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Concise and Efficient Synthesis of Indole−Indolone Scaffolds through MeOTf-Induced Annulation of *N*-(2-Cyanoaryl)indoles

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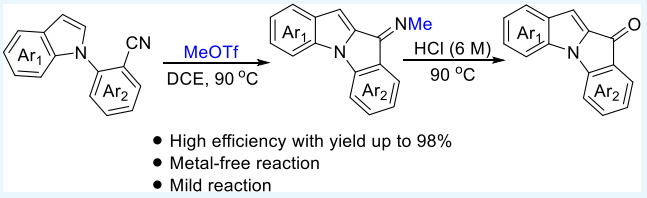
Supporting Information

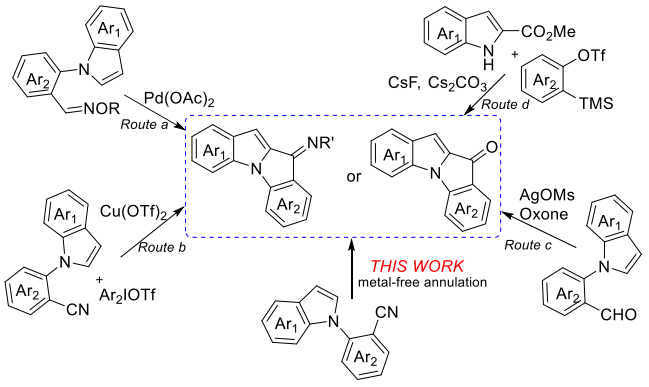
ABSTRACT: MeOTf-triggered annulation of *N*-(2-cyanoaryl)indoles to provide indolo[1,2-*a*]indol-10-imines and the corresponding indolo[1,2-*a*]indol-10-ones have been described under metal-free conditions. A variety of functional groups are tolerated in their scaffolds with good to excellent yields. The reaction could be carried to gram scale.



INTRODUCTION

Indole nuclei are the foundation for many well-known biologically active molecules and exhibiting various pharmacological properties.[1,2] Indolones are also valuable frameworks in medicinal chemistry and material chemistry.[3] Because both indoles and indolones are relevant core structures for medicines, a fusion of two frameworks could theoretically result in a range of biologically active compounds. Therefore, developing a strategy to assemble two biologically and medicinally interesting substructures into one skeletal structure is one of the interesting and important topics in organic synthetic chemistry. Transition-metal-catalyzed syntheses of indole−indolone scaffolds have been developed in recent years.[4] For example, Pd-catalyzed or Cu-catalyzed intramolecular annulation of indole-*N*-arylated aldoximes (Scheme 1, route a) or *N*-(2-cyanophenyl)indoles (route b) to afford indolo[1,2-*a*]indol-10-imines has been reported.[4a,b] Recently, Rao and co-workers reported an annulation reaction of *N*-(2-formylaryl)indoles to give indolo-[1,2-*a*]indol-10-ones via silver-catalyzed direct oxidative coupling between aldehyde C−H and sp^2 C−H bonds (route c).[4c] Larock and Ramtohul et al. have developed fluoride and inorganic base-mediated synthesis of indolo[1,2-*a*]indol-10-ones through the reaction of methyl indole-2-carboxylates with arynes (route d).[4d,e] Although significant progresses have been made to date, a new method for the synthesis of diverse indole−indolone scaffolds under metal-free conditions is still highly desirable, particularly in the drug scanning process. Herein, we report the methyl triflate (MeOTf)-induced annulation of *N*-(2-cyanoaryl)indoles to afford the indolo[1,2-*a*]indol-10-imines and the corresponding indolo[1,2-*a*]indol-10-ones under metal-free conditions.

Scheme 1. Synthetic Strategy Leading to Indolo[1,2-*a*]indol-10-imines or Indolo[1,2-*a*]indol-10-ones



RESULTS AND DISCUSSION

Learning from our previous studies in the area of triflate-induced annulation,[5,6] we initially explored the reaction of 2-(3-methyl-1*H*-indol-1-yl)benzonitrile **1a** and MeOTf **2a** with the ratio of 1:1.5 in dichloroethane (DCE) under different temperatures for 12 h (Table 1, entries 1−3), and 90 °C was found to be the optimal temperature for this reaction with the NMR yield up to 75% (entry 2). Then, different solvents were screened such as dichloromethane (CH_2Cl_2), chloroform ($CHCl_3$), tetrachloromethane (CCl_4), and toluene (entries 4−7). DCE was found to be a superior solvent for this reaction (entry 2). Furthermore, the effects of the reaction time were also examined (entry 2 and entries 8−9), the best time for approving yield was 24 h (entry 9). When the ratio of two components was converted to 1:1 and 1:2, the yield of **3a** was 79 and 85% (entries 10−11), respectively. We also tried the ratio of **1a** and **2a** in 1:1.2 and to our delight, 99% yield of **3a** was also obtained. On the basis of the above results, the optimal conditions are shown in entry 12.

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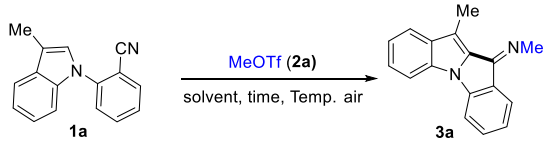
Table 1. Optimization of the Reaction Conditions for the Formation of 3a[a]

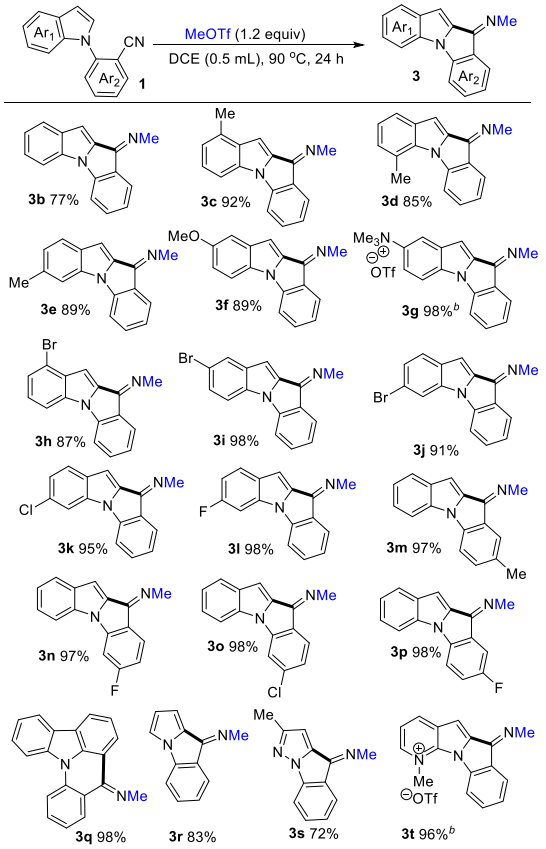


entry	temp (°C)	t (h)	solvent	yield/%[b]
1	60	12	DCE	64
2	90	12	DCE	75
3	120	12	DCE	43
4	90	12	DCM	54
5	90	12	$CHCl_3$	39
6	90	12	CCl_4	25
7	90	12	toluene	34
8	90	18	DCE	89
9	90	24	DCE	99 (95)[c]
10[d]	90	24	DCE	79
11[e]	90	24	DCE	85
12[f]	90	24	DCE	99

[a]Reaction conditions: 2-(3-methyl-1*H*-indol-1-yl)benzonitrile **1a** (0.5 mmol), MeOTf **2a** (0.75 mmol, 1.5 equiv) in 0.5 mL solvent under air ambience. [b]NMR yield based on CH_2Br_2 as internal standard. [c]Isolated yield. [d]MeOTf **2a** (0.5 mmol, 1.0 equiv). [e]MeOTf **2a** (1.0 mmol, 2.0 equiv). [f]MeOTf **2a** (0.6 mmol, 1.2 equiv).

With the optimized reaction conditions in hand (Table 1, entry 12), we probed the substrate scope and the representative results are summarized in Scheme 2. Suitable *N*-(2-cyanoaryl)-indole substrates **1** were prepared by the coupling reaction of commercially available indole derivatives and 2-bromobenzonitrile derivatives.[7] Generally, the *N*-(2-cyanophenyl)-indoles containing electron-rich or electron-deficient substituents could proceed smoothly to afford indolo[1,2-*a*]indol-10-imines in high yields. For example, *N*-(2-cyanophenyl)-indoles containing electron-donating groups such as Me, OMe, NMe_2 on the phenyl ring displayed higher reactivity to afford the corresponding products in excellent yields. Notably, when 2-(5-(dimethylamino)-1*H*-indol-1-yl)benzonitrile **2g** was employed under the same reaction conditions and *N*,*N*,*N*-trimethyl-10-(methylimino)-10*H*-indolo[1,2-*a*]indol-2-aminium trifluoromethanesulfonate **3g** was obtained in 75% yield. When 2.2 equiv of MeOTf were added, **3g** was obtained quantitatively. The *N*-(2-cyanophenyl)-indoles containing electron-withdrawing groups such as chlorine and fluorine also displayed higher reactivity to afford the corresponding products in excellent yields (**3h**−**3l**). To further expand the substrate scope, the benzonitrile units bearing either electron-donating groups such as methyl or electron-withdrawing groups such as chlorine and fluorine were tested, and all of them readily produce the desired products (**3m**−**3p**) in quantitative yields, respectively. The stereochemistries of **3b** and **3m** were determined by 2-D NMR. The nuclear Overhauser effect spectroscopy spectra revealed that the methyl group and the original indolyl group were in cis-fashion (see Figures S2 and S3 in the Supporting Information). In addition, 2-(9*H*-carbazol-9-yl)benzonitrile **1q**, 2-(1*H*-pyrrol-1-yl)benzonitrile **1r**, and 2-(3-methyl-1*H*-pyrazol-1-yl)-benzonitrile **1s** could be used as well to produce the corresponding compounds **3q**, **3r**, and **3s** in good yields, respectively. It is noteworthy that 2-(1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)benzonitrile **1t** was used in this reaction with 2.2 equiv of MeOTf and 1-methyl-6-(methylimino)-6*H*-pyrido[3′,2′:4,5]-

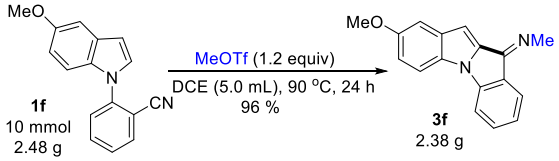
Scheme 2. Scope of Cyclization of (2-Cyanoaryl)indoles[a]



[a]Reaction conditions: *N*-(2-cyanoaryl)indoles **1** (0.5 mmol), MeOTf **2a** (0.6 mmol, 1.2 equiv) in 0.5 mL of DCE, 90 °C under air ambience, 24 h, isolated yield. [b]MeOTf **2a** (1.1 mmol, 2.2 equiv).

pyrrolo[1,2-*a*]indol-1-ium trifluoromethanesulfonate **3t** was obtained in 96% yield. Notably, when 2-(2-methyl-1*H*-indol-1-yl)benzonitrile was employed in this reaction, no product was obtained. The starting material remains.

In order to verify the applicability of the current method, the reaction was amplified to 10 mmol scale with the formation of indolo[1,2-*a*]indole **3f** in 96% yield (2.38 g) (eq 1).



(Eq. 1)

We also performed the reactions with hydrolysis to convert the imine into keto functionality using hydrochloric acid aqueous solution (6 M) at 90 °C for 12 h. The representative results are shown in Scheme 3. The indolo[1,2-*a*]indol-10-ones **4** were obtained in good to excellent yields. To our delight, the crystals of **4i**, **4t**, and **4u** were suitable for single crystal analysis, and their structures were fully characterized by X-ray diffraction analysis.[8] The structures of the compounds were further confirmed in the formation of indole−indolone scaffolds.

On the basis of the above results and related precedents,[5,9] a plausible mechanism is proposed as follows (Scheme 4): first, methylation of the *N*-(2-cyanoaryl)indole by MeOTf affords carbenium ion **A** or its resonance **B**. Then, intramolecular Friedel−Crafts reaction of **B** with the subsequent deprotonation

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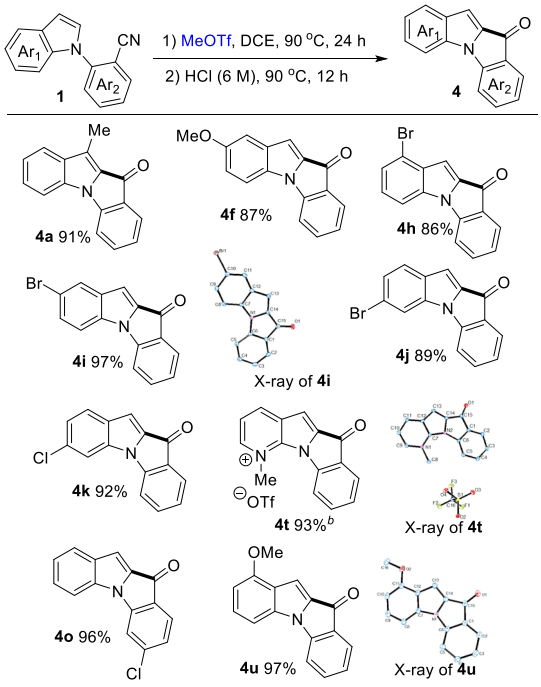
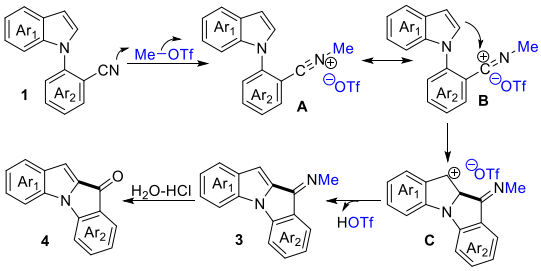
Scheme 3. Formation of (2-Cyanoaryl)indoles Subsequent Hydrolysis[a]



[a]Reaction conditions: (1) *N*-(2-cyanoaryl)indoles **1** (0.5 mmol), MeOTf **2a** (0.6 mmol, 1.2 equiv) in 0.5 mL of DCE under air ambience; (2) HCl (6 M, 5 mL), isolated yield. [b]MeOTf **2a** (1.1 mmol, 2.2 equiv).

Scheme 4. Plausible Mechanism of the Reaction



of intermediate **C** affords indole−indolone imine **3**, which undergoes hydrolysis with HCl aqueous solution to form indole−indolone scaffold **4**.

CONCLUSIONS

In summary, we have developed a MeOTf-induced intramolecular cyclization of *N*-(2-cyanoaryl)indoles for the synthesis of indolo[1,2-*a*]indol-10-imines and the corresponding indolo[1,2-*a*]indol-10-ones. This annulation represents a general entry for the construction of indole−indolone scaffolds in high yield under metal-free condition.

EXPERIMENTAL SECTION

General Information. All the reactions were carried out in air ambience. All materials were obtained from commercial sources and used as received. DCE and toluene were freshly distilled, whereas CH_2Cl_2, EtOAc, MeOH, and Et_3N were dried by an activated 4 Å molecular sieve. Column chromatography was performed on a silica column (particle size 300 mesh). ^1H NMR and $^{13}C\{^1H\}$ NMR spectra were recorded on 400 or 600 MHz at ambient temperature with $CDCl_3$ or CD_3OD as the solvent. Chemical shifts (δ) were given in ppm, in reference to the residual proton resonance of $CDCl_3$ (7.26) or CD_3OD (3.31), to the carbon resonance of $CDCl_3$ (77.16) or CD_3OD (49.0). Coupling constants (J) were given in Hertz (Hz). The terms m, q, t, d, s referred to multiplet, quartet, triplet, doublet, singlet. High-resolution mass spectra were recorded on electrospray mass spectrometer (ESI-TOF).

General Procedure for the Synthesis of Starting Materials.[7a] A sealed tube (25 mL) charged with indole derivatives (5 mmol), K_3PO_4 (10.2 mmol), CuI (10 mol %), 1,10-phenanthroline hydrate (40 mol %), and toluene (13 mL) was stirred for 10 min. Then, 2-bromobenzonitrile (6 mmol) was slowly added into above tube. The reaction mixture was stirred at 110 °C for 24−36 h under nitrogen atmosphere. After extraction with dichloromethane three times, the combined organic layer was dried by Na_2SO_4, evaporated, and isolated by silica gel flash chromatography (petroleum ether/ethyl acetate: 5/1) to obtain the starting material **1**.

General Procedure for the Synthesis of Product 3. A sealed tube (25 mL) charged with *N*-(2-cyanoaryl)-indoles (0.5 mmol), MeOTf (0.6 mmol), and DCE (0.5 mL) was stirred at 90 °C for 24 h under. After extraction with dichloromethane three times, the combined organic layer was dried by Na_2SO_4, evaporated, and isolated by silica gel flash chromatography (petroleum ether/ethyl acetate/triethylamine: 10/1/5) to obtain the corresponding product **3**.

Hydrolysis Procedure for Product 4. HCl (6 M, 5 mL) was added to a 25 mL sealed tube with product **3**. The solution was stirred at 90 °C for 12 h. After extraction with dichloromethane three times, the combined organic layer was dried by Na_2SO_4, evaporated, and isolated by silica gel flash chromatography (petroleum ether/EtOAc: 10/1) to obtain the corresponding product **4**.

(Z)-N,11-Dimethyl-10H-indolo[1,2-a]indol-10-imine (***3a***). Yellow solid, 95% isolated yield (116.9 mg); mp 137−139 °C; ^1H NMR (400 MHz, chloroform-*d*): δ 7.84 (d, J = 7.7 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.1 Hz, 1H), 7.44−7.38 (m, 2H), 7.32 (t, J = 7.7 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 7.0−6.98 (m, 1H), 3.88 (s, 3H), 2.53 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 157.3, 143.4, 135.3, 134.3, 132.2, 132.0, 128.5, 127.0, 125.1, 122.3, 121.2, 120.8, 114.1, 111.1, 111.0, 41.6, 8.9. IR ($CHCl_3$, cm^{-1}): 3057, 2970, 1640, 1457. HRMS (ESI): $[M + H]^+$ calcd for $C_{17}H_{15}N_2^+$, 247.1230; found, 247.1232.

(Z)-N-Methyl-10H-indolo[1,2-a]indol-10-imine (***3b***). Yellow solid, 77% isolated yield (89.3 mg); mp 142−143 °C; ^1H NMR (400 MHz, chloroform-*d*): δ 7.80 (d, J = 7.7 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.45 (d, J = 3.5 Hz, 2H), 7.43−7.36 (m, 1H), 7.23−7.10 (m, 2H), 6.94 (s, 1H), 3.73 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 156.4, 142.5, 132.9, 132.5, 132.1, 131.8, 131.3, 126.2, 123.7, 123.6, 123.1, 121.5, 111.2, 110.8, 107.3, 42.6. IR ($CHCl_3$, cm^{-1}): 3067, 2976, 1643, 1452. HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{13}N_2^+$, 233.1073; found, 233.1071.

(Z)-N,1-Dimethyl-10H-indolo[1,2-a]indol-10-imine (***3c***). Yellow solid, 92% isolated yield (113.2 mg); mp 145−147 °C; ^1H NMR (400 MHz, chloroform-*d*): δ 7.68 (d, J = 7.5 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.25−7.14 (m, 3H), 7.03 (t, J = 7.5 Hz, 1H), 6.84 (d, J = 7.0 Hz, 1H), 6.68 (s, 1H), 3.60 (s, 3H), 2.43 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 156.1, 142.2, 133.0, 132.5, 131.6, 131.6, 131.5, 131.0, 126.0, 123.2, 122.7, 121.6, 110.6, 108.6, 105.5, 42.4, 18.7. IR ($CHCl_3$, cm^{-1}): 3056,

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2978, 1648, 1482. HRMS (ESI): $[M + H]^+$ calcd for $C_{17}H_{15}N_2^+$, 247.1230; found, 247.1228.

(Z)-N,4-Dimethyl-10H-indolo[1,2-a]indol-10-imine (**3d**). Yellow solid, 85% isolated yield (104.6 mg); mp 156−158 °C; ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.58−8.52 (m, 1H), 8.07 (dd, *J* = 7.9, 2.8 Hz, 1H), 7.78 (dd, *J* = 4.0, 2.8 Hz, 1H), 7.72−7.65 (m, 1H), 7.61−7.55 (m, 1H), 7.54−7.48 (m, 1H), 7.42 (d, *J* = 4.5 Hz, 1H), 7.18 (d, *J* = 3.1 Hz, 1H), 3.59 (s, 1H), 2.81 (s, 1H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 164.6, 139.3, 136.6, 132.8, 129.7, 129.2, 128.6, 128.5, 127.5, 125.2, 123.7, 121.6, 121.2, 120.4, 118.2, 40.3, 16.7. IR ($CHCl_3$, cm^{-1}): 3076, 2970, 1645, 1456. HRMS (ESI): $[M + H]^+$ calcd for $C_{17}H_{15}N_2^+$, 247.1230; found, 247.1231.

(Z)-N,3-Dimethyl-10H-indolo[1,2-a]indol-10-imine (**3e**). Yellow solid, 89% isolated yield (109.5 mg); mp 152−153 °C; ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.76 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 8.1 Hz, 1H), 7.40 (dd, *J* = 3.6, 2.0 Hz, 2H), 7.37 (s, 1H), 7.11−7.07 (m, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 6.84 (s, 1H), 3.67 (s, 3H), 2.50 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 156.4, 142.4, 136.5, 132.5, 132.1, 131.6, 131.3, 130.7, 123.3, 123.3, 123.2, 122.9, 111.2, 110.8, 107.3, 42.5, 22.3. IR ($CHCl_3$, cm^{-1}): 3074, 2973, 1643, 1459. HRMS (ESI): $[M + H]^+$ calcd for $C_{17}H_{15}N_2^+$, 247.1230; found, 247.1233.

(Z)-2-Methoxy-N-methyl-10H-indolo[1,2-a]indol-10-imine (**3f**). Yellow solid, 89% isolated yield (116.6 mg); mp 149−150 °C; ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.77 (d, *J* = 7.5 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.43−7.37 (m, 2H), 7.12−7.08 (m, 2H), 7.05−7.03 (m, 1H), 6.85 (s, 1H), 3.87 (s, 3H), 3.71 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 156.5, 155.1, 142.5, 133.5, 132.9, 131.7, 131.1, 127.5, 123.3, 123.0, 116.6, 111.9, 110.3, 106.8, 104.8, 55.9, 42.6. IR ($CHCl_3$, cm^{-1}): 3074, 2962, 1649, 1458. HRMS (ESI): $[M + H]^+$ calcd for $C_{17}H_{15}N_2O^+$, 263.1179; found, 263.1180.

(Z)-N,N,N-Trimethyl-10-(methylimino)-10H-indolo[1,2-a]-indol-2-aminium (**3g**). Yellow solid, 98% isolated yield (215.2 mg); mp 185−186 °C; ^{1}H NMR (400 MHz, methanol-d_3): δ 8.11 (d, *J* = 2.5 Hz, 1H), 7.78 (dd, *J* = 12.0, 2.6 Hz, 1H), 7.55 (d, *J* = 9.2 Hz, 1H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 7.7 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 1H), 6.92 (t, *J* = 7.5 Hz, 1H), 6.86 (s, 1H), 4.74 (s, 3H), 3.70 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, methanol-d_3): δ 157.0, 142.1, 134.8, 133.6, 132.1, 130.8, 125.4, 123.9, 119.0, 116.4, 113.8, 112.4, 109.6, 58.4, 42.5, 8.0. IR ($CHCl_3$, cm^{-1}): 3203, 2963, 1642, 1446. HRMS (ESI): $[M + H]^+$ calcd for $C_{20}H_{21}F_3N_3O_3S^+$, 440.1250; found, 440.1253.

(Z)-1-Bromo-N-methyl-10H-indolo[1,2-a]indol-10-imine (**3h**). Yellow solid, 87% isolated yield (134.9 mg); mp 150−152 °C; ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.72 (d, *J* = 7.5 Hz, 1H), 7.40−7.38 (m, 2H), 7.25−7.27 (m, 2H), 7.16−7.08 (m, 2H), 6.79 (s, 1H), 3.67 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 155.7, 141.8, 133.1, 132.2, 132.0, 131.7, 131.0, 126.7, 124.3, 124.0, 123.1, 117.1, 110.8, 110.1, 106.7, 42.7. IR ($CHCl_3$, cm^{-1}): 3071, 2974, 1647, 1449. HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{12}BrN_2^+$, 311.0178; found, 311.0180.

(Z)-2-Bromo-N-methyl-10H-indolo[1,2-a]indol-10-imine (**3i**). Yellow solid, 98% isolated yield (151.9 mg); mp 154−156 °C; ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.66 (d, *J* = 7.5 Hz, 1H), 7.58 (d, *J* = 1.7 Hz, 1H), 7.38−7.23 (m, 2H), 7.18 (d, *J* = 8.7 Hz, 1H), 7.13−7.00 (m, 2H), 6.56 (s, 1H), 3.57 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 155.6, 141.6, 134.1, 132.8, 131.6, 130.8, 130.1, 128.7, 125.8, 123.7, 122.9, 114.2, 112.1, 110.5, 105.8, 42.5. IR ($CHCl_3$, cm^{-1}): 3083, 2965, 1643, 1456. HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{12}BrN_2^+$, 311.0178; found, 311.0181.

(Z)-3-Bromo-N-methyl-10H-indolo[1,2-a]indol-10-imine (**3j**). Yellow solid, 91% isolated yield (141.1 mg); mp 148−149 °C; ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.78−7.77 (m, 1H), 7.73 (s, 1H), 7.51−7.49 (m, 1H), 7.47−7.43 (m, 1H), 7.38−7.36 (m, 1H), 7.26−7.24 (m, 1H), 7.17−7.13 (m, 1H), 6.86 (s, 1H), 3.70 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 155.9, 141.8, 132.7, 132.4, 131.9, 131.6, 131.1, 124.8, 124.7, 124.0, 123.2, 119.8, 114.2, 110.9, 106.9, 42.6. IR ($CHCl_3$, cm^{-1}): 3065, 2970, 1643, 1450. HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{12}BrN_2^+$, 311.0178; found, 311.0177.

(Z)-3-Chloro-N-methyl-10H-indolo[1,2-a]indol-10-imine (**3k**). Yellow solid, 95% isolated yield (126.4 mg); mp 146−147 °C; ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.71 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.42−7.36 (m, 2H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.14−7.02 (m, 2H), 6.73 (s, 1H), 3.63 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 155.9, 141.8, 132.7, 132.4, 131.9, 131.6, 131.1, 124.8, 124.7, 124.0, 123.2, 119.8, 114.2, 110.9, 106.9, 42.6. IR ($CHCl_3$, cm^{-1}): 3074, 2973, 1641, 1454. HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{12}ClN_2^+$, 267.0684; found, 267.0686.

(Z)-3-Fluoro-N-methyl-10H-indolo[1,2-a]indol-10-imine (**3l**). Yellow solid, 98% isolated yield (122.5 mg); mp 137−138 °C; ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.72 (d, *J* = 7.5 Hz, 1H), 7.52−7.48 (m, 1H), 7.40−7.36 (m, 1H), 7.21 (d, *J* = 7.9 Hz, 1H), 7.15−7.07 (m, 2H), 6.89−6.84 (m, 1H), 6.76 (s, 1H), 3.62 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 161.99 (d, *J* = 243.7 Hz), 155.8, 141.7, 132.97 (d, *J* = 3.8 Hz), 131.8, 131.7, 130.11 (d, *J* = 191.8 Hz), 124.51 (d, *J* = 10.4 Hz), 123.8, 123.0, 110.6, 110.23 (d, *J* = 24.8 Hz), 107.0, 97.76 (d, *J* = 27.2 Hz), 42.5. ^{19}F NMR (565 MHz, chloroform-*d*): δ −113.92 (td, *J* = 9.5, 5.5 Hz). IR ($CHCl_3$, cm^{-1}): 3058, 2966, 1649, 1439. HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{12}FN_2^+$, 251.0979; found, 251.0982.

(Z)-N,8-Dimethyl-10H-indolo[1,2-a]indol-10-imine (**3m**). Yellow solid, 97% isolated yield (119.3 mg); mp 134−135 °C; ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.63 (d, *J* = 8.1 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.38−7.29 (m, 1H), 7.27−7.21 (m, 1H), 7.20−7.08 (m, 2H), 6.85 (s, 1H), 3.67 (s, 3H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 156.5, 140.2, 133.1, 132.7, 132.6, 132.1, 132.0, 131.2, 126.0, 123.6, 123.5, 121.2, 111.1, 110.4, 106.9, 42.4, 21.1. IR ($CHCl_3$, cm^{-1}): 3047, 2987, 1644, 1465. HRMS (ESI): $[M + H]^+$ calcd for $C_{17}H_{15}N_2^+$, 247.1230; found, 247.1232.

(Z)-7-Fluoro-N-methyl-10H-indolo[1,2-a]indol-10-imine (**3n**). Yellow solid, 97% isolated yield (121.3 mg); mp 124−126 °C; ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.71−7.63 (m, 2H), 7.51−7.49 (m, 1H), 7.40−7.36 (m, 1H), 7.19−7.15 (m, 1H), 7.05−7.06 (m, 1H), 6.88 (s, 1H), 6.80−6.75 (m, 1H), 3.67 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 165.4 (d, *J* = 249.7 Hz), 155.1, 143.3 (d, *J* = 12.3 Hz), 132.9 (d, *J* = 6.2 Hz), 131.9, 127.1, 126.4, 124.3 (d, *J* = 10.5 Hz), 123.8, 121.9, 111.0, 110.1 (d, *J* = 23.1 Hz), 107.6, 99.3 (d, *J* = 28.1 Hz), 42.5. ^{19}F NMR (565 MHz, chloroform-*d*): δ −107.03. IR ($CHCl_3$, cm^{-1}): 3069, 2954, 1639, 1469. HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{12}FN_2^+$, 251.0979; found, 251.0981.

(Z)-7-Chloro-N-methyl-10H-indolo[1,2-a]indol-10-imine (**3o**). Yellow solid, 98% isolated yield (130.4 mg); mp 135−136 °C; ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.59−7.55 (m, 2H), 7.40−7.38 (m, 1H), 7.35−7.25 (m, 1H), 7.18 (s, 1H), 7.15−7.11 (m, 1H), 7.01−6.98 (m, 1H), 6.77 (s, 1H), 3.60 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 155.1, 142.7, 137.4,

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132.8, 132.4, 131.7, 129.6, 126.4, 123.7, 123.6, 123.4, 121.8, 111.2, 111.1, 107.6, 42.5. IR ($CHCl_3$, cm^{-1}): 3061, 2984, 1638, 1459. HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{12}ClN_2^+$, 267.0684; found, 267.0686.

(Z)-8-Fluoro-N-methyl-10H-indolo[1,2-a]indol-10-imine (**3p**). Yellow solid, 98% isolated yield (122.5 mg); mp 129−130 °C; ^1H NMR (400 MHz, chloroform-*d*): δ 7.58−7.56 (m, 1H), 7.38−7.36 (m, 2H), 7.33−7.29 (m, 1H), 7.14−7.09 (m, 2H), 7.03−7.01 (m, 1H), 6.75 (s, 1H), 3.59 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 159.6 (d, *J* = 242.2 Hz), 155.5, 138.5, 132.6, 132.2 (d, *J* = 73.3 Hz), 126.3, 123.8, 121.5, 118.1, 118.0 (d, *J* = 24.7 Hz), 111.2, 110.8, 110.7, 110.4, 110.52 (d, *J* = 24.9 Hz), 42.5. ^{19}F NMR (565 MHz, chloroform-*d*): δ −119.20 to −119.26 (m). IR ($CHCl_3$, cm^{-1}): 3063, 2944, 1646, 1456. HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{12}FN_2^+$, 251.0979; found, 251.0979.

(Z)-N-Methyl-8H-indolo[3,2,1-de]acridin-8-imine (**3q**). Yellow solid, 98% isolated yield (138.2 mg); mp 196−197 °C; ^1H NMR (400 MHz, chloroform-*d*): δ 8.39−8.38 (m, 1H), 8.04−8.02 (m, 3H), 7.99−7.95 (m, 2H), 7.50−7.44 (m, 2H), 7.33−7.27 (m, 2H), 7.25−7.22 (m, 1H), 3.84 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 154.0, 138.2, 138.0, 136.8, 130.4, 127.9, 127.5, 127.1, 126.7, 125.8, 124.1, 123.7, 121.9, 121.8, 121.3, 121.0, 116.7, 114.4, 113.9, 41.7. IR ($CHCl_3$, cm^{-1}): 3021, 2868, 2674, 1627, 1460. HRMS (ESI): $[M + H]^+$ calcd for $C_{20}H_{15}N_2^+$, 283.1230; found, 283.1233.

(Z)-N-Methyl-9H-pyrrolo[1,2-a]indol-9-imine (**3r**). Yellow solid, 83% isolated yield (75.5 mg); mp 133−135 °C; ^1H NMR (400 MHz, chloroform-*d*): δ 7.73−7.71 (m, 1H), 7.35−7.33 (m, 1H), 7.16−7.09 (m, 2H), 7.07 (m, 1H), 6.59−6.58 (m, 1H), 6.38−6.3 (m, 1H), 3.62 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 155.7, 141.6, 132.0, 131.0, 128.6, 124.7, 122.8, 115.2, 114.8, 112.8, 109.9, 42.3. IR ($CHCl_3$, cm^{-1}): 1641, 1492, 1457, 1269, 752. HRMS (ESI): $[M + H]^+$ calcd for $C_{12}H_{11}N_2^+$, 183.0917; found, 183.0915.

(Z)-N,2-Dimethyl-4H-pyrazolo[1,5-a]indol-4-imine (**3s**). Brown solid, 72% isolated yield (70.9 mg); mp 105−106 °C; ^1H NMR (400 MHz, methanol-d_3): δ 8.76−8.75 (m, 1H), 8.28−8.26 (m, 1H), 8.19−8.17 (m, 1H), 8.14−8.10 (m, 1H), 7.14 (s, 1H), 3.99 (s, 3H), 2.81 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, methanol-d_3): δ 152.1, 139.7, 136.3, 135.9, 134.7, 131.6, 123.3, 120.1, 113.7, 110.5, 35.1, 12.3. IR ($CHCl_3$, cm^{-1}): 3021, 2674, 1647, 1460. HRMS (ESI): $[M + H]^+$ calcd for $C_{12}H_{12}N_3^+$, 198.1026; found, 198.1029.

(Z)-1-Methyl-6-(methylimino)-6H-pyrido[3′,2′:4,5]pyrrolo-[1,2-a]indol-1-ium Trifluoromethanesulfonate (**3t**). Yellow solid, 96% isolated yield (190.6 mg); mp 172−173 °C; ^1H NMR (600 MHz, methanol-d_3): δ 8.90−8.89 (m, 1H), 8.81−8.80 (m, 1H), 8.38 (s, 1H), 8.23−8.82 (m, 1H), 8.14−8.13 (m, 1H), 7.92−7.89 (m, 1H), 7.76−7.73 (m, 1H), 7.53−7.51 (m, 1H), 4.92 (s, 3H), 3.80 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, methanol-d_3): δ 161.4, 147.8, 144.5, 143.6, 141.7, 140.7, 136.3, 133.5, 129.0, 128.4, 126.2, 123.2, 121.0, 120.3, 120.0, 118.4, 36.6. IR ($CHCl_3$, cm^{-1}): 3076, 2970, 1645, 1451. HRMS (ESI): $[M + H]^+$ calcd for $C_{17}H_{15}F_3N_3O_3S^+$, 398.0781; found, 398.0783.

11-Methyl-10H-indolo[1,2-a]indol-10-one (**4a**).[10] Yellow solid, 91% isolated yield (106.1 mg); mp 121−123 °C; ^1H NMR (400 MHz, chloroform-*d*): δ 7.59−7.58 (m, 1H), 7.54−7.52 (m, 1H), 7.46−7.42 (m, 1H), 7.37−7.36 (m, 2H), 7.26−7.22 (m, 1H), 7.10−7.06 (m, 1H), 7.03−7.01 (m, 1H), 2.51 (s, 3H). $^{13}C\{^1H\}$ ^{13}C NMR (101 MHz, chloroform-*d*): δ 182.0, 145.0, 135.1, 134.2, 133.6, 132.8, 129.9, 128.3, 124.9, 123.2, 122.9, 122.4, 121.4, 111.3, 111.1, 9.4. IR ($CHCl_3$, cm^{-1}): 3069, 2971, 1634, 1465. HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{12}NO^+$, 234.0913; found, 234.0915.

2-Methoxy-10H-indolo[1,2-a]indol-10-one (**4f**).[4e] Yellow solid, 87% isolated yield (108.3 mg); mp 132−133 °C; ^1H NMR (600 MHz, chloroform-*d*): δ 7.61−7.60 (m, 1H), 7.49−7.46 (m, 1H), 7.39−7.37 (m, 1H), 7.27−7.25 (m, 1H), 7.07−7.02 (m, 4H), 3.84 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, chloroform-*d*): δ 181.7, 155.4, 145.7, 136.3, 135.5, 133.3, 129.8, 129.5, 125.2, 123.8, 119.2, 112.2, 110.9, 107.6, 105.6, 55.8. IR ($CHCl_3$, cm^{-1}): 3049, 2964, 1637, 1475. HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{12}NO_2^+$, 250.0863; found, 250.0862.

1-Bromo-10H-indolo[1,2-a]indol-10-one (**4h**).[4c] Yellow solid, 86% isolated yield (128.1 mg); mp 134−135 °C; ^1H NMR (400 MHz, chloroform-*d*): δ 7.69−7.68 (m, 1H), 7.58−7.54 (m, 1H), 7.50−7.48 (m, 1H), 7.39−7.37 (m, 1H), 7.33−7.26 (m, 2H), 7.21 (s, 1H), 7.16−7.13 (m, 1H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6): δ 179.9, 144.2, 135.8, 135.1, 133.6, 131.9, 128.7, 128.0, 124.5, 124.4, 124.3, 116.7, 112.0, 111.0, 105.9. IR ($CHCl_3$, cm^{-1}): 3054, 2985, 1627, 1460. HRMS (ESI): $[M + H]^+$ calcd for $C_{15}H_9BrNO^+$, 297.9862; found, 297.9860.

2-Bromo-10H-indolo[1,2-a]indol-10-one (**4i**).[4e] Yellow solid, 97% isolated yield (144.0 mg); mp 136−137 °C; ^1H NMR (400 MHz, chloroform-*d*): δ 7.76−7.65 (m, 1H), 7.65−7.62 (m, 1H), 7.52−7.45 (m, 2H), 7.37−7.26 (m, 2H), 7.13−7.09 (m, 1H), 7.02−7.00 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 181.4, 145.3, 136.6, 135.8, 134.2, 132.7, 131.0, 129.3, 127.5, 125.5, 124.4, 115.1, 112.6, 111.5, 106.8. IR ($CHCl_3$, cm^{-1}): 3078, 2981, 1631, 1456. HRMS (ESI): $[M + H]^+$ calcd for $C_{15}H_9BrNO^+$, 297.9862; found, 297.9863.

3-Bromo-10H-indolo[1,2-a]indol-10-one (**4j**).[4e] Yellow solid, 89% isolated yield (132.2 mg); mp 128−129 °C; ^1H NMR (400 MHz, chloroform-*d*): δ 7.63−7.61 (m, 2H), 7.53−7.44 (m, 2H), 7.29−7.25 (m, 1H), 7.21−7.19 (m, 1H), 7.11−7.08 (m, 1H), 7.03 (s, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 181.2, 145.1, 136.2, 135.7, 134.6, 131.4, 129.4, 126.1, 125.5, 125.4, 124.5, 122.2, 114.4, 111.5, 107.7. IR ($CHCl_3$, cm^{-1}): 3064, 2969, 1631, 1443. HRMS (ESI): $[M + H]^+$ calcd for $C_{15}H_9BrNO^+$, 297.9862; found, 297.9861.

3-Chloro-10H-indolo[1,2-a]indol-10-one (**4k**).[4c] Yellow solid, 92% isolated yield (116.3 mg); mp 125−126 °C; ^1H NMR (400 MHz, chloroform-*d*): δ 7.62 (m, 1H), 7.52−7.48 (m, 2H), 7.43 (s, 1H), 7.27−7.25 (m, 1H), 7.11−7.08 (m, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 181.2, 145.1, 136.4, 135.7, 134.3, 134.2, 131.1, 129.4, 125.8, 125.4, 124.5, 122.9, 111.5, 111.4, 107.7. IR ($CHCl_3$, cm^{-1}): 3074, 2986, 1630, 1454. HRMS (ESI): $[M + H]^+$ calcd for $C_{15}H_9ClNO^+$, 254.0367; found, 254.0366.

7-Chloro-10H-indolo[1,2-a]indol-10-one (**4o**). Yellow solid, 96% isolated yield (121.4 mg); mp 119−120 °C; ^1H NMR (400 MHz, chloroform-*d*): δ 7.63 (d, *J* = 8.1 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.46−7.40 (m, 2H), 7.30 (s, 1H), 7.17−7.10 (m, 2H), 7.04 (dd, *J* = 8.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 180.3, 146.2, 141.8, 136.1, 134.3, 132.8, 128.6, 128.0, 126.1, 125.3, 124.1, 122.6, 112.1, 111.4, 108.9. IR ($CHCl_3$, cm^{-1}): 3061, 2930, 1627, 1446. HRMS (ESI): $[M + H]^+$ calcd for $C_{15}H_9ClNO^+$, 254.0367; found, 254.0369.

1-Methyl-6-oxo-6H pyrido[3′,2′:4,5]pyrrolo[1,2-a]indol-1-ium Trifluoromethane-Sulfonate (**4t**). Yellow solid, 93% isolated yield (178.6 mg); mp 141−142 °C; ^1H NMR (400 MHz, methanol-d_3): δ 8.88 (d, *J* = 8.0 Hz, 1H), 8.87 (d, *J* = 8.0 Hz, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 7.93−7.76 (m, 2H), 7.74−7.72 (m, 2H), 7.55−7.51 (m, 1H), 4.99 (s, 3H). $^{13}C\{^1H\}$ NMR

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(151 MHz, methanol-d_3): δ 180.6, 145.6, 145.3, 143.4, 141.0, 140.2, 138.4, 133.8, 131.0, 128.8, 126.9, 122.8, 120.7, 119.9, 117.8, 107.6. IR ($CHCl_3$, cm^{-1}): 3045, 2964, 1633, 1459. HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{12}F_3N_2O_4S^+$, 385.0464; found, 385.0467.

*1-Methoxy-10H-indolo[1,2-a]indol-10-one (**4u**).*[4d] Yellow solid, 97% isolated yield (121.3 mg); mp 144−145 °C; ^1H NMR (400 MHz, chloroform-*d*): δ 7.64 (d, J = 8.1 Hz, 1H), 7.49 (s, 1H), 7.35−7.31 (m, 2H), 7.25 (d, J = 8.0 Hz, 1H), 7.10−7.08 (m, 2H), 6.50 (d, J = 8.0 Hz, 1H), 3.94 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 181.4, 156.2, 145.5, 135.6, 135.3, 134.6, 129.8, 129.7, 125.2, 124.0, 123.6, 111.5, 106.1, 104.4, 101.8, 55.6. IR ($CHCl_3$, cm^{-1}): 3058, 2985, 1629, 1450. HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{12}NO_2^+$, 250.0863; found, 250.0865.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.9b02679.

Experimental details, NMR data, ^1H NMR, and $^{13}C\{^1H\}$ NMR spectra (PDF)

Crystallographic data of **4i** (CIF)

Crystallographic data of **4t** (TXT)

Crystallographic data of **4u**(CIF)

Accession Codes

CCDC (1921810 for **4i**), (1921809 for **4t**), and (1921808 for **4u**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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