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Copper-Mediated Intramolecular Oxidative C−H/C−H Cross-Coupling of α-Oxo Ketene *N,S*-Acetals for Indole Synthesis

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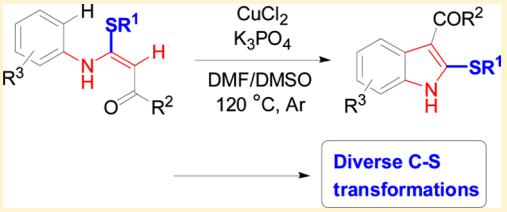
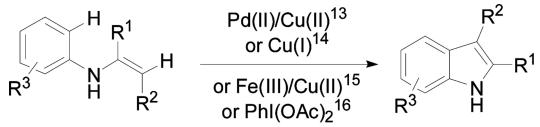
Supporting Information

ABSTRACT: $CuCl_2$-mediated intramolecular C−H/C−H cross-dehydrogenative coupling (CDC) of thioalkyl-substituted α-acetyl or α-aroyl ketene *N,S*-acetals afforded 2-thioalkyl indoles. Tunable C−S bond transformations of the resultant indoles led to highly functionalized N-heterocyclic compounds. A β-thioalkyl is necessary to activate the *N,S*-acetal substrate and enable the CDC reaction to occur, and the relevant mechanism studies revealed that the CDC reaction follows a radical pathway.



Indole motifs are abundant in natural products and are also featured in many pharmaceuticals. Diverse synthetic methods have been developed to access indole derivatives since the Fischer indole synthesis was reported in 1883.[1] Unfortunately, functionalized indoles can only be prepared through specific synthetic methods[2] or by functionalization of structurally simple indoles.[3] As cross-coupling via transition-metal-catalyzed C−H activation has recently become a promising straightforward route to form carbon−carbon and carbon−heteroatom bonds, catalytic C−H/C−halo cross-coupling[4] and C−H amination[5] have been reported for the direct synthesis of indoles. Palladium-catalyzed cyclization of 2-alkynylanilid(n)es[6] or *N*-alkynylanilines[7] and Rh(III)-promoted reactions of anilides with alkenes[8] have been applied for the construction of indole nuclei. On the basis of the pioneering work of Åkermark and Knölker on palladium-promoted intramolecular C−H/C−H cross-coupling of ArXAr′ (X = O, NY) for the synthesis of carbazoles and dibenzofurans,[9] intramolecular cross-dehydrogenative coupling (CDC)[10] has become a promising protocol for the synthesis of indoles from enamines and imines,[11] although photoredox-catalyzed intramolecular C−H/C−H cross-coupling[12a] and the Larock protocol[12b] can also be utilized for the same purpose. Palladium(II)-catalyzed, copper(II)-mediated cyclization of the enamine methyl (*Z*)-3-(phenylamino)but-2-enoate and its analogues formed indoles,[13] and Cu(I)-catalyzed oxidative cyclization of *N*-aryl enaminones afforded multisubstituted indoles.[14] Iron(III)-catalyzed, Cu(II)-mediated CDC reactions of methyl 3-(arylamino)but-2-enoates also gave indole derivatives,[15] and a process involving $PhI(OAc)_2$ was also reported for the construction of functionalized indoles[16] (Scheme 1). Pd(II)-catalyzed aerobic oxidative cyclization of *N*-aryl imines produced 2-substituted indoles,[17] and a combination of I_2 and NBS was also effective for the same purpose.[18] It is noted that 2,3-disubstituted indoles have been obtained from N-substituted anilines under palladium catalysis.[6d,19]

Scheme 1. Indole Synthesis via CDC Reactions of *N*-Aryl Enamines[13−16]



R^1 = Me or Ph
R^2 = CO_2Me, COPh, CN
R^3 = Me, OMe, Cl, Br, F, COMe, COOEt, $CONEt_2$, CN

up to 72-83%

Electron-withdrawing group (EWG)-substituted (α-oxo) ketene *S,S*-acetals[20] and *N,O*-acetals[21] are versatile building blocks in organic synthesis. However, their analogues, that is, α-oxo ketene *N,S*-acetals, have been paid much less attention.[22] We recently found that olefinic C−H and C−S bonds of α-oxo ketene *S,S*-acetals could be activated by palladium catalysts to participate in various cross-coupling reactions.[23] Keeping the knowledge of indole synthesis[13−19] in mind, we reasonably envisioned that α-oxo ketene *N,S*-acetals might be utilized for direct indole synthesis through their intramolecular C−H/C−H CDC reactions. Herein we report a thioalkyl-dependent, copper(II)-mediated CDC reaction of α-oxo ketene *N,S*-acetals for the synthesis of highly functionalized indoles.

Initially, the reaction of α-acetyl ketene *N,S*-acetal **1a** was performed under the known CDC conditions.[13−17] With the protocols developed by Åkermark and Knölker [10 mol % $Pd(OAc)_2$/HOAc/O_2/95 °C],[9] Glorius [10 mol % $Pd(OAc)_2$/$Cu(OAc)_2$/K_2CO_3/DMF/140 °C],[13] or Zhao [$PhI(OAc)_2$/DCE/60 °C],[16] **1a** reacted to afford acetanilide (MeCONHPh) as the product in 45−56% yield without the formation of the desired product, 2-thiomethyl-3-acetylindole (**2a**). Under

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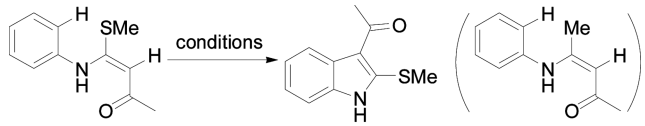
Cacchi's (5 mol % CuI/phen/Li_2CO_3/DMF/air/100 °C)[14] or Yoshikai's [10 mol % $Pd(OAc)_2$/Bu_4NBr/DMSO/O_2/60 °C][17] conditions, no reaction occurred. Using Liang's procedure [10 mol % $FeCl_3$/$Cu(OAc)_2$·$CuCl_2$/K_2CO_3/DMF/120 °C][15] led to a mixture of **2a** and acetanilide. These results reveal that both metallic and organic acetates easily cleave the olefinic C−N bond in **1a** to form acetanilide and that neither Pd(II)/oxidant nor Cu(I)/air promoted the intramolecular CDC reaction of **1a**. Intramolecular hydrogen bonding between the N−H moiety and the carbonyl oxygen seems to activate the *β*-olefinic C−N bond of **1a**, allowing nucleophilic attack of stoichiometric AcO^- anion at the *β*-carbon followed by attack of the nitrogen atom at the acetyl carbon in the *β*-C-attached OAc, resulting in acetanilide. Such a reactivity difference between **1a** and the reported *N*-aryl enamines and imines[13−17] is presumably attributed to the stronger push−pull electronic effect in the *α*-oxo ketene *N*,*S*-acetal substrate enhanced by the *β*-thioalkyl functionality. To our delight, stoichiometric $CuCl_2$ mediated the intramolecular CDC reaction of **1a** to yield **2a** without using an additional transition-metal catalyst.

The reaction of **1a** was then conducted to screen the reaction conditions. In the presence of both $CuCl_2$ and K_2CO_3 (3 equiv each) under an argon atmosphere, **1a** reacted to give indole **2a** in 31% yield in DMSO at 120 °C within 2 h (Table 1, entry 1). Using DMF as the solvent obviously improved the reaction efficiency, and a mixture of DMF and DMSO (7:1 v/v) acted as the most suitable reaction medium, enhancing the yield of **2a** to 88% (Table 1, entries 2−4). Using K_3PO_4 as the base further improved the formation of **2a** (94% isolated yield; Table 1, entries 4−8). Elevating the temperature to 140 °C did not further improve the reaction efficiency, while using a lower temperature (100 °C) deteriorated the product yield (Table 1, entries 9 and 10). It was found that employing an air atmosphere dramatically lessened the yield of **2a** to 68% and that an oxygen atmosphere nearly prohibited the reaction (Table 1, entries 11 and 12). Using a smaller amount of $CuCl_2$ obviously reduced the formation of **2a** (Table 1, entries 13 and 14). $CuCl_2$·$2H_2O$ was not an effective promoter, whereas $CuBr_2$ behaved as efficiently as $CuCl_2$ did (Table 1, entries 15 and 16). It should be noted that enamine **1a′** did not undergo the same CDC reaction, demonstrating that the compatible push−pull effect of the electron-donating/withdrawing functionalities on the C=C backbone of **1a** is crucial for the intramolecular C−H/C−H CDC reaction to occur.

Next, the generality of the protocol was explored by using various *α*-oxo ketene *N*,*S*-acetals **1** as the substrates (Table 2). Substituents such as *p*-Me, *o*-Me, *p*-OMe, and *p*-OEt on the NAr functionality were tolerated, efficiently giving the desired products **2b** and **2d**−**2f**, respectively (90−96%). Two isomeric products, **2c** (55%) and **2c′** (28%), were obtained when two reactive sites were present in the NAr group of **1c**. A 2-methoxy group exhibited a negative steric effect on the formation of **2g** (65%). Electron-withdrawing chloro and fluoro substituents lessened the yields of **2h**−**j** to 68−78%. Increased bulkiness in the *N*-aryl moiety deteriorated the reaction efficiency in the formation of **2k** (73%) and **2l** (79%). The corresponding thioethyl-bearing analogues (i.e., **1m**−**q**) also efficiently reacted to form the target products **2m**−**q** (81−96%). In a similar fashion, *α*-aroyl ketene *N*,*S*-acetals reacted to afford **2r**−**x** in 65−89% yield, demonstrating an obvious steric effect of the aroyl moiety.

In contrast to the indole derivatives obtained by the synthetic protocols depicted in Scheme 1, the 2-positions of the target

Table 1. Screening of the Reaction Conditions[a]



1a **2a** **1a'**, unreactive

entry	[Cu]	base	solvent (v:v)	*T* (°C)	yield (%)[b]
1	$CuCl_2$	K_2CO_3	DMSO	120	31
2	$CuCl_2$	K_2CO_3	DMF	120	76 (72)[c]
3	$CuCl_2$	K_2CO_3	DMF/DMSO (5:1)	120	83
4	$CuCl_2$	K_2CO_3	DMF/DMSO (7:1)	120	88
5	$CuCl_2$	Li_2CO_3	DMF/DMSO (7:1)	120	87
6	**$CuCl_2$**	**K_3PO_4**	**DMF/DMSO (7:1)**	**120**	**97 (94)**[c]
7	$CuCl_2$	K_3PO_4[d]	DMF/DMSO (7:1)	120	83
8	$CuCl_2$	K_3PO_4[e]	DMF/DMSO (7:1)	120	73
9	$CuCl_2$	K_3PO_4	DMF/DMSO (7:1)	140	96 (94)[c]
10	$CuCl_2$	K_3PO_4	DMF/DMSO (7:1)	100	81
11[f]	$CuCl_2$	K_3PO_4	DMF/DMSO (7:1)	120	68
12[g]	$CuCl_2$	K_3PO_4	DMF/DMSO (7:1)	120	7
13	$CuCl_2$[d]	K_3PO_4	DMF/DMSO (7:1)	120	52
14	$CuCl_2$[e]	K_3PO_4	DMF/DMSO (7:1)	120	6
15	$CuCl_2$·$2H_2O$	K_3PO_4	DMF/DMSO (7:1)	120	76
16	$CuBr_2$	K_3PO_4	DMF/DMSO (7:1)	120	95

[a]Conditions: **1a** (0.2 mmol), [Cu] (0.6 mmol), base (0.6 mmol), solvent (2 mL), Ar (0.1 MPa), 2 h. [b]GC yields with mesitylene as the internal standard. [c]The isolated yield is given in parentheses. [d]2 equiv. [e]1 equiv. [f]In air. [g]In O_2 (1 atm).

indole products **2** could be further functionalized by Liebeskind−Srogl cross-coupling[20b] or nucleophilic condensation (Scheme 2). These transformations render our method an alternative route that provides access to diverse indole derivatives. It is noteworthy that indoles **2d**, **2x**, and **3b** were structurally characterized by X-ray crystallography (see the Supporting Information).

In order to probe into the reaction mechanism, kinetic isotope effect (KIE) experiments on **1r**[D_5] were performed (eq 1). At 0.5 h, k_H/k_D = 1.07 was observed, suggesting that C−H bond cleavage in the *N*-aryl moiety of **1** is not involved in the rate-determining step.[24] At the present time, **1r**[D_7] was not successfully prepared for KIE experiments relevant to the olefinic C−D/C−H bonds. On the basis of the observation that both air and oxygen atmospheres deteriorated the reaction efficiency of **1a** (Table 1), radicals are considered to be involved in the C−H/C−H CDC reactions of **1**.

Addition of the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (1 or 2 equiv) resulted in complete inhibition of the reaction of **1a** (see the Experimental Section), suggesting involvement of radicals in the reaction. *N*-2′,6′-Dimethylphenyl ketene *N*,*S*-acetal **1y** could not undergo the reaction to form the chlorinated product **1y′**, and substrate **1i**

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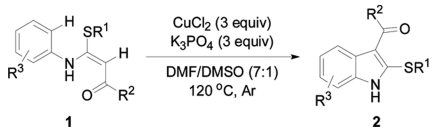
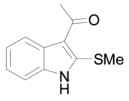
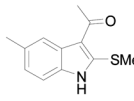
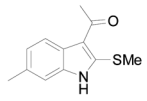
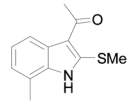
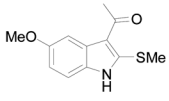
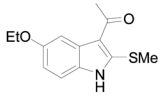
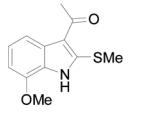
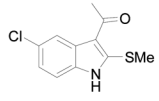
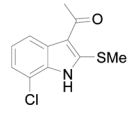
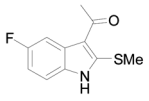
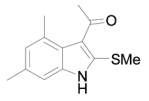
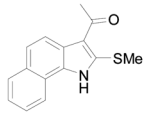
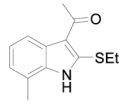
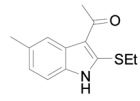
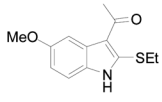
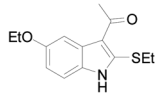
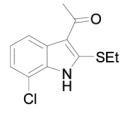
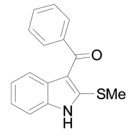
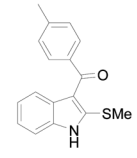
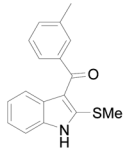
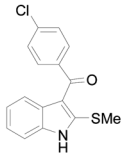
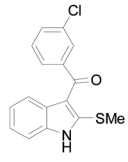
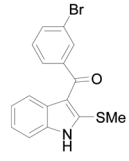
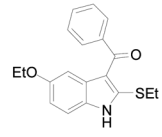
Table 2. CDC Reactions of α-Acetyl/Aroyl Ketene *N,S*-Acetals (1) To Form Indoles (2)[a,b]

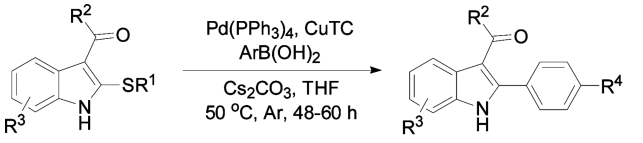


1 → 2

 **2a**, 94%	 **2b**, 95%	 **2c**, 55% + **2c′**, 28%		 **2d**, 90%
 **2e**, 93%	 **2f**, 96%	 **2g**, 65%	 **2h**, 72%	 **2i**, 78%
 **2j**, 68%	 **2k**, 73%	 **2l**, 79%	 **2m**, 92%	 **2n**, 91%
 **2o**, 94%	 **2p**, 96%	 **2q**, 81%	 **2r**, 71%	 **2s**, 73%
 **2t**, 72%	 **2u**, 67%	 **2v**, 65%	 **2w**, 66%	 **2x**, 89%

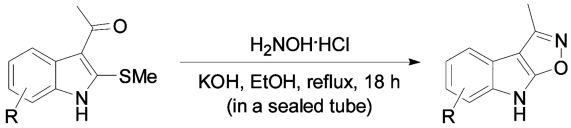
[a]Conditions: **1** (0.5 mmol), $CuCl_2$ (1.5 mmol), K_3PO_4 (1.5 mmol), DMF/DMSO (7:1 v/v, 5 mL), Ar (0.1 MPa), 120 °C, 2 h. [b]Yields refer to the isolated products.

Scheme 2. Functionalization of 2-Thioalkylindoles 2



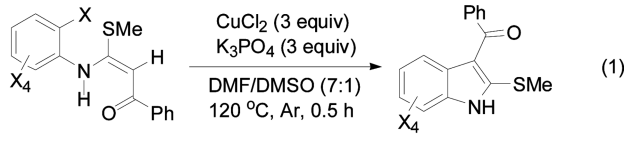
2b (R^1, R^2 = Me, R^3 = 5-Me)
2c (R^1, R^2 = Me, R^3 = 6-Me)
2m (R^1 = Et, R^2 = Me, R^3 = 7-Me)
2x (R^1 = Et, R^2 = Ph, R^3 = 5-OEt)

3a, 79% (from **2b**, R^4 = H)
3b, 72% (from **2c**, R^4 = H)
3c, 66% (from **2m**, R^4 = Cl)
3d, 63% (from **2x**, R^4 = Me)



2c (R = 6-Me)
2d (R = 7-Me)

4a, 72% (from **2c**)
4b, 64% (from **2d**)



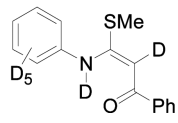
(1)

1r[D5] (X = D)
1r (X = H)

k_H/k_D = 1.07

2r[D4] (X = D), 67%
2r (X = H), 72%

1r[D7] =



could not be converted into **2a**. These results revealed that chlorinated intermediate of the type **1y′** cannot be generated during the reaction, so intramolecular C−H/C−Cl cross-coupling can be excluded from the reaction pathway of **1** (Scheme 3). Consequently, a plausible mechanism involving radicals and single-electron transfer (SET) is proposed (Scheme 4).

In summary, $CuCl_2$-mediated intramolecular C−H/C−H CDC reactions of α-acetyl/aroyl ketene *N,S*-acetals afford 2-thioalkylindoles. Readily tunable C−S bond transformations of the resultant products render the present method a promising

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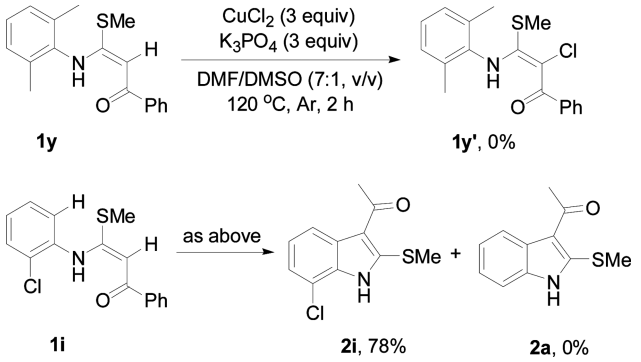
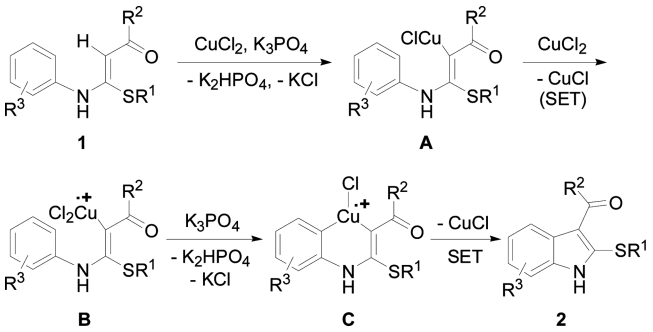
Scheme 3. Exclusion of Intramolecular C−H/C−Cl Cross-Coupling



Scheme 4. Proposed Mechanism



alternative route to access highly functionalized indole derivatives.

EXPERIMENTAL SECTION

General Considerations. The solvents were dried and distilled by literature methods prior to use. ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on a 400 and 100 MHz FT-NMR spectrometer, and all chemical shift values refer to δ_{TMS} = 0.00 ppm or to $CDCl_3$ [$\delta(^1H)$ = 7.26 ppm; $\delta(^{13}C)$ = 77.16 ppm] or DMSO-d_6 [$\delta(^1H)$ = 2.50 ppm; $\delta(^{13}C)$ = 39.52 ppm]. HRMS (EI) analysis was performed on a Waters GC-TOF mass spectrometer. All of the chemical reagents were purchased from commercial sources and used as received, unless otherwise indicated. (*E*)-4-Thiomethyl-4-(phenylamino)but-3-en-2-one (**1a**),[25a] (*E*)-3-thiomethyl-1-phenyl-3-(phenylamino)prop-2-en-1-one (**1r**),[25a] (*E*)-3-thiomethyl-3-phenylamino-1-(*p*-tolyl)prop-2-en-1-one (**1s**),[25b] and (*E*)-1-(4-chlorophenyl)-3-thiomethyl-3-(phenylamino)-prop-2-en-1-one (**1u**)[25b] are known compounds and were prepared by the literature methods. 2-Thiomethyl-3-acetyl-1*H*-indole (**2a**) and 2-thiomethyl-3-benzoyl-1*H*-indole (**2r**) are known compounds and were identified by comparison of their NMR features with the reported data for the authentic samples.[25c]

Typical Procedure for the Synthesis of 1: Synthesis of 1a. To a stirred solution of the ketene *S*,*S*-acetal 4,4-bis(methylthio)but-3-en-2-one (1.62 g, 10 mmol) and aniline (1.40 mL, 15 mmol) in toluene (30 mL) was added $BF_3{\cdot}Et_2O$ (0.13 mL, 1.0 mmol), and the resulting mixture was heated to reflux. When TLC monitoring on silica gel indicated complete consumption of the acetal, the mixture was cooled to ambient temperature, and all of the volatiles were evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography [eluent: petroleum ether (60−90 °C)/AcOEt = 30:1 v/v], affording *N*,*S*-acetal **1a** (1.30 g, 63%) as a yellow liquid.

*(E)-4-(Thiomethyl)-4-(phenylamino)but-3-en-2-one (**1a**).* 1.30 g, yield 63%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.95 (s, 1H), 7.26 (t, J = 7.6 Hz, 2H), 7.18 (d, J = 7.9 Hz, 2H), 7.12 (m, 1H), 5.13 (s, 1H), 2.21 (d, 3H), 2.08 (d, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.6, 165.5, 137.9, 128.7, 125.9, 124.8, 91.4, 29.0, 14.2.

*(E)-4-(Thiomethyl)-4-(p-tolylamino)but-3-en-2-one (**1b**).* 1.44 g, yield 65%; white solid, mp 43−45 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.82 (s, 1H), 7.13 (s, 4H), 5.15 (s, 1H), 2.33 (s, 3H), 2.29 (s, 3H), 2.13 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.8, 166.4, 136.4, 135.5, 129.6, 125.5, 91.2, 29.2, 21.0, 14.5; HRMS (EI) calcd for $C_{12}H_{15}NOS$ 221.0874, found 221.0874.

*(E)-4-(Thiomethyl)-4-(m-tolylamino)but-3-en-2-one (**1c**).* 1.44 g, yield 65%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.91 (s, 1H), 7.20 (t, J = 8.1 Hz, 1H), 7.05 (d, J = 6.6 Hz, 2H), 7.01 (d, J = 7.7 Hz, 1H), 5.16 (s, 1H), 2.32 (s, 3H), 2.28 (s, 3H), 2.12 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.8, 165.9, 138.9, 138.0, 128.7, 127.0, 125.8, 122.2, 91.4, 29.2, 21.3, 14.5; HRMS (EI) calcd for $C_{12}H_{15}NOS$ 221.0874, found 221.0877.

*(E)-4-(Thiomethyl)-4-(o-tolylamino)but-3-en-2-one (**1d**).* 1.37 g, yield 62%; white solid, mp 75−77 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.72 (s, 1H), 7.24 and 7.18 (m each, 2:2H), 5.17 (s, 1H), 2.29 (s, 6H), 2.15 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 193.0, 167.2, 137.0, 134.7, 130.8, 127.3, 127.1, 126.3, 90.9, 29.2, 18.0, 14.5; HRMS (EI) calcd for $C_{12}H_{15}NOS$ 221.0874, found 221.0878.

*(E)-4-(4-Methoxyphenylamino)-4-(thiomethyl)but-3-en-2-one (**1e**).* 1.59 g, yield 67%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.66 (s, 1H), 7.14 and 6.85 (d each, J = 8.8 Hz, 2:2H), 5.13 (s, 1H), 3.78 (s, 3H), 2.28 (s, 3H), 2.12 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.9, 167.1, 158.2, 130.9, 127.5, 114.2, 90.9, 55.5, 29.3, 14.5; HRMS (EI) calcd for $C_{12}H_{15}NO_2S$ 237.0823, found 237.0829.

*(E)-4-(4-Ethoxyphenylamino)-4-(thiomethyl)but-3-en-2-one (**1f**).* 1.73 g, yield 69%; yellow solid, mp 62−65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.66 (s, 1H), 7.13 and 6.84 (d each, J = 8.8 Hz, 2:2H), 5.13 (s, 1H), 4.00 (q, J = 7.0 Hz, 2H), 2.28 (s, 3H), 2.12 (s, 3H), 1.39 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.9, 167.2, 157.8, 130.8, 127.5, 114.7, 90.9, 63.7, 29.3, 14.9, 14.6; HRMS (EI) calcd for $C_{13}H_{17}NO_2S$ 251.0980, found 251.0988.

*(E)-4-(2-Methoxyphenylamino)-4-(thiomethyl)but-3-en-2-one (**1g**).* 1.52 g, yield 64%; yellow solid, mp 51−53 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.75 (s, 1H), 7.39 (d, J = 7.8 Hz, 1H), 7.16 (t, J = 7.8 Hz, 1H), 6.90 (t, J = 7.3 Hz, 2H), 5.19 (s, 1H), 3.84 (s, 3H), 2.31 (s, 3H), 2.14 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.9, 165.7, 152.9, 127.5, 127.0, 125.6, 120.0, 111.3, 92.1, 55.8, 29.3, 14.8; HRMS (EI) calcd for $C_{12}H_{15}NO_2S$ 237.0823, found 237.0826.

*(E)-4-(4-Chlorophenylamino)-4-(thiomethyl)but-3-en-2-one (**1h**).* 1.69 g, yield 70%; white solid, mp 60−62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.92 (s, 1H), 7.28 and 7.18 (d each, J = 8.6 Hz, 2:2H), 5.20 (s, 1H), 2.31 (s, 3H), 2.13 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 193.2, 165.4, 136.8, 131.6, 129.0, 126.4, 92.1, 29.2, 14.5; HRMS (EI) calcd for $C_{11}H_{12}NOSCl$ 241.0328, found 241.0335.

*(E)-4-(2-Chlorophenylamino)-4-(thiomethyl)but-3-en-2-one (**1i**).* 1.52 g, yield 63%; white solid, mp 87−90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.89 (br, 1H), 7.40 (m), 7.20 (m), and 7.12 (m) (2:1:1H), 5.22 (s, 1H), 2.29 (s, 3H), 2.13 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 193.5, 165.4, 135.9, 129.8, 130.0, 127.3, 137.0, 92.8, 29.3, 14.7; HRMS (EI) calcd for $C_{11}H_{12}NOSCl$ 241.0328, found 241.0333.

*(E)-4-(4-Fluorophenylamino)-4-(thiomethyl)but-3-en-2-one (**1j**).* 1.53 g, yield 68%; white solid, mp 73−75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.77 (s, 1H), 7.18 and 7.00 (m each, 2:2H), 5.16 (s, 1H), 2.29 (s, 3H), 2.12 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 193.3, 166.4, 161 (d and Cq, J = 246.4 Hz), 134.2, 127.6 (d, J = 8.3 Hz), 115.8 (d, J = 22.7 Hz), 91.5, 29.3, 14.5; HRMS (EI) calcd for $C_{11}H_{12}NOSF$ 225.0624, found 225.0628.

*(E)-4-(3,5-Dimethylphenylamino)-4-(thiomethyl)but-3-en-2-one (**1k**).* 1.43 g, yield 61%; white solid, mp 60−62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.87 (s, 1H), 6.87 and 6.85 (s each, 2:1H), 5.16 (s, 1H), 2.31 (s, 3H), 2.30 (s, 6H), 2.13 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.8, 166.1, 138.7, 138.0, 128.0, 123.0, 91.3, 29.3, 21.3, 14.6; HRMS (EI) calcd for $C_{13}H_{17}NOS$ 235.1031, found 235.1031.

*(E)-4-(Thiomethyl)-4-(naphthalen-1-ylamino)but-3-en-2-one (**1l**).* 1.26 g, yield 49%; white solid, mp 96−98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.29 (s, 1H), 8.07 and 7.78 (d each, J = 7.8 Hz, 1:1H), 7.87 and 7.49 (d each, J = 7.6 Hz, 1:1H), 7.54 and 7.44 (m each, 2:1H), 5.30 (s, 1H), 2.26 (d, J = 1.8 Hz, 3H), 2.24 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 193.3, 167.7, 134.3, 134.2, 129.7, 128.2, 127.5,

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126.9, 126.6, 125.0, 124.1, 122.8, 91.6, 29.3, 14.5; HRMS (EI) calcd for $C_{15}H_{15}NOS$ 257.0874, found 257.0873.

*(E)-4-(Thioethyl)-4-(o-tolylamino)but-3-en-2-one (**1m**).* 1.88 g, yield 80%; yellow solid, mp 48−51 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.89 (s, 1H), 7.33 and 7.26 (m each, 2:2H), 5.33 (s, 1H), 2.91 (q, J = 7.4 Hz, 2H), 2.39 (s, 3H), 2.24 (s, 3H), 1.38 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.8, 166.2, 136.9, 134.5, 130.7, 127.1, 127.0, 126.2, 91.5, 29.1, 25.6, 18.0, 13.3; HRMS (EI) calcd for $C_{13}H_{17}NOS$ 235.1031, found 235.1037.

*(E)-4-(Thioethyl)-4-(p-tolylamino)but-3-en-2-one (**1n**).* 2.10 g, yield 89%; yellow solid, mp 39−42 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.88 (s, 1H), 7.10 (s, 4H), 5.20 (s, 1H), 2.79 (q, J = 7.4 Hz, 2H), 2.30 (s, 3H), 2.10 (s, 3H), 1.26 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.6, 165.2, 136.0, 135.5, 129.4, 125.2, 91.8, 29.0, 25.6, 20.9, 13.2; HRMS (EI) calcd for $C_{13}H_{17}NOS$ 235.1031, found 235.1038.

*(E)-4-(Thioethyl)-4-(4-methoxyphenylamino)but-3-en-2-one (**1o**).* 1.56 g, yield 62%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.72 (br, 1H), 7.16 and 6.87 (d each, J = 8.8 Hz, 2:2H), 5.18 (s, 1H), 3.80 (s, 3H), 2.83 (q, J = 7.4 Hz, 2H), 2.13 (s, 3H), 1.30 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.8, 166.3, 158.3, 131.0, 127.5, 114.2, 91.6, 55.5, 29.2, 25.8, 13.4; HRMS (EI) calcd for $C_{13}H_{17}NO_2S$ 251.0980, found 251.0986.

*(E)-4-(4-Ethoxyphenylamino)-4-(thioethyl)but-3-en-2-one (**1p**).* 1.62 g, yield 61%; yellow solid, mp 88−91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.71 (s, 1H), 7.14 and 6.85 (d each, J = 8.6 Hz, 2:2H), 5.18 (s, 1H), 4.01 (q, J = 6.9 Hz, 2H), 2.82 (q, J = 7.4 Hz, 2H), 2.12 (s, 3H), 1.40 (t, J = 7.0 Hz, 3H), 1.29 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.8, 166.1, 157.7, 130.9, 127.4, 114.7, 91.6, 63.7, 29.3, 25.8, 14.9, 13.4; HRMS (EI) calcd for $C_{14}H_{19}NO_2S$ 265.1136, found 265.1139.

*(E)-4-(2-Chlorophenylamino)-4-(thioethyl)but-3-en-2-one (**1q**).* 1.60 g, yield 63%; white solid, mp 66−69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.90 (br, 1H), 7.43 (t, J = 8.3 Hz), 7.23 (m), and 7.15 (m) (2:1:1H), 5.29 (s, 1H), 2.83 (q, J = 7.4 Hz, 2H), 2.15 (s, 3H), 1.30 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 193.5, 164.3, 136.1, 130.0, 127.4, 127.3, 126.9, 129.9, 93.8, 29.0, 26.1, 13.3; HRMS (EI) calcd for $C_{12}H_{14}NOSCl$ 255.0485, found 255.0489.

*(E)-3-(Thiomethyl)-1-phenyl-3-(phenylamino)prop-2-en-1-one (**1r**).* 2.15 g, yield 80%; yellow solid, mp 58 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.58 (s, 1H), 7.96 and 7.48 (m each, 2:3H), 7.39 and 7.28 (m each, 4:1H), 5.93 (s, 1H), 2.45 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 186.1, 167.6, 140.3, 138.3, 131.0, 129.1, 128.4, 127.1, 126.4, 125.3, 88.8, 14.8.

*Synthesis of (E)-3-(Thiomethyl)-1-phenyl-3-(D$_5$-phenylamino)-prop-2-en-1-one (**1r[D$_5$]**).* To a stirred solution of ketene *S*,*S*-acetal 3,3-bis(methylthio)-1-phenylprop-2-en-1-one (1.12 g, 5 mmol) and aniline-d_7 (0.50 mL, 5.5 mmol) in toluene (10 mL) was added BF_3·Et_2O (65 mL, 0.05 mmol), and the resulting mixture was heated to reflux. When TLC monitoring on silica gel indicated complete consumption of the acetal, the mixture was cooled to ambient temperature, and all of the volatiles were evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent: petroleum ether (60−90 °C)/AcOEt = 30:1 v/v) to afford ketene *N*,*S*-acetal **1r**[$\mathbf{D_5}$] (0.99 g, 72%, 98% D) as a yellow solid. Mp 51−53 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.57 (s, 1H), 7.93 and 7.38 (m each, 2:3H), 5.91 (s, 1H), 2.42 (d, J = 1.7 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 186.1, 167.6, 140.3, 138.1, 130.9, 128.4, 127.1, 128.8, 128.6, 125.1, 124.8, 124.6, 88.8, 14.8; HRMS (EI) calcd for $C_{16}H_{11}D_5NOS$ [M + H]$^+$ 275.1266, found 275.1278.

*(E)-3-(Thiomethyl)-3-(phenylamino)-1-(p-tolyl)prop-2-en-1-one (**1s**).* 2.49 g, yield 88%; yellow solid, mp 61−64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.56 (s, 1H), 7.87 (d, J = 8.1 Hz) and 7.27 (d, J = 7.8 Hz) (2:3H), 7.47−7.32 (m, 4H), 5.93 (s, 1H), 2.46 (s, 3H), 2.44 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 186.1, 167.2, 141.4, 138.4, 137.5, 129.1, 127.2, 126.4, 125.3, 88.6, 21.6, 14.8.

*(E)-3-(Thiomethyl)-3-(phenylamino)-1-(m-tolyl)prop-2-en-1-one (**1t**).* 2.66 g, yield 94%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.57 (s, 1H), 7.75 (s), 7.71 (d, J = 7.4 Hz), 7.30 (d, J = 7.6 Hz), and 7.26 (m) (1:1:1:1H), 7.39 and 7.34 (m each, 2:3H), 5.89 (s, 1H), 2.44 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 186.4, 167.5, 140.3, 138.3, 138.1, 131.8, 129.1, 128.3, 127.8, 126.4, 125.3, 124.2, 88.9, 21.6, 14.9; HRMS (EI) calcd for $C_{17}H_{17}NOS$ 283.1031, found 283.1039.

*(E)-1-(4-Chlorophenyl)-3-(thiomethyl)-3-(phenylamino)prop-2-en-1-one (**1u**).* 2.51 g, yield 83%; yellow solid, mp 84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.49 (s, 1H), 7.83 and 7.39 (d each, J = 8.2 Hz, 2:2H), 7.36 and 7.31 (d each, J = 7.7 and 7.6 Hz, 2:2H), 7.24 (t, J = 7.2 Hz, 1H), 5.81 (s, 1H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 184.6, 168.2, 138.6, 138.1, 137.1, 129.2, 128.6, 128.5, 126.7, 125.4, 88.3, 14.9.

*(E)-1-(3-Chlorophenyl)-3-(thiomethyl)-3-(phenylamino)prop-2-en-1-one (**1v**).* 2.56 g, yield 85%; yellow solid, mp 56−58 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.49 (s, 1H), 7.86 (t, J = 1.7 Hz), 7.76 (d, J = 7.7 Hz), 7.41 (m), and 7.24 (t, J = 7.2 Hz) (1:1:1:1H), 7.39−7.27 (m, 5H), 5.79 (s, 1H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 184.3, 168.5, 142.1, 138.0, 134.5, 130.8, 129.7, 129.2, 127.3, 126.7, 125.4, 125.2, 88.4, 14.9; HRMS (EI) calcd for $C_{16}H_{14}NOSCl$ 303.0485, found 303.0494.

*(E)-1-(3-Bromophenyl)-3-(thiomethyl)-3-(phenylamino)prop-2-en-1-one (**1w**).* 2.32 g, yield 67%; red liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.51 (s, 1H), 8.01 (t, J = 1.5 Hz), 7.78 (d, J = 7.8 Hz), 7.52 (m), 7.32 (m), 7.27 (m), 7.21 (m) (1:1:1:2:2:2H), 5.76 (s, 1H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 183.8, 168.3, 142.1, 137.8, 133.5, 130.0, 129.8, 129.0, 126.5, 125.5, 125.1, 122.6, 88.3, 14.7; HRMS (ESI) calcd for $C_{16}H_{14}NOSBrNa$ [M + Na]$^+$ 369.9877, found 369.9883.

*(E)-3-(4-Ethoxyphenylamino)-3-(thioethyl)-1-phenylprop-2-en-1-one (**1x**).* 1.58 g, yield 48%; yellow solid, mp 86−88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.36 (s, 1H), 7.90 and 7.45 (m each, 2:3H), 7.22 and 6.89 (d each, J = 8.8 Hz, 2:2H), 5.90 (s, 1H), 4.02 (q, J = 7.0 Hz, 2H), 2.94 (q, J = 7.4 Hz, 2H), 1.41 (t, J = 7.0 Hz, 3H), 1.36 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 185.8, 167.8, 157.7, 140.4, 130.7, 130.8, 128.3, 127.2, 127.0, 114.7, 88.6, 63.6, 26.0, 14.9, 13.4; HRMS (EI) calcd for $C_{19}H_{21}NO_2S$ 327.1293, found 327.1304.

*(E)-3-(2,6-Dimethylphenylamino)-3-(thiomethyl)-1-phenylprop-2-en-1-one (**1y**).* 1.37 g, yield 46%; white solid, mp 130−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.98 (s, 1H), 7.98 (dd, J = 7.4 and 1.9 Hz) and 7.13 (d, J = 7.4 Hz) (2:2H), 7.46 and 7.19 (m each, 3:1H), 5.91 (s, 1H), 2.40 (s, 3H), 2.32 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 186.0, 170.2, 140.4, 136.8, 136.0, 130.8, 128.3, 128.2, 128.1, 127.1, 86.9, 18.2, 14.3; HRMS (EI) calcd for $C_{18}H_{20}NOS$ 298.1266, found 298.1269.

Typical Procedure for the Synthesis of Indoles 2: Synthesis of 2a. Under an argon atmosphere, a mixture of ketene *N*,*S*-acetal **1a** (104 mg, 0.5 mmol), $CuCl_2$ (202 mg, 1.5 mmol), and K_3PO_4 (318 mg, 1.5 mmol) in 5 mL of DMF/DMSO (7:1 v/v) was stirred at 120 °C for 2 h. The resulting mixture was cooled to ambient temperature, filtered through a short pad of Celite, rinsed with 20 mL of AcOEt, and washed with 10% aqueous NH_3·H_2O (2 × 10 mL) and brine (10 mL). The organic phase was dried over anhydrous Na_2SO_4 and filtered. All of the volatiles were evaporated under reduced pressure. The resultant residue was purified by silica gel column chromatography [eluent: petroleum ether (60−90 °C)/AcOEt = 10:1 v/v] to afford **2a** as a white solid (96 mg, 94%).

*2-(Thiomethyl)-3-acetyl-1H-indole (**2a**).* 96 mg, yield 94%; yellow solid, mp 170 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.75 (s, 1H), 7.83, 7.45, and 7.15 (m each, 1:1:2H), 2.62 (s, 3H), 2.54 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 191.2, 145.0, 136.9, 126.6, 121.6, 121.4, 119.3, 111.3, 113.7, 30.3, 14.4; HRMS (EI) calcd for $C_{11}H_{11}NOS$ 205.0561, found 205.0569.

*2-(Thiomethyl)-3-acetyl-5-methyl-1H-indole (**2b**).* 104 mg, yield 95%; white solid, mp 212−215 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.66 (s, 1H), 7.67 (s), 7.36 (d, J = 6.4 Hz), and 7.01 (d, J = 5.5 Hz) (1:1:1H), 2.64, 2.56, and 2.44 (s each, 9H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 191.1, 144.8, 135.2, 130.3, 126.8, 122.8, 119.2, 113.4, 110.9, 30.3, 21.5, 14.3; HRMS (EI) calcd for $C_{12}H_{13}NOS$ 219.0718, found 219.0709.

*2-(Thiomethyl)-3-acetyl-6-methyl-1H-indole (**2c**).* 60 mg, yield 55%; white solid, mp 216−218 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ

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11.60 (s, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.23 (s, 1H), 6.96 (d, J = 8.1 Hz, 1H), 2.59 (s, 3H), 2.50 (s, 3H), 2.38 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 191.1, 143.9, 137.2, 130.6, 124.4, 123.0, 119.1, 111.1, 113.7, 30.2, 21.2, 14.5; HRMS (EI) calcd for $C_{12}H_{13}NOS$ 219.0718, found 219.0710.

*2-(Thiomethyl)-3-acetyl-4-methyl-1H-indole (**2c'**).* 31 mg, yield 28%; yellow solid, mp 141−143 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.76 (s, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 6.87 (d, J = 7.2 Hz, 1H), 2.62 (s, 3H), 2.60 (s, 3H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 195.3, 137.0, 136.6, 129.7, 125.0, 123.1, 122.5, 108.7, 119.4, 32.0, 21.9, 17.0; HRMS (EI) calcd for $C_{12}H_{13}NOS$ 219.0718, found 219.0713.

*2-(Thiomethyl)-3-acetyl-7-methyl-1H-indole (**2d**).* 99 mg, yield 90%; white solid, mp 186−189 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.18 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 6.95 (d, J = 7.2 Hz, 1H), 2.69 (s, 3H), 2.58 (s, 3H), 2.52 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 191.9, 142.8, 136.0, 126.5, 123.0, 121.8, 117.5, 120.7, 115.7, 30.5, 17.1, 15.7; HRMS (EI) calcd for $C_{12}H_{13}NOS$ 219.0718, found 219.0714.

*2-(Thiomethyl)-3-acetyl-5-methoxy-1H-indole (**2e**).* 109 mg, yield 93%; white solid, mp 192−194 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.61 (s, 1H), 7.34 (d, J = 8.7 Hz, 2H), 6.79 (dd, J = 8.7 and 2.0 Hz, 1H), 3.79 (s, 3H), 2.61 (s, 3H), 2.53 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 191.1, 155.1, 144.6, 131.8, 127.4, 113.8, 111.8, 110.4, 102.5, 55.3, 30.3, 14.5; HRMS (EI) calcd for $C_{12}H_{13}NO_2S$ 235.0667, found 235.0668.

*2-(Thiomethyl)-3-acetyl-5-ethoxy-1H-indole (**2f**).* 120 mg, yield 96%; white solid, mp 152−154 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.60 (s, 1H), 7.33 (m, 2H), 6.77 (d, J = 8.8 Hz, 1H), 4.03 (q, J = 6.9 Hz, 2H), 2.60 (s, 3H), 2.51 (s, 3H), 1.34 (t, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 191.2, 154.4, 144.7, 131.8, 127.4, 113.8, 111.8, 110.8, 103.4, 63.4, 30.3, 14.9, 14.5; HRMS (EI) calcd for $C_{13}H_{15}NO_2S$ 249.0823, found 249.0826.

*2-(Thiomethyl)-3-acetyl-7-methoxy-1H-indole (**2g**).* 76 mg, yield 65%; white solid, mp 197−200 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.66 (s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.09 (t, J = 8.0 Hz, 1H), 6.76 (d, J = 7.9 Hz, 1H), 3.94 (s, 3H), 2.67 (s, 3H), 2.55 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 191.8, 145.4, 143.2, 128.1, 126.6, 122.4, 112.4, 103.0, 115.5, 55.3, 30.5, 15.3; HRMS (EI) calcd for $C_{12}H_{13}NO_2S$ 235.0667, found 235.0674.

*2-(Thiomethyl)-3-acetyl-5-chloro-1H-indole (**2h**).* 86 mg, yield 72%; yellow solid, mp 232−234 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 7.82 (d, J = 1.6 Hz, 1H), 7.43 (d, J = 8.5 Hz, 1H), 7.14 (dd, J = 8.5 and 1.8 Hz, 1H), 2.63 (s, 3H), 2.52 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 191.1, 146.5, 135.3, 127.8, 126.3, 121.4, 118.6, 112.6, 113.3, 30.3, 14.4; HRMS (EI) calcd for $C_{11}H_{10}NOSCl$ 239.0172, found 239.0178.

*2-(Thiomethyl)-3-acetyl-7-chloro-1H-indole (**2i**).* 93 mg, yield 78%; yellow solid, mp 168−171 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.69 (s, 1H), 7.92 (m, 1H), 7.25 (m, 1H), 7.17 (d, J = 7.9 Hz, 1H), 2.73 (s, 3H), 2.59 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 192.1, 144.5, 133.6, 128.5, 122.8, 121.9, 118.9, 116.2, 115.5, 30.6, 15.8; HRMS (EI) calcd for $C_{11}H_{10}NOSCl$ 239.0172, found 239.0172.

*2-(Thiomethyl)-3-acetyl-5-fluoro-1H-indole (**2j**).* 76 mg, yield 68%; pale-yellow solid, mp 202−204 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.69 (s, 1H), 7.45, 7.31, and 6.86 (m each, 1:1:1H), 2.51 (s, 3H), 2.40 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 191.1, 158.5 (d and Cq, J = 233.7 Hz), 146.5, 133.4, 127.3 (d and Cq, J = 10.8 Hz), 113.8 (d and Cq, J = 3.9 Hz), 112.1 (d, J = 9.9 Hz), 109.1 (d, J = 25.7 Hz), 104.8 (d, J = 25.4 Hz), 30.1, 14.4; HRMS (EI) calcd for $C_{11}H_{10}NOSF$ 223.0467, found 223.0474.

*2-(Thiomethyl)-3-acetyl-4,6-dimethyl-1H-indole (**2k**).* 85 mg, yield 73%; pale-red solid, mp 149−151 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.62 (s, 1H), 7.01 and 6.71 (s each, 1:1H), 2.59 (s, 3H), 2.58 (s, 3H), 2.40 (s, 3H), 2.33 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 195.2, 137.5, 135.6, 131.7, 129.5, 123.0, 124.9, 108.6, 119.5, 31.9, 21.8, 21.0, 17.3; HRMS (EI) calcd for $C_{13}H_{15}NOS$ 233.0874, found 233.0874.

*2-(Thiomethyl)-3-acetyl-1H-benzo[g]indole (**2l**).* 101 mg, yield 79%; brown solid, mp 206−208 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 12.23 (s, 1H), 8.61 and 7.94 (d each, J = 7.8 Hz, 1:1H), 8.14 (d, J = 8.5 Hz, 1H), 7.61 (m, 2H), 7.46 (t, J = 6.8 Hz, 1H), 2.74 (s, 3H), 2.67 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 192.8, 138.9, 131.3, 129.8, 120.9, 122.9, 128.3, 125.8, 124.5, 122.4, 121.4, 120.0, 117.6, 30.6, 16.9; HRMS (EI) calcd for $C_{15}H_{13}NOS$ 255.0718, found 255.0728.

*2-(Thioethyl)-3-acetyl-7-methyl-1H-indole (**2m**).* 107 mg, yield 92%; white solid, mp 114−116 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.57 (s, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 7.00 (d, J = 7.1 Hz, 1H), 3.25 (q, J = 7.3 Hz, 2H), 2.66 (s, 3H), 2.55 (s, 3H), 1.28 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 192.7, 138.8, 136.0, 126.5, 123.4, 121.8, 118.2, 120.7, 117.7, 30.7, 27.9, 17.0, 14.4; HRMS (EI) calcd for $C_{13}H_{15}NOS$ 233.0874, found 233.0878.

*2-(Thioethyl)-3-acetyl-5-methyl-1H-indole (**2n**).* 106 mg, yield 91%; white solid, mp 186−188 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.70 (s, 1H), 7.71 (s, 1H), 7.31 (d, J = 8.2 Hz, 1H), 6.97 (d, J = 8.2 Hz, 1H), 3.13 (q, J = 7.3 Hz, 2H), 2.54 (s, 3H), 2.40 (s, 3H), 1.30 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 191.5, 142.1, 135.3, 130.2, 126.8, 123.0, 119.5, 111.0, 114.4, 30.5, 25.8, 21.5, 14.3; HRMS (EI) calcd for $C_{13}H_{15}NOS$ 233.0874, found 233.0880.

*2-(Thioethyl)-3-acetyl-5-methoxy-1H-indole (**2o**).* 117 mg, yield 94%; white solid, mp 148−150 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.72 (s, 1H), 7.44 (s) and 7.32 and 6.80 (d each, J = 8.6 Hz) (1:1:1H), 3.78 (s, 3H), 3.13 (q, J = 7.1 Hz, 2H), 2.55 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 191.7, 155.2, 141.6, 131.7, 127.4, 115.0, 111.8, 111.0, 102.7, 55.3, 30.4, 26.1, 14.3; HRMS (EI) calcd for $C_{13}H_{15}NO_2S$ 249.0823, found 249.0826.

*2-(Thioethyl)-3-acetyl-5-ethoxy-1H-indole (**2p**).* 126 mg, yield 96%; white solid, mp 157−160 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.70 (s, 1H), 7.41 (s), 7.31 (d, J = 8.7 Hz), and 6.78 (d, J = 7.7 Hz) (1:1:1H), 4.03 (q, J = 6.8 Hz, 2H), 3.13 (q, J = 7.2 Hz, 2H), 2.54 (s, 3H), 1.34 and 1.29 (t each, J = 6.9 and 7.3 Hz, 3:3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 191.6, 154.4, 141.7, 131.7, 127.4, 114.9, 111.8, 111.4, 103.5, 63.3, 30.4, 26.0, 14.9, 14.3; HRMS (EI) calcd for $C_{14}H_{17}NO_2S$ 263.0980, found 263.0982.

*2-(Thioethyl)-3-acetyl-7-chloro-1H-indole (**2q**).* 102 mg, yield 81%; white solid, mp 135−137 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 12.02 (s, 1H), 8.01 (d, J = 7.7 Hz), 7.26 (d, J = 7.6 Hz), and 7.16 (t, J = 7.9 Hz) (1:1:1H), 3.27 (q, J = 7.3 Hz, 2H), 2.63 (s, 3H), 1.23 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 192.8, 140.8, 133.6, 128.5, 122.7, 122.4, 119.5, 118.2, 115.5, 30.8, 27.9, 14.3; HRMS (EI) calcd for $C_{12}H_{12}NOSCl$ 253.0328, found 253.0330.

*2-(Thiomethyl)-3-benzoyl-1H-indole (**2r**).* 95 mg, yield 71%; yellow solid, mp 159−161 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 12.00 (s, 1H), 7.58 (s) and 7.52−7.43 (m) (1:3H), 7.56 (t, J = 3.3 Hz), 7.08 (dt, J = 8.2 and 4.2 Hz), and 6.94 (d, J = 4.0 Hz) (2:1:2H), 2.60 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 190.2, 146.2, 141.3, 137.2, 131.3, 128.7, 128.1, 122.0, 121.5, 119.2, 111.6, 127.1, 113.3, 14.9; HRMS (EI) calcd for $C_{16}H_{13}NOS$ 267.0718, found 267.0727.

*2-(Thiomethyl)-3-benzoyl-4,5,6,7-D_4-1H-indole (**2r[D_4]**).* 91 mg, yield 67%; yellow solid, mp 164−166 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 7.58 and 7.50 (m each, 3:2H), 2.62 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 189.6, 145.7, 141.1, 136.8, 126.7, 113.0, 137.4, 129.7, 128.6, 127.6, 131.0, 128.3, 127.8, 14.6; HRMS (ESI) calcd for $C_{16}H_{10}D_4NOS$ $[M + H]^+$ 272.1047, found 272.1046.

*2-(Thiomethyl)-3-(4-methylbenzoyl)-1H-indole (**2s**).* 103 mg, yield 73%; white solid, mp 170−172 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 7.52 and 7.30 (d each, J = 7.9 Hz, 2:2H), 7.45 (d, J = 8.0 Hz), 7.10 (t, J = 7.5 Hz), 7.04 (d, J = 7.9 Hz), and 6.97 (t, J = 7.5 Hz) (1:1:1:1H), 2.61 (s, 3H), 2.39 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 189.5, 145.1, 141.1, 138.2, 136.8, 128.9, 128.3, 121.6, 121.1, 119.0, 111.2, 126.8, 113.3, 21.1, 14.7; HRMS (EI) calcd for $C_{17}H_{15}NOS$ 281.0874, found 281.0879.

*2-(Thiomethyl)-3-(3-methylbenzoyl)-1H-indole (**2t**).* 101 mg, yield 72%; yellow solid, mp 105−108 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 7.45 (d, J = 8.0 Hz), 7.08 (m), and 6.96 (m) (1:1:2H), 7.39 (d, J = 8.3 Hz, 4H), 2.62 (s, 3H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 189.8, 145.6, 141.2, 137.6,

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136.9, 131.6, 128.3, 128.2, 125.1, 121.6, 121.1, 118.9, 111.3, 126.9, 113.1, 20.9, 14.7; HRMS (EI) calcd for $C_{17}H_{15}NOS$ 281.0874, found 281.0879.

*2-(Thiomethyl)-3-(4-chlorobenzoyl)-1H-indole (**2u**).* 101 mg, yield 67%; yellow solid, mp 199−201 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.00 (s, 1H), 7.62 and 7.56 (d each, J = 8.4 Hz, 2:2H), 7.46 (d), 7.11 (m), and 7.01 (m) (1:1:2H), 2.63 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 188.3, 146.1, 139.7, 136.9, 135.8, 129.9, 128.5, 121.8, 121.4, 118.9, 111.4, 126.7, 112.8, 14.7; HRMS (EI) calcd for $C_{16}H_{12}NOSCl$ 301.0328, found 301.0334.

*2-(Thiomethyl)-3-(3-chlorobenzoyl)-1H-indole (**2v**).* 98 mg, yield 65%; yellow solid, mp 168−170 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.02 (s, 1H), 7.64 (m), 7.54 (d, J = 4.8 Hz), and 7.47 (d, J = 8.0 Hz) (1:2:1H), 7.59 (s), 7.11 (m), and 7.00 (d, J = 3.5 Hz) (1:1:2H), 2.63 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 187.8, 146.5, 143.1, 137.0, 133.2, 130.7, 130.4, 127.5, 126.4, 121.8, 121.4, 118.8, 111.4, 126.7, 112.6, 14.7; HRMS (EI) calcd for $C_{16}H_{12}NOSCl$ 301.0328, found 301.0326.

*2-(Thiomethyl)-3-(3-bromobenzoyl)-1H-indole (**2w**).* 114 mg, yield 66%; white solid, mp 168−170 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.03 (s, 1H), 7.77 (d, J = 7.9 Hz), 7.58 (d, J = 7.6 Hz), and 7.46 (m) (1:1:2H), 7.72 (s) and 7.12 and 7.10 (m each) (1:1:2H), 2.63 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 187.8, 146.6, 143.3, 137.0, 133.6, 130.8, 130.4, 126.8, 121.9, 121.5, 118.8, 111.4, 126.7, 121.7, 112.6, 14.7; HRMS (ESI) calcd for $C_{16}H_{12}NOSBrNa$ $[M + Na]^+$ 367.9721, found 367.9729.

*2-(Thioethyl)-3-benzoyl-5-ethoxy-1H-indole (**2x**).* 145 mg, yield 89%; white solid, mp 151−153 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 7.58 and 7.50 (m each, 3:2H), 7.32 (d, J = 8.7 Hz), 6.74 (dd, J = 8.7 and 2.3 Hz), and 6.51 (d, J = 2.1 Hz) (1:1:1H), 3.75 (q, J = 6.9 Hz, 2H), 3.10 (q, J = 7.3 Hz, 2H), 1.25 and 1.22 (t each, J = 6.9 and 7.3 Hz, 3:3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 189.9, 153.8, 142.8, 141.1, 131.8, 131.0, 128.3, 128.0, 111.9, 111.5, 102.7, 127.6, 114.0, 63.0, 25.9, 14.7, 14.2; HRMS (EI) calcd for $C_{19}H_{19}NO_2S$ 325.1136, found 325.1144.

Typical Procedure for the Reactions of 2 with Arylboronic Acids: Synthesis of 3a. Under a nitrogen atmosphere, a mixture of **2b** (110 mg, 0.5 mmol), phenylboronic acid (92 mg, 0.75 mmol), $Pd(PPh_3)_4$ (43 mg, 0.0375 mmol), CuTC (191 mg, 1.0 mmol), and Cs_2CO_3 (326 mg, 1.0 mmol) in 5 mL of THF was stirred at 50 °C for 48 h. The resulting mixture was cooled to ambient temperature, filtered through a short pad of Celite, and rinsed with 10 mL of CH_2Cl_2. All of the volatiles were evaporated from the combined filtrate under reduced pressure. The resultant residue was purified by silica gel column chromatography [eluent: petroleum ether (60−90 °C)/AcOEt = 30:1 v/v] to afford **3a** as a white solid (99 mg, 79%).

*2-Phenyl-3-acetyl-5-methyl-1H-indole (**3a**).* 99 mg, yield 79%; white solid, mp 231−233 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.97 (s, 1H), 8.03 (s, 1H), 7.62 and 7.53 (m each, 2:3H), 7.32 and 7.05 (d each, J = 8.2 Hz, 1:1H), 2.42 (s, 3H), 2.06 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 193.6, 144.9, 133.8, 132.9, 130.5, 127.3, 114.0, 130.0, 129.3, 128.4, 124.3, 121.3, 111.3, 30.1, 21.5; HRMS (ESI) calcd for $C_{17}H_{15}NONa$ $[M + Na]^+$ 272.1051, found 272.1042.

*2-Phenyl-3-acetyl-6-methyl-1H-indole (**3b**).* 90 mg, yield 72%; white solid, mp 219−222 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.94 (s, 1H), 8.09 and 7.04 (d each, J = 8.2 Hz, 1:1H), 7.62 and 7.53 (m each, 2:3H), 7.23 (s, 1H), 2.42 (s, 3H), 2.08 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 193.5, 144.4, 135.9, 132.9, 132.1, 124.9, 114.2, 130.0, 129.2, 128.4, 123.4, 121.3, 111.3, 30.02, 21.28; HRMS (ESI) calcd for $C_{17}H_{15}NONa$ $[M + Na]^+$ 272.1051, found 272.1047.

*2-(4-Chlorophenyl)-3-acetyl-7-methyl-1H-indole (**3c**).* 93 mg, yield 66%; white solid, mp 174−175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.37 (s, 4H), 7.22 (d, J = 8.0 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 6.99 (d, J = 7.0 Hz, 1H), 2.54 (s, 3H), 2.25 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 200.9, 138.4, 136.0, 135.5, 131.8, 130.8, 125.5, 118.4, 130.1, 129.3, 123.9, 109.0, 32.7, 21.4; HRMS (EI) calcd for $C_{17}H_{15}NOCl$ $[M + H]^+$ 284.0842, found 284.0832.

*2-(4-Methylphenyl)-3-benzoyl-5-ethoxy-1H-indole (**3d**).* 112 mg, yield 63%; white solid, mp 182−184 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.98 (s, 1H), 7.51 and 7.35 (m each, 2:1H), 7.39 and 6.87 (d each, J = 8.8 Hz, 1:1H), 7.22 (m, 5H), 7.03 (d, J = 7.9 Hz, 2H), 3.95 (q, J = 6.9 Hz, 2H), 2.22 (s, 3H), 1.31 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.1, 154.2, 144.6, 140.0, 137.8, 130.8, 129.0, 128.8, 111.8, 131.1, 129.3, 128.9, 128.5, 127.7, 113.1, 112.5, 103.4, 63.3, 20.7, 14.8; HRMS (EI) calcd for $C_{24}H_{22}NO_2$ $[M + H]^+$ 356.1651, found 356.1641.

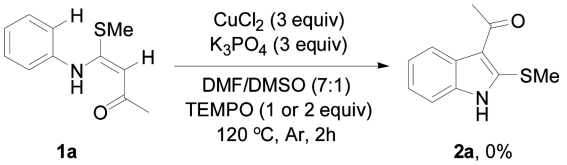
Typical Procedure for the Reactions of 2 with Hydroxylamine Hydrochloride: Synthesis of 4a. A mixture of **2c** (110 mg, 0.50 mmol), hydroxylamine hydrochloride (52 mg, 0.75 mmol), and potassium hydroxide (42 mg, 0.75 mmol) in ethanol (5 mL) was stirred at 100 °C for 18 h. After the reaction was complete as determined by TLC monitoring on silica gel, the mixture was cooled to ambient temperature, and all of the volatiles were removed under reduced pressure. The resultant residue was dissolved in 15 mL of water, and the solution was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with water (2 × 10 mL) and dried over anhydrous Na_2SO_4, and all of the volatiles were evaporated under reduced pressure. Purification by silica gel column chromatography [eluent: petroleum ether (60−90 °C)/AcOEt = 50:1 v/v] afforded **4a** as a white solid (67 mg, 72%).

*3,6-Dimethyl-8H-isoxazolo[5,4-b]indole (**4a**).* 67 mg, yield 72%; white solid, mp 141−144 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.60 (s, 1H), 7.72 and 7.01 (d each, J = 8.0 Hz, 1:1H), 7.32 (s, 1H), 2.66 (d, 3H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 158.4, 156.6, 144.4, 132.5, 125.0, 118.1, 121.5, 118.4, 112.2, 21.5, 18.5; HRMS (EI) calcd for $C_{11}H_{11}N_2O$ $[M + H]^+$ 187.0871, found 187.0876.

*3,7-Dimethyl-8H-isoxazolo[5,4-b]indole (**4b**).* 60 mg, yield 64%; white solid, mp 212−215 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.85 (s, 1H), 7.70 and 7.11 (m each, 1:2H), 2.69 (s, 3H), 2.51 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 158.3, 156.9, 143.2, 125.4, 121.0, 119.8, 123.7, 120.1, 116.3, 18.4, 16.7; HRMS (EI) calcd for $C_{11}H_{11}N_2O$ $[M + H]^+$ 187.0871, found 187.0879.

KIE Experiments. The deuterated derivative of **1r**, that is, **1r**[D_5], was prepared using aniline-d_7 as the starting material in a fashion similar to the preparation of **1r**. Two sets of reactions of **1r**[D_5] and **1r** were carried out on a 0.3 mmol scale in a parallel manner under the optimized conditions shown in Table 2. The reactions were monitored by GC analysis, and the yields were carefully checked by integration of the signals of the desired products using mesitylene as the internal standard. At 20 min, a sample of the reaction mixture was withdrawn for GC analysis, and yields of 63% and 66% were measured for **2r**[D_4] and **2r**, respectively; at 0.5 h, the yields increased to 67% for **2r**[D_4] and 72% for **2r**. The corresponding k_H/k_D values of 1.05 (0.66/0.63) at 20 min and 1.07 (0.72/0.67) at 0.5 h were thus obtained.

Radical Trapping Study. Under an argon atmosphere, a mixture of ketene *N*,*S*-acetal **1a** (104 mg, 0.5 mmol), $CuCl_2$ (202 mg, 1.5 mmol), TEMPO (0.5 or 1.0 mmol), and K_3PO_4 (318 mg, 1.5 mmol) in 5 mL of DMF/DMSO (7:1 v/v) was stirred at 120 °C for 2 h. The resultant mixture was cooled to ambient temperature and subjected to GC analysis using mesitylene as the internal standard. The desired product **2a** was not detected in the reaction mixture.



1a **2a**, 0%

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Optimization of the reaction conditions, ^{1}H and ^{13}C NMR spectra of all of the compounds, and X-ray structural information for **2d**, **2x**, and **3b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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