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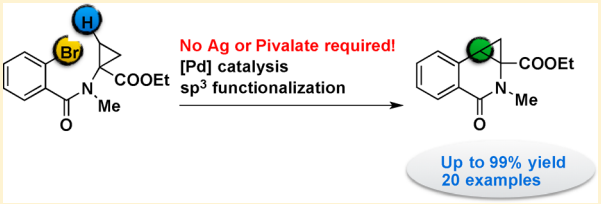
Intramolecular sp^3 Functionalization of Cyclopropyl α-Amino Acid-Derived Benzamides

Carolyn L. Ladd, Audrey V. Belouin, and André B. Charette*

Centre in Green Chemistry and Catalysis, Faculty of Arts and Sciences, Department of Chemistry, Université de Montreal, P.O. Box 6128, Station Downtown, Montreal, Quebec H3C 3J7, Canada

Supporting Information

ABSTRACT: Intramolecular Pd-catalyzed functionalization of cyclopropyl α-amino acid-derived benzamides proceeds without silver or pivalate additives. Both electronically and sterically diverse ethyl 1,2,3,4-tetrahydroisoquinolone-3-carboxylates were accessible in good to excellent yields.



The search for milder, simpler and more environmentally benign methodologies to form C−C bonds continues to motivate the chemical community.[1] Despite significant efforts toward developing C−H functionalization processes over the past decade,[2] many of these methods often require both high temperatures and additives such as silver and carboxylate-based reagents.

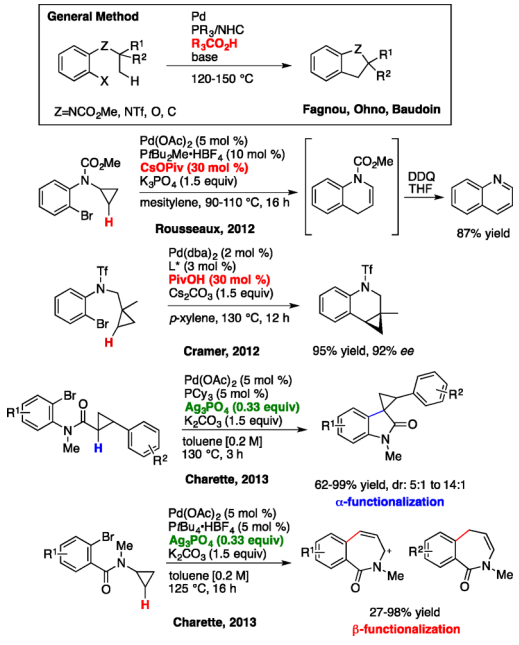
Our group has been actively developing C−H functionalization protocols to access heterocycles in a more environmentally benign fashion, including employing less toxic metals and metal-free methodologies.[3] Additionally, we have held a long-standing interest in both accessing[4] and functionalizing cyclopropanes.[5]

Overcoming high C−H bond dissociation energies remains a major challenge in C−H functionalization, particularly for sp^3 centers;[6] however, a general approach has been established relying on carboxylate-based additives for Pd-catalyzed intramolecular C(sp^3)−H bond arylation.[7]

Compared to other sp^3 systems, cyclopropanes afford distinct advantages including enhanced C−H bond acidity and increased reactivity from ring strain. Despite these advantageous properties, cyclopropane functionalization still requires high reaction temperatures and additional carboxylate-based[8] or silver additives[9] to promote C−H insertion, in addition to minimizing undesirable ring-opening processes (Scheme 1).[10]

Recently, the C−H functionalization of amino acids, and, in particular, cyclopropyl amino acids, has gained interest.[11] Despite recent advances, accessing cyclopropyl α-amino acids[12] and their derivatives[13] remains a challenging endeavor. We previously studied the C−H functionalization of cyclopropyl benzamides under silver and pivalate conditions, which suffered from ring-opening.[14] Inspired by cyclopropyl α-amino acids, we designed a benzamide derivative possessing an ester moiety that we postulated could access a milder, less-energetically demanding process for cyclopropyl C−H insertion.[15] Herein, we report the intramolecular C−H functionalization of cyclopropanes to access ethyl 1,2,3,4-tetrahydroisoquinolone-3-carboxylates without requiring pivalate or silver additives.[16]

Scheme 1. Pivalate- and Silver-Mediated Intramolecular Pd−Catalyzed Arylation of Cyclopropanes



We synthesized cyclopropyl α-amino acid-derived benzamide **1a** from commercially available ethyl 1-amino-1-cyclopropanecarboxylate and 2-bromobenzoic acid. Much to our delight, substrate **1a** afforded cyclopropyl-fused tetrahydroisoquinolone carboxylate **2a** as the sole product in excellent yield employing silver or pivalate.[17] Upon further examinination, we observed

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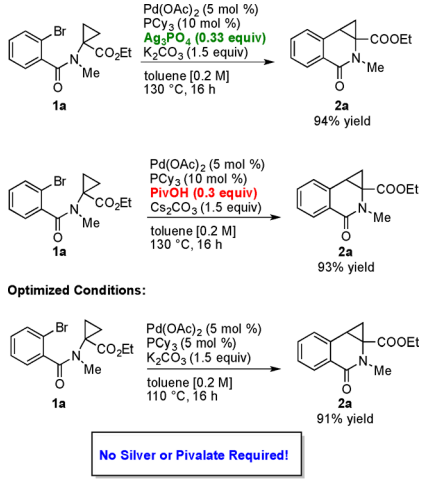
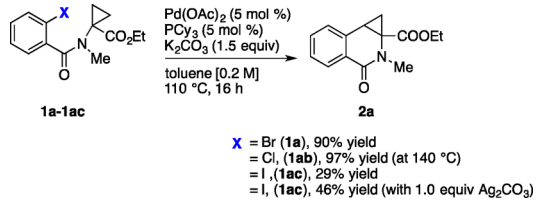
that the reaction proceeds at reduced temperatures without silver or pivalate (Scheme 2).[18]

Scheme 2. Reaction Optimization toward Milder Arylation Conditions



Using optimized conditions, we explored other halide partners (Scheme 3). Chloro analogue (**1ab**) also provided

Scheme 3. Effect of Halide Partner

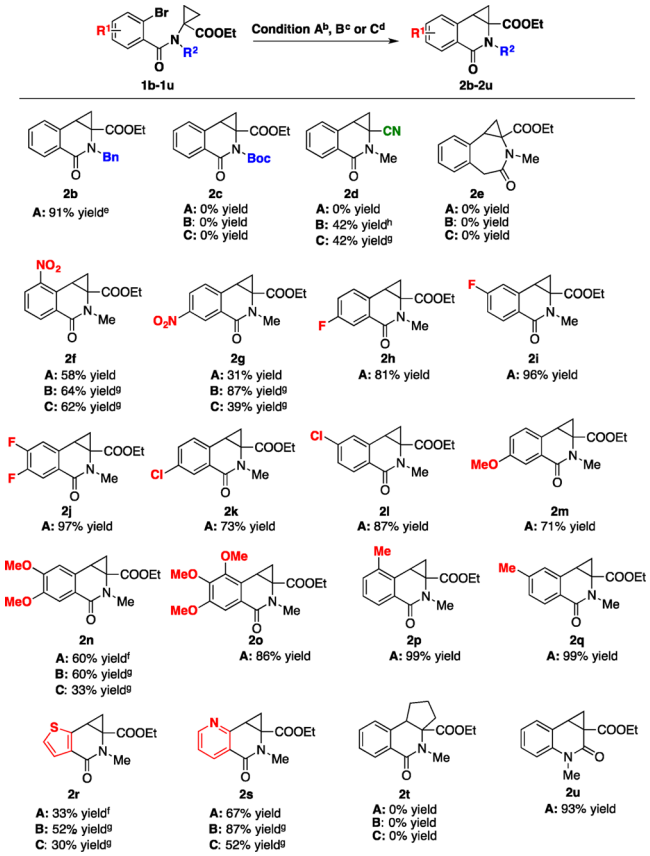


high yields, albeit higher temperatures were required.[19] Due to tendency toward dehalogenation, iodo analogue **1ac** gave diminished conversions; however, adding 1.0 equiv of cationic silver improved reactivity.[20]

The scope and limitations were then investigated employing various functional groups (Scheme 4).

Both electron-withdrawing and electron-donating substrates afforded good to excellent yields under additive-free conditions (Conditions A), supporting a concerted-metalation deprotonation process.[21] Low-yielding substrates produced dehalogenation or starting materials as identifiable byproducts; no ring-opening was observed. Substrates with yields <70% were compared to pivalate and silver conditions (Conditions B and C). The *N*-benzyl derivative could also be employed providing product **2b** in excellent yield; however, the *N*-Boc group was incompatible.[22] Replacing the ester moiety with a cyano group (**2c**) gave trace conversions; albeit, both silver and pivalate additives enhanced reactivity.[23] Homologated benzamide **2e** failed to cyclize.[24] Strongly electron-withdrawing functionalities such as the nitro group were tolerated (**2f**–**2g**). Notably, yields for product **2g** could be dramatically improved with pivalate; however, no improvement was observed for product **2f**.[25] Both fluoro- and chloro-substitution (**2e**–**2i**) performed well. Electron-donating groups were also viable (**2m**–**2q**). *Bis*-methoxy-substituted **2n** produced moderate yields additional additives were not beneficial.[26] *Tris*-methoxy-substitution was also feasible, affording **2o** in good yield. Notably, thienyl and

Scheme 4. Scope of Direct β-Functionalization of Cyclopropyl Benzamides[a]

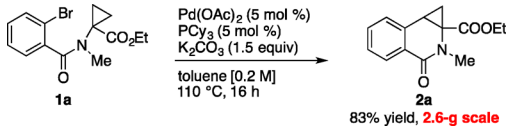


[a]Isolated yield, 0.5 mmol scale. [b]Conditions A: $Pd(OAc)_2$ (5 mol %), PCy_3 (5 mol %), K_2CO_3 (1.5 equiv), toluene [0.2 M], 110 °C, 16 h. [c]Conditions B: $Pd(OAc)_2$ (5 mol %), $PtBu_2Me{\cdot}HBF_4$ (5 mol %), CsOPiv (0.3 equiv), K_3PO_4 (1.5 equiv), toluene [0.2 M], 110 °C, 16 h. [d]Conditions C: $Pd(OAc)_2$ (5 mol %), PCy_3 (5 mol %), Ag_3PO_4 (0.3 equiv), K_2CO_3 (1.5 equiv), toluene [0.2 M], 110 °C, 16 h. [e]1.0 mmol scale. [f]with $PtBu_2Me{\cdot}HBF_4$. [g]0.2 mmol scale, ^1H NMR yield with 1,3,5-trimethoxybenzene as an internal standard. [h]Isolated yield, 0.2 mmol scale.

pyridyl substrates (**2r**–**2s**) produced modest to good yields, which could be improved with pivalate.[27] Cyclopentyl derivative **2t** was unable to cyclize.[28] Finally, tetrahydroquinolone **2u** could be obtained.[29]

Additionally, 2.6 g of product **2a** was accessible in good yield using a reflux condenser exposed to air and moisture, illustrating the robust nature of this protocol (Scheme 5).

Scheme 5. Robust Gram-Scale Synthesis of 2a



On the basis of our findings, we postulate that the reaction without pivalate or silver occurs via a Pd(0)–Pd(II) cycle (Figure 1).[30] Oxidative addition of Pd into the Ar–Br bond generates **A**. Acetate then serves as a proton shuttle to mediate the concerted metalation-deprotonation event **B**,[31] producing seven-membered palladacycle **C**,[32] stabilized by the rigid

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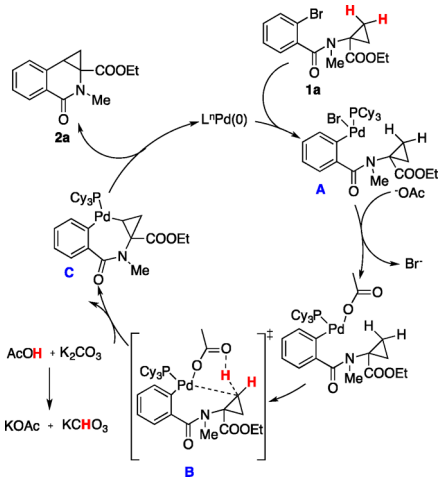

Figure 1. Proposed catalytic cycle.

cyclopropyl moiety. Reductive elimination from **C** regenerates Pd(0) and liberates product **2a**.

In conclusion, we have developed a β-functionalization process for cyclopropyl α-amino-acid-derived benzamides, which readily undergo C−H insertion to provide ethyl 1,2,3,4-tetrahydroisoquinolone-3-carboxylates. Pivalate or silver additives may not always be required for direct functionalization processes; however, such additives can be beneficial for more challenging substrates. Therefore, it is important to consider the subtle role of such additives in reaction development to avoid employing unnecessary reagents.

EXPERIMENTAL SECTION

General Considerations. All nonaqueous reactions were run under argon atmosphere with flame-dried glassware using standard techniques for manipulating air-sensitive compounds.[33] Anhydrous solvents were obtained by filtration through drying columns or by distillation over calcium hydride or sodium. Flash column chromatography was performed using 230−400 mesh silica and basic alumina (pH ∼ 10−11) by hand or performed on an automatic purification system using the indicated solvent system Prepacked normal phase silica gel columns were used for separation of products. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel plates and visualized by UV absorbance (254 nm), and/or potassium permanganate ($KMnO_4$). Nuclear magnetic resonance spectra were recorded on an 400, 300, or 400 MHz (^{1}H,^{13}C, ^{19}F) spectrometer. Chemical shifts for ^{1}H NMR spectra are recorded in parts per million (ppm) from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CHCl_3$, δ = 7.26 ppm). The data was reported as follows: chemical shift, multiplicity (s = singlet, s (br) = broad singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, ddd = doublet of doublets of doublets, t = triplet, q = quadruplet, m = multiplet, br m= broad multiplet), coupling constant in Hz and integration. Chemical shifts for ^{13}C NMR spectra were recorded in parts per million from tetramethylsilane using the central peak of $CDCl_3$ (77.16 ppm) as the internal standard. All ^{13}C NMR spectra were obtained with complete proton decoupling. Infrared spectra were taken using FTIR (neat) and are reported in reciprocal centimeters (cm^{-1}). Melting points were obtained using a melting point apparatus and are uncorrected. High-resolution mass spectrometry (HRMS) spectra were obtained on a TOF-MS utilizing electrospray ionization (ESI) in positive-ion mode.

Materials. Commercial reagents were used as supplied or purified by standard techniques where necessary. Starting materials not listed below were obtained commercially and the reagents were used without further purification. Ethyl 1-((*tert*-butoxycarbonyl)amino)-cyclopropane-1-carboxylate was synthesized according to literature procedure[34] and converted to its TFA salt for subsequent use.[35] 2-bromoanilide **1u** was synthesized in the same fashion as previously reported from 2-bromo aniline and 1-(ethoxycarbonyl)cyclopropane-1-carboxylic acid.[36] Benzyl-protected substrate **2b** was synthesized by the general procedure and benzylated as previously reported.[37]

General Procedure for Cyclopropyl Benzamide Synthesis of 1a−1u. *Ethyl 1-[N-methyl(2-bromophenyl)amido]cyclopropane-1-carboxylate (**1a**).* To a 100 mL round-bottom flask flame-dried and cooled under Ar (g) was added 2-bromobenzoic acid (1.91 g, 12.19 mmol) dissolved in either MeCN or DCM (25 mL). To this was added EDC·HCl (1.89 g, 12.19 mmol and HOBt (1.71 g, 11.18 mmol). In a separate 50 mL round-bottom flask containing the cyclopropane TFA salt (2.45 g, 10.16 mmol) dissolved in MeCN or DCM was added DIPEA (4.20 mL, 25.40 mmol), evolving white fumes; this mixture was canulated into the reaction mixture and subsequently stirred for 24 h at ambient temperature. The reaction was transferred into a separatory funnel and diluted with 75 mL of EtOAc. The organics were then washed in the following order: HCl 1.0 N (50 mL), distilled water (50 mL), saturated $NaHCO_3$ (50 mL) and brine (2×'s, 50 mL each). The combined organics were dried with sodium sulfate anhydrous, filtered and concentrated in vacuo to give a golden brown solid, which was used crude in the following methylation step.

To a 250 mL round-bottom flask containing ethyl 1-[(2-bromophenyl)amido]cyclopropane-1-carboxylate (1.94 g, 6.22 mmol) and purged with argon was added anhydrous THF (50 mL) and NaH (22.4 mg, 9.33 mmol) (bubbling was observed) The reaction was stirred for 10 min. MeI (1.5 mL, 24.88 mmol) was added and this was stirred overnight at room temperature. The reaction was quenched with 50 mL of water and then transferred into a separatory funnel. The aqueous layer was extracted (3×'s, 50 mL) with EtOAc. The combined organics were washed with brine (50 mL), dried with sodium sulfate, filtered and concentrated in vacuo to give a dark-orange brown oil. The crude was then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes. The desired product was isolated as a pale yellow oil (1.59 g, 4.86 mmol, 78% yield over two steps). Reported as a mixture of rotamers. R_f 0.58 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48−7.42 (m, 1H), 7.29−7.08 (m, 3H), 4.13−4.06 (q, J = 7.3 Hz, 2H), 3.08 (s, 1.3H), 2.75 (s, 1.8H), 1.65−1.04 (m, 7H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.1, 171.6, 170.63, 170.43, 139.3, 138.4, 133.0, 132.7, 130.3, 130.1, 127.9, 127.8, 127.1, 126.4, 119.5, 118.7, 77.7, 77.3, 76.9, 61.6, 61.3, 43.1, 40.4, 36.9, 34.7, 20.6, 19.1 (br), 18.4, 17.3(br), 14.2, −2.4 (br). FTIR (cm^{-1}) (neat) 2979, 1725, 1435, 1296, 1023, 770.5, 748.9, 501.3, 448.6; HRMS (ESI, Pos) calcd for $C_{14}H_{16}BrNO_3$ $(M + H)^+$ 326.03959, found 326.03863.

*Ethyl 1-(2-chloro-N-methylbenzamido)cyclopropanecarboxylate (**1ab**).* The title compound was prepared by the general synthesis on a 10.16 mmol scale and then purified via column chromatography (10−30% EtOAc/Hex) to give a golden yellow oil (2.298 g, 8.16 mmol, 80% yield over two steps). Reported as a mixture of rotamers. R_f 0.39 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42−7.16 (m, 4H), 4.20 (q, J = 7.1 Hz, 2H), 3.17 (s, 1.4H), 2.85 (s, 1.6H), 1.94−1.10 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.9, 171.4, 169.8, 169.6, 137.1, 136.2, 130.0, 129.83, 129.78, 129.65, 129.3, 127.6, 127.0, 126.4, 126.2, 61.4, 61.1, 42.9, 40.3, 36.6, 34.4, 20.1, 18.7 (br), 18.1, 17.6 (br), 14.0, −2.6 (br); FTIR (cm^{-1}) (neat) 2981, 1725, 1654, 1382, 1186, 1134, 1039, 748; HRMS (ESI, Pos) calcd for $C_{14}H_{16}ClNO_3$ $(M + H)^+$ 282.08811, found 282.08915 *m/z*.

*Ethyl 1-(2-iodo-N-methylbenzamido)cyclopropanecarboxylate (**1ac**).* The title compound was prepared by the general synthesis on a 12.71 mmol scale and then purified via column chromatography (10−30% EtOAc/Hex) to give a yellow oil (0.666 g, 1.78 mmol, in 14% yield over two steps). Reported as a mixture of rotamers. R_f 0.41 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.77−7.64 (m, 1H), 7.37−7.24 (m, 1H), 7.23−7.04 (m, 1H), 7,02−6.90 (m, 1H), 4,10 (q, J = 7.1 Hz, 2H), 3.08 (s, 1.1H), 2.74 (s, 1.9H), 1.86−0.94 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.0, 171.9, 171.7, 171.4, 143.0, 142.2, 139.3, 138.9, 130.1, 130.0, 128.3, 127.6, 127.2, 125.8, 93.7, 91.7, 61.5, 61.2, 43.0, 40.3, 37.0, 34.7, 21.1, 18.9 (br), 18.4, 17.2 (br), 14.1, −2.4 (br); FTIR (cm^{-1}) (neat) 2981, 1725, 1650, 1384, 1186, 1014,

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730, 440; HRMS (ESI, Pos) calcd for $C_{14}H_{16}INO_3$ $(M + H)^+$ 374.02331, found 374.02476 *m/z*.

*Ethyl 1-(N-benzyl-2-bromobenzamido)cyclopropane-1-carboxylate (**1b**).* The title compound was prepared by the general synthesis on a 2.568 mmol scale and then purified via column chromatography (10−60% EtOAc/Hexanes) to give a clear oil (0.9298 g, 2.311 mmol, 90% yield). Reported as a mixture of rotamers. R_f 0.46 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67−7.24 (m, 10H), 5.53 (d, J = 15.4 Hz, 0.7H), 4.45−4.15 (m, 3.7H), 1.45−1.08 (m, 7H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.6, 171.8, 171.5, 139.4, 138.5, 133.3, 132.9, 130.43, 130.28, 128.60, 128.43, 127.7, 127.2, 126.6, 119.9, 119.4, 61.9, 61.4, 53.8, 52.46, 52.41, 43.3, 19.5, 17.5, 14.4; FTIR (cm^{-1}) (neat) 2980, 1724, 1652, 1177, 1156, 747.5, 501.5; HRMS (ESI, Pos) calcd for $C_{20}H_{20}BrNO_3$ $(M + H)^+$ 402.07141, found 402.06993 *m/z*.

*Ethyl 1-(N-benzyl-2-bromobenzamido)cyclopropane-1-carboxylate (**1b**).* The title compound was prepared by the general synthesis on a 2.568 mmol scale and then purified via column chromatography (10−60% EtOAc/Hexanes) to give a clear oil (0.9298 g, 2.311 mmol, 90% yield). Reported as a mixture of rotamers. R_f 0.46 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67−7.24 (m, 10H), 5.53 (d, J = 15.4 Hz, 0.7H), 4.45−4.15 (m, 3.7H), 1.45−1.08 (m, 7H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.6, 171.8, 171.5, 139.4, 138.5, 133.3, 132.9, 130.43, 130.28, 128.60, 128.43, 127.7, 127.2, 126.6, 119.9, 119.4, 61.9, 61.4, 53.8, 52.46, 52.41, 43.3, 19.5, 17.5, 14.4; FTIR (cm^{-1}) (neat) 2980, 1724, 1652, 1177, 1156, 747.5, 501.5; HRMS (ESI, Pos) calcd for $C_{20}H_{20}BrNO_3$ $(M + H)^+$ 402.07141, found 402.06993 *m/z*.

*2-Bromo-N-(1-cyanocyclopropyl)-N-methylbenzamide (**1d**).* The title compound was prepared by the general synthesis on a 4.434 mmol scale and then purified via column chromatography (10−60% EtOAc/Hexanes) to give a clear oil (0.389 g, 1.394 mmol, 31% yield). Reported as a mixture of rotamers. R_f 0.46 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66−7.28 (m, 4H), 3.24 (s, 1.09H), 2.92 (s, 1.72H), 1.70−1.27 (m, 4H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.1, 136.7, 132.9, 132.5, 130.64, 130.53, 127.6, 127.29, 127.24, 127.04, 119.5, 119.03, 118.85, 118.6, 35.9, 33.6, 27.5; FTIR (cm^{-1}) (neat) 2921, 2237,1657, 1369, 1076, 695, 565 ; HRMS (ESI, Pos) calcd for $C_{12}H_{11}BrN_2O$ $(M + H)^+$ 279.01275, found 279.01407 *m/z*.

*Ethyl 1-(2-bromo-N-methyl-3-nitrobenzamido)cyclopropane-1-carboxylate (**1f**).* The title compound was prepared by the general synthesis on a 6.272 mmol scale and then purified via column chromatography (10−60% EtOAc/Hexanes) to give an orange oil (0.773 g, 3.596 mmol, 57% yield over two steps). Reported as a mixture of rotamers. R_f 0.59 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42−6.92 (m, 4H), 4.27−4.18 (m, 2H), 3.28−3.20 (m, 0.8H), 2.93 (s, 1.7H), 1.89−1.19 (m, 7H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 171.5, 170.5, 165.9, 159.9, 157.4, 131.91, 131.83, 131.23, 131.14, 131.04, 128.8, 128.5, 127.1, 126.9, 119.89, 119.85, 115.1, 114.9, 61.84, 61.74, 61.5, 40.5, 36.4, 14.14, 14.01; FTIR (cm^{-1}) (neat) 2982, 1724, 1661,1445, 1188, 871.9, 676.6, 662.6, 469.1; HRMS (ESI, Pos) calcd for $C_{14}H_{15}BrN_2O_5$ $(M + H)^+$ 371.02554, found 371.02371 *m/z*.

*Ethyl 1-(2-bromo-N-methyl-5-nitrobenzamido)-cyclopropanecarboxylate (**1g**).* The title compound was prepared by the general synthesis on a 4.26 mmol scale and then purified via column chromatography (10−30% EtOAc/Petroleum Et2O) to give a yellow solid (0.773 g, 2.08 mmol, 55% yield over two steps). Reported as a mixture of rotamers. mp 80−86 °C; R_f 0.39 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11−7.94 (m, 2H), 7.74−7.65 (m, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.11 (s, 1.6H), 2.80 (s, 1.4H), 1.77−1.03 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz); δ 171.7, 171.1, 168.4, 168.3, 147.1, 146.6, 140.6, 139.8, 134.4, 134.2, 127.1, 126.2, 124.8, 124.7, 122.9, 121.6, 62.3, 61.5, 43.1, 40.6, 36.9, 34.7, 20.7, 19.0 (br), 18.3, 17.4 (br), 14.2, 14.12, 14.07; FTIR (cm^{-1}) (neat) 2982, 1654, 1526, 1338, 1183, 1135, 1026, 752, 739; HRMS (ESI, Pos) calcd for $C_{14}H_{15}BrN_2O_5$ $(M + H)^+$ 371.02429, found 371.02371 *m/z*.

*Ethyl 1-(2-bromo-5-fluoro-N-methylbenzamido)cyclopropane-1-carboxylate (**1h**).* The title compound was prepared by the general synthesis on a 4.822 mmol scale and then purified via column chromatography (10−30% EtOAc/Hex) to give a white solid (1.044 g, 3.032 mmol, 63% yield over two steps). Reported as a mixture of rotamers. mp 66−68 °C R_f 0.52 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54−7.45 (m, 1H), 7.03−6.90 (m, 2H), 4.26−4.13 (m, 2H), 3.15 (s, 1.4H), 2.86 (s, 1.6H), 1.42−1.17 (m, 7H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.1, 171.6, 169.5, 169.3, 162.3 (d, J = 249.6 Hz), 161.6 (d, J = 249.5 Hz), 141.0 (d, J = 7.4 Hz), 140.1 (d, J = 6.9 Hz), 134.7 (d, J = 8.0 Hz), 134.5(d, J = 8.1 Hz), 117.8 (d, J = 22.5 Hz), 117.5 (d, J = 22.4 Hz),115.4 (d, J = 24.2 Hz),114.3, (d, J = 24.5 Hz), 113.2, 62.0, 61.6, 43.2, 40.7, 37.0, 34.9, 20.7, 18.4, 14.3; ^{19}F NMR ($CDCl_3$, 282 MHz):δ −114.7 (m), −115.2 (m); FTIR (cm^{-1}) (neat) 2984, 1729, 1658, 1407, 1193, 1148, 868, 749, 591; HRMS (ESI, Pos) calcd for $C_{14}H_{15}BrFNO_3$ $(M + H)^+$ 344.03039, found 344.02921 *m/z*.

*Ethyl 1-(2-bromo-4-fluoro-N-methylbenzamido)-cyclopropanecarboxylate (**1i**).* The title compound was prepared by the general synthesis on a 3.09 mmol scale and then purified via column chromatography (10−30% EtOAc/Hex) to give a light yellow oil (0.235 g, 0.68 mmol, 22% yield over two steps). Reported as a mixture of rotamers. R_f 0.38 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38−7.22 (m, 2H), 7.04 (dtd, J = 30.9, 10.7, 2.4 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.18 (s, 1.3H), 2.86 (s, 1.7H), 1.86−1.12 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.0, 171.5 170.0, 169.8, 164.0 (d, J = 253.2 Hz), 160.6 (d, J = 252.9 Hz), 135.7 (d, J = 4.0 Hz), 134.9 (d, J = 4.0 Hz), 129.5 (d, J = 8.7 Hz), 127.9 (d, J = 8.7 Hz), 120.7 (d, J = 24.6 Hz), 120.4 (d, J = 9.4 Hz), 120.2 (d, J = 24.7 Hz), 119.5 (d, J = 9.4 Hz), 115.3 (d, J = 21.4 Hz), 114.5 (d, J = 21.3 Hz), 61.7, 61.3, 43.1, 40.5, 36.9, 34.7, 20.6, 19.1 (br), 18.3, 17.6 (br), 14.1; ^{19}F NMR ($CDCl_3$, 282 MHz) δ −109.5 (m), −109.8 (m); FTIR (cm^{-1}) (neat) 2981, 1726, 1655, 1381, 1189, 1027, 752; HRMS (ESI, Pos) calcd for $C_{14}H_{15}BrFNO_3$ $(M + H)^+$ 344.03021, found 344.02921 *m/z*.

*Ethyl 1-(2-bromo-4,5-difluoro-N-methylbenzamido)-cyclopropane-1-carboxylate (**1j**).* The title compound was prepared by the general synthesis on a 5.882 mmol scale and then purified via column chromatography (10−30% EtOAc/Hex) to give a clear oil (1.605 g, 4.431 mmol, 75% yield over two steps). Reported as a mixture of rotamers. R_f 0.48 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.41−7.35 (m, 1H), 7.14−7.09 (m, 1H), 4.17−4.12 (m, 2H), 3.10 (s, 1.4H), 2.83 (s, 1.6H), 1.65−1.18 (m, 7H) ; ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.0, 171.4, 168.80, 168.61, 151.65, 151.52, 151.37, 151.23, 151.10, 150.58, 150.46, 149.11, 148.98, 148.83, 148.70, 148.0, 136.00, 135.95, 135.11, 135.06, 122.5, 122.27, 122.13, 121.93, 117.2, 117.0, 115.95, 115.75, 113.88, 62.03, 61.55, 43.18, 40.68, 36.96, 34.85, 29.71, 20.72, 18.25, 14.29,14.26; ^{19}F NMR ($CDCl_3$, 282 MHz) δ −133.2 (m), −133.5 (m), −136.8(m), −137.5(m); FTIR (cm^{-1}) (neat) 2981, 1724, 1651, 1287, 1149, 750.1, 576.1, 458.0 ; HRMS (ESI, Pos)calcd for $C_{14}H_{15}BrF_2NO_3$ $(M + H)^+$ 362.02137, found 362.01979 *m/z*.

*Ethyl 1-(2-bromo-5-chloro-N-methylbenzamido)-cyclopropanecarboxylate (**1k**).* The title compound was prepared by the general synthesis on a 3.87 mmol scale and then purified via column chromatography (10−40% EtOAc/Hex) to give a cream white solid (0.681 g, 7.89 mmol, 49% yield over two steps). Reported as a mixture of rotamers. mp 98−104 °C; R_f 0.48 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.49 (t, J = 8.3 Hz, 1H), 7.33−7.16 (m, 2H), 4.21 (q, J = 7.1 Hz, 2H), 3.17 (s, 1.4H), 2.88 (s, 1.6H), 1.93−1.08 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz); δ 172.1, 171.5, 169.4, 169.2, 140.7, 139.9, 134.3, 134.1, 133.5, 130.6, 130.3, 128.1, 126.9, 117.6, 116.8, 62.1, 61.6, 61.3, 43.2, 40.6, 37.0, 34.8, 28.3, 20.7, 19.0 (br), 18.4, 17.7 (br), 14.4, 14.3; FTIR (cm^{-1}) (neat) 3341, 2979, 1718, 1645, 1389, 1595, 1026, 754, 502; HRMS (ESI, Pos) calcd for $C_{14}H_{15}BrClNO_3$ $(M + H)^+$ 360.00014, found 359.99966 *m/z*.

*Ethyl 1-(2-bromo-4-chloro-N-methylbenzamido)cyclopropane-1-carboxylate (**1l**).* The title compound was prepared by the general synthesis on a 5.962 mmol scale and then purified via column chromatography (10−40% EtOAc/Hex) to give a light yellow oil (0.8074 g, 2.239 mmol, 38% yield over two steps). Reported as a mixture of rotamers. R_f 0.44 (1:1 ethyl acetate:hexanes); ^{1}H NMR

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($CDCl_3$, 400 MHz) δ 7.62−7.58 (m, 1H), 7.38−7.20 (m, 2H), 4.24−4.19 (m, 2H), 3.18 (s, 1.3H), 2.87 (s, 1.6H), 1.47−1.19 (m, 7H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 171.7, 171.1, 169.55, 169.37, 137.5, 136.6, 135.2, 134.9, 132.5, 132.1, 128.5, 127.8, 127.07, 127.03, 119.9, 119.0, 61.5, 61.1, 42.8, 40.2, 36.6, 34.5, 20.4, 18.1, 13.9 ; FTIR (cm^{-1}) (neat) 2980, 1725, 1652, 1367, 1327, 1078, 725.8, 507.2, 445.3; HRMS (ESI, Pos) calcd calcd for $C_{14}H_{15}BrClNO_3$ $(M + H)^+$ 360.00086, found 359.99966 *m/z*.

*Ethyl 1-(2-bromo-5-methoxy-N-methylbenzamido)-cyclopropanecarboxylate (**1m**).* The title compound was prepared by the general synthesis on a 4.04 mmol scale and then purified via column chromatography (10−30% EtOAc/Hex) to give a light yellow oil (0.486 g, 1.37 mmol, 34% yield over two steps). Reported as a mixture of rotamers. R_f 0.41 (1:1 ethyl acetate:hexanes); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.30 (m, 1H), 6.79−6.65 (m, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.72 (s, 1.7H), 3.64 (s, 1.3H), 3.10 (s, 1.3H), 2.80 (s, 1.7H), 1.83−1.07 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.0, 171.5, 170.9, 170.6, 139.7, 138.90, 138.89, 138.6, 130.8, 130.7, 127.4, 126.8, 124.9, 123.6, 121.6, 120.7, 61.4, 61.1, 43.0, 40.2, 36.7, 34.4, 23.1, 22.9, 20.2, 18.9 (br), 18.2, 17.3 (br), 14.1, 14.0; FTIR (cm^{-1}) (neat) 2980, 1726, 1655, 1467, 1291, 1238, 1040, 751; HRMS (ESI, Pos) calcd for $C_{15}H_{18}BrNO_4$ $(M + H)^+$ 356.04746, found 356.0492 *m/z*.

*Ethyl 1-(2-bromo-4,5-dimethoxy-N-methylbenzamido)-cyclopropanecarboxylate (**1n**).* The title compound was prepared by the general synthesis on a 6.71 mmol scale and then purified via column chromatography (50−75% EtOAc/Petroleum Et_2O) to give a white solid (0.879 g, 2.28 mmol, 34% yield over two steps). Reported as a mixture of rotamers. mp 104−106 °C; R_f 0.19 (1:1 ethyl acetate:hexanes); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.01 (d, J = 13.8 Hz, 1H), 6.87−6.71 (m, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.94−3.70 (m, 6H), 3.16 (s, 1.3H), 2.89 (s, 1.5H), 1.85−1.13 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.0, 171.2, 170.08, 170.06, 149.5, 149.2, 148.4, 147.5, 130.8, 129.8, 115.2, 114.8, 110.1, 109.6, 109.2, 108.8, 61.2, 60.8, 55.8, 55.74, 55.72, 55.4, 42.8, 40.1, 36.5, 34.3, 20.2, 18.5 (br), 18.0, 17.2 (br), 13.85, 13.79; FTIR (cm^{-1}) (neat) 2981, 1720, 1506, 1255, 1160, 1027, 863, 754; HRMS (ESI, Pos) calcd for $C_{16}H_{20}BrNO_5$ $(M + H)^+$ 386.06031, found 386.05976 *m/z*.

*Ethyl 1-(2-bromo-3,4,5-trimethoxy-N-methylbenzamido)-cyclopropanecarboxylate (**1o**).* The title compound was prepared by the general synthesis on a 3.75 mmol scale and then purified via column chromatography (20−50% EtOAc/Petroleum Et_2O) to give a clear oil (0.996 g, 2.39 mmol, 63% yield over two steps). Reported as a mixture of rotamers. R_f 0.54 (1:1 ethyl acetate:petroleum ether); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.63−6.51 (m, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.87−3.70 (m, 8H), 3.65 (s, 1H), 3.06 (s, 1.3H), 2.78 (s, 1.7H), 1.81−1.04 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz); δ 172.2, 171.5, 170.2, 170.1, 153.4, 152.7, 151.2, 150.8, 143.4, 143.1, 134.5, 133.6, 106.3, 106.0, 105.6, 105.2, 61.5, 61.2, 61.0, 60.0, 56.1, 55.8, 43.1, 40.4, 36.8, 34.6, 20.3, 19.0 (br), 18.2, 17.2 (br), 14.09, 14.07; FTIR (cm^{-1}) (neat) 2939, 1726, 1656, 1382, 1242, 1106, 1009, 752; HRMS (ESI, Pos) calcd for $C_{17}H_{22}BrNO_6$ $(M + H)^+$ 416.0706, found 416.07033 *m/z*.

*Ethyl 1-(2-bromo-N,3-dimethylbenzamido)-cyclopropanecarboxylate (**1p**).* The title compound was prepared by the general synthesis on a 5.61 mmol scale and then purified via column chromatography (10−40% EtOAc/Hex) to give a yellow oil (0.495 g, 1.46 mmol, 26% yield over two steps). Reported as a mixture of rotamers. R_f 0.37 (1:1 ethyl acetate:hexanes); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.25−7.03 (m, 3H), 4.21 (q, J = 7.1 Hz, 2H), 3.19 (s, 1.2H), 2.85 (s, 1.8H), 2.42 (s, 3H), 1.91−1.22 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz); δ 172.2, 171.6, 170.4, 170.2, 159.1, 158.5, 139.9, 139.0, 133.7, 133.5, 116.6, 116.2, 113.0, 112.1, 109.6, 108.8, 61.6, 61.3, 55.5, 55.3, 43.1, 40.4, 36.8, 34.6, 20.5, 19.1 (br), 18.3, 17.4 (br), 14.17, 14.15, −2.4 (br); FTIR (cm^{-1}) (neat) 2980, 1727, 1656, 1383, 1193, 1138, 1026, 791, 749; HRMS (ESI, Pos) calcd for $C_{15}H_{18}BrNO_3$ $(M + H)^+$ 340.05468, found 340.05428 *m/z*.

*Ethyl 1-(2-bromo-N,4-dimethylbenzamido)-cyclopropanecarboxylate (**1q**).* The title compound was prepared by the general synthesis on a 5.68 mmol scale and then purified via column chromatography (10−30% Et_2O/Hex) to give a cream yellow solid (0.975 g, 2.87 mmol, 50% yield over two steps). Reported as a mixture of rotamers. mp 70−74 °C; R_f 0.39 (1:1 ethyl acetate:hexanes); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.38 (d, J = 9.4 Hz, 1H), 7.22−7.01 (m, 2H), 4.19 (q, J = 7.1 Hz, 2H), 3.17 (s, 1.3H), 2.85 (s, 1.7H), 2.32 (s, 3H), 1.85−1.11 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.9, 171.4, 170.5, 170.4, 140.5, 140.2, 136.2, 135.3, 133.1, 132.7, 128.2, 127.5, 127.4, 126.0, 119.0, 118.3, 61.3, 61.0, 42.9, 40.2, 36.7, 34.4, 20.64, 20.62, 20.4, 18.7 (br), 18.2, 17.7 (br), 14.0, −2.5 (br); FTIR (cm^{-1}) (neat) 2980, 1726, 1653, 1380, 1186, 1029, 752; HRMS (ESI, Pos) calcd for $C_{15}H_{18}BrNO_3$ $(M + H)^+$ 340.05298, found 340.05428 *m/z*.

*Ethyl 1-(2-bromo-N-methylthiophene-3-carboxamido)-cyclopropane-1-carboxylate (**1r**).* The title compound was prepared by the general synthesis on a 5.28 mmol scale and then purified via column chromatography (10−60% EtOAc/Hexanes) to give a clear oil (0.7096 g, 2.136 mmol, 40% yield over two steps). Reported as a mixture of rotamers. R_f 0.46 (1:1 ethyl acetate:hexanes); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32−7.26 (m, 1H), 6.92 (s, 1H), 4.16 (t, J = 6.5 Hz, 2H), 3.06 (d, J = 37.3 Hz, 3H), 1.64−1.16 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz); δ 171.8, 171.0, 164.9, 132.36, 132.33, 131.7, 129.88, 129.78, 127.2, 126.2, 110.5, 109.4, 61.6, 61.0, 43.1, 40.6, 37.2, 34.9, 21.5, 18.4, 13.8; FTIR (cm^{-1}) (neat) 2980, 1725, 1643, 1123, 909.6, 751.4, 551.1; HRMS (ESI, Pos) calcd for $C_{12}H_{14}BrNO_3S$ $(M + H)^+$ 331.99659, found 331.99505 *m/z*.

*Ethyl 1-(2-bromo-N-methylnicotinamido)cyclopropane-1-carboxylate (**1s**).* The title compound was prepared by the general synthesis on a 9.111 mmol scale and then purified via column chromatography (10−60% EtOAc/Hexanes) to give a brown oil (0.770 g, 2.354 mmol, 28% yield over two steps). Reported as a mixture of rotamers. R_f 0.46 (1:1 ethyl acetate:hexanes); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.43−8.38 (m, 1H), 7.67−7.24 (m, 2H), 4.25−4.19 (m, 2H), 3.19 (s, 1.6H), 2.92 (s, 1.8H), 1.52−1.21 (m, 7H); ^{13}C NMR ($CDCl_3$, 101 MHz); δ 172.0, 171.4, 169.2, 168.7, 150.4, 150.1, 139.2, 138.1, 136.7, 136.4, 135.6, 134.9, 123.1, 122.2, 61.9, 61.60, 61.55, 43.2, 40.7, 37.0, 34.8, 20.9, 18.4, 14.30, 14.28; FTIR (cm^{-1}) (neat) 2980, 1724, 1652, 1381, 1036, 754.1, 454.1; HRMS (ESI, Pos) calcd for $C_{13}H_{15}BrN_2O_3$ $(M + H)^+$ 327.03505, found 327.03388 *m/z*.

*1-(2-Bromophenyl) 1-ethyl cyclopropane-1,1-dicarboxylate (**1u**).* The title compound was prepared as directed (see SM synthesis) on a 8.283 mmol scale and then purified via column chromatography (10−60% EtOAc/Hexanes) to give a light yellow oil (1.729 g, 5.301 mmol, 64% yield over two steps). R_f 0.48 (1:1 ethyl acetate:hexanes); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.68−7.63 (m, 1H), 7.39−7.20 (m, 3H), 4.35−4.02 (m, 2H), 3.33 (s, 0.9H), 3.26 (s, 2H), 1.67−0.97 (m, 7H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 171.3, 171.0, 168.1, 167.8, 142.4, 141.8, 134.0, 133.6, 130.3, 129.8, 129.32, 129.30, 128.8, 128.5, 123.2, 122.4, 61.7, 61.3, 37.8, 37.3, 30.2, 29.3, 17.1, 16.5, 16.2, 14.9, 14.4, 14.2; FTIR (cm^{-1}) (neat) 2979, 1720, 1655, 1584, 1476,1436, 1368, 1057, 765.0, 729.7, 455.6; HRMS (ESI, Pos) calcd for $C_{14}H_{16}BrNO_3$ $(M + H)^+$ 326.03966, found 326.03863 *m/z*.

General Procedure A for Pd-Catalyzed Cyclization. A 5.0 mL microwave vial containing 2-halobenzamide (0.5 mmol) was taken into a glovebox and to this was added in the following order: $Pd(OAc)_2$ (5 mol %, 0.025 mmol, 5.6 mg), PCy_3 (5 mol %, 0.025 mmol, 7.0 mg), and K_2CO_3 (1.5 equiv, 0.75 mmol, 104 mg). The vial was crimped shut. Outside of the glovebox was added 2.5 mL of toluene. The yellowish-orange solution was then heated to 110 °C in an oil bath for 16 h. The reaction was cooled to ambient temperature, filtered over a cotton-Celite plug, and rinsed with 25 mL of ethyl acetate. It was then concentrated in vacuo to give the crude product. The crude was then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% Ethyl Acetate/Hexanes to give the desired products.

General Procedure B for Pd-Catalyzed Cyclization. A 5.0 mL microwave vial containing 2-bromobenzamide (0.5 mmol) was taken into a glovebox and to this was added in the following order: $Pd(OAc)_2$ (5 mol %, 0.025 mmol, 5.6 mg), $PtBu_2Me{\cdot}HBF_4$ (5 mol %, 0.025 mmol, 6.2 mg), CsOPiv (0.3 equiv, 0.15 mmol, 35.1 mg), K_3PO_4 (1.5 equiv, 0.75 mmol, 159 mg). The vial was crimped shut. Outside of the glovebox was added 2.5 mL of toluene. The yellowish-orange

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solution was then heated to 110 °C in an oil bath for 16 h. The reaction was cooled to ambient temperature, filtered over a cotton-Celite plug, and rinsed with 25 mL of ethyl acetate. It was then concentrated in vacuo to give the crude product. The crude was then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% Ethyl Acetate/Hexanes to give the resulting products.

General Procedure C for Pd-Catalyzed Cyclization. Preocedure C was identical to Procedure A except 0.3 equiv of Ag_3PO_4 was additionally added in a glovebox.

*Ethyl 2-methyl-3-oxo-1,2,3,7b-tetrahydro-1aH-cyclopropa[c]-isoquinoline-1a-carboxylate (**2a**).* The title compound was prepared by general procedure A on a 0.9921 mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a pale yellow solid in 96% yield (0.2339g, 0.9536 mmol). R_f 0.46 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.14−8.12 (m, 1H), 7.48−7.41 (m, 1H), 7.36−7.30 (m, 2H), 4.33−4.14 (m, 2H), 3.24 (s, 3H), 2.72 (dd, J = 10.4, 7.2 Hz, 1H), 2.15 (dd, J = 10.4, 4.6 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H), 0.86 (dd, J = 7.2, 4.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.0, 162.3, 136.4, 132.1, 129.1, 128.2, 127.5, 125.1, 62.1, 45.0, 34.7, 26.4, 20.1, 14.3; FTIR (cm^{-1}) (neat) 2981, 1720, 1648, 1249, 798.1, 748.9, 523.9; HRMS (ESI, Pos) calcd for $C_{14}H_{15}NO_3$ $(M + H)^+$ 246.11316, found 246.11247 *m/z*.

*Ethyl 2-benzyl-3-oxo-1,2,3,7b-tetrahydro-1aH-cyclopropa[c]-isoquinoline-1a-carboxylate (**2b**).* The title compound was prepared by general procedure A on a 0.4994 mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a yellow crystalline solid in 96% yield (0.1282 g, 0.4944 mmol). mp 98−101 °C; R_f 0.45 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25 (d, J = 7.8 Hz, 1H), 7.47−7.27 (m, 8H), 5.79 (d, J = 14.6 Hz, 1H), 4.49 (d, J = 14.6 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 2.61 (dd, J = 10.4, 7.3 Hz, 1H), 1.99 (dd, J = 10.5, 5.0 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H), 0.46 (dd, J = 7.2, 5.0 Hz, 1H);^{13}C NMR ($CDCl_3$, 101 MHz) δ 169.7, 161.8, 136.5, 136.3, 132.2, 129.43, 129.35, 128.3, 128.0, 127.5, 127.3, 125.3, 61.9, 49.2, 43.0, 25.1, 21.4, 14.1; FTIR (cm^{-1}) (neat) 3002, 2926, 1722, 1647, 1359, 1105, 7021, 455.8; HRMS (ESI, Pos) calcd for $C_{20}H_{19}NO_3$ $(M + Na)^+$ 344.12571, found 344.12704 *m/z*.

*6-Methyl-5-oxo-5H,6H,6aH,7H,7aH-cyclopropa[c]isoquinoline-6a-carbonitrile (**2d**).* The title compound was prepared by general procedure B on a 0.1975 mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a light cream-colored solid in 42% yield (0.01644 g, 0.08295 mmol). R_f 0.44 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz); δ 8.17−8.15 (m, 1H), 7.54−7.51 (m, 1H), 7.44−7.39 (m, 2H), 3.38 (s, 3H), 3.02−2.97 (m, 1H), 2.01−1.97 (m, 1H), 0.99−0.96 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.6, 134.4, 132.6, 129.4, 128.19, 128.10, 124.2, 117.5, 77.4, 77.0, 76.5, 33.1, 23.5, 21.4; FTIR (cm^{-1}) (neat) 3095, 2921, 2237, 1655, 1369, 1049, 1027, 753.9, 533.8 ; HRMS (ESI, Pos) calcd for $C_{12}H_{10}N_2O$ $(M + H)^+$ 199.08659, found 199.08733 *m/z*.

*Ethyl 2-methyl-7-nitro-3-oxo-1,2,3,7b-tetrahydro-1aH-cyclopropa[c]isoquinoline-1a-carboxylate (**2f**).* The title compound was prepared by general procedure A on a 0.4995 mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a light brown crystalline solid in 31% yield (0.0444 g, 0.153 mmol). mp 144−146 °C; R_f 0.44 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz δ 7.45−7.38 (m, 1H), 7.17−7.14 (m, 1H), 7.06−6.99 (m, 1H), 4.32−4.18 (m, 2H), 3.19 (s, 3H), 2.75−2.71 (m, 1H), 2.17−2.12 (m, 1H), 1.33−1.28 (m, 3H), 0.91−0.87 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.8, 161.1, 134.8, 133.7, 132.2, 129.7, 129.1, 126.7, 62.3, 45.1, 34.9, 25.9, 20.2, 14.3 FTIR (cm^{-1}) (neat) 3101, 2989, 2908, 1718, 1649, 1214, 1034, 687.4, 483.5; HRMS (ESI, Pos) calcd for $C_{14}H_{14}N_2O_5$ $(M + H)^+$ 291.09842, found 291.09827 *m/z*.

*Ethyl 2-methyl-5-nitro-3-oxo-1,2,3,7b-tetrahydro-1aH-cyclopropa[c]isoquinoline-1a-carboxylate (**2g**).* The title compound was prepared by general procedure A on a 0.5 mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a crystalline light brown solid in 58% yield (0.0838 g, 0.2887 mmol). mp 116−117 °C; R_f 0.44 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.97−8.96 (m, 1H), 8.30 (ddd, J = 8.4, 2.5, 1.4 Hz, 1H), 7.56 (dd, J = 8.4, 1.3 Hz, 1H), 4.35−4.20 (m, 2H), 3.29 (s, 3H), 2.85−2.80 (m,, 1H), 2.33−2.28 (m, 1H), 1.34−1.30 (m, 3H), 1.01−0.98 (m, 1H).; ^{13}C NMR ($CDCl_3$, 101 MHz) δ 169.1, 160.1, 147.6, 143.3, 129.7, 126.65, 126.48, 124.7, 62.5, 45.6, 35.0, 26.0, 21.0, 14.3; FTIR (cm^{-1}) (neat) 2931, 1728, 1645, 1242, 1034, 783.1, 504.1, 448.7; HRMS (ESI, Pos) calcd for $C_{14}H_{14}N_2O_5$ $(M + H)^+$ 291.09842, found 291.09755 *m/z*.

*Ethyl 5-fluoro-2-methyl-3-oxo-1,2,3,7b-tetrahydro-1aH-cyclopropa[c]isoquinoline-1a-carboxylate (**2h**).* The title compound was prepared by general procedure A on a 0.5 mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a light crystalline solid in 81% yield (0.1071 g, 0.4068 mmol). mp 80−82 °C; R_f 0.5 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85 (dt, J = 9.3, 2.2 Hz, 1H), 7.38−7.35 (m, 1H), 7.19 (ddd, J = 9.1, 7.4, 2.8 Hz, 1H), 4.32−4.21 (m, 2H), 3.27 (s, 3H), 2.76−2.72 (m, 1H), 2.17 (ddd, J = 10.3, 4.7, 1.6 Hz, 1H), 1.35−1.31 (m, 3H), 0.87 (ddd, J = 7.2, 4.7, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.7, 162.4 (d, J = 246.3 Hz), 161.1, 132 (d, J = 3.2 Hz), 130 (d, J = 7.6 Hz), 127.1 (d, J = 7.7 Hz), 119.4 (d, J = 22.3 Hz), 115.6 (d, J = 23.8 Hz), 62.1, 44.9, 34.7, 25.7, 19.9, 14.2; ^{19}F NMR ($CDCl_3$, 282 MHz) δ −113.5 (m); FTIR (cm^{-1}) (neat) ; 2928, 1722, 1646, 1194, 1077, 533.9, 447.2; HRMS (ESI, Pos) calcd for $C_{14}H_{14}FNO_3$ $(M + H)^+$ 264.10432, found 264.10305 *m/z*.

*Ethyl 6-fluoro-2-methyl-3-oxo-1,2,3,7b-tetrahydro-1aH-cyclopropa[c]isoquinoline-1a-carboxylate (**2i**).* The title compound was prepared by general procedure A on a 0.4838 mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a yellow solid in 96% yield (0.1224 g, 0.4649 mmol). R_f 0.48 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16−8.11 (m, 1H), 7.05−6.97 (m, 2H), 4.32−4.17 (m, 2H), 3.22 (s, 3H), 2.71−2.65 (m, 1H), 2.20−2.14 (m, 1H), 1.32−1.27 (m, 3H), 0.89 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.7, 165.1 (d, J = 253.7 Hz), 161.5, 139.1 (d, J = 9.4 Hz), 132.1 (d, J = 9.6 Hz), 121.5 (d, J = 2.7 Hz), 115.1 (d, J = 21.7 Hz), 114.8 (d, J = 22.5 Hz), 62.2, 45.2, 34.7, 26.12, 26.09, 20.3, 14.3 ; ^{19}F NMR ($CDCl_3$, 282 MHz) δ −107.2 (m); FTIR (cm^{-1}) (neat) 2924, 1727, 1646, 1242, 995.2, 685.2, 497.1; HRMS (ESI, Pos) calcd for $C_{14}H_{14}FNO_3$ $(M + H)^+$ 264.10424, found 264.10305 *m/z*.

*Ethyl 5,6-difluoro-2-methyl-3-oxo-1,2,3,7b-tetrahydro-1aH-cyclopropa[c]isoquinoline-1a-carboxylate (**2j**).* The title compound was prepared by general procedure A on a 0.5 mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a yellow solid in 81% yield (0.1365 g, 0.4853 mmol). R_f 0.44 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99−7.93 (m, 1H), 7.21−7.16 (m, 1H), 4.35−4.20 (m, 2H), 3.25 (s, 3H), 2.68 (ddd, J = 11.2, 6.0, 2.2 Hz, 1H), 2.21−2.17 (m, 1H), 1.35−1.31 (m, 3H), 0.91 (ddd, J = 7.0, 4.8, 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.4, 160.4, 154.4 (d, J = 13.5 Hz), 153 (d, J = 235.4 Hz), 151.3 (d, J = 12.8 Hz), 152.8 (d, J = 234.7 Hz), 151.1 (d, J = 13.5 Hz), 148 (d, J = 12.8 Hz), 133.6 (d, J = 3.7 Hz), 133.5 (d, J = 3.8 Hz), 122.4 (d, J= 3.2 Hz), 122.3 (d, J= 3.2), 118.3 (d, J = 19.2 Hz), 118.3 (d, J = 19.2 Hz), 116.9 (d, J= 18.5 Hz), 62.2, 45.0, 34.6, 19.9, 14.1; ^{19}F NMR ($CDCl_3$, 282 MHz) δ −133.1 (m), −139.5 (m); FTIR (cm^{-1}) (neat) 3055, 2931, 1727, 1650, 1337, 1267, 720.4, 504.1, 411.7; HRMS (ESI, Pos) calcd for $C_{14}H_{13}F_2NO_3$ $(M + H)^+$ 282.0945, found 282.09363 *m/z*.

*Ethyl 5-chloro-2-methyl-3-oxo-1,2,3,7b-tetrahydro-1aH-cyclopropa[c]isoquinoline-1a-carboxylate (**2k**).* The title compound was prepared by general procedure A on a 0.5 mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a light crystalline yellow solid in 73% yield (0.1024 g, 0.3661 mmol). mp 79−80 °C; R_f 0.44 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08−8.08 (m, 1H), 7.38 (dd, J = 8.2, 2.2 Hz, 1H), 7.28−7.22 (m, 1H), 4.28−4.15 (m, 2H), 3.21 (s, 3H), 2.67 (dd, J = 10.3, 7.2 Hz, 1H,

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2.14 (dd, J = 10.4, 4.7 Hz, 1H), 1.27 (t, J = 7.1 Hz, 3H), 0.83 (dd, J = 7.2, 4.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.8, 161.1, 134.8, 133.7, 132.2, 129.7, 129.1, 126.7, 62.3, 45.1, 34.9, 25.9, 20.2, 14.3 FTIR (cm^{-1}) (neat) 2977, 1727, 1596, 1170, 974.9, 791.4, 695.3, 458.6 ; HRMS (ESI, Pos) calcd for $C_{14}H_{14}ClNO_3$ (M + H)$^+$ 280.07436, found 280.0735 *m/z*.

*Ethyl 6-chloro-2-methyl-3-oxo-1,2,3,7b-tetrahydro-1aH-cyclopropa[c]isoquinoline-1a-carboxylate (**2l**).* The title compound was prepared by general procedure A on a 0.5 mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a light yellow solid in 87% yield (0.1217 g, 0.4351 mmol). mp 108−110 °C; R_f 0.44 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (s, 1H), 4.32−4.20 (m, 2H), 3.96−3.91 (m, 9), 3.24 (s, 3H), 2.90−2.83 (m, 1H), 2.22−2.12 (1H), 1.38−129 (m, 3H), 0.83−0.80 (m, 1H).; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.3, 162.0, 152.8, 150.8, 145.5, 123.5, 120.8, 107.5, 62.1, 61.4, 61.1, 56.3, 44.9, 34.8, 21.8, 19.1, 14.3; FTIR (cm^{-1}) (neat) 2919, 1724, 1650, 1246, 1216, 927.5, 738.9, 546.1, 449.0; HRMS (ESI, Pos) calcd for $C_{14}H_{14}ClNO_3$ (M + H)$^+$ 280.07433, found 280.0735 *m/z*.

*Ethyl 5-methoxy-2-methyl-3-oxo-1,2,3,7b-tetrahydro-1aH-cyclopropa[c]isoquinoline-1a-carboxylate (**2m**).* The title compound was prepared by general procedure A on a 0.5 mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give an off-white crystalline solid in 71% yield (0.0982 g, 0.3567 mmol). mp 78−80 °C; R_f 0.44 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66 (d, J = 2.8 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.02 (dd, J = 8.4, 2.8 Hz, 1H), 4.24 (dtd, J = 19.8, 12.6, 7.2 Hz, 2H), 3.83 (s, 3H), 3.25 (s, 3H), 2.69 (dd, J = 10.2, 7.2 Hz, 1H), 2.11 (dd, J = 10.2, 4.5 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H), 0.81 (dd, J = 7.2, 4.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.1, 162.2, 159.1, 129.3, 128.5, 126.1, 119.9, 112.0, 62.0, 55.6, 44.8, 34.7, 25.9, 19.8, 14.2; FTIR (cm^{-1}) (neat) 2933, 1726, 1650, 1278, 1079, 859.0, 576.7; HRMS (ESI, Pos) calcd for $C_{15}H_{17}NO_4$ (M + H)$^+$ 276.12383, found 276.12303 *m/z*.

*Ethyl 5,6-dimethoxy-2-methyl-3-oxo-1,2,3,7b-tetrahydro-1aH-cyclopropa[c]isoquinoline-1a-carboxylate (**2n**).* The title compound was prepared by general procedure A on a 0.4971 mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a light beige crystalline solid in 93% yield (0.1413 g, 0.4628 mmol). mp 124−126 °C; R_f 0.44 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62 (s, 1H), 6.80 (s, 1H), 4.30−4.17 (m, 2H), 3.91 (d, J = 7.9 Hz, 6H), 3.22 (s, 3H), 2.66 (dd, J = 10.1, 7.2 Hz, 1H), 2.13−2.09 (m, 1H), 1.32−1.28 (m, 3H), 0.81 (dt, J = 7.5, 2.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.1, 162.3, 152.3, 148.4, 130.1, 117.9, 111.0, 110.0, 62.0, 56.17, 56.14, 44.9, 34.6, 26.2, 19.5, 14.2; FTIR (cm^{-1}) (neat) 3000, 2840, 1712, 1646, 1265, 847.9, 649.4, 514.1 ; HRMS (ESI, Pos) calcd for $C_{16}H_{19}NO_5$ (M + H)$^+$ 306.1346, found 306.1336 *m/z*.

*Ethyl 5,6,7-trimethoxy-2-methyl-3-oxo-1,2,3,7b-tetrahydro-1aH-cyclopropa[c]isoquinoline-1a-carboxylate (**2o**).* The title compound was prepared by general procedure A on a 0.5 mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a white solid in 86% yield (0.1448 g, 0.4318 mmol). R_f 0.44 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (s, 1H), 4.32−4.20 (m, 2H), 3.96−3.91 (m, 9), 3.24 (s, 3H), 2.90−2.83 (m, 1H), 2.22−2.12 (1H), 1.38−129 (m, 3H), 0.83−0.80 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.3, 162.0, 152.8, 150.8, 145.5, 123.5, 120.8, 107.5, 62.1, 61.4, 61.1, 56.3, 44.9, 34.8, 21.8, 19.1, 14.3; FTIR (cm^{-1}) (neat) 2939, 1727, 1649, 1595, 1415, 1096, 700, 519.4; HRMS (ESI, Pos) calcd for $C_{17}H_{21}NO_6$ (M + H)$^+$ 336.14416, found 336.14524 *m/z*.

*Ethyl 2,7-dimethyl-3-oxo-1,2,3,7b-tetrahydro-1aH-cyclopropa[c]-isoquinoline-1a-carboxylate (**2p**).* The title compound was prepared by general procedure A on a 0.4994 mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a light orange solid in 99% yield (0.1282 g, 0.4944 mmol). R_f 0.45 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95−7.92 (m, 1H), 7.24−7.13 (m, 2H), 4.27−4.10 (m, 2H), 3.16 (s, 3H), 2.57 (dd, J = 10.3, 7.3 Hz, 1H), 2.34 (s, 3H), 2.11 (dd, J = 10.4, 4.3 Hz, 1H), 1.23 (t, J = 7.1 Hz, 3H), 0.78 (dd, J = 7.3, 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.4, 162.5, 136.1, 134.9, 133.3, 127.1, 62.1, 44.7, 34.7, 24.3, 18.89, 18.81, 14.2; FTIR (cm^{-1}) (neat) 2922, 2852, 1715, 1645, 1368, 750.1, 723.7, 431.4; HRMS (ESI, Pos) calcd for $C_{15}H_{17}NO_3$ (M + H)$^+$ 260.12922, found 260.12812 *m/z*.

*Ethyl 2,6-dimethyl-3-oxo-1,2,3,7b-tetrahydro-1aH-cyclopropa[c]-isoquinoline-1a-carboxylate (**2q**).* The title compound was prepared by general procedure A on a 0.4988 mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a light crystalline yellow solid in 99% yield (0.128 g, 0.4938 mmol). mp 104−105 °C; R_f 0.45 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99 (d, J = 7.5 Hz, 1H), 7.14−7.10 (m, 2H), 4.29−4.15 (m, 2H), 3.21 (s, 3H), 2.66 (dd, J = 9.8, 7.2 Hz, 1H), 2.34 (s, 3H), 2.11 (dd, J = 10.4, 7.2 Hz, 1H), 1.29−1.25 (m, 3H), 0.83−0.80 (m, 1H); ^{13}C NMR ($CDCl_3$, 101 MHzδ 169.9, 162.3, 142.6, 136.3, 129.0, 128.5, 128.3, 122.4, 61.9, 44.9, 34.4, 26.3, 21.4, 19.9, 14.1; FTIR (cm^{-1}) (neat) 2975, 1719, 1649, 1210, 1138, 613.4, 501.3; HRMS (ESI, Pos) calcd for $C_{15}H_{17}NO_3$ (M + H)$^+$ 260.12916, found 260.12812 *m/z*.

*Ethyl 5-methyl-4-oxo-4,5,6,6a-tetrahydro-5aH-cyclopropa[b]-thieno[2,3-d]pyridine-5a-carboxylate (**2r**).* The title compound was prepared by general procedure A on a 0.4985 mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a light crystalline yellow solid in 33% yield (0.04134 g, 0.1645 mmol). mp 78−80 °C; R_f 0.44 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 (d, J = 5.0 Hz, 1H), 7.05 (d, J = 5.0 Hz, 1H), 4.30−4.17 (m, 2H), 3.21 (s, 3H), 2.73 (dd, J = 10.1, 7.1 Hz, 1H), 2.15 (dd, J = 10.1, 4.8 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H), 0.84 (dd, J = 7.1, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 169.8, 159.3, 141.9, 132.2, 129.3, 127.2, 62.2, 46.6, 33.7, 25.2, 18.2, 14.3 ; FTIR (cm^{-1}) (neat) 3097, 2981, 1719, 1635, 1234, 1166, 485.6, 468.2; HRMS (ESI, Pos) calcd for $C_{12}H_{13}NO_3S$ (M + H)$^+$ 252.06988, found 252.06889 *m/z*.

*Ethyl 6-methyl-5-oxo-5,6,7,7a-tetrahydro-6aH-cyclopropa[h]-[1,6]naphthyridine-6a-carboxylate (**2s**).* The title compound was prepared by general procedure A on a 0.5 mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a bright yellow crystalline solid in 67% yield (0.0821 g, 0.3334 mmol). mp 78−80 °C; R_f 0.44 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.63 (d, J = 3.2 Hz, 1H), 8.40−8.37 (m, 1H), 7.35−7.28 (m, 1H), 4.33−4.17 (m, 2H), 3.27 (s, 3H), 3.02−2.96 (m, 1H), 2.32−2.26 (m, 1H), 1.30 (m, 3H), 1.02−0.94 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.2, 161.6, 155.5, 152.5, 136.8, 122.8, 121.1, 62.1, 44.9, 34.4, 28.5, 19.8, 14.1; FTIR (cm^{-1}) (neat) 3105, 2981, 1725, 1585, 1446, 1421, 726.1, 489.3; HRMS (ESI, Pos) calcd for $C_{13}H_{14}N_2O_3$ (M + H)$^+$ 247.10895, found 247.10772 *m/z*.

*Ethyl 3-methyl-2-oxo-1,2,3,7b-tetrahydro-1aH-cyclopropa[c]-quinoline-1a-carboxylate (**2u**).* The title compound was prepared by general procedure A on a 0.4936 mmol scale and then purified via column chromatography over silica using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a light yellow solid in 93% yield (0.1129 g, 0.4603 mmol). R_f 0.48 (1:1 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37−7.35 (m, 1H), 7.31−7.27 (m, 1H), 7.10−7.06 (m, 1H), 6.99 (d, J = 8.4 Hz, 1H), 4.30−4.24 (m, 2H), 3.39 (d, J = 1.1 Hz, 3H), 2.83−2.79 (m, 1H), 2.32 (ddd, J = 9.3, 4.6, 1.2 Hz, 1H), 1.35−1.29 (m, 3H), 1.07 (ddd, J = 6.7, 4.2, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 168.9, 165.0, 137.3, 128.5, 127.9, 122.9, 122.1, 114.8, 30.8, 29.6, 29.1, 17.2, 14.3; FTIR (cm^{-1}) (neat) 2928, 1718, 1655, 1363, 1303, 1048, 747.4, 679.5; HRMS (ESI, Pos) calcd for $C_{14}H_{15}NO_3$ (M + H)$^+$ 246.11366, found 246.11247 *m/z*.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01916.

Optimization tables, sample spectra and compound characterization data. (PDF)

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AUTHOR INFORMATION

Corresponding Author

*E-mail: andre.charette@umontreal.ca.

Notes

The authors declare no competing financial interest.

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(23) The decreased reactivity of the cyano group indicates that the beneficial effects of the ester moiety may not be solely electronic in nature. Further investigations are warranted.

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