vinylpyridine (21.5 µL, 0.2 mmol, 1 equiv) as a colorless oil in 70% yield (40.7 mg). Hexane containing ethyl acetate (25–50%) was used as the eluent for silica gel chromatography. Compound (±)-**3c** is known and the published characterization data matched our own in all respects.[62] R_f = 0.37 in EtOAc/Hexanes 50:50v/v. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 8.51–8.48 (m, 1H), 7.55 (app td, *J* = 7.7, 1.9 Hz, 1H), 7.12 (app d, *J* = 7.8 Hz, 1H), 7.07 (ddd, *J* = 7.7, 7.4, 1.2 Hz, 1H), 4.34–4.25 (m, 1H), 4.02–3.91 (m, 1H), 2.84–2.62 (m, 3H), 2.19–2.07 (m, 1H), 1.87–1.75 (m, 1H), 1.68–1.52 (m, 5H), 1.44–1.39 (s, 10H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 161.5, 154.8, 149.4, 136.5, 122.9, 121.2, 80.0, 69.3, 67.1, 51.3, 40.0, 35.0, 28.9, 28.5. HRMS (ESI-TOF): Calculated for $C_{17}H_{27}N_2O_2$ $[M + H]^+$: 291.2067, found: 291.2075.

***tert*-Butyl 2-[2-(pyridin-2-yl)ethyl]azepane-1-carboxylate (3d)**: Following general procedure A, compound (±)-**3d** was obtained from *tert*-butyl azepane-1-carboxylate (119.6 mg, 0.6 mmol, 3 equiv) and 2-vinylpyridine (21.5 µL, 0.2 mmol, 1 equiv) as a colorless oil in 41% yield (25.0 mg). Hexane containing ethyl acetate (10–30%) was used as the eluent for silica gel chromatography. R_f = 0.33 in EtOAc/Hexanes 30:70v/v. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 8.53–8.45 (m, 1H), 7.60–7.50 (m, 1H), 7.19–7.03 (m, 2H), 4.24–3.93 (m, 1H), 3.76–3.51 (m, 1H), 2.85–2.63 (m, 3H), 2.15–2.03 (m, 1H), 1.86–1.69 (m, 4H), 1.65–1.54 (m, 2H), 1.46–1.41 (m, 9H), 1.28–1.14 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 162.3, 162.0, 156.3, 155.9, 149.3, 149.2, 136.4, 136.4, 123.1, 122.8, 121.1, 121.0, 79.2, 78.9, 55.3, 54.3, 41.9, 41.6, 35.4, 35.3, 35.2, 35.0, 34.9, 34.7, 30.0, 29.0, 28.7, 28.4, 25.2, 24.9. HRMS (ESI-TOF): Calculated for $C_{18}H_{29}N_2O_2$ $[M + H]^+$: 305.2224, found: 305.2229.

***tert*-Butyl 3-[2-(pyridin-2-yl)ethyl]morpholine-4-carboxylate (3e)**: Following general procedure A, compound (±)-**3e** was obtained from *tert*-butyl morpholine-4-carboxylate (112.3 mg, 0.6 mmol, 3 equiv) and 2-vinylpyridine (21.5 µL, 0.2 mmol, 1 equiv) as a colorless oil in 44% yield (25.7 mg). Hexane containing ethyl acetate (35–80%) was used as the eluent for silica gel chromatography. R_f = 0.33 in EtOAc/Hexanes 80:20 v/v. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 8.52–8.49 (m, 1H), 7.57 (app td, *J* = 7.7, 1.8 Hz, 1H), 7.15 (app d, *J* = 7.8 Hz, 1H), 7.10–7.06 (m, 1H), 4.07–3.95 (m, 1H), 3.85–3.72 (m, 3H), 3.55 (dd, *J* = 11.6, 3.2 Hz, 1H), 3.43 (app td, *J* = 11.8, 2.8 Hz, 1H), 3.21–3.10 (m, 1H), 2.87–2.78 (m, 1H), 2.76–2.68 (m, 1H), 2.27–2.17 (m, 1H), 2.11–2.01 (m, 1H), 1.44–1.40 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 161.5, 154.8, 149.4, 136.5, 122.9, 121.2, 80.0, 69.3, 67.1, 51.9, 39.8, 35.0, 28.9, 28.5. HRMS (ESI-TOF): Calculated for $C_{16}H_{25}N_2O_3$ $[M + H]^+$: 293.1860, found: 293.1865.

***tert*-Butyl (2*R**,4*S**)-4-methyl-2-[2-(pyridin-2-yl)ethyl]piperidine-1-carboxylate (3f):** Following general procedure A, compound (±)-**3f** was obtained from *tert*-butyl 4-methylpiperidine-1-carboxylate (119.6 mg, 0.6 mmol, 3 equiv) and 2-vinylpyridine (21.5 µL, 0.2 mmol, 1 equiv) as a colorless oil in 77% yield (46.9 mg) and > 20:1 diastereomeric ratio. Hexane containing ethyl acetate (25–50%) was used as the eluent for silica gel

chromatography. R_f = 0.45 in EtOAc/Hexanes 50:50 v/v. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 8.51–8.47 (m, 1H), 7.55 (app t, *J* = 7.6 Hz, 1H), 7.17–7.02 (m, 2H), 4.46–4.20 (m, 1H), 4.12–3.83 (m, 1H), 2.90–2.63 (m, 3H), 2.14–2.00 (m, 1H), 1.90–1.66 (m, 2H), 1.62–1.49 (m, 2H), 1.45 (s, 9H), 1.22 (ddd, *J* = 13.0, 13.0, 5.9 Hz, 1H), 1.08–0.92 (m, 1H), 0.85 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 162.1, 161.8, 155.2, 149.4, 136.4, 123.1, 122.9, 121.1, 79.3, 79.1, 51.2, 50.3, 39.5, 38.3, 37.8, 37.4, 35.4, 34.2, 30.7, 28.6, 25.5. HRMS (ESI-TOF): Calculated for $C_{18}H_{29}N_2O_2$ $[M + H]^+$: 305.2224, found: 305.2229. Relative stereochemistry was assigned by analogy to similar compounds synthesized from our group.[38]

***tert*-Butyl 7-[2-(pyridin-2-yl)ethyl]-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (3g)**: Following general procedure A, compound (±)-**3g** was obtained from *tert*-butyl 1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (146.0 mg, 0.6 mmol, 3 equiv) and 2-vinylpyridine (21.5 µL, 0.2 mmol, 1 equiv) as a colorless oil in 57% yield (39.7 mg). Hexane containing ethyl acetate (35–70%) was used as the eluent for silica gel chromatography. R_f = 0.35 in EtOAc/Hexanes 80:20 v/v. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 8.51–8.48 (m, 1H), 7.56 (app td, *J* = 7.7, 1.8 Hz, 1H), 7.15–7.12 (m, 1H), 7.07 (ddd, *J* = 7.7, 7.5, 1.1 Hz, 1H), 4.56–4.35 (m, 1H), 4.13–4.01 (m, 1H), 3.96–3.83 (m, 4H), 3.10–2.98 (m, 1H), 2.81–2.65 (m, 2H), 2.34–2.23 (m, 1H), 2.00–1.89 (m, 1H), 1.83 (dd, J = 13.7, 6.7 Hz, 1H), 1.74–1.68 (m, 1H), 1.66–1.59 (m, 2H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 161.9, 154.9, 149.3, 136.4, 123.0, 121.1, 107.4, 79.7, 64.8, 63.9, 50.8, 37.3, 36.4, 35.7, 34.8, 31.4, 28.5. HRMS (ESI-TOF): Calculated for $C_{19}H_{29}N_2O_4$ $[M + H]^+$: 349.2122, found: 349.2130.

***tert*-Butyl (2*S**,6*S**)-2-methyl-6-[2-(pyridin-2-yl)ethyl]piperidine-1-carboxylate (3h):** Following general procedure A, compound (±)-**3h** was obtained from *tert*-butyl 2-methylpiperidine-1-carboxylate (119.6 mg, 0.6 mmol, 3 equiv) and 2-vinylpyridine (21.5 µL, 0.2 mmol, 1 equiv) as a colorless oil in 60% yield (36.5 mg) and > 10:1 diastereomeric ratio. Hexane containing ethyl acetate (25–50%) was used as the eluent for silica gel chromatography. R_f = 0.47 in EtOAc/Hexanes 50:50 v/v. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.52–8.49 (m, 1H), 7.57 (app td, *J* = 7.7, 1.9 Hz, 1H), 7.14 (app d, *J* = 7.7 Hz, 1H), 7.08 (ddd, *J* = 7.7, 7.3, 1.2 Hz, 1H), 4.36–4.28 (m, 1H), 4.23–4.15 (m, 1H), 2.88–2.77 (m, 1H), 2.76–2.67 (m, 1H), 2.01–1.89 (m, 2H), 1.74–1.50 (m, 5H), 1.46–1.41 (s, 10H), 1.18 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 162.1, 155.5, 149.4, 136.5, 122.8, 121.1, 79.7, 50.4, 45.8, 36.7, 35.5, 30.4, 28.6, 27.8, 20.7, 14.3. HRMS (ESI-TOF): Calculated for $C_{18}H_{29}N_2O_2$ $[M + H]^+$: 305.2224, found: 305.2235. Note: Relative stereochemistry was determined from compound **5b** after Boc-deprotection.

***tert*-Butyl cyclohexyl[3-(pyridin-2-yl)propyl]carbamate (3i):** Following general procedure A, compound **3i** was obtained from *tert*-butyl cyclohexyl(methyl)carbamate (128.0 mg, 0.6 mmol, 3 equiv) and 2-vinylpyridine (21.5 µL, 0.2 mmol, 1 equiv) as a light yellow oil in 23% yield (14.6 mg). Hexane containing ethyl acetate (0–20%) was used as the eluent for silica gel chromatography. R_f = 0.17 in EtOAc/Hexanes 25:75 v/v. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 8.53–8.49 (m, 1H), 7.58 (app td, *J* = 7.7, 1.6 Hz, 1H), 7.18–7.06 (m, 2H), 3.93–3.43 (m 1H), 3.24–3.01 (m, 2H), 2.75 (t, *J* = 7.8 Hz, 2H), 1.97–1.85 (m, 2H), 1.80–1.65 (m, 4H), 1.63–1.55 (m, 1H), 1.47–1.38 (m, 10H), 1.35–1.25 (m, 3H), 1.09–0.97 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 161.8, 155.6, 149.4, 136.5, 122.8, 121.2, 79.2, 55.2, 43.0, 36.2, 31.5, 31.2, 28.6, 26.2, 25.7. HRMS (ESI-TOF): Calculated for $C_{19}H_{31}N_2O_2$ $[M + H]^+$: 319.2380, found: 319.2397.

***tert*-Butyl 2-[2-(pyridin-4-yl)ethyl]piperidine-1-carboxylate (3j):** Following general procedure B, compound (±)-**3j** was obtained from *tert*-butyl piperidine-1-carboxylate (111.1 mg, 0.6 mmol, 3 equiv) and 4-vinylpyridine (21.5 µL, 0.2 mmol, 1 equiv) as a colorless oil in 47% yield (27.3 mg). Hexane containing ethyl acetate (25–50%) was used as the eluent for silica gel chromatography. R_f = 0.25 in EtOAc/Hexanes 50:50 v/v. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 8.50–8.44 (m, 2H), 7.11–7.08 (m, 2H), 4.33–4.21 (m, 1H), 4.04–3.93 (m,

1H), 2.79–2.70 (m, 1H), 2.63–2.45 (m, 2H), 2.08–1.95 (m, 1H), 1.73–1.51 (m, 6H), 1.47–1.34 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 155.2, 151.2, 149.8, 123.9, 79.4, 50.2, 38.98, 32.2, 30.7, 28.7, 28.6, 25.7, 19.2. HRMS (ESI-TOF): Calculated for $C_{17}H_{27}N_2O_2$ $[M + H]^+$: 291.2067, found: 291.2073.

***tert*-Butyl 2-[2-(pyridin-3-yl)ethyl]piperidine-1-carboxylate (3k):** Following general procedure B, compound (±)-**3k** was obtained from *tert*-butyl piperidine-1-carboxylate (111.1 mg, 0.6 mmol, 3 equiv) and 3-vinylpyridine (5 M stock solution in MeCN, 40 µL, 0.2 mmol, 1 equiv) as a colorless oil in 27% yield (15.7 mg). Hexane containing ethyl acetate (30–50%) was used as the eluent for silica gel chromatography. R_f = 0.17 in EtOAc/Hexanes 50:50 v/v. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 8.57–8.41 (m, 2H), 7.52–7.48 (m, 1H), 7.20 (dd, *J* = 7.7, 4.8 Hz, 1H), 4.34–4.22 (m, 1H), 4.07–3.95 (s, 1H), 3.82–2.72 (m, 1H), 2.64–2.47 (m, 2H), 2.07–1.89 (m, 2H), 1.73–1.54 (m, 6H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 155.3, 150.0, 147.5, 137.5, 135.9, 123.4, 79.4, 50.2, 38.8, 31.6, 30.0, 28.6, 28.3, 25.7, 19.2. HRMS (ESI-TOF): Calculated for $C_{17}H_{27}N_2O_2$ $[M + H]^+$: 291.2067, found: 291.2073.

***tert*-Butyl 2-[2-(6-bromopyridin-2-yl)ethyl]piperidine-1-carboxylate (3l):** Following general procedure B, compound (±)-**3l** was obtained from *tert*-butyl piperidine-1-carboxylate (111.1 mg, 0.6 mmol, 3 equiv) and 2-bromo-6-vinylpyridine (5 M stock solution in MeCN, 40 µL, 0.2 mmol, 1 equiv) as a colorless oil in 32% yield (23.6 mg). Hexane containing ethyl acetate (0–10%) was used as the eluent for silica gel chromatography. R_f = 0.31 in EtOAc/Hexanes 85:15 v/v. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 7.43 (app t, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 7.7 Hz 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 4.35–4.24 (m, 1H), 4.04–3.91 (m, 1H), 2.83–2.62 (m, 3H), 2.19–2.07 (m, 1H), 1.86–1.75 (m, 1H), 1.61–1.53 (m, 5H), 1.47–1.34 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 163.8, 155.2, 141.7, 138.8, 125.5, 121.9, 80.1, 35.1, 30.0, 28.9, 28.6, 25.8, 19.2. HRMS (ESI-TOF): Calculated for $C_{17}H_{26}BrN_2O_2$ $[M + H]^+$: 369.1172, found: 369.1177.

***tert*-Butyl 2-[2-(6-methoxypyridin-2-yl)ethyl]piperidine-1-carboxylate (3m):** Following general procedure B, compound (±)-**3m** was obtained from *tert*-butyl piperidine-1-carboxylate (111.1 mg, 0.6 mmol, 3 equiv) and 2-methoxy-6-vinylpyridine (5 M stock solution in MeCN, 40 µL, 0.2 mmol, 1 equiv) as a colorless oil in 42% yield (26.9 mg). Hexane containing ethyl acetate (0–10%) was used as the eluent for silica gel chromatography. R_f = 0.58 in EtOAc/Hexanes 85:15 v/v. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 7.45 (dd, *J* = 8.3, 7.2 Hz, 1H), 6.70 (d, *J* = 7.2 Hz, 1H), 6.53 (d, *J* = 8.3 Hz, 1H), 4.35–4.25 (m, 1H), 4.04–3.95 (m, 1H), 3.91 (s, 3H), 2.86–2.76 (m, 1H), 2.71–2.55 (m, 2H), 2.18–2.06 (m, 1H), 1.90–1.80 (m, 1H), 1.64–1.53 (m, 5H), 1.46–1.36 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 163.8, 159.8, 155.3, 138.9, 115.3, 107.4, 79.2, 53.3, 50.5, 39.1, 34.8, 29.5, 28.8, 28.6, 25.8, 19.2. HRMS (ESI-TOF): Calculated for $C_{18}H_{29}N_2O_3$ $[M + H]^+$: 321.2173, found: 321.2180.

***tert*-Butyl 2-[2-(*1H*-imidazol-2-yl)ethyl]piperidine-1-carboxylate (3n):** Following general procedure C, compound (±)-**3n** was obtained from *tert*-butyl piperidine-1-carboxylate (111.1 mg, 0.6 mmol, 3 equiv) and 2-vinyl-*1H*-imidazole (18.8 mg, 0.2 mmol, 1 equiv) as a light yellow oil in 48% yield (26.8 mg). Ethyl acetate containing isopropyl amine (0–1%) was used as the eluent for silica gel chromatography. R_f = 0.22 in EtOAc/MeOH/IPA 90:9:1 v/v. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 6.94 (s, 2H), 4.34–4.26 (m, 1H), 4.02–3.93 (m, 1H), 2.93–2.73 (m, 2H), 2.46–2.34 (m, 1H), 2.29–2.17 (m, 1H), 1.69–1.54 (m, 4H), 1.52–1.42 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 156.7, 148.2, 80.3, 48.4, 39.5, 29.4, 28.60, 28.56, 25.8, 24.4, 19.2. HRMS (ESI-TOF): Calculated for $C_{15}H_{26}N_3O_2$ $[M + H]^+$: 280.2020, found: 280.2034.

***tert*-Butyl cyclohexyl[3-phenyl-3-(pyridin-2-yl)propyl]carbamate (3o)**: Following general procedure B, compound (±)-**3o** was obtained from *tert*-butyl cyclohexyl(methyl)carbamate (128.0 mg, 0.6 mmol, 3 equiv) and 2-(1-phenylvinyl)pyridine (5 M stock solution in MeCN, 40 µL, 0.2 mmol, 1 equiv) as a colorless oil in 59% yield (46.7 mg). Hexane containing ethyl acetate (5–15%) was used as the eluent for silica gel chromatography. R_f = 0.42 in EtOAc/Hexanes 25:75 v/v. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ = 8.61–8.55 (m,

1H), 7.57 (app t, *J* = 7.7 Hz, 1H), 7.39–7.28 (m, 4H), 7.24–7.15 (m, 2H), 7.15–7.09 (m, 1H), 4.10–3.81 (m, 2H), 3.11–2.91 (m, 2H), 2.54–2.41 (m, 1H), 2.37–2.26 (m, 1H), 1.79–1.65 (m, 5H), 1.63–1.57 (m, 1H), 1.44 (s, 9H), 1.33–1.24 (m, 3H), 1.07–0.96 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, mixture of rotamers): δ= 163.5, 155.6, 149.4, 143.4, 136.6, 128.7, 128.0, 126.6, 122.7, 121.5, 79.2, 55.2, 52.2, 42.2, 35.8, 31.4, 28.7, 26.1, 25.7. HRMS (ESI-TOF): Calculated for $C_{25}H_{35}N_2O_2$ $[M + H]^+$: 395.2693, found: 395.2698.

2-{2-[(2*R,4*S**)-4-Methylpiperidin-2-yl]ethyl}pyridine (5a)**: To a 25 mL round bottom flask was added a stir bar and (±)-**3f** (63.9 mg, 0.21 mmol, 1 equiv). TFA (2.1 mL) was added, and the reaction was left to stir at room temperature for 16 hours. The TFA was removed via vacuum and 1 M NaOH (10 mL) was added to the crude residue and stirred for 10 minutes. The NaOH was extracted with diethyl ether (4 × 5 mL) and the combined organic layers were dried over Na_2SO_4. The dried organic layer was filtered, and the solvent was removed under reduced pressure resulting in a light-yellow oil in 96% yield (41.2 mg) and >20:1 diastereomeric ratio. No further purification was performed. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 8.50–8.48 (m, 1H), 7.56 (app td, *J* = 7.7, 1.8 Hz, 1H), 7.13 (app d, *J* = 7.7 Hz, 1H), 7.07 (app dd, *J* = 7.6, 7.2 Hz, 1H), 2.87–2.75 (m, 5H), 2.54 (s, 1H), 1.93–1.83 (m, 2H), 1.81–1.74 (m, 1H), 1.67–1.61 (m, 1H), 1.48–1.38 (m, 2H), 1.27–1.20 (m, 1H), 0.93 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C): δ = 162.1, 149.3, 136.5, 122.8, 121.1, 51.0, 40.8, 38.7, 35.3, 34.9, 33.4, 26.0, 19.9. HRMS (ESI-TOF): Calculated for $C_{13}H_{21}N_2$ $[M + H]^+$: 205.1699, found: 205.1715.

2-{2-[(2*S,6*S**)-6-Methylpiperidin-2-yl]ethyl}pyridine (5b)**: To a 25 mL round bottom flask was added a stir bar and (±)-**3h** (57.0 mg, 0.19 mmol, 1 equiv). TFA (1.9 mL) was added, and the reaction was left to stir at room temperature for 16 hours. The TFA was removed via vacuum and 1 M NaOH (10 mL) was added to the crude residue and stirred for 10 minutes. The NaOH was extracted with diethyl ether (4 × 5 mL) and the combined organic layers were dried over Na_2SO_4. The dried organic layer was filtered, and the solvent was removed under reduced pressure resulting in a light-yellow oil in 93% yield (36.1 mg) and >10:1 diastereomeric ratio. No further purification was performed. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 8.50–8.47 (m, 1H), 7.56 (app td, *J* = 7.7, 1.9 Hz, 1H), 7.12 (app d, *J* = 7.7 Hz, 1H), 7.07 (app dd, *J* = 7.7, 7.0 Hz, 1H), 2.82 (t, *J* = 8.0 Hz, 2H), 2.59 (dqd, *J* = 12.6, 6.3, 2.6 Hz, 1H), 2.54 (dtd, *J* = 10.9, 6.4, 2.5 Hz, 1H), 1.83–1.72 (m, 4H), 1.68–1.64 (m, 1H), 1.58–1.54 (m, 1H), 1.30 (app qt, *J* = 13.1, 3.9 Hz 1H), 1.07–0.97 (m, 5H). ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C): δ = 162.1, 149.3, 136.4, 122.7, 121.1, 56.7, 52.5, 37.5, 35.0, 34.4, 32.2, 24.9, 23.2. HRMS (ESI-TOF): Calculated for $C_{13}H_{21}N_2$ $[M + H]^+$: 205.1699, found: 205.1711. Note: Relative stereochemistry was determined from the coupling constants for the α and α' protons.

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Supplementary Material

Copies of the ^{1}H and ^{13}C NMR spectra for all title compounds are provided in the supplementary material.

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