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Disulfide Catalyzed Iodination of Electron-rich Aromatic Compounds

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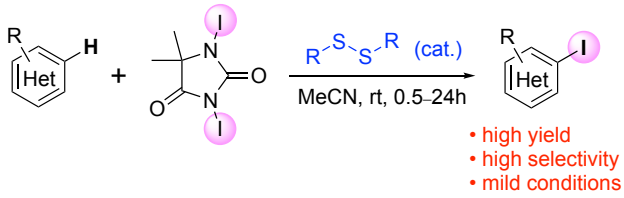


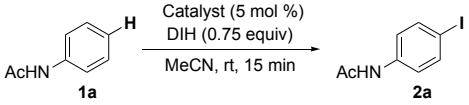
ABSTRACT: Herein, a disulfide-catalyzed electrophilic iodination of aromatic compounds using 1,3-diiodo-5,5-dimethylhydantoin (DIH) has been developed. The disulfide activates DIH as a Lewis base to promote the iodination reaction in acetonitrile under mild conditions. This system is applicable to a wide range of electron-rich aromatic compounds, including acetanilide, anisole, imidazole and pyrazole derivatives.

Iodinated aromatic compounds are widely used in a number of metal-catalyzed coupling reactions[1] pharmaceutical drugs[2] and X-ray contrast media.[3] One of the synthetic methods used to prepare these compounds is the electrophilic aromatic substitution reaction, which is the most fundamental reaction to produce the iodinated aromatic compounds. Elemental iodine is known as a general and low-cost reagent for iodination, though it shows relatively low reactivity and generates hydrogen iodide during the reaction. Nevertheless, elemental iodine is still a useful reagent due to its advantage of atom economy, since "I^-" can be oxidized into the iodonium species "I^+".[4] On the other hand, many electrophilic iodinating reagents have been developed aimed towards more active iodonium species. Representative examples are iodine monochloride (ICl), bis(pyridinium)iodonium(I) tetrafluoroborate (IPy_2BF_4),[5] *N*-iodosuccinimide (NIS),[6,7] and 1,3-diiodo-5,5-dimethylhydantoin (DIH).[8]

Over the last few decades, Brønsted/Lewis acids or metal catalysts have been used to enhance the iodinating ability of these reagents, including, trifluoroacetic acid,[9,10] sulfuric acid,[11] BF_3•H_2O,[12] $ZrCl_4$,[13] $Ph_3PAuNTf_2$,[14] $In(OTf)_3$,[15] $Fe(NTf_2)_3$,[16] and $AgNTf_2$.[17] Recently, Lewis base catalysis has been reported to promote the electrophilic halogenation reaction, and has been recognized as an efficient and mild halogenation method.[18-20] In particular, Lewis basic nitrogen or sulfur atoms can interact with an electrophilic halogenating reagent to give a reactive halonium cation-Lewis base complex. This class of nucleophilic catalyst has been shown to be an effective activator of halogen transfer reagents.[21-26] Herein, we report the use of disulfides as efficient catalysts for the iodination of aromatic compounds using 1,3-diiodo-5,5-dimethylhydantoin (DIH) as the iodinating reagent. A wide variety of aromatic compounds have been iodinated in good to excellent yield with high regioselectivity using this protocol.

We have focused on electron-rich disulfides, which can potentially activate electrophilic iodinating reagents.[27,28] Our initial study was performed investigating the electrophilic iodination of the C-4 position of acetanilide using DIH in acetonitrile (Table 1). In the absence of a catalyst, the desired product was obtained in 13% yield after 15 min (entry 1). To our delight, when diphenyl disulfide (**3a**) was used as a catalyst, the yield was dramatically improved to 76% (entry 2). In addition, an alkyl substituted disulfide (**3f** and **3g**) was also successful in the reaction (entries 7 and 8). Furthermore, we investigated the substituent effects on the disulfide catalyst. Using electron-rich disulfides (**3b** and **3c**) as the catalyst further improved the yield (entries 3 and 4). In particular, 4-methoxyphenyl disulfide (**3c**) gave an excellent reaction yield of 99% (entry 4). Moreover, the amount of **3c** can be reduced to 1 mol % without decreasing the reaction yield. In contrast, electron-poor disulfides (**3d** and **3e**) proved to be less efficient catalysts in the reaction. In addition, diphenyl sulfide (**3h**) and diphenyl diselenide (**3i**) were ineffective (entries 9 and 10). We also investigated a variety of nucleophilic bases (i.e., **3j**, **k** as tertiary amines, **3l-n** as highly nucleophilic amines, and triphenylphosphine **3o**) in the reaction, which can activate halogenation reagents.[22,24,29,30] However, the nitrogenous and phosphorous bases did not promote the iodination reaction under the reaction conditions. Subsequently, we explored other conventional iodination reagents under these reaction conditions (Table 2). Whereas NIS or I_2 alone showed poor reactivity, the combination of a stoichiometric amount of NIS and a catalytic amount of I_2 promoted the reaction, as previously reported.[31-37] However, its reactivity was sluggish when compared to DIH. Finally, the solvent effect was investigated, which showed MeCN gave the most satisfactory results.

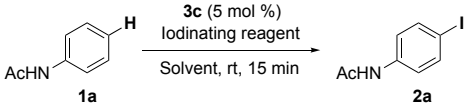
Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst	Yield (%)[b]
1	none	13
2	Ph_2S_2 (**3a**)	76
3	$(4\text{-}MeC_6H_4)_2S_2$ (**3b**)	89
4	$(4\text{-}MeOC_6H_4)_2S_2$ (**3c**)	99 (99)[c-e]
5	$(4\text{-}ClC_6H_4)_2S_2$ (**3d**)	23
6	$(4\text{-}NO_2C_6H_4)_2S_2$ (**3e**)	7
7	Me_2S_2 (**3f**)	89
8	*t*-Bu_2S_2 (**3g**)	80
9	PhSPh (**3h**)[24]	9
10	Ph_2Se_2 (**3i**)	16
11	Et_3N (**3j**)	<1
12	DIPEA (**3k**)	<1
13	DABCO (**3l**)	<1
14	Pyridine (**3m**)	<1
15	DMAP (**3n**)	<1
16	PPh_3 (**3o**)	<1

[a] Reaction conditions: **1a** (0.3 mmol), catalyst (5 mol %), DIH (0.75 equiv), MeCN (1 mL), rt, 15 min. [b] The yield was determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c] Isolated yield. [d] 1 mol % of catalyst was used. [e] The reaction time was 30 min.

Table 2. Investigation of the iodinating reagent and solvent used in the reaction.[a]

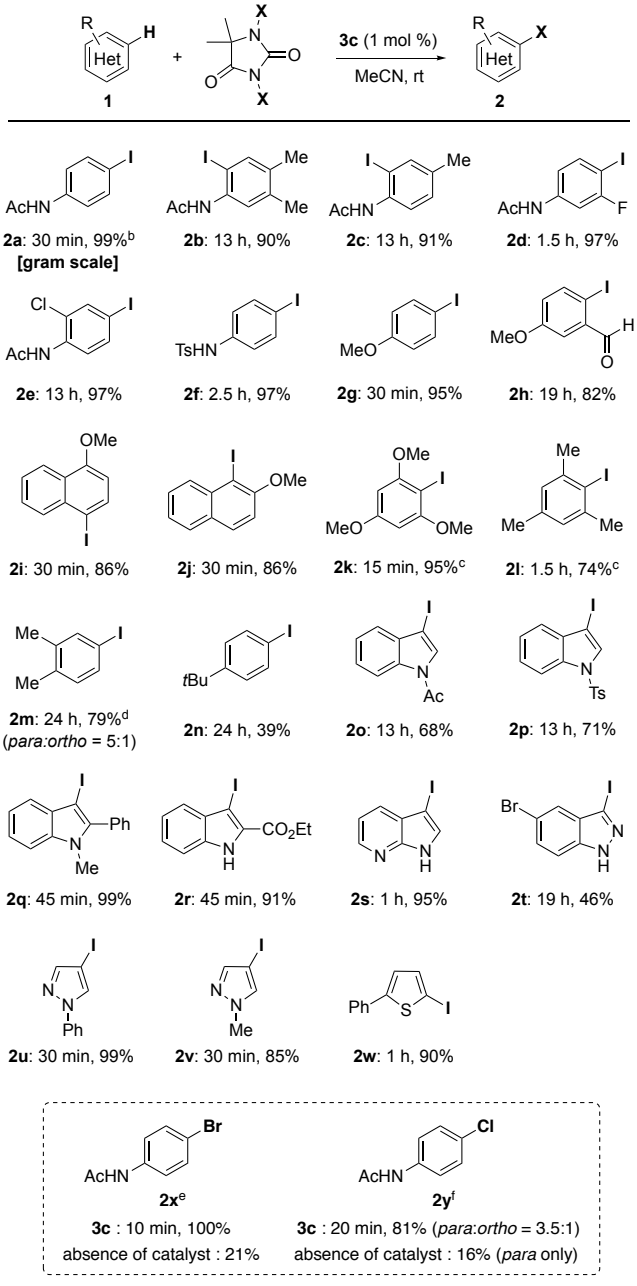


Entry	Iodinating reagent	Solvent	Yield (%)[b]
1	DIH (0.75 equiv)	MeCN	99
2	I_2 (1.5 equiv)	MeCN	<1
3	NIS (1.5 equiv)	MeCN	4
4	NIS (1.5 equiv) + I_2 (0.2 equiv)	MeCN	52
5	DIH (0.75 equiv)	1,4-dioxane	45
6	DIH (0.75 equiv)	THF	5
7	DIH (0.75 equiv)	DMSO	12
8	DIH (0.75 equiv)	CH_2Cl_2	89
9	DIH (0.75 equiv)	$CHCl_3$	1

[a] Reaction conditions: **1a** (0.3 mmol), catalyst (5 mol %), solvent (1 mL), rt, 15 min. [b] The yield was determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

With the optimized reaction conditions in hand, a variety of substrates were examined (Scheme 1). Several anilides (**2a**-**f**), anisoles (**2g**, **2h**) and methoxynaphthalenes (**2i**, **2j**), trimethoxybenzene (**2k**) and mesitylene (**2l**) were iodinated in good to excellent yield with high regioselectivity, whereas *o*- xylene (**2m**) and *t*Bu-benzene (**2n**) showed low regioselectivity and poor reactivity, respectively. Notably, *m*-anisaldeyde **2h** was iodinated without any oxidation of the aldehyde moiety. In addition, heteroarenes such as indoles (**2o**-**s**), indazole (**2t**) pyrazoles (**2u**, **2v**) and a thiophene derivative (**2w**) gave their corresponding mono-iodinated products. We also found that catalyst **3c** promoted bromination and chlorination of **1a** in the prescence of 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) and 1,3-dichloro-5,5-dimethylhydantoin (DCDMH), respectively (**2x**, **2y**).

Scheme 1. The scope of the iodination reaction of aromatic compounds.[a]



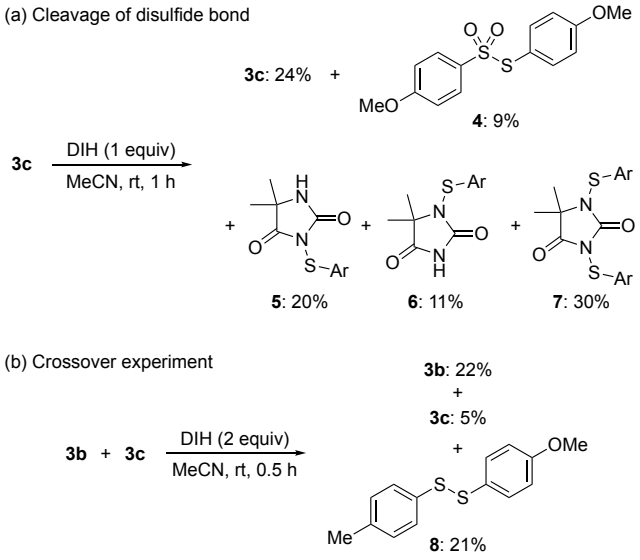
[a] Reaction conditions: **1** (0.6 mmol), **3c** (1 mol%), DIH (0.75 equiv), MeCN (2 mL), rt, 0.25–24 h. [b] Conducted on a 9.0 mmol scale. [c] 0.55 equiv of DIH was used. [d] **2m** was obtained as inseparable mixture with regioisomer, and product was determined by ^{1}H NMR. [e] 0.75 equiv of DBDMH was used. [f] 1.00 equiv of DCDMH was used.

To probe the mechanism of the reaction, disulfide **3c** was treated with DIH in the absence of the substrate for 1 h. As a result, the corresponding thiosulfonate **4** and *N*-sulfenyl hydantoin products (**5**-**7**) were obtained (Scheme 2-a). Importantly,

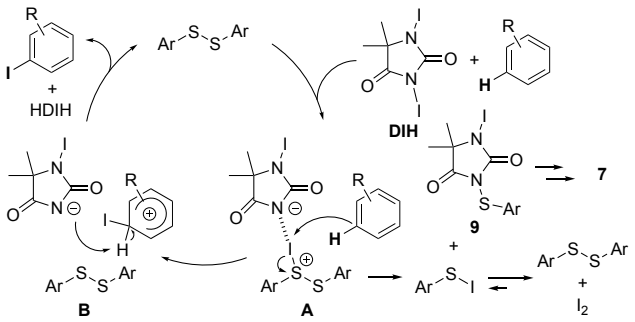
these products did not promote the iodination reaction under the optimal reaction conditions (see Supporting Information). Moreover, when the crossover reaction between disulfides **3b** and **3c** was carried out for 30 min in the presence of DIH (2 equiv), we isolated the crossover product **8** in 21% yield, which indicated that the disulfide bond is possible to be cleaved *in situ* (Scheme 2-b). From these results, we concluded that the disulfide acts as a catalyst, and any other cleavage products originating from the disulfide did not.

Based on our experimental results, we have proposed a mechanism of the reaction, as shown in Scheme 3. First, activation of DIH with disulfide occurs forming the transient halogen-bonding adduct **A**.[38] To support the formation of this transient halogen-bonding adduct, we conducted an NMR experiment. After disulfide **3c** (1 equiv) was exposed to DIH (1 equiv), the ^{1}H NMR spectrum was recorded. Although the *N*-sulfenyl hydantoin species were present, no other species were observed. Meanwhile, when a similar experiment was conducted in the presence of 1,3-dichloro-5,5-dimethylhydantoin (DCDMH), *N*-sulfenyl hydantoin species and sulfenyl chloride were produced (see Supporting Information). In addition, disulfide **3c** (1 equiv) was exposed to ICl (1 equiv) as an iodine source to confirm the halogen-sulfur interaction. As a result, the aromatic protons were broadened and slightly shifted downfield (see Supporting Information). Furthermore, a similar change in the NMR spectrum was observed upon the addition of Selectfluor™, which has been previously used for the oxidation of disulfides to give the corresponding thiosulfonates.[39] This suggests the formation of the transient halogen-bonding adduct **A**. Subsequently, the aromatic compound can be iodinated via an ionic pathway from this electrophilic intermediate (**A**) to give the desired products with the regeneration of the disulfide catalyst.[40,41] During this process, the disulfide is gradually decomposed into *N*-sulfenyl hydantoin **9** and sulfenyl iodide.[42,43] Since sulfenyl iodides are relatively unstable without the protection of a bulky substituent,[44] they readily convert into the disulfide and iodine.[45]

Scheme 2. Mechanistic investigation of the disulfide-catalyzed aromatic iodination reaction.



Scheme 3. Proposed reaction mechanism.



In summary, we have developed a mild and efficient aromatic iodination reaction using a readily available disulfide as the catalyst. The disulfide generates a powerful iodination species in the presence of DIH, which is effective for the iodination of a wide range of aromatic compounds. Further development of disulfide-derived catalysts and their application in other reactions are currently underway in our laboratory.

EXPERIMENTAL SECTION

General. Analytical thin layer chromatography (TLC) was performed on glass plates coated with 0.25 mm 230-400 mesh silica gel containing a fluorescent indicator (Merck, #1.05715.0009). Silica gel column chromatography was performed on Kanto silica gel 60 (spherical, 40-100 μm). ^{1}H and ^{13}C NMR spectra were recorded on JEOL ECS-400 (400 MHz), ECA-500 (500 MHz) and ECX-400 (400 MHz) spectrometers. In case of ^{1}H-NMR in $CDCl_3$, chemical shifts of spectra were reported relative to tetramethylsilane ($\delta = 0$). The other spectra are referenced internally according to residual solvent signals of $CDCl_3$ (^{13}C NMR; $\delta = 77.0$ ppm), DMSO-d_6 (^{1}H NMR; $\delta = 2.49$ ppm, ^{13}C NMR; $\delta = 39.5$ ppm) and acetonitrile-d_3 (^{1}H NMR; $\delta = 1.94$ ppm). Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet; br, broad), integration, coupling constant (Hz). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). High- resolution mass spectra were recorded by Thermo Fisher Scientific Exactive Orbitrap mass spectrometers. Starting materials, solvents, and reagents including disulfides were received from commercial sources (Sigma Aldrich, TCI, Wako, Kanto Chemicals and Nippoh Chemicals), unless otherwise noted and were used without purification.

General procedure for iodination of aromatic compounds. To a solution of substrate (1.0 equiv) and catalyst (1 mol %) in acetonitrile (0.3 M) at room temperature was added 1,3-diiodo-5,5-dimethylhydantoin (DIH) (0.75 or 0.55 equiv) with stirring. The reaction was monitored by thin layer chromatography. After no further conversion was observed, aqueous $Na_2S_2O_3$ solution was added to the crude reaction mixture and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtrated and concentrated *in vacuo*. The residue was purified on silica gel flash column chromatography.

***N*-(4-iodophenyl)acetamide (2a).** Acetanilide (1.22 g, 9.0 mmol), bis(4-methoxyphenyl) disulfide **3c** (25.1 mg, 0.09 mmol) and DIH (2.56 g, 6.75 mmol) in acetonitrile (30 mL) for 30 min to afford **2a** (2.35 g, 100% yield) purified by flash column chromatography (Hexane/AcOEt = 3:2) as a white solid; ^{1}H NMR (400MHz, DMSO-d_6) $\delta = 10.02$ (s, 1H), 7.60 (d, $J = 8.9$ Hz, 2H), 7.40 (d, $J = 8.9$ Hz, 2H), 2.02 (s, 3H). The NMR spectrum was identical to that previously reported.[25]

***N*-(2-iodo-4,5-dimethylphenyl)acetamide (2b).** According to the general procedure, 3,4-dimethylacetanilide (97.9 mg, 0.6 mmol), bis(4-methoxyphenyl) disulfide **3c** (1.7 mg, 6 μmol) and DIH (171.0 mg, 0.45 mmol) in acetonitrile (2 mL) for 13 h to afford

2b (155.8 mg, 90% yield) purified by flash column chromatography (Hexane/AcOEt = 3:2) as a white solid; ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.93 (s, 1H), 7.53 (s, 1H), 2.23 (s, 6H), 2.18 (s, 3H). The NMR spectrum was identical to that previously reported.[46]

***N*-(2-iodo-4-methylphenyl)acetamide (2c).** According to the general procedure, 4-methylacetanilide (89.5 mg, 0.6 mmol), bis(4-methoxyphenyl) disulfide **3c** (1.7 mg, 6 μmol) and DIH (171.0 mg, 0.45 mmol) in acetonitrile (2 mL) for 13 h to afford **2c** (150.4 mg, 91% yield) purified by flash column chromatography (Hexane/AcOEt = 3:2) as a pale pink solid; ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.03 (d, J = 8.3 Hz, 1H), 7.61 (s, 1H), 7.32 (br, 1H), 7.15 (d, J = 8.3 Hz, 1H), 2.28 (s, 3H), 2.23 (s, 3H). The NMR spectrum was identical to that previously reported.[47]

***N*-(3-fluoro-4-iodophenyl)acetamide (2d).** According to the general procedure, 3-fluoroacetanilide (91.9 mg, 0.6 mmol), bis(4-methoxyphenyl) disulfide **3c** (1.7 mg, 6 μmol) and DIH (171.0 mg, 0.45 mmol) in acetonitrile (2 mL) for 1.5 h to afford **2d** (162.9 mg, 97% yield) purified by flash column chromatography (Hexane/AcOEt = 3:2) as a white solid; ^{1}H NMR (500MHz, DMSO-d_6) δ = 10.23 (s, 1H), 7.71 (dd, J = 8.6, 7.5 Hz, 1H), 7.65 (dd, J = 10.9, 2.3 Hz, 1H), 7.11 (dd, J = 8.6, 2.3 Hz, 1H), 2.04 (s, 3H); ^{13}C{^{1}H } NMR (100MHz, DMSO-d_6) δ = 168.8, 162.2, 159.8, 141.3, 141.2, 138.9, 138.8, 116.7, 106.2, 105.9, 73.2, 73.0, 24.1; HRMS (ESI) *m/z*: $[M - H]^-$ Calcd for C_8H_6NOFI 277.9484; Found: 277.9492.

***N*-(2-chloro-4-iodophenyl)acetamide (2e).** According to the general procedure, 2-chloroacetanilide (101.8 mg, 0.6 mmol), bis(4-methoxyphenyl) disulfide **3c** (1.7 mg, 6 μmol) and DIH (171.0 mg, 0.45 mmol) in acetonitrile (2 mL) for 13 h to afford **2e** (172.8 mg, 97% yield) purified by flash column chromatography (Hexane/AcOEt = 3:2) as a white solid; ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.17 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 2.0 Hz, 1H), 7.58−7.55 (m, 2H), 2.24 (s, 3H). The NMR spectrum was identical to that previously reported.[17]

***N*-(4-iodophenyl)-4-methylbenzenesulfonamide (2f).** According to the general procedure, 4-methyl-*N*-phenylbenzenesulfonamide (148.4 mg, 0.6 mmol), bis(4-methoxyphenyl) disulfide **3c** (1.7 mg, 6 μmol) and DIH (171.0 mg, 0.45 mmol) in acetonitrile (2 mL) for 2.5 h to afford **2f** (217.1 mg, 97% yield) purified by flash column chromatography (Hexane/AcOEt = 3:2) as a white solid; ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.65 (d, J = 8.3 Hz, 2H), 7.54 (d, J = 8.5 Hz, 2H), 7.25 (d, J = 8.2 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 6.64 (s, 1H), 2.39 (s, 3H). The NMR spectrum was identical to that previously reported.[48]

1-iodo-4-methoxybenzene (2g). According to the general procedure, anisole (65.2 μL, 0.6 mmol), bis(4-methoxyphenyl) disulfide **3c** (1.7 mg, 6 μmol) and DIH (171.0 mg, 0.45 mmol) in acetonitrile (2 mL) for 30 min to afford **2g** (133.5 mg, 95% yield) purified by flash column chromatography (Hexane/AcOEt = 9:1) as a white solid; ^{1}H NMR (500MHz, $CDCl_3$) δ = 7.56 (d, J = 9.2 Hz, 2H), 6.68 (d, J = 9.2 Hz, 2H), 3.78 (s, 3H). The NMR spectrum was identical to that previously reported.[25]

2-iodo-5-methoxybenzaldehyde (2h). According to the general procedure, 3-methoxybenzaldehyde (72.9 μL, 0.6 mmol), bis(4-methoxyphenyl) disulfide **3c** (1.7 mg, 6 μmol) and DIH (171.0 mg, 0.45 mmol) in acetonitrile (2 mL) for 19 h to afford **2h** (129.0 mg, 82% yield) purified by flash column chromatography (Hexane/AcOEt = 9:1) as a white solid; ^{1}H NMR (500MHz, $CDCl_3$) δ = 10.02 (s, 1H), 7.81 (d, J = 8.6 Hz, 1H), 7.43 (d, J = 3.2 Hz, 1H), 6.92 (dd, J = 8.6, 3.2 Hz, 1H), 3.85 (s, 3H). The NMR spectrum was identical to that previously reported.[25]

1-iodo-4-methoxynaphthalene (2i). According to the general procedure, 1-methoxynaphthalene (86.3 μL, 0.6 mmol), bis(4-methoxyphenyl) disulfide **3c** (1.7 mg, 6 μmol) and DIH (171.0 mg, 0.45 mmol) in acetonitrile (2 mL) for 30 min to afford **2i** (146.5 mg, 82% yield) purified by flash column chromatography (Hexane/AcOEt = 9:1) as a brown solid; ^{1}H NMR (500MHz, $CDCl_3$) δ = 8.23 (d, J = 8.3 Hz, 1H), 8.02 (d, J = 8.6 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2H), 7.60−7.57 (m, 1H), 7.53−7.49 (m, 1H), 6.61 (d, J = 8.0 Hz, 1H), 4.00 (s, 3H). The NMR spectrum was identical to that previously reported.[25]

1-iodo-2-methoxynaphthalene (2j). According to the general procedure, 2-methoxynaphthalene (94.9 mg, 0.6 mmol), bis(4-methoxyphenyl) disulfide **3c** (1.7 mg, 6 μmol) and DIH (171.0 mg, 0.45 mmol) in acetonitrile (2 mL) for 30 min to afford **2j** (146.0 mg, 82% yield) purified by flash column chromatography (Hexane/AcOEt = 9:1) as a white solid; ^{1}H NMR (500MHz, $CDCl_3$) δ = 8.14 (d, J = 8.5 Hz, 1H), 7.84 (d, J = 8.9 Hz, 1H), 7.75 (d, J = 8.3 Hz, 2H), 7.56-7.53 (m, 1H), 7.40-7.37 (m, 1H), 7.22 (d, J = 8.9 Hz, 1H), 4.03 (s, 3H). The NMR spectrum was identical to that previously reported.[25]

1-iodo-2,4,6-trimethoxybenzene (2k). According to the general procedure, 1,3,5-trimethoxybenzene (100.9 mg, 0.6 mmol), bis(4-methoxyphenyl) disulfide **3c** (1.7 mg, 6 μmol) and DIH (125.4 mg, 0.33 mmol) in acetonitrile (2 mL) for 15 min to afford **2l** (167.6 mg, 95% yield) purified by flash column chromatography (Hexane/AcOEt = 9:1) as a white solid; ^{1}H NMR (500MHz, $CDCl_3$) δ = 6.15 (s, 2H), 3.87 (s, 6H), 3.83 (s, 3H). The NMR spectrum was identical to that previously reported.[25]

1-iodo-2,4,6-trimethylbenzene (2l). According to the general procedure, 1,3,5-trimethylbenzene (82.9 μL, 0.6 mmol), bis(4-methoxyphenyl) disulfide **3c** (1.7 mg, 6 μmol) and DIH (125.4 mg, 0.33 mmol) in acetonitrile (2 mL) for 1.5 h to afford **2k** (110.0 mg, 74% yield) purified by flash column chromatography (Hexane/AcOEt = 9:1) as a white solid; ^{1}H NMR (500MHz, $CDCl_3$) δ = 6.89 (s, 2H), 2.43 (s, 6H), 2.24 (s, 3H). The NMR spectrum was identical to that previously reported.[25]

4-iodo-1,2-dimethylbenzene/1-iodo-2,3-dimethylbenzene (2m/2m'; 5/1). According to the general procedure, *o*-xylene (72.4 μL, 0.6 mmol), bis(4-methoxyphenyl) disulfide **3c** (1.7 mg, 6 μmol) and DIH (171.0 mg, 0.45 mmol) in acetonitrile (2 mL) for 24 h to afford **2m/2m'** as inseparable mixture (110.1 mg, 79% yield) purified by flash column chromatography (Hexane/AcOEt = 95:5) as a colorless oil; ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.67 (d, J = 7.9 Hz, 0.2 × 1H), 7.46 (s, 1.0 × 1H), 7.40 (d, J = 7.9 Hz, 1.0 × 1H), 7.09 (d, J = 7.5 Hz, 0.2 × 1H), 6.85 (d, J = 7.9 Hz, 1.0 × 1H), 6.76 (dd, J = 7.9 7.5 Hz, 0.2 × 1H), 2.40 (s, 0.2 × 3H), 2.33 (s, 0.2 × 3H), 2.19 (s, 1.0 × 6H). The NMR spectra were identical to those previously reported.[25]

1-(*tert*-butyl)-4-iodobenzene (2n). According to the general procedure, *tert*-butylbenzene (92.6 μL, 0.6 mmol), bis(4-methoxyphenyl) disulfide **3c** (1.7 mg, 6 μmol) and DIH (125.4 mg, 0.33 mmol) in acetonitrile (2 mL) for 24 h to afford **2n** (60.8 mg, 39% yield) purified by flash column chromatography (Hexane/AcOEt = 95:5) as a colorless oil; ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.60 (d, J = 8.1 Hz, 1H), 7.13 (d, J = 8.1 Hz, 1H), 1.29 (s, 9H). The NMR spectrum was identical to that previously reported.[49]

1-(3-iodo-*1H*-indol-1-yl)ethan-1-one (2o). According to the general procedure, 1-acetylindole (68.9 μL, 0.6 mmol), bis(4-methoxyphenyl) disulfide **3c** (1.7 mg, 6 μmol) and DIH (171.0 mg, 0.45 mmol) in acetonitrile (2 mL) for 13 h to afford **2o** (116.7 mg, 68% yield) purified by flash column chromatography (Hexane/AcOEt = 3:1) as a brown solid; ^{1}H NMR (500MHz, $CDCl_3$) δ = 8.41 (d, J = 8.0 Hz, 1H), 7.59 (s, 1H), 7.44−7.36 (m, 3H), 2.65 (s, 3H). The NMR spectrum was identical to that previously reported.[50]

3-iodo-1-[(4-methylphenyl)sulfonyl]-*1*H-indole (2p). According to the general procedure, 1-tosylindole (162.8 mg, 0.6 mmol), bis(4-methoxyphenyl) disulfide **3c** (1.7 mg, 6 μmol) and DIH (171.0 mg, 0.45 mmol) in acetonitrile (2 mL) for 30 min to afford **2p** (170.2 mg, 71% yield) purified by flash column chromatography (Hexane/AcOEt = 3:1) as a pale yellow solid; ^{1}H NMR (500MHz, $CDCl_3$) δ = 7.96 (d, J = 8.9 Hz, 1H), 7.78 (d, J = 8.3 Hz, 2H), 7.70 (s, 1H), 7.39−7.29 (m, 3H), 7.24 (d, J = 8.0 Hz, 2H), 2.36

(s, 3H). The NMR spectrum was identical to that previously reported.[51]

3-iodo-1-methyl-2-phenyl-*1*H-indole (2q). According to the general procedure, 1-methyl-2-phenylindole (124.4 mg, 0.6 mmol), bis(4-methoxyphenyl) disulfide **3c** (1.7 mg, 6 μmol) and DIH (171.0 mg, 0.45 mmol) in acetonitrile (2 mL) for 45 min to afford **2q** (198.7 mg, 99% yield) purified by flash column chromatography (Hexane/AcOEt = 9:1) as a colorless oil; ^{1}H NMR (500MHz, $CDCl_3$) δ = 7.68−7.56 (m, 6H), 7.46−7.37 (m, 3H), 3.74 (s, 3H). The NMR spectrum was identical to that previously reported.[52]

ethyl 3-iodo-*1*H-indole-2-carboxylate (2r). According to the general procedure, ethyl indole-2-carboxylate (113.5 mg, 0.6 mmol), bis(4-methoxyphenyl) disulfide **3c** (1.7 mg, 6 μmol) and DIH (171.0 mg, 0.45 mmol) in acetonitrile (2 mL) for 45 min to afford **2r** (172.7 mg, 99% yield) purified by flash column chromatography (Hexane/AcOEt = 9:1) as a white solid; ^{1}H NMR (500MHz, $CDCl_3$) δ = 9.18 (s, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.40−7.36 (m, 2H), 7.26−7.22 (m, 1H), 4.47 (q, J = 7.2 Hz, 2H), 1.47 (t, J = 7.2 Hz, 3H). The NMR spectrum was identical to that previously reported.[53]

3-iodo-*1*H-pyrrolo[2,3-b]pyridine (2s). According to the general procedure, 7-azaindole (70.9 mg, 0.6 mmol), bis(4-methoxyphenyl) disulfide **3c** (1.7 mg, 6 μmol) and DIH (171.0 mg, 0.45 mmol) in acetonitrile (2 mL) for 1 h to afford **2s** (138.6 mg, 95% yield) purified by flash column chromatography (Hexane/AcOEt = 3:1) as a pale yellow solid; ^{1}H NMR (500MHz, $CDCl_3$) δ = 8.34 (d, J = 4.9 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.43 (s, 1H), 7.18 (dd, J = 8.1, 4.9 Hz, 1H). The NMR spectrum was identical to that previously reported.[54]

5-bromo-3-iodo-1*H*-indazole (2t). According to the general procedure, 5-bromo-*1*H-indazole (118.2 mg, 0.6 mmol), bis(4-methoxyphenyl) disulfide **3c** (1.7 mg, 6 μmol) and DIH (171.0 mg, 0.45 mmol) in acetonitrile (2 mL) for 19 h to afford **2s** (89.4 mg, 46% yield) purified by flash column chromatography (Hexane/AcOEt = 4:1) as a white solid; ^{1}H NMR (400MHz, DMSO-d_6) δ = 13.70 (s, 1H), 7.60 (s, 1H), 7.54−7.53 (m, 1H). The NMR spectrum was identical to that previously reported.[55]

4-iodo-1-phenyl-*1*H-pyrazole (2u). According to the general procedure, 1-phenylpyrazole (77.9 μL, 0.6 mmol), bis(4-methoxyphenyl) disulfide **3c** (1.7 mg, 6 μmol) and DIH (171.0 mg, 0.45 mmol) in acetonitrile (2 mL) for 30 min to afford **2u** (161.2 mg, 99% yield) purified by flash column chromatography (Hexane/AcOEt = 9:1) as a white solid; ^{1}H NMR (500MHz, $CDCl_3$) δ = 7.97 (s, 1H), 7.72 (s, 1H), 7.66−7.64 (m, 1H), 7.48-7.45 (m, 2H), 7.34−7.31 (m, 1H). The NMR spectrum was identical to that previously reported.[56]

4-iodo-1-methyl-*1*H-pyrazole (2v). According to the general procedure, 1-methylpyrazole (49.8 μL, 0.6 mmol), bis(4-methoxyphenyl) disulfide **3c** (1.7 mg, 6 μmol) and DIH (171.0 mg, 0.45 mmol) in acetonitrile (2 mL) for 30 min to afford **2v** (106.1 mg, 85% yield) purified by flash column chromatography (Hexane/AcOEt = 9:1) as a white solid; ^{1}H NMR (500MHz, $CDCl_3$) δ = 7.49 (s, 1H), 7.41 (s, 1H), 3.92 (s, 3H). The NMR spectrum was identical to that previously reported.[52]

2-iodo-5-phenylthiophene (2w). According to the general procedure, 2-phenylthiophene (96.1 mg, 0.6 mmol), bis(4-methoxyphenyl) disulfide **3c** (1.7 mg, 6 μmol) and DIH (171.0 mg, 0.45 mmol) in acetonitrile (2 mL) for 30 min to afford **2w** (154.6 mg, 90% yield) purified by flash column chromatography (Hexane: AcOEt = 9:1) as a white solid; ^{1}H NMR (500MHz, $CDCl_3$) δ = 7.53−7.51 (m, 2H), 7.39−7.36 (m, 2H), 7.31−7.28 (m, 1H), 7.22 (d, J = 3.7 Hz, 1H), 6.98 (d, J = 3.7 Hz, 1H). The NMR spectrum was identical to that previously reported.[57]

***N*-(4-bromophenyl)acetamide (2x).** Acetanilide (81.1 mg, 0.6 mmol), bis(4-methoxyphenyl) disulfide **3c** (1.7 mg, 6 μmol) and DBDMH (128.7 mg, 0.45 mmol) in acetonitrile (2 mL) for 10 min to afford **2x** (128.5 mg, 100% yield) purified by flash column chromatography (Hexane/AcOEt = 3:2) as a white solid; ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.46−7.37 (m, 4H), 7.30 (s, 1H), 2.17 (s, 3H). The NMR spectrum was identical to that previously reported.[58]

***N*-(4-chlorophenyl)acetamide/*N*-(2-chlorophenyl)acetamide (2y/2y'; 3.5/1).** T Acetanilide (81.1 g, 0.6 mmol), bis(4-methoxyphenyl) disulfide **3c** (1.7 mg, 6 μmol) and DBDMH (118.2 mg, 0.6 mmol) in acetonitrile (2 mL) for 20 min to afford **2y** (64.0 mg, 63% yield) and **2y'** (18.0 mg, 18%) purified by flash column chromatography (Hexane/Acetone = 3:2) as a white solid. **2y**; ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.45 (d, J = 8.8 Hz, 2H), 7.33 (s, 1H), 7.27 (d, J = 8.8 Hz, 2H), 2,17 (s, 3H). **2y'**; (400MHz, $CDCl_3$) δ = 8.36 (d, J = 8.1 Hz, 2H), 7.64 (s, 1H), 7.36 (dd, J = 8.1, 1.4 Hz, 2H), 7.27 (td, J = 7.9, 1.6 Hz, 2H), 7.04 (t, J = 7.6 Hz, 1H), 2,24 (s, 3H). The NMR spectra was identical to those previously reported.[58,59]

Catalyst deactivation caused by decomposition of disulfide To a solution of bis(4-methoxyphenyl) disulfide **3c** (278.4 mg, 1 mmol) in acetonitrile (2 mL), was added DIH (379.9 mg, 1 mmol) and stirred for 1 h at room temperature. The resulting mixture was directly purified by silica gel flash column chromatography eluting 0% to 40% AcOEt in hexane to give **5** (106.4 mg, 20% yield) and **6** (59.8 mg, 11% yield), and **3c** (67.0 mg, 24% yield) was recovered. Subsequently, further purification was conducted by silica gel flash column chromatography eluting 0% to 4% AcOEt in toluene to give **4** (26.7 mg, 9% yield) and **7** (122.0 mg, 30% yield).

S-4-methoxyphenyl 4-methoxybenzenesulfonothioate (4) ^{1}H NMR (500MHz, $CDCl_3$) δ = 7.51 (d, J = 9.2 Hz, 2H), 7.28 (d, J = 8.9 Hz, 2H), 6.88 (d, J = 9.2 Hz, 1H), 6.85 (d, J = 8.9 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H). The NMR spectrum was identical to that previously reported.[60]

3-[(4-methoxyphenyl)thio]-5,5-dimethylimidazolidine-2,4-dione (5) ^{1}H NMR (500MHz, $CDCl_3$) δ = 7.71 (d, J = 8.9 Hz, 2H), 6.86 (d, J = 8.9 Hz, 2H), 6.01 (s, 1H), 3.81 (s, 3H), 1.41 (s, 6H); ^{13}C{^{1}H } NMR (125MHz, $CDCl_3$) δ = 177.6, 161.3, 156.1, 135.7, 125.1, 114.6, 59.6, 55.3, 25.0; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{14}N_2O_3S$ 267.0798; Found: 267.0800.

1-[(4-methoxyphenyl)thio]-5,5-dimethylimidazolidine-2,4-dione (6) ^{1}H NMR (500MHz, $CDCl_3$) δ = 8.16 (s, 1 H), 7.62 (d, J = 8.9 Hz, 2H), 6.87 (d, J = 8.9 Hz, 2H), 3.81 (s, 3H), 1.38 (s, 6H); ^{13}C{^{1}H } NMR (125MHz, $CDCl_3$) δ = 176.8, 160.7, 157.2, 134.1, 127.6, 114.6, 66.8, 55.3, 23.2; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{15}N_2O_3S$ 267.0798; Found: 267.0799.

1,3-bis[(4-methoxyphenyl)thio]-5,5-dimethylimidazolidine-2,4-dione (7) ^{1}H NMR (500MHz, $CDCl_3$) δ = 7.74 (d, J = 8.9 Hz, 2H), 7.61 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.9 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 1.32 (s, 6H); ^{13}C{^{1}H } NMR (125MHz, $CDCl_3$) δ = 176.1, 161.6, 160.9, 157.0, 136.7, 134.6, 127.4, 124.9, 114.7, 114.6, 66.1, 55.4, 55.3, 23.5; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{20}N_2O_4S_2$ 405.0937; Found: 405.0935.

Crossover experiment To a solution of bis(4-methelphenyl) disulfide **3b** (24.6 mg, 0.1 mmol) and bis(4-methoxyphenyl) disulfide **3c** (27.8 mg, 0.1 mmol) in acetonitrile (1 mL), was added DIH (76 mg, 0.2 mmol) at room temperature. After stirring for 30 min, aqueous $Na_2S_2O_3$ solution was added to the crude reaction mixture and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtrated and concentrated *in vacuo*. The residue was purified on silica gel flash column chromatography (Hexane) to recover **3b** (11.0 mg, 22% yield). Subsequently, further purification was conducted by PLC (Silica gel 60, 0.5 mm, Merck; Hexane) to give **8** (10.9 mg, 21% yield), and **3c** (2.9 mg, 5% yield) was recovered.

4-methoxyphenyl 4-tolyl disulfide (8) ^{1}H NMR (500MHz, $CDCl_3$) δ = 7.53 (d, J = 8.9 Hz, 2H), 7.38 (d, J = 8.0 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 8.9 Hz, 1H), 3.79 (s, 3H), 2.33 (s, 3H). The NMR spectrum was identical to that previously reported.[61]

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SUPPORTING INFORMATION

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Mechanistic studies, as well as ^{1}H and ^{13}C NMR spectra of compounds in the disulfide catalyzed aromatic iodination reaction.

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