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Iodide-Mediated Synthesis of Spirooxindolo Dihydrofurans from Iodonium Ylides and 3-Alkylidene-2-oxindoles

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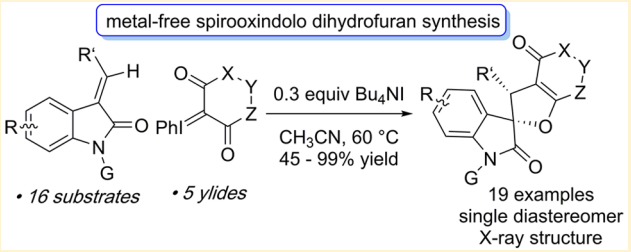
Supporting Information

ABSTRACT: An iodide-mediated reaction between cyclic iodonium ylides of 1,3-dicarbonyls and 3-alkylidene-2-oxindoles results in 3*H*-spiro[furan-2,3′-indolin]-2′-ones. The reaction was tolerant to substitutions on both the alkylidene and ylide substrates and provided access to 19 new, densely functionalized polycyclic spirocycles in typically high yield.



Iodonium ylides of 1,3-dicarbonyls are an important class of synthetically useful hypervalent iodine (HVI) compounds that can be synthesized easily from active methylene compounds and $PhI(OAc)_2$.[1] Iodonium ylides of cyclic 1,3-dicarbonyls are generally easier to isolate and handle, more thermally stable,[2] and more soluble in common organic solvents than the acyclic counterparts. Such ylides can be used in a variety of different reactions, including with nucleophiles,[3] as diazo surrogates in carbenoid reactions,[4] and in cycloaddition reactions.[5] Suitable dipolarophiles for cycloaddition reactions include alkenes,[6] alkynes,[7] arynes,[5a] ketenes,[8] isocyanates,[5c] isothiocyanates,[5c] nitriles,[5b] CS_2,[5c] and carbodiimides,[9] which can provide access to a variety of polycyclic synthetic building blocks with carbocyclic or heterocyclic scaffolds.

Reactions between iodonium ylides and functionalized dipolarophiles can result in new methods for preparing valuable classes of compounds, such as spirocyclic oxindoles. The family of compounds containing (or derived from) 3,3′-spirooxindolo dihydrofurans are represented by a variety of naturally occurring compounds[10] (Figure 1a). Previous preparations of this motif employed diazo chemistry,[11] intramolecular cyclizations,[12] [3 + 2] cycloadditions,[13] intramolecular Friedel−Crafts reactions,[14] and annulation strategies.[15] As part of our investigations of iodonium ylides acting as diazo surrogates,[16] we recently discovered that iodonium ylides react with electron-rich styrenes, under the action of $PhI(OAc)_2$ and Bu_4NI, to give dihydrofurans (Figure 1b).[17] We envisioned that more rigid, cyclic iodonium ylides (e.g., **2a**) would react with 3-alkylidene-2-oxindoles (**1**) to generate 3,3′-spirooxindolo dihydrofurans. This chemistry would offer a mild, metal-free and environmentally benign alternative to existing methodologies, and we report here that under Bu_4NI catalysis, cyclic iodonium ylides react with alkenes (**1**) to chemo-, diastereo-, and regioselectively generate spirocyclic dihydrofurans **3** (Figure 1c).

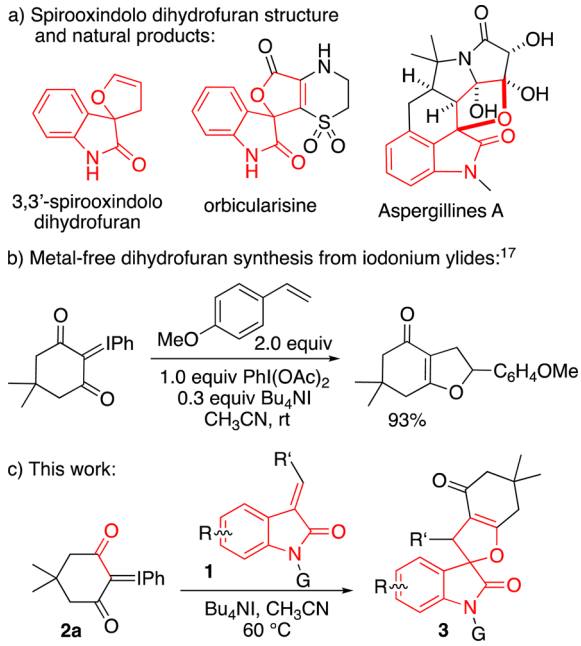


Figure 1. Motivation, background, and synthetic plan for a new 3,3′-spirooxindolo dihydrofuran synthesis.

We began this investigation using the previously optimized reactions conditions (Figure 1, b), anticipating recovery of two possible regioisomeric dihydrofurans **3a** and/or **3a′** (Table 1, entry 1). Complete consumption of **1a** was observed within 5 h; however, the product was only recovered in 64% yield. Presuming the excess $PhI(OAc)_2$ to be problematic, we decreased its loading and recovered **3a** in 83% yield (entry

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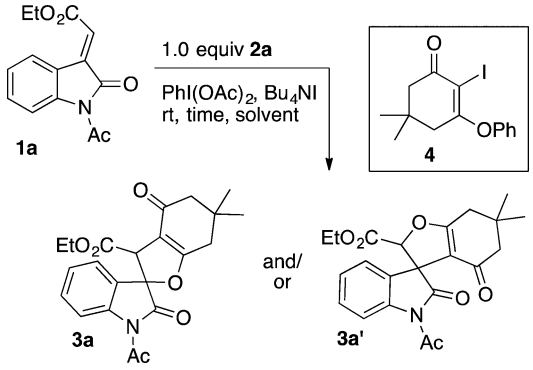
Table 1. Optimization of the Reaction[a]



entry	$PhI(OAc)_2$ (equiv)	Bu_4NI (equiv)	time (h)	conv.[b,c]	yield[b]
1	1.0	0.3	5	100%	64%
2	0.3	0.3	5	>95%	83%
3[d]	0.3	0.3	5	42%	38%
4[d]	0.3	0.3	25	60%	54%
5[e]	0.3	0.3	5	63%	46%
6[f]	0.3	0.3	5	>95%	78%
7	–	–	5	8%	<5%
8	0.3	–	5	19%	10%
9	–	0.3	5	83%	81%
10	–	0.1	20	54%	48%
11	–	0.3	20	>95%	94%
12[g]	–	0.3	5	>95%	96%
13[h]	–	0.3	3	>95%	93%
14[g,i]	–	0.3	1	100%	97% (91%)

[a]Reaction Conditions: **1a** (0.1 mmol) is combined with **2a**, $PhI(OAc)_2$, and Bu_4NI in solvent (0.1 M), and the reaction is stirred at the indicated temperature for the indicated length of time. [b]Conversion and yield determined by ^1H NMR, using hexamethyldisiloxane as internal standard. [c]Conversions listed as >95% indicate that <5 mol % of **1a** remained according to ^1H NMR. [d]Solvent was DCM. [e]Solvent was DCE. [f]Solvent was toluene. [g]Reaction at 60 °C. [h]Reaction at reflux. [i]1.1 equiv **2a** used.

2). Changing the solvent offered no improvement, with incomplete conversion observed even after 25 h (entries 3–6). A control experiment lacking both $PhI(OAc)_2$ and Bu_4NI failed (entry 7), and while the reaction containing 0.3 equiv of $PhI(OAc)_2$ also failed (10% yield, entry 8), the reaction proceeded in 81% yield when only Bu_4NI was present. Though the conversion decreased when $PhI(OAc)_2$ was omitted (compare entry 9 with entry 2), the yield of **3a** was nearly equal in both instances. Decreasing the loading of Bu_4NI resulted in decreased conversion, but a longer reaction gave the product in 94% NMR yield (entries 10, 11). Increasing the temperature to either 60 °C or reflux resulted in decreased reaction times (entries 12, 13), and despite the elevated temperature, we did not observe any of iodoether **4**, a known byproduct of thermal reactions of **2a**.[5b,18] Incomplete consumption of **1a** was still problematic, but increasing the loading of **2a** to 1.1 equiv resulted in complete consumption of **1a**, with **3a** observed in 97% NMR yield (91% isolated, entry 14). Thus, straightforward synthesis of spirooxindolo dihydrofurans could be achieved using nearly equimolar loading of ylide and alkene.

NMR analysis of the product indicated that the reaction proceeded chemoselectively to give **3a** as the sole product.[20] The 87.8 ppm ^{13}C peak (4°, R_3C–O) (Figure 2a) and the long-range H–H coupling between the 4.33 ppm methine proton and the 2.53 ppm diasterotopic methylene (Figure 2b, green arrow) are consistent with **3a**. HMBC crosspeaks from the methine proton showed all the expected 2- and 3-bond correlations (Figure 2b, blue arrows) except the crucial 193.2 ppm crosspeak, which would have distinguished between **3a** and **3a′**. The product was crystallized from CH_2Cl_2 (4 °C, 16 h), and X-ray analysis proved the structure and stereochemistry to be as shown in Figure 2c. This regioisomer is consistent with previous dihydrofuran syntheses employing iodonium ylides, with the oxygen bound to the more substituted of alkene carbons.[19]

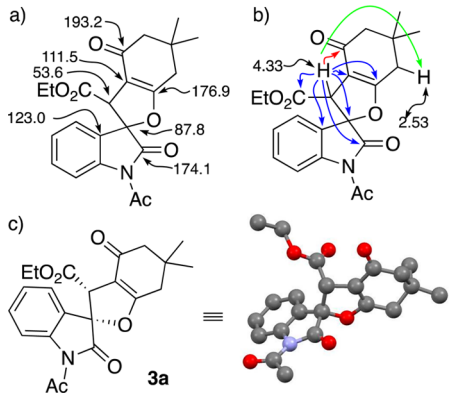


Figure 2. Structural elucidation of the spirooxindolo dihydrofuran product. (a) Diagnostic ^{13}C NMR peaks. (b) COSY (green) and HMBC (blue) peaks, and the missing key peak (red). (c) X-ray structure of **3a**.

Having optimized the reaction, we conducted it at the 1.0 mmol scale, where **3a** was recovered in 90% yield (Scheme 1). The *N*-CBZ (**1b**), *N*-Boc (**1c**), and *N*-Ts derivatives gave products **3b**, **3c**, and **3d** in 90%, 99%, and 90% yields, respectively. Changing the polarity of the N-substituent from electron-withdrawing to electron-donating groups was also acceptable, as the *N*-Bn (**1e**), *N*-allyl (**1f**), and *N*-Me (**1g**) substrates gave products **3e**, **3f**, and **3g** in 97%, 85%, and 98% yields, albeit over longer reaction times. Halogenated alkylidenes possessing either *N*-Me (5-F, **1h**), (5-Cl, **1i**), or (5-Br, **1j**) or *N*-Boc (5-F, **1k**), (5-Cl, **1l**), or (5-Br, **1m**) substituents also gave the desired products in generally high yield. Benzoyl and acetyl alkylidene substituents were tested and gave **3n** and **3o** in 99% and 89% yields. Lastly, an electron-neutral phenyl substituent on the alkylidene was tested, and it gave **3p** in 82% yield. This is noteworthy since the switch from electron-poor to electron-neutral alkylidene substituents failed to alter the regioisomeric outcome (e.g., **3p** vs **3p′**) of the reaction.

We investigated other cyclic iodonium ylides in the reaction with alkylidene **1a**, and the iodonium ylide of cyclohexane dione (**2b**) gave the dihydrofuran in 97% yield (Scheme 2). Meldrum's acid iodonium ylide (**2c**) failed, but a *β*-ketoester-derived ylide (**2d**) gave **3s** in 54% yield, with the ester carbonyl participating in dihydrofuran formation. Lastly, the pyrimidine derived iodonium ylide **2e** gave **3t** in 45% yield.

We attempted to circumvent isolation of the iodonium ylide by developing a one-pot, multistep synthesis of **3a**, with in situ generation of **2a** (eq 1).[1b,21] Alkene **1a** was combined with dimedone, $PhI(OAc)_2$, Bu_4NI, and Cs_2CO_3 and stirred at 60 °C in CH_3CN. Though the alkene was consumed, no trace of **3a** was observed. We believe the alkene decomposition occurred

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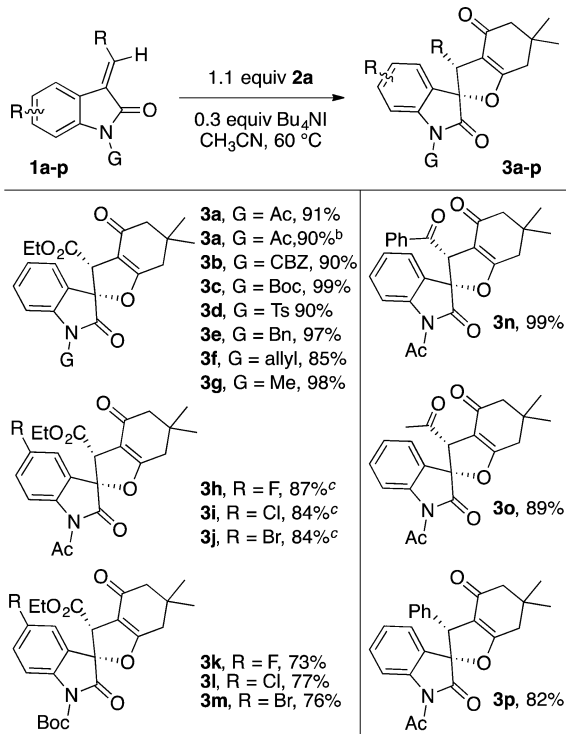
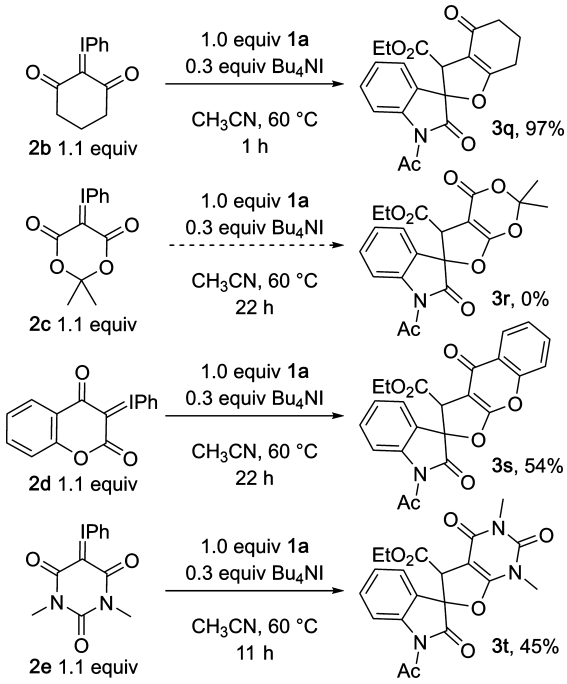
Scheme 1. Synthesis of Spirooxindolo Dihydrofurans[a]



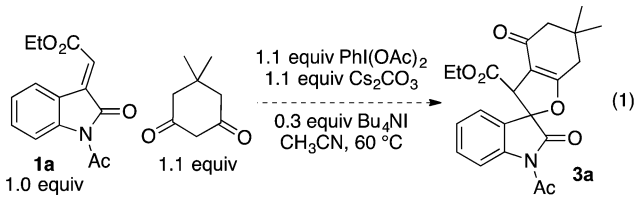
[a]Reaction conditions: Alkene **1** (0.3 mmol, 1 equiv) is combined with **2a** (1.1 equiv) and Bu_4NI (0.3 equiv) in CH_3CN (0.1 M), and the reaction is stirred at reflux. [b]Reaction carried out at the 1.0 mmol scale. [c]^1H NMR yield using hexamethyldisiloxane as internal standard.

Scheme 2. Synthesis of Spirooxindolo Dihydrofurans Using Cyclic Iodonium Ylides of 1,3-Dicarbonyls



due to an undesired side reaction with $PhI(OAc)_2$, as previously observed (see Table 1, entry 1).

We probed the reaction mechanism by substituting Bu_4NI with NaI (55% yield), Bu_4NBr (31% yield), Bu_4NCl (17% yield), and with I_2, which failed (see Table SI-2). It is improbable that thermally or photochemically generated free carbenes are involved since the reaction proceeds well at room temperature, and since iodoether **4** was not observed.[5b,18] The intermediacy of cyclopropanes is also unlikely because these do not readily rearrange to dihydrofurans.[19] To test for radical chemistry, we added BHT (0.3 equiv), but **3a** was still recovered in 95% yield. Adding DDQ (0.3 equiv) completely consumed ylide **2a**, presumably though chemical degradation. We therefore propose an ionic mechanism[22] in which iodide activates ylide **2a**, giving **A** (Figure 3). Ligand exchange with



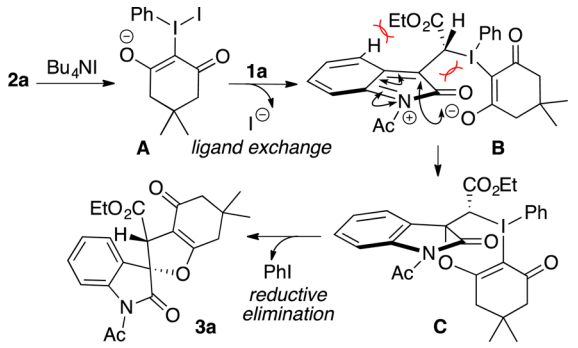


Figure 3. Proposed mechanism for the formation of **3a**.

the nucleophilic vinylogous enamine gives **B**.[23] Steric repulsion with the stereogenic methine substituents prevents bond rotation, forcing the C−O bond to be forged from the α-face, giving **C** as a single diastereomer. Reductive elimination of iodobenzene from **C** generates **3a**. We believe the differing reactivity observed for cyclic and acyclic[17] iodonium ylides with **1** (e.g., dihydrofuran vs cyclopropane formation) stems from (a) the fixed proximity of the cyclic enolate oxygen atom with the electrophile (see **B**) and (b) the unfavorable steric interactions necessary for cyclopropane formation to occur.

In conclusion, we report here a novel, metal-free synthesis of spirooxindolo dihydrofurans from substituted 3-alkylidene-2-oxindoles and iodonium ylides of 1,3-dicarbonyls. The optimized procedure was catalyzed by Bu_4NI and provided the desired spirocycles in excellent yield. The reaction was tolerant to both electron-rich and electron-poor substituents on the oxindole as well as keto, ester, and aryl substituents on the alkylidene. Variations in the iodonium ylide were also tolerated, with ylides derived from cyclic 1,3-diketones, 1,3-ketoesters, and pyrimidines all undergoing the spirocycle formation.

EXPERIMENTAL SECTION

General Information. All reactions were carried out in flame-dried glassware under a nitrogen atmosphere. Transfer of anhydrous solvents and reagents was accomplished with oven-dried syringes. Thin-layer chromatography was performed on glass plates precoated with 0.25 mm Kieselgel 60 F254. Flash chromatography columns were packed with 230−400 mesh silica gel. Melting points were recorded on a MEL-TEMP II instrument and are uncorrected. Proton NMR

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spectra (^{1}H NMR) were recorded at 300 or 500 MHz and are reported (ppm) relative to the residual chloroform peak (7.26 ppm), and coupling constants (J) are reported in hertz (Hz). Carbon NMR spectra (^{13}C NMR) were recorded at 125 MHz and are reported (ppm) relative to the center line of the triplet from chloroform-d (77.0 ppm). ^{19}F NMR spectra were recorded at 282 MHz and are reported relative to TFA. Positive ion electrospray (ESI) mass spectrometry experiments were performed with a ThermoFisher Scientific Q-Exactive Orbitrap hybrid mass spectrometer, with accurate mass determinations performed at a mass resolution of 70,000. For ESI, samples were infused at 10 μL/min in 1:1 CH_3OH/H_2O + 0.1% formic acid.

The 3-alkylidene-2-oxindoles **2a**–**o** were prepared by Wittig olefinations of the isatins.[24] Compounds **2p** was prepared by aldol condensation of benzaldehyde onto *N*-acetyl-2-oxindole.

General Procedure A: Dihydrofuran Synthesis. The alkylidene **1** (0.3 mmol, 1.0 equiv) was added to a flame-dried round-bottom flask equipped with a magnetic stir bar and a septum, and to this was added CH_3CN (3.0 mL, 0.1 M). To this was added Bu_4NI (33 mg, 0.09 mmol, 0.3 equiv), followed by **2a** (113 mg, 0.33 mmol, 1.1 equiv), and the reaction was immersed in a preheated 60 °C oil bath. The resulting mixture was stirred until TLC analysis (eluting with 40% EtOAc in hexanes) indicated consumption of **1**. Upon completion, the CH_3CN was evaporated by rotary evaporation, and the resulting residue was dissolved in a minimum volume of CH_2Cl_2 and charged onto a silica gel column. The product was eluted using a gradient of 10, 20, 30, then 40% EtOAc in hexanes, and the recovered product was azeotropically dried using chloroform, reconcentrated, and dried under high vacuum.

3a. General Procedure A was followed using **1a** (78 mg, 0.3 mmol). The reaction was complete after 1 h at 60 °C, and **3a** was recovered as a white solid (109 mg) in 91% yield.

General Procedure A was also followed using **1a** (259 mg, 1.0 mmol). The reaction was complete after 1 h at 60 °C, and **3a** was recovered as a white solid (356 mg) in 90% yield. R_f = 0.40 (40% EtOAc/hexanes, UV active); m.p.: 146–148 °C; IR (ATR): 2958, 1771, 1737, 1717, 1646, 1175, 1166 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (t, J = 7.2 Hz, 3H), 1.20 (s, 3H), 1.26 (s, 3H), 2.35 (d, J_{AB} = 16.3 Hz, 1H), 2.39 (d, J_{AB} = 16.3 Hz, 1H), 2.48 (d, J_{AB} = 17.7 Hz, 1H), 2.52 (d, J_{AB} = 17.7 Hz, 1H), 2.71 (s, 3H), 3.83 (m, 2H), 4.33 (br s, 1H), 7.21 (dd, J = 7.7, 7.7 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.45 (dd, J = 8.0, 8.0 Hz, 1H), 8.26 (d, J = 8.3 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 13.6, 26.5, 28.1, 28.8, 34.7, 37.6, 50.9, 53.6, 61.5, 87.7, 111.5, 116.9, 122.9, 125.3, 125.6, 131.8, 140.5, 167.6, 170.2, 174.0, 176.9, 193.2; HRMS (ESI) calcd for $C_{22}H_{24}O_6N$ [M + H]$^+$ 398.1604; found 398.1599.

3b. General Procedure A was followed using **1b** (105 mg, 0.3 mmol). The reaction was complete after 1 h at 60 °C, and **3b** was recovered as a white solid (132 mg) in 90% yield. R_f = 0.37 (40% EtOAc/hexanes, UV active); m.p.: 116–118 °C; IR (ATR): 2963, 1777, 1742, 1645, 1608, 1344, 1286, 1231, 1169 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (t, J = 7.2 Hz, 3H), 1.19 (s, 3H), 1.24 (s, 3H), 2.33 (d, J_{AB} = 16.3 Hz, 1H), 2.36 (d, J_{AB} = 16.3 Hz, 1H), 2.45 (d, J_{AB} = 17.7 Hz, 1H), 2.50 (d, J_{AB} = 17.7 Hz, 1H), 3.82 (m, 2H), 4.32 (s, 1H), 5.46 (s, 2H), 7.18 (dd, J = 7.8, 7.8 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 7.2 Hz, 1H), 7.42 (m, 3H), 7.51 (d, J = 6.9 Hz, 2H), 7.97 (d, J = 8.3 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 13.6, 28.1, 28.8, 34.7, 37.6, 50.9, 53.5, 61.4, 69.2, 87.5, 111.5, 115.5, 122.8, 125.2, 125.5, 128.2 (2C), 128.70, 128.74 (2C), 131.8, 134.4, 139.7, 150.2, 167.8, 171.3, 176.9, 193.2; HRMS (ESI) calcd for $C_{28}H_{28}O_7N$ [M + H]$^+$ 490.1860; found 490.1860.

3c. General Procedure A was followed using **1c** (95 mg, 0.3 mmol). The reaction was complete after 1 h at 60 °C, and **3c** was recovered by column chromatography, eluting with 10, 20, and then 30% EtOAc/hexanes, which gave an oil that solidified upon standing (136 mg) in 99% yield. R_f = 0.39 (40% EtOAc/hexanes, UV active); m.p.: 138–140 °C; IR (ATR): 2965, 1787, 1730, 1652, 1470, 1347, 1292, 1151 cm^{-1}; ^{1}H (500 MHz, $CDCl_3$) δ 0.85 (t, J = 7.2 Hz, 3H), 1.18 (s, 3H), 1.23 (s, 3H), 1.63 (s, 9H), 2.33 (s, 2H), 2.44 (d, J_{AB} = 17.7 Hz, 1H), 2.50 (d, J_{AB} = 17.7 Hz, 1H), 3.83 (m, 2H), 4.23 (s, 1H), 7.14 (dd, J = 7.7, 7.7 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.41 (dd, J = 7.6, 7.6 Hz, 1H), 7.91 (d, J = 8.3 Hz, 1H); ^{13}C{^{1}H} (125 MHz, $CDCl_3$) δ 13.6, 28.0 (4C), 28.9, 34.6, 37.6, 50.8, 53.4, 61.3, 85.3, 87.5, 111.5, 115.4, 122.6, 124.8, 125.4, 131.7, 140.3, 148.6, 167.9, 171.5, 177.0, 193.2; HRMS (ESI) calcd for $C_{25}H_{30}O_7N$ [M + H]$^+$ 456.2017; found 456.2016.

3d. General Procedure A was followed using **1d** (111 mg, 0.3 mmol). The reaction was complete after 1 h at 60 °C, and **3d** was recovered as an orange solid (138 mg) in 90% yield. R_f = 0.27 (40% EtOAc/hexanes, UV active); m.p.: 117–118 °C; IR (ATR): 2960, 1770, 1739, 1651, 1606, 1464, 1384, 1178, 1161 cm^{-1}; ^{1}H (500 MHz, $CDCl_3$) δ 0.75 (t, J = 7.1 Hz, 3H), 1.13 (s, 3H), 1.19 (s, 3H), 2.27 (d, J_{AB} = 16.3 Hz, 1H), 2.31 (d, J_{AB} = 16.3 Hz, 1H), 2.39 (d, J_{AB} = 17.8 Hz, 1H), 2.42 (s, 3H), 2.44 (d, J_{AB} = 17.8 Hz, 1H), 3.72 (m, 2H), 4.11 (s, 1H), 7.15 (dd, J = 7.6, 7.6 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 7.33 (d, J = 8.2 Hz, 2H), 7.44 (dd, J = 7.9, 7.9 Hz, 1H), 7.91 (d, J = 8.3 Hz, 1H), 7.94 (d, J = 8.3 Hz, 2H); ^{13}C{^{1}H} (125 MHz, $CDCl_3$) δ 13.5, 21.7, 28.0, 28.6, 34.6, 37.4, 50.7, 53.5, 61.3, 87.3, 111.1, 113.8, 122.9, 125.2, 125.7, 127.9 (2C), 129.9 (2C), 132.0, 134.3, 139.4, 146.3, 167.3, 171.4, 177.0, 193.1; HRMS (ESI) calcd for $C_{27}H_{28}O_7NS$ [M + H]$^+$ 510.1581; found 510.1581.

3e. General Procedure A was followed using **1e** (92 mg, 0.3 mmol). The reaction was complete after 4 h at 60 °C, and **3e** was recovered as a white solid (130 mg) in 97% yield. R_f = 0.33 (40% EtOAc/hexanes, UV active); m.p.: 151–153 °C, IR (ATR): 2966, 2929, 1728, 1641, 1611, 1489, 1468, 1397, 1376, 1365, 1351, 1233, 1180 cm^{-1}; ^{1}H (500 MHz, $CDCl_3$) δ 0.74 (t, J = 7.2, 3H), 1.20 (s, 3H), 1.25 (s, 3H), 2.34 (d, J_{AB} = 16.3 Hz, 1H), 2.38 (d, J_{AB} = 16.3 Hz, 1H), 2.47 (d, J_{AB} = 17.7 Hz, 1H), 2.54 (d, J_{AB} = 17.7 Hz, 1H), 3.79 (m, 2H), 4.41 (s, 1H), 4.78 (d, J = 15.9 Hz, 1H), 5.06 (d, J = 15.9 Hz, 1H), 6.69 (d, J = 7.9 Hz, 1H), 7.00 (dd, J = 7.6, 7.6 Hz, 1H), 7.24 (dd, J = 7.9, 7.9 Hz, 1H), 7.30 (m, 6H); ^{13}C{^{1}H} (125 MHz, $CDCl_3$) δ 13.5, 28.1, 28.9, 34.6, 37.7, 43.9, 50.9, 53.0, 61.1, 87.8, 109.7, 111.6, 123.1, 124.1, 125.6, 127.0 (2C), 127.9, 128.9 (2C), 131.2, 134.7, 143.0, 168.0, 173.5, 177.1, 193.2; HRMS (ESI) calcd for $C_{27}H_{28}O_5N$ [M + H]$^+$ 446.1962; found 446.1961.

3f. General Procedure A was followed using **1f** (68 mg, 0.3 mmol). The reaction was complete after 4 h at 60 °C, and **3f** was recovered by column chromatography, eluting with 5, 10, 20, and then 30% EtOAc/hexanes, which gave a white solid (101 mg) in 85% yield. R_f = 0.29 (40% EtOAc/hexanes, UV active); m.p.: 173–174 °C; IR (ATR): 2961, 1736, 1726, 1648, 1613, 1465, 1395, 1366, 1226, 1184, 1169 cm^{-1}; ^{1}H (500 MHz, $CDCl_3$) δ 0.80 (t, J = 7.1 Hz, 3H), 1.17 (s, 3H), 1.23 (s, 3H), 2.33 (s, 2H), 2.43 (d, J_{AB} = 17.7 Hz, 1H), 2.50 (d, J_{AB} = 17.7 Hz, 1H), 3.81 (m, 2H), 4.24 (dd, J = 16.7, 4.5 Hz, 1H), 4.31 (s, 1H), 4.41 (dd, J = 16.7, 4.5 Hz, 1H), 5.23 (d, J = 13.1 Hz, 2H), 5.83 (m, 1H), 6.82 (d, J = 7.8 Hz, 1H), 7.02 (dd, J = 7.5, 7.5 Hz, 1H), 7.25 (d, J = 7 Hz, 1H), 7.32 (dd, J = 7.7, 7.7 Hz, 1H); ^{13}C{^{1}H} (125 MHz, $CDCl_3$) δ 13.5, 28.0, 28.9, 34.6, 37.6, 42.3, 50.8, 52.8, 61.1, 87.7, 109.5, 111.6, 117.6, 123.1, 123.9, 125.6, 130.3, 131.3, 143.1, 168.1, 173.0, 177.1, 193.2; HRMS (ESI) calcd for $C_{23}H_{26}O_5N$ [M + H]$^+$ 396.1806; found 396.1806.

3g. General Procedure A was followed using **1g** (69 mg, 0.3 mmol). The reaction was complete after 6 h at 60 °C, and **3g** was recovered as an oil that solidified upon standing (108 mg) in 98% yield. R_f = 0.23 (40% EtOAc/hexanes, UV active); m.p.: 102–103 °C; IR (ATR): 2970, 2930, 1736, 1636, 1612, 1467, 1347, 1187 cm^{-1}; ^{1}H (500 MHz, $CDCl_3$) δ 0.85 (t, J = 7.2 Hz, 3H), 1.18 (s, 3H), 1.23 (s, 3H), 2.33 (s, 2H), 2.43 (d, J_{AB} = 17.7 Hz, 1H), 2.50 (d, J_{AB} = 17.7 Hz, 1H), 3.21 (s, 3H), 3.84 (q, J = 7.2 Hz, 2H), 4.26 (s, 1H), 6.84 (d, J = 7.9 Hz, 1H), 7.04 (dd, J = 7.6, 7.6 Hz, 1H), 7.27 (d, J = 6.8 Hz, 1H), 7.37 (dd, J = 7.8, 7.8 Hz, 1H); ^{13}C{^{1}H} (125 MHz, $CDCl_3$) δ 13.6, 26.5, 27.9, 28.9, 34.6, 37.6, 50.8, 52.5, 61.1, 87.8, 108.6, 111.8, 123.1, 123.8, 125.6, 131.4, 144.1, 168.3, 173.2, 177.1, 193.2; HRMS (ESI) calcd for $C_{21}H_{24}O_5N$ [M + H]$^+$ 370.1649; found 370.1648.

3h. General Procedure A was followed using **1h** (83 mg, 0.3 mmol). The reaction was complete after 1 h at 60 °C, and **3h** was observed in 87% NMR yield. An analytically pure sample was recovered by column chromatography, eluting with 5, 10, 15, 20, and then 30% EtOAc/hexanes, which gave a pale-yellow solid that was characterized. R_f = 0.45 (40% EtOAc/hexanes, UV active); m.p.: 179–181 °C; IR (ATR):

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2959, 1785, 1736, 1715, 1646, 1604, 1480, 1397, 1371, 1328, 1288, 1259, 1224, 1182, 1166, 1117 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 0.91 (t, J = 7.1 Hz, 3H), 1.19 (s, 3H), 1.24 (s, 3H), 2.33 (d, J_{AB} = 16.4 Hz, 1H), 2.37 (d, J_{AB} = 16.4 Hz, 1H), 2.47 (d, J_{AB} = 18.2 Hz, 1H), 2.51 (d, J_{AB} = 18.2 Hz, 1H), 2.68 (s, 3H), 3.90 (q, J = 7.1 Hz, 2H), 4.29 (s, 1H), 7.06 (dd, J = 7.5, 2.7 Hz, 1H), 7.14 (ddd, J = 8.9, 8.9, 2.7 Hz, 1H), 8.26 (dd, J = 9.0, 4.5 Hz, 1H); $^{13}C\{^1H\}$ (125 MHz, $CDCl_3$) δ 13.7, 26.4, 28.1, 28.7, 34.7, 37.5, 50.8, 53.7, 61.7, 87.2, 111.5, 112.8 (d, J = 25.1 Hz, 1C), 118.41 (d, J = 22.4 Hz, 1C), 118.47 (d, J = 7.5 Hz, 1C), 124.6 (d, J = 8.1 Hz), 136.5, 160.0 (d, J = 245.5 Hz, 1C), 167.4, 169.9, 173.6, 176.8, 193.2; $^{19}F\{^1H\}$ (470 MHz, $CDCl_3$) δ −115.0; HRMS (ESI) calcd for $C_{22}H_{23}O_6NF$ $[M + H]^+$ 416.1504; found 416.1503.

3i. General Procedure A was followed using **1i** (88 mg, 0.3 mmol). **1i** did not dissolve in CH_3CN, and the reaction proceeded as a suspension. The reaction was complete after 1 h at 60 °C, and **3i** was observed in 84% NMR yield. An analytically pure sample was recovered by column chromatography, eluting with 5, 10, 15, 20, and then 30% EtOAc/hexanes, which gave a white solid that was characterized. R_f = 0.49 (40% EtOAc/hexanes, UV active); m.p.: 197−199 °C; IR (ATR): 2956, 1782, 1737, 1717, 1646, 1468, 1224, 1189, 1174, 1166 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 0.92 (t, J = 7.2 Hz, 3H), 1.20 (s, 3H), 1.25 (s, 3H), 2.34 (d, J_{AB} = 16.4 Hz, 1H), 2.38 (d, J_{AB} = 16.4 Hz, 1H), 2.48 (d, J_{AB} = 18.3 Hz, 1H), 2.52 (d, J_{AB} = 18.3 Hz, 1H), 2.69 (s, 3H), 3.92 (m, 2H), 4.28 (s, 1H), 7.31 (d, J = 2.2 Hz, 1H), 7.42 (dd, J = 8.8, 2.2 Hz, 1H), 8.22 (d, J = 8.8 Hz, 1H); $^{13}C\{^1H\}$ (125 MHz, $CDCl_3$) δ 13.7, 26.4, 28.2, 28.8, 34.8, 37.6, 50.9, 53.7, 61.8, 87.1, 111.5, 118.2, 124.6, 125.5, 131.2, 131.8, 139.0, 167.4, 170.0, 173.3, 176.8, 193.2; HRMS (ESI) calcd for $C_{22}H_{23}O_6NCl$ $[M + H]^+$ 432.1208; found 432.1209.

3j. General Procedure A was followed using **1j** (101 mg, 0.3 mmol). **1j** did not dissolve in CH_3CN, and the reaction proceeded as a suspension. The reaction was complete after 1 h at 60 °C, and **3c** was observed in 84% NMR yield. An analytically pure sample was recovered by column chromatography, eluting with 5, 10, 15, 20, and then 30% EtOAc/hexanes, which gave a white solid that was characterized. R_f = 0.48 (40% EtOAc/hexanes, UV active); m.p.: 198−200 °C; IR (ATR): 2954, 1787, 1737, 1717, 1646, 1466, 1372, 1315, 1254, 1224, 1188, 1166 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 0.94 (t, J = 7.1 Hz, 3H), 1.20 (s, 3H), 1.25 (s, 3H), 2.34 (d, J_{AB} = 16.4 Hz, 1H), 2.38 (d, J_{AB} = 16.4 Hz, 1H), 2.50 (s, 2H), 2.68 (s, 3H), 3.83 (m, 2H), 4.28 (s, 1H), 7.45 (s, 1H), 7.57 (d, J = 8.7 Hz, 1H), 8.17 (d, J = 8.8 Hz, 1H); $^{13}C\{^1H\}$ (125 MHz, $CDCl_3$) δ 13.7, 26.5, 28.1, 28.7, 34.7, 37.5, 50.9, 53.7, 61.8, 87.0, 111.5, 118.50, 118.60, 124.8, 128.3, 134.7, 139.5, 167.4, 170.0, 173.2, 176.8, 193.2; HRMS (ESI) calcd for $C_{22}H_{23}O_6NBr$ $[M + H]^+$ 476.0703; found 476.0705.

3k. General Procedure A was followed using **1k** (101 mg, 0.3 mmol). The reaction was complete after 1 h at 60 °C, and **3k** was recovered by column chromatography, eluting with 5, 10, 20, and then 30% EtOAc/hexanes, which gave a white solid (104 mg) in 73% yield. R_f = 0.48 (40% EtOAc/hexanes, UV active); m.p.: 161−162 °C; IR (ATR): 2965, 1784, 1728, 1652, 1486, 1162, 1144, 1116 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 0.93 (t, J = 7.2 Hz, 3H), 1.17 (s, 3H), 1.22 (s, 3H), 1.62 (s, 9H), 2.32 (s, 2H), 2.44 (d, J_{AB} = 17.7 Hz, 1H), 2.50 (d, J_{AB} = 17.7 Hz, 1H), 3.91 (q, J = 7.2 Hz, 2H), 4.29 (s, 1H), 7.04 (dd, J = 7.5, 2.7 Hz, 1H), 7.12 (ddd, J = 8.9, 8.9, 2.7 Hz, 1H), 7.92 (dd, J = 9.0, 4.4 Hz, 1H); $^{13}C\{^1H\}$ (125 MHz, $CDCl_3$) δ 13.7, 27.9, 28.9 (4C), 34.7, 37.5, 50.8, 53.4, 61.6, 85.5, 87.1, 111.5, 113.0 (d, J = 25.0 Hz), 116.9 (d, J = 7.6 Hz), 118.3 (d, J = 22.6 Hz), 124.1 (d, J = 8.3 Hz), 136.2 (d, J = 2.4 Hz), 148.5, 159.7 (d, J = 244.5 Hz), 167.7, 171.1, 176.9, 193.1; $^{19}F\{^1H\}$ (470 MHz, $CDCl_3$) δ −115.0; HRMS (ESI) calcd for $C_{25}H_{29}O_7NF$ $[M + H]^+$ 474.1923; found 474.1923.

3l. General Procedure A was followed using **1l** (106 mg, 0.3 mmol). The reaction was complete after 1 h at 60 °C, and **3l** was recovered by column chromatography, eluting with 5, 10, 20, and then 30% EtOAc/hexanes, which gave a pale yellow solid (113 mg) in 77% yield. R_f = 0.50 (40% EtOAc/hexanes, UV active); m.p.: 139−141 °C; IR (ATR): 2961, 1781, 1736, 1653, 1470, 1328, 1250, 1148, 1120 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 0.94 (t, J = 7.1 Hz, 3H), 1.18 (s, 3H), 1.23 (s, 3H), 1.62 (s, 9H), 2.33 (s, 2H), 2.44 (d, J_{AB} = 17.8 Hz, 1H), 2.50 (d, J_{AB} = 17.8 Hz, 1H), 3.93 (m, 2H), 4.28 (s, 1H), 7.29 (s, 1H), 7.39 (d, J = 8.7 Hz, 1H), 7.89 (d, J = 8.8 Hz, 1H); $^{13}C\{^1H\}$ (125 MHz, $CDCl_3$) δ 13.7, 27.9 (4C), 28.9, 34.7, 37.5, 50.8, 53.5, 61.7, 85.7, 87.0, 111.5, 116.8, 124.2, 125.6, 130.4, 131.6, 138.7, 148.4, 167.7, 170.8, 176.9, 193.2; HRMS (ESI) calcd for $C_{25}H_{29}O_7NCl$ $[M + H]^+$ 490.1627; found 490.1628.

3m. General Procedure A was followed using **1m** (119 mg, 0.3 mmol). The reaction was complete after 1 h at 60 °C, and **3m** was recovered by column chromatography, eluting with 5, 10, 20, and then 30% EtOAc/hexanes, which gave a yellow solid (121 mg) in 76% yield. R_f = 0.48 (40% EtOAc/hexanes, UV active); m.p.: 125−126 °C; IR (ATR): 2961, 1781, 1736, 1652, 1605, 1470, 1394, 1370, 1328, 1250, 1163, 1147, 1122 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 0.94 (t, J = 7.2 Hz, 3H), 1.16 (s, 3H), 1.21 (s, 3H), 1.61 (s, 9H), 2.31 (s, 2H), 2.43 (d, J_{ab} = 17.7 Hz, 1H), 2.49 (d, J_{ab} = 17.7 Hz, 1H), 3.91 (m, 2H), 4.25 (s, 1H), 7.40 (d, J = 1.9 Hz, 1H), 7.53 (dd, J = 8.8, 2.1 Hz, 1H), 7.82 (d, J = 8.8 Hz, 1H); $^{13}C\{^1H\}$ (125 MHz, $CDCl_3$) δ 13.7, 27.89 (3C), 27.93, 28.8, 34.7, 37.4, 50.8, 53.4, 61.7, 85.6, 86.8, 111.5, 117.1, 117.7, 124.4, 128.3, 134.5, 139.2, 148.3, 167.6, 170.6, 176.8, 193.1; HRMS (ESI) calcd for $C_{25}H_{29}O_7NBr$ $[M + H]^+$ 534.1122; found 534.1122.

3n. General Procedure A was followed using **1n** (87 mg, 0.3 mmol). The reaction was complete after 1 h at 60 °C, and **3n** was recovered by column chromatography, eluting with 5, 10, 20, and then 30% EtOAc/hexanes, which gave a yellow/orange oil (129 mg) in 99% yield. R_f = 0.36 (40% EtOAc/hexanes, UV active); IR (ATR): 2959, 1768, 1718, 1646, 1466, 1370, 1338, 1270, 1218, 1168 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 1.22 (s, 3H), 1.31 (s, 3H), 2.36 (d, J_{AB} = 16.3 Hz, 1H), 2.43 (d, J_{AB} = 16.3 Hz, 1H), 2.54 (s, 2H), 2.73 (s, 3H), 5.31 (s, 1H), 7.01 (dd, J = 7.6, 7.6 Hz, 1H), 7.16 (dd, J = 6.8, 6.8 Hz, 2H), 7.21 (dd, J = 7.6, 7.6 Hz, 2H), 7.37 (dd, J = 7.4, 7.4 Hz, 1H), 7.46 (d, J = 7.5 Hz, 2H), 7.94 (d, J = 8.3 Hz, 1H); $^{13}C\{^1H\}$ (125 MHz, $CDCl_3$) δ 26.5, 28.3, 28.7, 34.7, 37.7, 50.9, 54.2, 87.7, 112.4, 116.4, 122.4, 125.6, 126.4, 127.7 (2C), 128.4 (2C), 131.4, 133.4, 136.3, 139.9, 169.9, 174.4, 176.7, 193.2, 193.9; HRMS (ESI) calcd for $C_{26}H_{24}O_5N$ $[M + H]^+$ 430.1649; found 430.1650.

3o. General Procedure A was followed using **1o** (69 mg, 0.3 mmol). The reaction was complete after 1 h at 60 °C, and **3o** was recovered as a yellow/orange solid (98 mg) in 89% yield. R_f = 0.34 (40% EtOAc/hexanes, UV active); m.p.: 193−194 °C; IR (ATR): 2962, 2932, 1777, 1713, 1645, 1606, 1468 1395, 1367, 1340, 1272, 1220, 1177 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.24 (s, 3H), 1.81 (s, 3H), 2.33 (s, 2H), 2.50 (s, 2H), 2.69 (s, 3H), 4.37 (s, 1H), 7.20 (d, J = 4.1 Hz, 2H), 7.44 (m, 1H), 8.26 (d, J = 8.2 Hz, 1H); $^{13}C\{^1H\}$ (125 MHz, $CDCl_3$) δ 26.6, 28.3, 28.7, 31.4, 34.7, 37.5, 50.7, 58.5, 87.5, 112.6, 116.9, 121.9, 125.9, 126.2, 131.9, 140.3, 170.2, 174.0, 177.2, 193.5, 202.8; HRMS (ESI) calcd for $C_{21}H_{22}O_5N$ $[M + H]^+$ 368.1493; found 368.1492.

3p. General Procedure A was followed using **1p** (79 mg, 0.3 mmol). The reaction was complete after 15 h at 60 °C, and **3p** was recovered by column chromatography, eluting with 5, 10, 15, 20, and then 30% EtOAc/hexanes, which gave a pale yellow solid (99 mg) in 82% yield. R_f = 0.44 (40% EtOAc/hexanes, UV active); m.p.: 164−166 °C; IR (ATR): 2961, 1763, 1717, 1607, 1466, 1265, 1171 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.33 (s, 3H), 2.42 (s, 2H), 2.59 (d, J_{AB} = 18.9 Hz, 1H), 2.63 (d, J_{AB} = 18.9 Hz, 1H), 2.72 (s, 3H), 4.69 (s, 1H), 6.39 (d, J = 7.6 Hz, 1H), 6.77 (dd, J = 7.5, 7.5 Hz, 1H), 6.83 (s, 2H), 7.14 (s, 3H), 7.22 (dd, J = 8.2, 8.2 Hz, 1H), 8.16 (d, J = 8.1 Hz, 1H); $^{13}C\{^1H\}$ (125 MHz, $CDCl_3$) δ 26.6, 28.6, 29.1, 34.3, 37.9, 51.4, 53.3, 90.7, 113.7, 116.3, 122.9, 124.8, 126.2, 127.8, 128.3 (2C), 128.4 (2C), 130.7, 135.8, 140.1, 170.4, 175.2, 177.0, 193.6; HRMS (ESI) calcd for $C_{25}H_{24}O_4N$ $[M + H]^+$ 402.1700; found 402.1700.

3q. General Procedure A was followed using **1a** (78 mg, 0.3 mmol). The reaction was complete after 1 h at 60 °C, and **3q** was recovered as a white solid (108 mg) in 97% yield. R_f = 0.23 (40% EtOAc/hexanes, UV active); m.p.: 142−143 °C; IR (ATR): 2998, 2952, 1775, 1733, 1709, 1648, 1603, 1171 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 0.80 (t, J = 7.2 Hz, 3H), 2.21 (m, 2H), 2.49 (m, 2H), 2.65 (m, 2H), 2.71 (s, 3H), 3.81 (m, 2H), 4.34 (s, 1H), 7.21 (dd, J = 7.6, 7.6 Hz, 1H), 7.35 (d, J = 7.0 Hz, 1H), 7.45 (ddd, J = 7.9, 7.9, 1.4 Hz, 1H), 8.26 (d, J = 8.3 Hz, 1H); $^{13}C\{^1H\}$ (125 MHz, $CDCl_3$) δ 13.5, 21.5, 23.8, 26.5, 36.4, 53.8, 61.4, 87.4, 112.6, 116.8, 123.0, 125.3, 125.6, 131.8, 140.5, 167.4, 170.1,

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174.1, 177.7, 193.7; HRMS (ESI) calcd for $C_{20}H_{20}O_6N$ $[M + H]^+$ 370.1285; found 370.1284.

3s. General Procedure A was followed using **1a** (52 mg, 0.2 mmol). The reaction was complete after 22 h at 60 °C, and **3s** was recovered by column chromatography, eluting with 5, 10, 20, and then 30% EtOAc/hexanes, which gave a white solid (45 mg) in 54% yield. R_f = 0.43 (40% EtOAc/hexanes, UV active); m.p.: 186−188 °C; IR (ATR): 2979, 1770, 1744, 1723, 1661, 1607, 1371, 1276, 1165 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 0.85 (t, J = 7.1 Hz, 3H), 2.75 (s, 3H), 2.89 (m, 2H), 4.68 (s, 1H), 7.24 (dd, J = 7.6, 7.6 Hz, 1H), 7.32 (dd, J = 7.5, 7.5 Hz, 1H), 7.39 (d, J = 7.7 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.51 (dd, J = 7.6, 7.6 Hz, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.65 (dd, J = 7.6, 7.6 Hz, 1H), 8.32 (d, J = 8.3 Hz, 1H); $^{13}C\{^1H\}$ (125 MHz, $CDCl_3$) δ 13.6, 26.6, 54.2, 62.0, 89.0, 101.1, 111.7, 117.1, 117.3, 122.5, 123.2, 124.3, 125.5, 125.9, 132.4, 133.6, 140.8, 155.5, 158.8, 166.5, 167.2, 170.1, 173.5; HRMS (ESI) calcd for $C_{23}H_{18}O_7N$ $[M + H]^+$ 420.1078; found 420.1077.

3t. General Procedure A was followed using **1a** (52 mg, 0.2 mmol). The reaction was complete after 11 h at 60 °C, and **3t** was recovered by column chromatography, eluting with 10, 20, 30, 40, and then 50% EtOAc/hexanes, which gave a purple solid (37 mg) in 45% yield. R_f = 0.19 (40% EtOAc/hexanes, UV active); m.p.: 182−184 °C; IR (ATR): 2960, 1772, 1738, 1710, 1678, 1658, 1509, 1465, 1176. cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 0.82 (t, J = 7.1 Hz, 3H), 2.72 (s, 3H), 3.35 (s, 3H), 3.36 (s, 3H), 3.79 (m, 1H), 3.88 (m, 1H), 4.50 (s, 1H), 7.25 (dd, J = 7.6, 7.6 Hz, 1H), 7.40 (d, J = 7.7 Hz, 1H), 7.50 (dd, J = 7.8, 7.8 Hz, 1H), 8.29 (d, J = 8.3 Hz, 1H); $^{13}C\{^1H\}$ (125 MHz, $CDCl_3$) δ 13.6, 26.5, 28.2, 29.9, 53.3, 61.9, 85.8, 88.0, 117.1, 121.6, 125.4, 125.8, 132.5, 140.7, 151.2, 158.9, 162.2, 167.2, 170.0, 172.9 ; HRMS (ESI) calcd for $C_{20}H_{20}O_7N_3$ $[M + H]^+$ 414.1296; found 414.1297.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01639.

Reaction optimization and control experiment tables, NMR spectra used for elucidation of **3a**, and spectra of all new compounds (PDF)

Crystallographic data for **3a** (CIF)

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The authors declare no competing financial interest.

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