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Copper(I)-Catalyzed Thiolation of C–H Bonds for the Synthesis of Sulfenyl Pyrroles and Indoles

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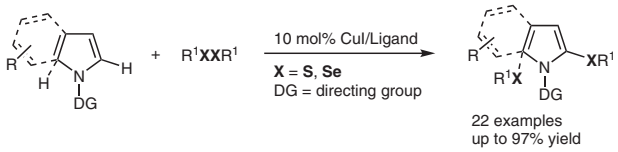

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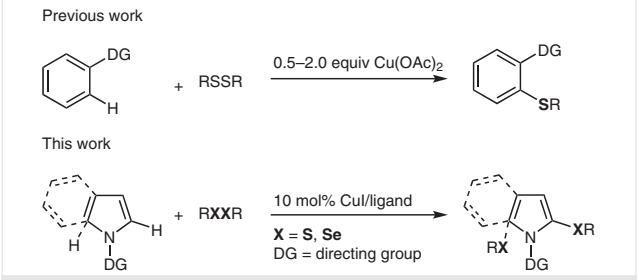
Abstract A novel and convenient copper(I)-catalyzed thiolation of C–H bonds of pyrroles and indoles is developed for the synthesis of sulfenyl pyrroles and indoles. Dual C–H thiolation reactions are observed for pyrroles. A wide range of pyrroles and indoles undergo the C–H thiolation smoothly with various disulfides and diselenides to generate the corresponding heteroaryl thioethers in moderate to excellent yields.

Key words copper(I) iodide, ligands, thiolation, pyrroles, indoles

Nitrogen-containing heterocycles play important roles in pharmaceuticals, materials, and agrochemicals.[1] Among these compounds, sulfenyl pyrroles and indoles are often found in natural and bioactive products that can be applied as therapeutics in many diseases, including cancer, obesity, ulcers, and heart disease.[2] Moreover, these N,S-containing heterocycles have been employed as ligands in organic synthesis.[3] As a consequence, the development of convenient and efficient methods for the preparation of these molecules is highly desirable.

Recently, strategies for the preparation of multisubstituted indole and pyrrole derivatives have focused on transition-metal-catalyzed direct C–H functionalizations due to the associated atom- and step-economic advantages.[4] For example, Li described an iron-catalyzed sulfenylation of indoles with disulfides. The employed catalytic system was found to demonstrate good functional group tolerance.[5] In 2015, Kambe and co-workers reported a palladium-catalyzed chalcogenation of indoles, carbazole and 2-phenylpyridine, which afforded excellent yields of the desired products.[4j] As a typical representative, cheap and abundant copper salts have attracted significant attention and have been widely used as catalysts or promoters in many C–H functionalizations.[6,7] However, stoichiometric or semi-stoichiometric amounts of copper salts were required in most cases. In addition, only copper(II) salts were reported as catalysts in most C–H activation reactions. For example, Yu,[8] Daugulis[9] and Kambe[10] reported on $Cu(OAc)_2$-mediated direct sp^2 C–H thiolations of arenes bearing a directing group with disulfides. While cuprous salts are rarely reported as catalysts in C–H functionalizations of heterocyclic compounds, the copper(I)-catalyzed C–H thiolation is especially challenging (Scheme 1). Alves described the CuI-catalyzed sulfenylation of pyrroles, with only mono-sulfenylation products being obtained due to the pyrroles being present in excess.[7] Herein, we report a novel and convenient CuI-catalyzed thiolation of pyrroles and indoles for the synthesis of 2,5-disulfenyl pyrroles and 2-sulfenyl indoles under base-free conditions.



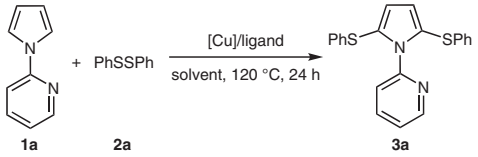
Scheme 1 Copper-mediated C–H thiolation

The reaction of 2-(1*H*-pyrrol-1-yl)pyridine (**1a**) with PhSSPh (**2a**) was chosen as a model reaction to determine the optimum conditions, and the results are summarized in Table 1. Initially, the reaction was performed in the presence of CuI (10 mol%) and PPh_3 (10 mol%) in DMSO at 120 °C for 24 hours, achieving a 56% yield of 2-[2,5-bis(phenylthio)-1*H*-pyrrol-1-yl]pyridine (**3a**) (Table 1, entry 1). Encouraged by this result, further investigations were

conducted by testing a series of ligands, and similar yields were observed for PCy_3, P(*t*-Bu)$_3$ and DPPP (Table 1, entries 2–4). To our delight, product **3a** was obtained in 86% yield when 10 mol% of XPhos was used as the ligand (Table 1, entry 5). However, the yield of **3a** decreased to 43% in the absence of a ligand (Table 1, entry 6). Subsequently, the effects of several cuprous and cupric salts were tested. Lower yields were obtained with CuBr and CuCl (Table 1, entries 7 and 8). No reaction took place when $Cu(OAc)_2$ was applied as the catalyst (Table 1, entry 9). These results suggested that this thiolation of pyrrole did not proceed through a copper(II)-catalyzed C–H activation pathway. In the absence of a copper catalyst, the reaction also failed (Table 1, entry 10). Next, different solvents were screened, including DMF, PrCN, THF and toluene, but all were completely ineffective (Table 1, entries 11–14). We believed that DMSO might act as an auxiliary ligand to promote the C–H thiolation. Thus we examined some other S-containing solvents. As expected, tetramethylene sulfoxide (TMSO) and dibutyl sulfoxide afforded **3a** in 65% and 35% yields, respectively (Table 1, entries 15 and 16). These results demonstrated that sulfoxide played a critical role as both a solvent and a promoter. The reaction performed under O_2 resulted in a 69% yield of the desired product (Table 1, entry 17). However, only a trace amount of product **3a** was obtained when the reaction was carried out under an N_2 atmosphere (Table 1, entry 18).

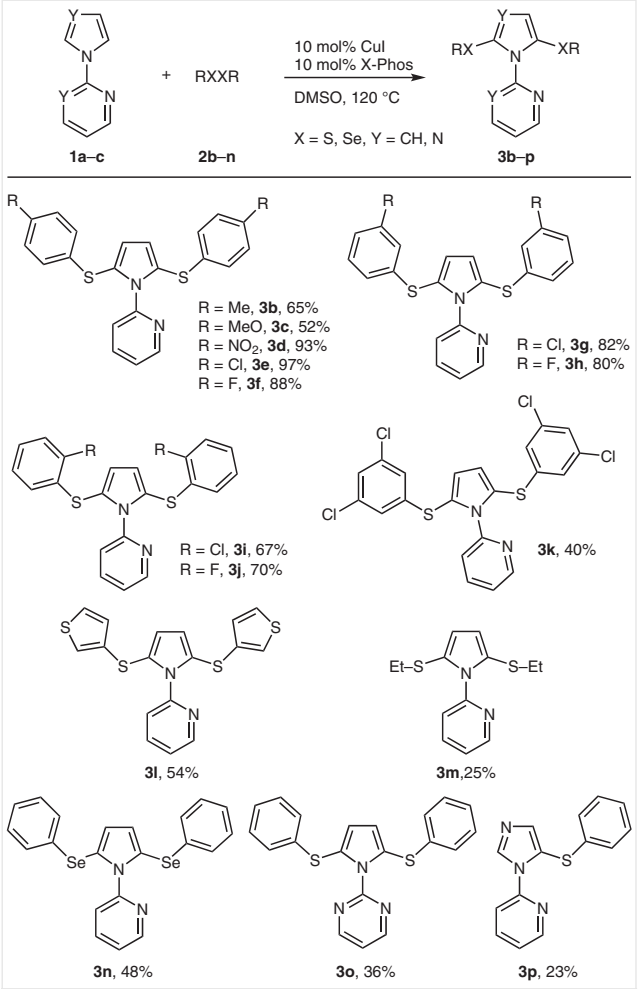
With optimized reaction conditions in hand, we next explored the scope of substrates **1** and **2** (Scheme 2). Initially, the electronic and steric effects of the sulfides were evaluated. The results showed that sulfides bearing electron-donating and electron-withdrawing groups on the aromatic

Table 1 Optimization of the Reaction Conditions[a]



Entry	[Cu]	Ligand	Solvent	Yield[b]
1	CuI	PPh_3	DMSO	56
2	CuI	PCy_3	DMSO	62
3	CuI	P(*t*-Bu)$_3$	DMSO	60
4	CuI	DPPP[c]	DMSO	56
5	CuI	XPhos[d]	DMSO	86
6	CuI	–	DMSO	43
7	CuBr	XPhos	DMSO	23
8	CuCl	XPhos	DMSO	12
9	$Cu(OAc)_2$	XPhos	DMSO	NR
10	–	XPhos	DMSO	NR
11	CuI	XPhos	DMF	NR
12	CuI	XPhos	PrCN	NR
13	CuI	XPhos	THF	NR
14	CuI	XPhos	toluene	NR
15[e]	CuI	XPhos	TMSO	65
16	CuI	XPhos	dibutyl sulfoxide	35
17[f]	CuI	XPhos	DMSO	69
18[g]	CuI	XPhos	DMSO	trace

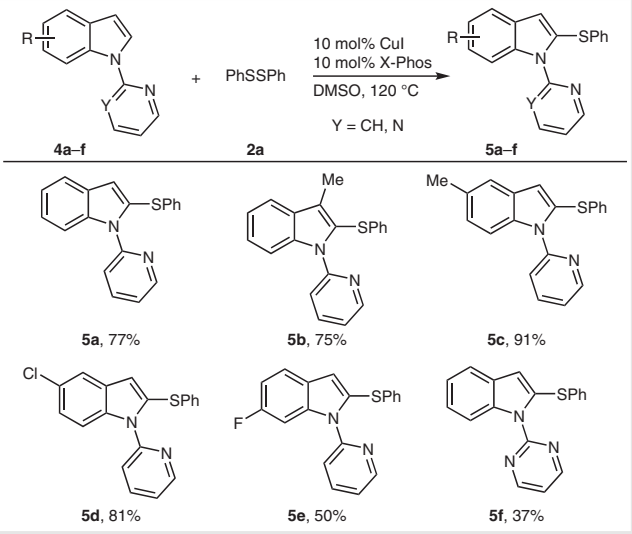
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), [Cu] (10 mol%), ligand (10 mol%), solvent (2 mL), 120 °C, air atmosphere, 24 h.
[b] Yield of isolated product; NR = no reaction.
[c] DPPP = 1,3-bis(diphenylphosphino)propane.
[d] XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.
[e] TMSO = tetramethylene sulfoxide.
[f] Reaction under O_2.
[g] Reaction under N_2



Scheme 2 CuI-catalyzed dual thiolation of pyrroles. *Reagents and conditions*: **1** (0.2 mmol), **2** (0.4 mmol), CuI (10 mol%), XPhos (10 mol%), DMSO (2 mL), 120 °C, air atmosphere, 24 h. Yields are those of isolated products

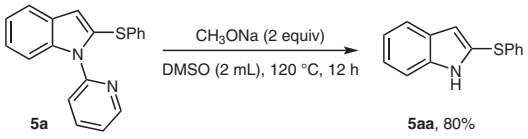
ring were well-tolerated. For example, sulfides with electron-donating groups such as *p*-Me and *p*-MeO on the phenyl ring facilitated the reaction to give products **3b**,**c** in 65% and 52% yields, respectively. Phenyl sulfides with electron-withdrawing groups such as *p*-NO_2, *p*-Cl and *p*-F reacted smoothly with **1a** to form products **3d–f** in excellent yields. *m*-Cl- and *m*-F-substituted phenyl sulfides afforded products **3g** and **3h** in 82% and 80% yield, respectively. The inhibition effect of steric hindrance on the aromatic ring was observed, with lower yields being obtained for *o*-substituted phenyl sulfides (67% and 70% for **3i** and **3j**). The structure of product **3i** was further confirmed by X-ray crystal analysis (see the Supporting Information). Furthermore, 3,5-dichlorophenyl disulfide (**2k**) gave the target product **3k** in 40% yield. A heterocyclic sulfide was also a suitable substrate for the reaction, affording **3l** in 54% yield. Importantly, the reaction of alkyl sulfide **2m** with **1a** proceeded smoothly, albeit furnishing a lower yield of 25% of **3m**. Gratifyingly, a diselenide also reacted successfully to produce **3n** in 48% yield. Pyrimidine-substituted substrate **1b** gave the corresponding thiolated product **3o** in a moderate 36% yield. It is noteworthy that mono-thiolated product **3p** was afforded in 23% yield when 2-(1*H*-imidazol-1-yl)pyridine (**1c**) was used as the substrate.

When the catalytic system was applied to indoles, the reaction also occurred smoothly, affording the target compounds in moderate to excellent yields (Scheme 3). For example, *N*-pyridine indole **4a** reacted with **2a** successfully under the optimized conditions to furnish **5a** in 77% yield. During the investigation of the electronic effects on the indoles, both electron-donating (3-Me, 5-Me) and electron-withdrawing groups (5-Cl and 6-F) were found to be compatible with the transformation leading to products **5b–e**. However, the reaction was sluggish when 1-(pyrimidin-2-yl)-1*H*-indole (**4f**) was used as the substrate, with only a 37% yield of product **5f** isolated.



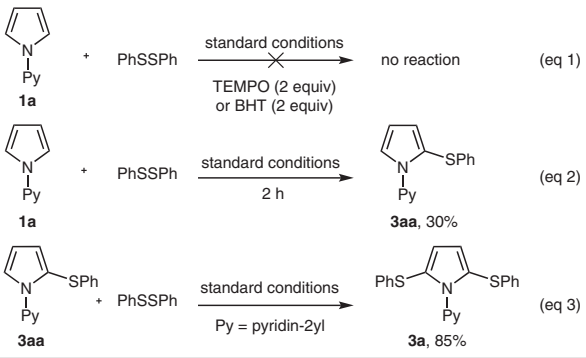
Scheme 3 CuI-catalyzed thiolation of indoles **4**. *Reagents and conditions*: **1** (0.2 mmol), **2** (0.4 mmol), CuI (10 mol%), XPhos (10 mol%), DMSO (2 mL), 120 °C, air atmosphere, 24 h. Yields are those of isolated products

To further demonstrate the synthetic application of this methodology, removal of the directing group was required to give medicinally useful N-unblocked indoles. As expected, the pyridinyl group on 2-phenylsulfenyl indole **5a** was readily removed by treatment with CH_3ONa in DMSO (Scheme 4).[10]



Scheme 4 Removal of the directing group

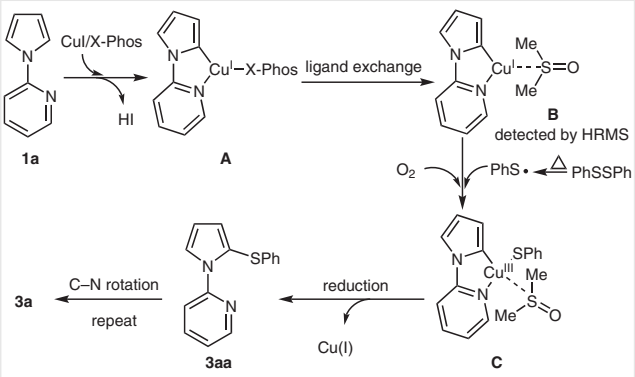
To probe the thiolation mechanism, several control experiments were conducted under standard conditions. Firstly, when two equivalents of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) or BHT (2,6-di-*tert*-butyl-4-methylphenol), two radical inhibitors, were added to the reaction, no target product was detected by GC-MS analysis, which implied that the reaction might be a radical process (Scheme 5, eq 1). Next, the reaction of **1a** with PhSSPh was quenched after running for 2 hours under standard conditions. A mono-substituted product, 2-[2-(phenylthio)-1*H*-pyrrol-1-yl]pyridine (**3aa**), was isolated in 30% yield (Scheme 5, eq 2). Finally, treatment of **3aa** with PhSSPh under the standard reaction conditions afforded **3a** in 85% yield (Scheme 5, eq 3). These results indicated that the dual thiolation of pyrrole might proceed through two stepwise C–H activations.



Scheme 5 Control experiments

Based on previous reports[5–8] and our present observed results, a possible mechanism has been proposed as outlined in Scheme 6. Initially, substrate **1a** combines with CuI and XPhos to generate Cu complex **A**. The Cu complex then undergoes ligand exchange with DMSO to give intermediate **B**, which was monitored by HRMS analysis (see the Sup-

porting Information). Subsequently, under oxidation by oxygen, complex **B**, through a one-electron oxidation pathway with a PhS radical, affords intermediate **C**.[6c,11] This intermediate furnishes product **3aa** through a reduction process and regenerates the Cu(I) species.[6e,10] Finally, **3aa** is converted into the target molecule **3a** via C–N bond rotation and a second C–H thiolation.



Scheme 6 Proposed mechanism

In summary, we have developed an efficient and convenient protocol for the synthesis of sulfenyl pyrrole and indole derivatives by CuI-catalyzed thiolation using disulfides as the sulfur source. A number of pyrroles and indoles were tolerated under the optimized reaction conditions, furnishing the corresponding products in moderate to excellent yields. Importantly, the reaction proceeds via a copper(I)-catalyzed C–H thiolation process rather than by way of a traditional stoichiometric copper(II)-mediated C–H thiolation.

Chemicals were either purchased or purified by standard techniques. All reactions were conducted under air an atmosphere using standard Schlenk techniques. Column chromatography was performed using EM silica gel 60 (300–400 mesh). Melting points were obtained using a SGW X-4 apparatus. ^{1}H NMR and ^{13}C NMR spectra were measured at room temperature on a Bruker ADVANCE-500 MHz spectrometer (^{1}H: 500 MHz, ^{13}C: 125 MHz) using $CDCl_3$ as the solvent and TMS as an internal standard. Chemical shifts (δ) are given in ppm relative to TMS and the coupling constants *J* are given in Hz. Low-resolution mass spectra (LRMS) were obtained using a Shimadazu GC-MS 2010 plus spectrometer. High-resolution mass spectra (HRMS) were recorded on an ESI-Q-TOF mass spectrometer.

2-[2,5-Bis(phenylthio)-1*H*-pyrrol-1-yl]pyridine (3a); Typical Procedure

Under an air atmosphere, a reaction tube was charged with 2-(1*H*-pyrrol-1-yl)pyridine (**1a**) (0.2 mmol), diphenyldisulfane (**2a**) (0.4 mmol), CuI (10 mol%), XPhos (2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl) (10 mol%) and DMSO (2 mL). The vessel was sealed and heated at 120 °C (oil bath temperature) for 24 h and then cooled to room temperature. The reaction mixture was washed with saturated $Na_2S_2O_3$ (2 × 15 mL) and then brine (15 mL). After the aqueous layer had been extracted with EtOAc, the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography (hexane/EtOAc) to afford the product **3a**.

Yield: 64.5 mg (86%); light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 4.5 Hz, 1 H), 7.52 (t, *J* = 7.5 Hz, 1 H), 7.20–7.14 (m, 5 H), 7.08 (t, *J* = 7.5 Hz, 2 H), 6.99 (d, *J* = 7.5 Hz, 4 H), 6.89 (d, *J* = 7.5 Hz, 1 H), 6.75 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.4, 148.7, 137.8, 137.0, 128.7, 127.1, 125.7, 124.1, 123.4, 123.2, 120.1.

LRMS (EI, 70 eV): *m*/*z* (%) = 360 (100), 251 (98), 218 (19), 174 (18), 78 (27).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{17}N_2S_2$: 361.0828; found: 361.0838.

2-[2,5-Bis(*p*-tolylthio)-1*H*-pyrrol-1-yl]pyridine (3b)

Yield: 48.2 mg (65%); light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.47 (dd, *J* = 5.0 Hz, *J* = 1.5 Hz, 1 H), 7.56 (td, *J* = 1.5 Hz, *J* = 7.5 Hz, 1 H), 7.21 (dd, *J* = 7.5 Hz, *J* = 5.0 Hz, 1 H), 6.97 (d, *J* = 8.0 Hz, 4 H), 6.94 (d, *J* = 8.0 Hz, 1 H), 6.90 (d, *J* = 8.0 Hz, 4 H), 6.69 (s, 2 H), 2.26 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.5, 148.6, 137.0, 135.7, 134.1, 129.5, 127.6, 124.6, 123.5, 123.2, 119.6, 20.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{21}N_2S_2$: 389.1141; found: 389.1145.

2-{2,5-Bis[(4-methoxyphenyl)thio]-1*H*-pyrrol-1-yl}pyridine (3c)

Yield: 47.4 mg (52%); light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.49 (dd, *J* = 5.0 Hz, *J* = 1.5 Hz, 1 H), 7.59 (td, *J* = 1.5 Hz, *J* = 7.5 Hz, 1 H), 7.25–7.22 (m, 1 H), 6.97–6.94 (m, 4 H), 6.92 (d, *J* = 7.5 Hz, 1 H), 6.71–6.68 (m, 4 H), 6.60 (s, 2 H), 3.73 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.5, 150.6, 148.6, 137.0, 130.4, 127.7, 125.5, 123.7, 123.1, 118.6, 114.4, 55.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{21}O_2N_2S_2$: 421.1039; found: 421.1049.

2-{2,5-Bis[(4-nitrophenyl)thio]-1*H*-pyrrol-1-yl}pyridine (3d)

Yield: 89.4 mg (93%); light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.33–8.32 (m, 1 H), 8.03–8.00 (m, 4 H), 7.64 (td, *J* = 2.0 Hz, *J* = 7.5 Hz, 1 H), 7.24–7.22 (m, 1 H), 7.07–7.04 (m, 5 H), 6.89 (d, *J* = 2.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.6, 149.0, 147.4, 145.6, 137.6, 125.9, 124.0, 123.9, 123.0, 122.3, 121.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{15}O_4N_4S_2$: 451.0529; found: 451.0538.

2-{2,5-Bis[(4-chlorophenyl)thio]-1*H*-pyrrol-1-yl}pyridine (3e)

Yield: 84.7 mg (97%); light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 4.0 Hz, 1 H), 7.58 (td, *J* = 1.5 Hz, *J* = 7.5 Hz, 1 H), 7.23 (dd, *J* = 5.0 Hz, *J* = 7.5 Hz, 1 H), 7.09 (t, *J* = 7.5 Hz, 2 H), 7.06–7.04 (m, 2 H), 6.94 (t, *J* = 1.5 Hz, 2 H), 6.90 (d, *J* = 7.5 Hz, 1 H), 6.87–6.85 (m, 2 H), 6.79 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.1, 148.9, 139.9, 137.2, 134.6, 129.8, 126.6, 125.9, 125.0, 123.6, 123.5, 123.3, 120.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{15}Cl_2N_2S_2$: 429.0048; found: 429.0064.

2-{2,5-Bis[(4-fluorophenyl)thio]-1*H*-pyrrol-1-yl}pyridine (3f)

Yield: 70.2 mg (88%); light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.43 (dd, *J* = 5.0 Hz, *J* = 1.5 Hz, 1 H), 7.57 (td, *J* = 8.0 Hz, *J* = 1.5 Hz, 1 H), 7.23–7.21 (m, 1 H), 7.14–7.10 (m, 2 H), 6.92 (d, *J* = 8.0 Hz, 1 H), 6.80 (s, 2 H), 6.79–6.75 (m, 4 H), 6.69 (dt, *J* = 9.0 Hz, *J* = 2.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.8 (d, J_{C-F} = 247.5 Hz), 150.1, 148.8, 140.3 (d, J_{C-F} = 7.5 Hz), 137.2, 130.0 (d, J_{C-F} = 8.8 Hz), 123.5 (d, J_{C-F} = 2.5 Hz), 123.2, 122.3 (d, J_{C-F} = 2.5 Hz), 120.7, 113.8 (d, J_{C-F} = 23.8 Hz), 112.7 (d, J_{C-F} = 21.3 Hz).

LRMS (EI, 70 eV): *m*/*z* (%) = 396 (26), 395 (100), 268 (77), 174 (12), 78 (18).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{15}F_2N_2S_2$: 397.0639; found: 397.0645.

2-{2,5-Bis[(3-chlorophenyl)thio]-1*H*-pyrrol-1-yl}pyridine (3g)

Yield: 66.9 mg (82%); light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.43 (d, *J* = 3.5 Hz, 1 H), 7.57 (t, *J* = 7.5 Hz, 1 H), 7.23–7.21 (m, 1 H), 7.12 (dd, *J* = 7.5 Hz, *J* = 14.0 Hz, 2 H), 6.93 (d, *J* = 7.5 Hz, 1 H), 6.80–6.75 (m, 6 H), 6.69 (d, *J* = 7.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.8, 161.8, 150.1, 148.8, 140.31, 140.26, 137.2, 130.0, 129.9, 122.33, 122.31, 120.7, 113.9, 113.7, 112.8, 112.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{15}Cl_2N_2S_2$: 429.0048; found: 429.0062.

2-{2,5-Bis[(3-fluorophenyl)thio]-1*H*-pyrrol-1-yl}pyridine (3h)

Yield: 71.0 mg (80%); light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 5.0 Hz, 1 H), 7.57 (td, *J* = 7.5 Hz, *J* = 1.5 Hz, 1 H), 7.22 (dd, *J* = 7.5 Hz, *J* = 5.0 Hz, 1 H), 7.14–7.10 (m, 2 H), 6.92 (d, *J* = 7.5 Hz, 1 H), 6.80 (s, 2 H), 6.79–6.75 (m, 4 H), 6.69 (dt, *J* = 9.0 Hz, *J* = 1.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.8 (d, J_{C-F} = 247.5 Hz), 150.1, 148.8, 140.3 (d, J_{C-F} = 7.5 Hz), 137.2, 130.0 (d, J_{C-F} = 8.8 Hz), 123.5, 123.2, 122.3 (d, J_{C-F} = 3.8 Hz), 120.7, 113.7 (d, J_{C-F} = 23.8 Hz), 112.7 (d, J_{C-F} = 21.3 Hz).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{15}F_2N_2S_2$: 397.0639; found: 397.0647.

2-{2,5-Bis[(2-chlorophenyl)thio]-1*H*-pyrrol-1-yl}pyridine (3i)

Yield: 58.8 mg (69%); white solid; mp 92–94 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.38 (d, *J* = 4.5 Hz, 1 H), 7.56 (td, *J* = 1.5 Hz, *J* = 7.5 Hz, 1 H), 7.19–7.16 (m, 3 H), 7.10 (t, *J* = 7.5 Hz, 2 H), 7.02–7.00 (m, 3 H), 6.85 (d, *J* = 7.5 Hz, 2 H), 6.82 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.9, 148.8, 137.3, 137.2, 130.7, 129.2, 128.0, 127.0, 126.5, 123.5, 123.1, 122.9, 121.2.

LRMS (EI, 70 eV): *m*/*z* (%) = 430 (61), 429 (21), 428 (76), 285 (100), 250 (26), 174 (43).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{15}Cl_2N_2S_2$: 429.0048; found: 429.0058.

2-{2,5-Bis[(2-fluorophenyl)thio]-1*H*-pyrrol-1-yl}pyridine (3j)

Yield: 54.6 mg (70%); light yellow solid; mp 72–74 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.43–8.42 (m, 1 H), 7.61 (td, *J* = 7.5 Hz, *J* = 1.5 Hz, 1 H), 7.23–7.21 (m, 1 H), 7.10–7.06 (m, 2 H), 7.02 (d, *J* = 7.5 Hz, 1 H), 6.97 (t, *J* = 7.5 Hz, 2 H), 6.92–6.87 (m, 4 H), 6.76 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2 (d, J_{C-F} = 243.8 Hz), 150.1, 148.7, 137.2, 129.9, 127.6 (d, J_{C-F} = 7.5 Hz), 124.8 (d, J_{C-F} = 16.3 Hz), 124.4 (d, J_{C-F} = 2.5 Hz), 123.4, 123.2, 122.6, 120.5, 115.2 (d, J_{C-F} = 21.3 Hz).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{15}F_2N_2S_2$: 397.0639; found: 397.0648.

2-{2,5-Bis[(3,5-dichlorophenyl)thio]-1*H*-pyrrol-1-yl}pyridine (3k)

Yield: 41.6 mg (40%); light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 3.5 Hz, 1 H), 7.66 (td, *J* = 7.5 Hz, *J* = 1.5 Hz, 1 H), 7.28 (dd, *J* = 7.5 Hz, *J* = 5.0 Hz, 1 H), 7.07 (t, *J* = 1.5 Hz, 2 H), 6.95 (d, *J* = 7.5 Hz, 1 H), 6.83 (d, *J* = 1.5 Hz, 4 H), 6.82 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.9, 149.0, 141.3, 137.4, 135.2, 126.0, 124.8, 123.8, 123.2, 122.9, 121.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{13}Cl_4N_2S_2$: 496.9269; found: 496.9267.

2-[2,5-Bis(thiophen-3-ylthio)-1*H*-pyrrol-1-yl]pyridine (3l)

Yield: 45.5 mg (54%); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.61 (dd, *J* = 5.0 Hz, *J* = 1.5 Hz, 1 H), 7.78 (td, *J* = 7.5 Hz, *J* = 1.5 Hz, 1 H), 7.38–7.36 (m, 1 H), 7.21–7.19 (m, 3 H), 6.80 (dd, *J* = 5.0 Hz, *J* = 3.5 Hz, 2 H), 6.72 (dd, *J* = 3.5 Hz, *J* = 1.5 Hz, 2 H), 6.55 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.3, 148.8, 137.3, 134.7, 131.6, 128.8, 127.1, 126.3, 123.8, 123.3, 117.8.

LRMS (EI, 70 eV): *m*/*z* (%) = 372 (28), 371 (52), 256 (100), 255 (19), 78 (23).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{13}N_2S_4$: 372.9956; found: 372.9956.

2-[2,5-Bis(ethylthio)-1*H*-pyrrol-1-yl]pyridine (3m)

Yield: 13.5 mg (25%); light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.63 (d, *J* = 4.5 Hz, 1 H), 7.86 (td, *J* = 7.5 Hz, *J* = 1.5 Hz, 1 H), 7.38 (dd, *J* = 7.5 Hz, *J* = 4.5 Hz, 1 H), 7.31 (d, *J* = 7.5 Hz, 1 H), 6.47 (s, 2 H), 2.48 (dd, *J* = 14.5 Hz, *J* = 7.5 Hz, 4 H), 1.08 (t, *J* = 7.5 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.5, 148.7, 137.4, 125.4, 124.2, 123.3, 117.9, 31.1, 14.4.

LRMS (EI, 70 eV): *m*/*z* (%) = 264 (100), 235 (70), 207 (16), 174 (48), 78 (34).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{17}N_2S_2$: 265.0828; found: 265.0828.

2-[2,5-Bis(phenylselanyl)-1*H*-pyrrol-1-yl]pyridine (3n)

Yield: 48.5 mg (48%); light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.46 (dd, *J* = 5.0 Hz, *J* = 1.5 Hz, 1 H), 7.55 (td, *J* = 7.5 Hz, *J* = 1.5 Hz, 1 H), 7.22 (dd, *J* = 7.5 Hz, *J* = 5.0 Hz, 1 H), 7.18–7.15 (m, 10 H), 6.92 (d, *J* = 7.5 Hz, 1 H), 6.70 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.8, 148.5, 137.0, 133.2, 130.0, 129.0, 126.5, 123.11, 123.09, 121.2, 119.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{17}N_2Se_2$: 456.9717; found: 456.9726.

2-[2,5-Bis(phenylthio)-1*H*-pyrrol-1-yl]pyrimidine (3o)

Yield: 26.0 mg (36%); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.66 (d, *J* = 5.0 Hz, 2 H), 7.19–7.15 (m, 5 H), 7.10–7.09 (m, 1 H), 7.08–7.06 (m, 5 H), 6.66 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.9, 156.7, 137.8, 128.7, 127.5, 125.8, 124.5, 120.1, 119.7.

LRMS (EI, 70 eV): *m*/*z* (%) = 361 (26), 360 (100), 351 (90), 147 (10), 77 (6).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{16}N_3S_2$: 362.0780; found: 362.0798.

2-[5-(Phenylthio)-1*H*-imidazol-1-yl]pyridine (3p)

Yield: 12.0 mg (23%); light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.48 (dd, *J* = 5.0 Hz, *J* = 1.5 Hz, 1 H), 7.76 (td, *J* = 7.5 Hz, *J* = 1.5 Hz, 1 H), 7.53 (s, 1 H), 7.48 (d, *J* = 7.5 Hz, 1 H), 7.25–7.19 (m, 6 H), 7.17–7.14 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.7, 148.9, 139.1, 138.3, 133.6, 130.4, 130.1, 129.1, 127.3, 122.8, 121.9, 118.3.

LRMS (EI, 70 eV): *m*/*z* (%) = 253 (13), 252 (54), 251 (100), 118 (26), 78 (23).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{12}N_3S$: 254.0747; found: 254.0752.

2-(Phenylthio)-1-(pyridin-2-yl)-1*H*-indole (5a)

Yield: 56.8 mg (77%); light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.59 (d, *J* = 4.0 Hz, 1 H), 8.26 (d, *J* = 8.0 Hz, 1 H), 8.02 (s, 1 H), 7.83 (t, *J* = 8.0 Hz, 1 H), 7.64 (d, *J* = 8.0 Hz, 1 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.37 (t, *J* = 8.0 Hz, 1 H), 7.25–7.17 (m, 6 H), 7.09 (t, *J* = 8.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.8, 149.0, 138.6, 138.2, 135.9, 131.8, 131.0, 128.7, 126.4, 125.1, 124.0, 122.1, 120.7, 120.0, 114.7, 113.4, 106.5.

LRMS (EI, 70 eV): *m*/*z* (%) = 302 (25), 301 (100), 300 (41), 268 (20), 223 (12).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{15}N_2S$: 303.0951; found: 303.0951.

3-Methyl-2-(phenylthio)-1-(pyridin-2-yl)-1*H*-indole (5b)

Yield: 44.2 mg (75%); light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.58 (d, *J* = 4.0 Hz, 1 H), 7.73 (t, *J* = 8.0 Hz, 1 H), 7.67 (d, *J* = 8.0 Hz, 1 H), 7.53 (d, *J* = 8.0 Hz, 1 H), 7.31–7.28 (m, 2 H), 7.25–7.22 (m, 2 H), 7.16–7.13 (m, 2 H), 7.07–7.04 (m, 1 H), 6.97–6.96 (m, 2 H), 2.49 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.0, 149.0, 138.2, 137.6, 137.2, 128.9, 128.3, 126.3, 125.4, 124.4, 123.7, 123.0, 122.1, 122.0, 120.7, 119.3, 111.6, 10.0.

LRMS (EI, 70 eV): *m*/*z* (%) = 316 (100), 287 (17), 207 (22), 156 (16), 78 (14).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{17}N_2S$: 317.1107; found: 317.1110.

5-Methyl-2-(phenylthio)-1-(pyridin-2-yl)-1*H*-indole (5c)

Yield: 73.1 mg (91%); light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.59 (d, *J* = 3.5 Hz, 1 H), 8.15 (d, *J* = 8.0 Hz, 1 H), 8.01 (s, 1 H), 7.83 (td, *J* = 1.5 Hz, *J* = 8.0 Hz, 1 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.45 (s, 1 H), 7.22–7.19 (m, 6 H), 7.12–7.08 (m, 1 H), 2.45 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.8, 149.0, 138.5, 134.2, 131.9, 131.7, 131.3, 128.7, 126.2, 125.6, 124.9, 120.5, 119.6, 114.4, 113.2, 105.8, 21.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{17}N_2S$: 317.1107; found: 317.1105.

5-Chloro-2-(phenylthio)-1-(pyridin-2-yl)-1*H*-indole (5d)

Yield: 55.3 mg (81%); light yellow solid; mp 83–85 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.59 (s, 1 H), 8.23 (d, *J* = 9.0 Hz, 1 H), 7.99 (s, 1 H), 7.85 (t, *J* = 9.0 Hz, 1 H), 7.60 (d, *J* = 1.5 Hz, 1 H), 7.46 (d, *J* = 9.0 Hz, 1 H), 7.30 (dd, *J* = 1.5 Hz, *J* = 9.0 Hz, 1 H), 7.25–7.22 (m, 1 H), 7.21–7.17 (m, 4 H), 7.11 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.5, 149.1, 138.7, 137.8, 134.3, 132.8, 132.3, 128.9, 128.0, 126.5, 125.4, 124.4, 121.0, 119.4, 115.0, 114.4, 106.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{14}ClN_2S$: 337.0561; found: 337.0566.

6-Fluoro-2-(phenylthio)-1-(pyridin-2-yl)-1*H*-indole (5e)

Yield: 32.2 mg (50%); light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.60 (d, *J* = 4.0 Hz, 1 H), 8.11 (dd, *J* = 2.0 Hz, *J* = 8.5 Hz, 1 H), 7.95 (s, 1 H), 7.85 (td, *J* = 2.0 Hz, *J* = 8.5 Hz, 1 H), 7.52 (dd, *J* = 5.5 Hz, *J* = 8.5 Hz, 1 H), 7.45 (d, *J* = 8.0 Hz, 1 H), 7.23 (dd, *J* = 5.5 Hz, *J* = 8.5 Hz, 1 H), 7.20–7.19 (m, 4 H), 7.12–7.09 (m, 1 H), 6.99 (td, *J* = 2.0 Hz, *J* = 8.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.0 (d, J_{C-F} = 237.5 Hz), 151.7, 149.0, 138.7, 137.9, 136.0, 135.9, 131.6 (d, J_{C-F} = 2.5 Hz), 128.8, 127.2, 126.5, 125.3, 120.8, 120.7 (d, J_{C-F} = 10.0 Hz), 114.1, 110.7 (d, J_{C-F} = 25.0 Hz), 106.9, 101.1, 100.9.

LRMS (EI, 70 eV): *m*/*z* (%) = 320 (23), 319 (100), 318 (45), 286 (16), 241 (15).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{14}FN_2S$: 321.0856; found: 321.0855.

2-(Phenylthio)-1-(pyrimidin-2-yl)-1*H*-indole (5f)[10]

Yield: 47.5 mg (37%); yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.84 (d, *J* = 8.5 Hz, 1 H), 8.70 (d, *J* = 4.5 Hz, 2 H), 8.58 (s, 1 H), 7.57 (d, *J* = 7.5 Hz, 1 H), 7.40–7.37 (m, 1 H), 7.24–7.22 (m, 3 H), 7.18 (t, *J* = 7.5 Hz, 2 H), 7.10–7.06 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.2, 157.3, 137.7, 136.0, 131.6, 131.4, 128.8, 126.8, 125.2, 124.5, 122.8, 119.8, 116.7, 116.5, 108.5.

LRMS (EI, 70 eV): *m*/*z* (%) = 303 (24), 302 (100), 301 (48), 300 (9), 269 (16).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}N_3S$: 304.0903; found: 304.0902.

2-[2-(Phenylthio)-1*H*-pyrrol-1-yl]pyridine (3aa)[7]

Yield: 15.1 mg (30%); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.45 (d, *J* = 4.5 Hz, 1 H), 7.68–7.65 (m, 1 H), 7.57–7.56 (m, 1 H), 7.52 (d, *J* = 8.5 Hz, 1 H), 7.19–7.15 (m, 3 H), 7.07–7.06 (m, 1 H), 6.75 (d, *J* = 7.5 Hz, 2 H), 6.76–6.75 (m, 1 H), 6.44–6.42 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.3, 148.8, 139.3, 137.8, 129.1, 127.7, 126.1, 126.0, 125.5, 123.5, 122.0, 119.1, 117.3, 110.4.

LRMS (EI, 70 eV): *m*/*z* (%) = 252 (100), 251 (36), 174 (19), 78 (38), 51 (21).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{12}N_2S$: 253.0721; found: 253.0801.

2-(Phenylthio)-1*H*-indole (5aa)[4b]

Yield: 36.0 mg (80%); white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 3.5 Hz, 1 H), 8.13 (d, *J* = 8.5 Hz, 1 H), 7.77–7.76 (m, 1 H), 7.66 (d, *J* = 3.5 Hz, 1 H), 7.59 (d, *J* = 8.5 Hz, 1 H), 7.43 (d, *J* = 8.5 Hz, 1 H), 7.23–7.09 (m, 4 H), 6.65 (d, *J* = 3.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.0, 138.4, 135.1, 130.5, 125.9, 123.1, 121.1, 120.0, 114.6, 112.9, 105.5.

LRMS (EI, 70 eV): *m*/*z* (%) = 225 (100), 224 (42), 193 (22), 148 (22), 121 (19), 112 (13), 77 (41), 51 (28).

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Supporting Information

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