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Aerobic Oxidative Sulfenylation of Pyrazolones and Pyrazoles Catalyzed by Metal-Free Flavin–Iodine Catalysis

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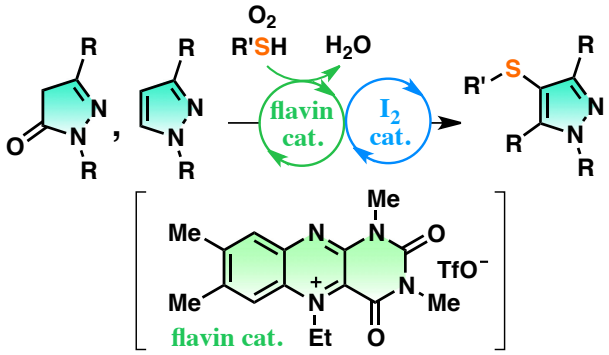


ABSTRACT: Two-component metal-free catalytic oxidative sulfenylation of pyrazolones with thiols has been achieved using the biomimetic flavin and iodine. The methodology is mild and eco-friendly, and proceeds in the presence of air or molecular oxygen (1 atm) as the sole sacrificial reagent, and generates water as the only by-product. The methodology was also extended to the sulfenylation of pyrazoles and electron-rich benzenes and afforded a series of thioethers in good yields.

Pyrazoles and their derivatives are an important class of aza-heterocycles, which display a wide range of pharmacological and biological activities.[1] Notably, commercially available drugs and agrochemicals such as Crizotinib (anticancer),[2] Sildenafil (erectile dysfunction therapeutic),[3] Celecoxib (anti-inflammatory),[4] and Fipronil (agricultural insecticide)[5] contain the pyrazole skeleton (Figure 1). Due to their widespread applications in medicinal chemistry, considerable efforts have been devoted toward the synthesis and functionalization of pyrazoles.[6,7] Among them, the sulfenylation of pyrazolones and pyrazoles by direct C-H functionalization has attracted increasing attention, due to the crucial contribution of C-S bond incorporation toward imparting diversity to pharmaceutical and material science-relevant molecules.[8] Indeed, sulfur-containing pyrazole derivatives have been recognized as promising candidates for medicinal and agrochemical compounds,[9] *e.g.* Sildenafil,[3] Celecoxib,[4] Fipronil,[5] potent anti-inflammatory agent **I**,[9d] and fungicidal active agent **II**[9e] (Figure 1).

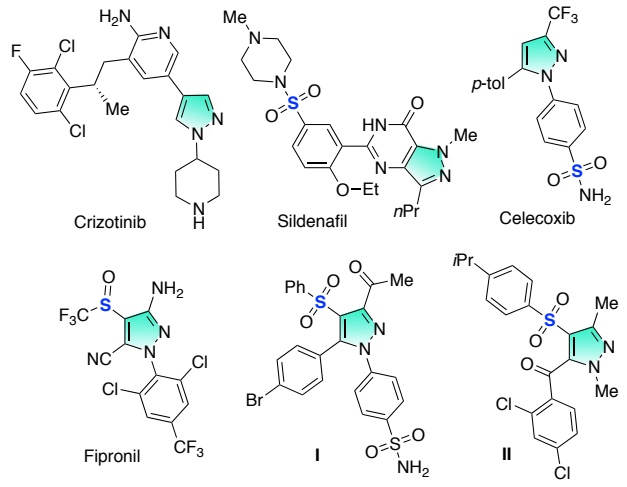


Figure 1. Biologically active pyrazole derivatives.

Several reagents have been reported for the direct sulfenylation of C-H bonds, such as thiols, disulfides, sulfenyl halides, sulfonyl hydrazides, sulfonyl cyanides, sulfinates, sulfinic acid, and 1-(substituted phenylthio)pyrrolidine-2,5-dione.[8,10] However, most of these C-H sulfenylation reagents require moisture-free reaction conditions or involve multiple synthetic manipulations. Since thiols are the

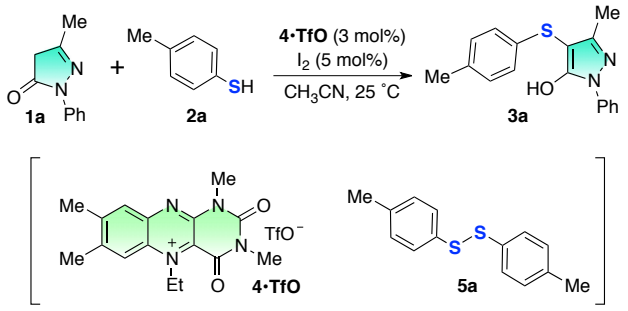
simplest, most atom-economical, and readily available sulfenylation reagents, the thiol-mediated oxidative sulfenylation has emerged as a highly reliable strategy for a variety of substrates. However, methods for the sulfenylation of pyrazolones[11] and pyrazoles[12] with thiols have been rather limited. Despite their potential advantages, these reported methods typically involve harsh reaction conditions and may require the use of expensive transition metal catalysts, and/or a stoichiometric amount of a base or oxidant.[11,12] The use of ambient molecular oxygen as the sole sacrificial reagent for oxidative sulfenylation would be an ideal approach because molecular oxygen is an atom-economical and low-polluting green oxidant which generates the non-hazardous water as the byproduct.[13] The recent demand for green and sustainable oxidative transformations has driven the use of ambient molecular oxygen in these processes. However, to the best of our knowledge, eco-friendly approaches to oxidative pyrazolone and pyrazole sulfenylation using molecular oxygen have not been reported.

Recently, we reported the development of a novel strategy for green metal-free oxidation by coupling flavin and iodine catalysis, which enabled the use of molecular oxygen as a terminal oxidant.[14] By the activation of O_2[15,16] under biomimetic flavin organocatalysis, formation thiadiazole rings by the reaction of N-tosylhydrazones with sulfur[14a] was successfully achieved using the two-component catalysis system under aerobic conditions, and the sulfenylation was further extended to the reaction of indole analogs with thiols.[14b,c] Building on the successes of these flavin-iodine coupled catalyses, we report herein, the first examples of the oxidative sulfenylations of pyrazolones and pyrazoles using molecular oxygen as the sole sacrificial reagent. Importantly, this methodology meets the growing demand for the development of green chemical transformations.

We began our study by probing the sulfenylation of 3-methyl-1-phenyl pyrazolone **1a** with *p*-tolyl thiol (**2a**) in the presence of I_2 and a flavin catalyst, and found that the I_2 and riboflavin-derived alloxazinium salt (**4•TfO**) smoothly promoted the catalytic oxidative sulfenylation of **1a** in CH_3CN, under an atmosphere of molecular oxygen to furnish the corresponding sulfenyl pyrazole **3a** (the effect of solvents and iodine sources was summarized in Table S1, Supporting Information). Further optimization

of the reaction conditions revealed that the sulfenylation proceeded in excellent yield in the presence of 3 mol% of **4•TfO** and 5 mol% of I_2 in CH_3CN at 25 ˚C and afforded the products in an excellent yield after 8 h (Table 1, entry 1). To our delight, a 90% yield of the products was obtained by using air (1 atm) as the terminal oxidant (entry 2), which indicated that the concentration of molecular oxygen in air was sufficient for this sulfenylation to proceed at a reasonable rate under the present mild condition.

Table 1. Catalytic sulfenylation of **1a** with **2a** under various conditions[a]



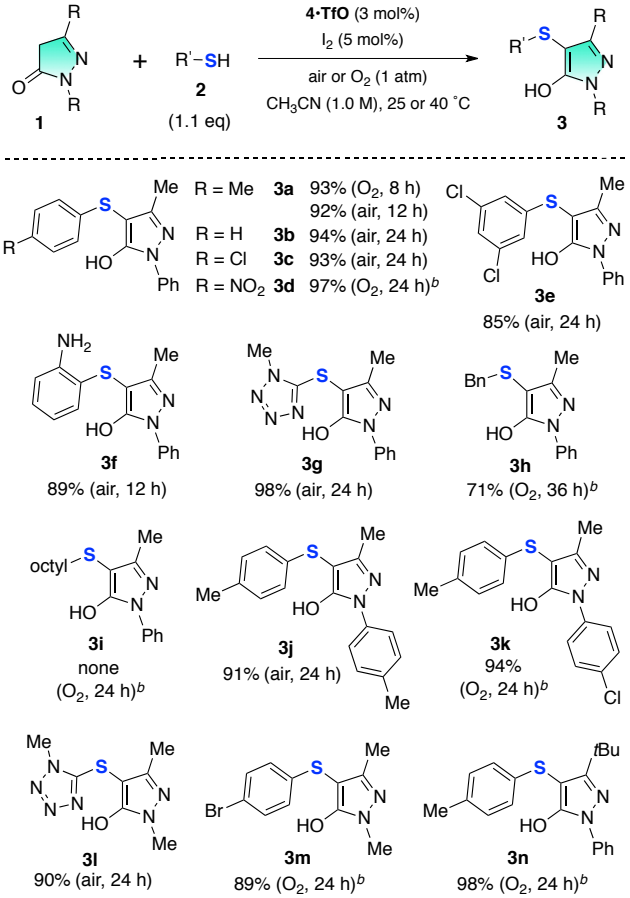
entry	flavin (mol%)	iodine source (mol%)	atmosphere	time (h)	yield (%)
1	**4•TfO** (3)	I_2 (5)	O_2	8	94
2	**4•TfO** (3)	I_2 (5)	air	12	90
3	None	I_2 (5)	O_2	8	2
4	**4•TfO** (3)	None	O_2	8	5
5	**4•TfO** (3)	I_2 (5)	N_2	8	3
6	None	I_2 (120)	N_2	8	25
7	**4•TfO** (3)	I_2 (5)	air	0.5	9 (91)[b]
8[c]	**4•TfO** (3)	I_2 (5)	air	12	93

[a]Conditions: **1a** (1.0 M), **2a** (1.1 M), **4•TfO**, I_2, and CH_3CN under air, O_2, or N_2 atmosphere (1 atm) at 25 °C. Yield was determined by ^1H NMR using 1,3,5-trioxane as an internal standard. [b]Yield of disulfide **5a** calculated on the bases of **2a**. [c]**5a** (0.55 M) was used instead of **2a**.

Having optimized the reaction conditions, we surveyed the substrate scope and limitations of the present methodology (Table 2). A series of aryl thiols bearing electron donating and withdrawing groups successfully reacted with pyrazolone generally at 25 ˚C under air and provided the corresponding sulfenylated products (**3a**-**3g**) in 85-98% yields, while the synthesis of **3d** was performed at 40 ˚C under molecular oxygen (1 atm) due to the poor solubility of **2d**. Because the sulfenylation with electron rich

thiols such as benzyl thiol (**2h**) was relatively slower than that with electron poor thiols, slightly higher temperature (40 ˚C) and molecular oxygen (1 atm) was used to promote the sulfenylation, thus gave the corresponding product **3f** in 71% yield. On the other hand, the reaction with alkyl thiol (**2i**) was sluggish (**3i**) probably due to the poor electrophilicity of the corresponding iodine adduct as described later. Pyrazolones bearing various substituents also underwent the sulfenylation to yield the desired products (**3j-3n**) in 89-98% yields. It is noteworthy that amino, chloro, and bromo functional groups are tolerated (**3c**, **3e**, **3f**, and **3m**) under the present reaction condition. The chemoselectivity of the transformation results from the efficient O_2-activation catalysis of flavin, that enables mild oxidative sulfenylation in the absence of stoichiometric quantities of strong oxidants.

Table 2. Aerobic sulfenylation of pyrazolones[a]

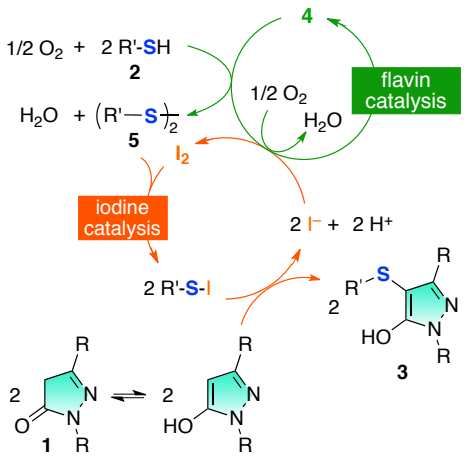


[a]Conditions: **1** (1.0 M), **2** (1.1 M), **4•TfO** (3 mol%), I_2 (5 mol%), and CH_3CN under air or O_2 (1 atm) at 25 °C. [b]At 40 °C.

With the assessment of the scope and limitations of the developed process complete, we conducted a series of control experiments to gain insight into the sulfenylation reaction. The reaction of **1a** with **2a** in the absence of **4·TfO**, I_2, or molecular oxygen was studied, and the sulfenylated product **3a** was obtained only in a trace quantity in each of these conditions, which indicated that the three components are essential for the desired outcome (Table 1, entries 3–5). The use of a super-stoichiometric quantity of I_2 (120 mol%) led to a lower yield of **3a** (entry 6), which further revealed the distinct advantage of the present dual catalytic system. To gain further insight, we analyzed the reaction mixture at 0.5 h and found the formation of the disulfide **5a**, which results from the oxidation of **2a**, in 91% yield along with the formation of **3a** in 9% yield (entry 7). Importantly, when **5a** (0.55 equiv) was used instead of **2a**, the sulfenylation occurred smoothly in good yield (entry 8). These results suggest that the sulfenylation of pyrazolones under the developed reaction conditions proceeds via generation of the disulfide.

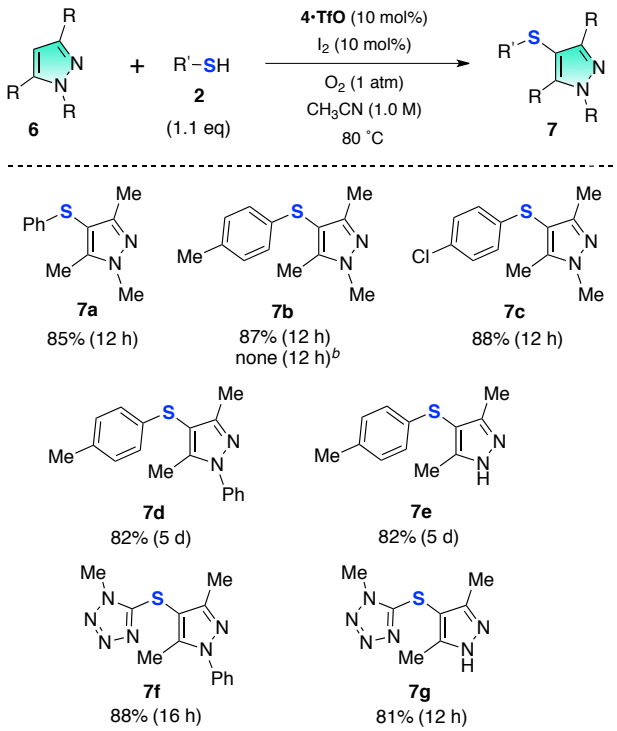
On the basis of these preliminary results along with related literature,[11e,12,14a,b] a tentative reaction mechanism is shown in Scheme 1. The basic mechanism of the flavin-iodine catalytic system is almost identical to that reported previously for indole sulfenylation.[14b] In this mechanism, the thiol is oxidatively converted to the corresponding disulfide, which reacts with I_2 to form the corresponding sulfenyl iodide (R-SI). The ensuing nucleophilic attack of pyrazolone onto R-SI provides the desired product. This is supported by the fact that the sulfenylation using relatively electron rich pyrazolones smoothly proceeded in the present reaction. In this system, the flavin catalyst oxidizes the thiol and I^- under aerobic conditions to generate disulfide and I_2, respectively. Although conventional conditions for sulfenylation of pyrazolones with thiols require heating,[11a-e] the developed pyrazolone sulfenylation occurs at ambient temperature (25 °C) due to the multiple beneficial roles of flavin catalysis which include O_2-activation and the oxidations of thiol and I^-.

Scheme 1. Proposed mechanism for aerobic sulfenylation catalyzed by flavin–iodine-catalyst.



We explored next, the sulfenylation of pyrazoles, which seem to be less reactive than pyrazolones. Indeed, the sulfenylation of pyrazoles with thiols has been limited to a single recent example, where DMSO was used as the oxidant.[12] We were pleased to find the successful sulfenylation of pyrazole **6a** using **4·TfO** and I_2 at 80 °C under a molecular oxygen atmosphere, and the desired thioether **7a** was obtained in 85% yield (Table 3). A series of thiols and pyrazoles were tested under these conditions, and the corresponding sulfenylated pyrazoles(**7b**-**7g**) were obtained in 81-88% yields, while the combination of the relatively electron-rich thiol with the relatively electron-deficient pyrazoles, which would decelerate the nucleophilic attack of pyrazole onto R-SI intermediate, required 5 d to yield the products (**7d** and **7e**) in 82% yields. In contrast to the result of the flavin-catalyzed system, the sulfenylated product **7b** was not obtained in the absence of **4·TfO**. To extend the scope of the sulfenylation system, electron-rich benzenes such as 1,3,5-trimethoxybenzene (**8a**) and 4-(methylthio)aniline (**8b**), which are expected to be nucleophilic towards R-SI, were also evaluated under the developed conditions. As a result, the sulfenylation was successfully performed, thus gave the corresponding sulfenylated products (**9a** and **9b**) in good yields (Scheme S1, Supporting Information). These results demonstrate the facile applicability of the developed flavin-iodine catalytic system for the development of metal-free O_2-driven reactions.

Table 3. Aerobic sulfenylation of pyrazoles[a]



[a]Conditions: **6** (1.0 M), **2** (1.1 M), **4•TfO** (10 mol%), I_2 (10 mol%), and CH_3CN under O_2 (1 atm) at 80 °C. [b]Without **4•TfO**.

The first aerobic oxidative sulfenylation of pyrazolones and pyrazoles with thiols mediated by the flavin-iodine dual catalytic system has been developed. The combination of biomimetic flavin with iodine enabled the catalytic sulfenylation to be driven by molecular oxygen, which is recognized as the ideal oxidant. Further, the molecular oxygen present in the air is sufficient to catalyze the reaction. Overall, the present method provides a green synthetic route with good economic advantages to access diverse sulfur-containing pyrazole derivatives, which are promising candidates for medicinal and agrochemical applications. Extension of this methodology to diverse C-S bond formations, and related C-N and C-C bond formations is currently under investigation.

Experimental Section

General Information. The NMR spectra were measured using JEOL JNM-L400 and JNM ECX-500 spectrometers (JEOL, Akishima, Japan) operating at 400 and 500 MHz, respectively, for ^{1}H and 100 and 126 MHz, respectively, for ^{13}C using tetramethylsilane (TMS) or a solvent residual peak as the internal standard. The electrospray ionization mass (ESI-MS) spectra were recorded using a Bruker microTOFII-SHIY3 mass spectrometer (Bruker, Billerica, MA). All starting materials were purchased from Aldrich (Milwaukee, WI), FUJIFILM Wako Pure Chemical Industries (Osaka, Japan), Nacalai tesque (Kyoto, Japan), HYDRUS CHEMICAL INC. (Tokyo, Japan), and Tokyo Kasei (TCI, Tokyo, Japan) and were used as received. 5-Ethyl-1,3,7,8-tetramethylalloxazinium triflate (**4·TfO**) was synthesized according to the previously reported methods.[17]

Typical Procedure for Catalytic Sulfenylation of Pyrazolones. A mixture of **1a** (174 mg, 1.0 mmol), **2a** (137 mg, 1.1 mmol), I_2 (12.7 mg, 0.050 mmol), **4·TfO** (13.5 mg, 0.030 mmol), and CH_3CN (1.0 mL) was stirred at 25 °C for 12 h under air (1 atm). Evaporation of the solvent and purification of the residue by column chromatography (SiO_2, chloroform/methanol = 100/0 to 99/1, v/v) afforded **3a** (272 mg, 92%) as a white solid. The results for the sulfenylation of pyrazolones are summarized in Table 2.

*Spectroscopic data of 3-methyl-1-phenyl-4-(p-tolylthio)-1H-pyrazol-5-ol (**3a**).*[18] ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C, δ): 12.12 (br s, 1H), 7.75 (d, J = 7.8 Hz, 2H), 7.47 (t, J = 7.9 Hz, 2H), 7.27 (t, J = 7.4 Hz, 1H), 7.09 (d, J = 8.1 Hz, 2H), 7.00 (d, J = 8.1 Hz, 2H), 2.23 (s, 3H), 2.13 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6, 25 °C, δ): 155.5, 151.8, 138.3, 134.8, 134.3, 129.7, 128.9, 125.7, 125.3, 120.8, 87.3, 20.4, 12.3.

*Spectroscopic data of 3-methyl-1-phenyl-4-(phenylthio)-1H-pyrazol-5-ol (**3b**).*[18] Column chromatography (SiO_2, chloroform/methanol = 100/0 to 99/1, v/v) afforded the desired product (159 mg, 94%) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C, δ): 12.18 (br s, 1H), 7.76 (d, J = 7.8 Hz, 2H), 7.48 (t, J = 7.9 Hz, 2H), 7.28 (t, J = 7.6 Hz, 3H), 7.15–7.03 (m, 3H), 2.14 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6, 25 °C, δ): 155.6, 152.0, 138.4, 138.1, 129.1, 129.0, 125.8, 124.94, 124.89, 120.8, 86.9, 12.3.

*Spectroscopic data of 4-(4-chlorophenylthio)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**3c**).*[19] Column chromatography (SiO_2, chloroform/methanol = 100/0 to 99/1, v/v) afforded the desired product (176 mg, 93%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C, δ): 12.27 (br s, 1H), 7.75 (d, J = 7.7 Hz, 2H), 7.47 (t, J = 7.9 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 7.28 (t, J = 7.4 Hz, 1H), 7.09 (d, J = 8.5 Hz, 2H), 2.13 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6, 25 °C, δ): 155.9, 151.8, 138.1, 137.6, 129.5, 129.0, 126.6, 125.8, 120.8, 86.5, 12.3.

*Spectroscopic data of 3-methyl-4-(4-nitrophenylthio)-1-phenyl-1H-pyrazol-5-ol (**3d**).* Column chromatography (SiO_2, chloroform/methanol = 100/0 to 9/1, v/v) afforded the desired product (190 mg, 97%) as a yellow solid. Mp: 215.1-216.3 °C. IR (KBr, cm^{-1}): 1620, 1504, 1399, 1340, 1089. ^1H NMR (500 MHz, DMSO-d_6, 25 °C, δ): 8.13 (d, J = 9.0 Hz, 2H), 7.76 (d, J = 7.7 Hz, 2H), 7.49 (t, J = 7.9 Hz, 2H), 7.34−7.25 (m, 3H), 2.14 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6, 25 °C, δ): 156.9, 151.9, 148.9, 144.7, 138.0, 129.0, 126.0, 124.9, 124.2, 120.9, 85.2, 12.2. HRMS (ESI+) (m/z): ($M + Na^+$) calculated for $C_{16}H_{13}N_3O_3SNa$, 350.0570; found, 350.0565.

*Spectroscopic data of 4-(3,5-dichlorophenylthio)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**3e**).*[20] Column chromatography (SiO_2, hexane/ethyl acetate = 2/1, v/v) afforded the desired product (178 mg, 85%) as a white solid. ^1H NMR (500 MHz, DMSO-d_6, 25 °C, δ): 7.76 (d, J = 7.6 Hz, 2H), 7.47 (t, J = 8.0 Hz, 2H), 7.33−7.25 (m, 2H), 7.07 (d, J = 1.7 Hz, 2H), 2.15 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6, 25 °C, δ): 157.1, 151.9, 143.5, 137.9, 134.7, 129.0, 125.9, 124.6, 122.9, 120.9, 85.8, 12.2.

*Spectroscopic data of 4-(2-aminophenylthio)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**3f**).*[21] Column chromatography (SiO_2, chloroform/methanol = 100/0 to 99/1, v/v) afforded the desired product (158 mg, 89%) as a pale yellow solid. ^1H NMR (500 MHz, DMSO-d_6, 25 °C, δ): 7.70 (d, J = 7.7 Hz, 2H), 7.46 (t, J = 7.8 Hz, 2H), 7.25 (t, J = 7.4 Hz, 1H), 7.15 (d, J = 5.4 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 6.68 (d, J = 7.8 Hz, 1H), 6.50 (t, J = 7.2 Hz, 1H), 2.20 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-*d6*, 25 °C, δ): 159.3, 152.1, 147.8, 137.6, 132.3, 129.0, 128.4, 125.5, 120.2, 118.6, 116.7, 114.9, 92.5, 12.1.

*Spectroscopic data of 3-methyl-4-((1-methyl-1H-tetrazol-5-yl)thio)-1-phenyl-1H-pyrazol-5-ol (**3g**).*[18] Column chromatography (SiO_2, chloroform/methanol = 99/1 to 9/1, v/v) afforded the desired product (170 mg, 98%) as a pale yellow solid. ^1H NMR (500 MHz, DMSO-d_6, 25 °C, δ): 12.48 (br s, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.48 (t, J = 7.9 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 4.05 (s, 3H), 2.24 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6, 25 °C, δ): 156.8, 153.7, 152.0, 137.7, 129.0, 126.0, 120.8, 83.1, 33.9, 12.3.

*Spectroscopic data of 4-(benzylthio)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**3h**).*[18] Column chromatography (SiO_2, chloroform/methanol = 100/0 to 99/1, v/v) afforded the desired product (126 mg, 71%) as a pale yellow solid. ^1H NMR (500 MHz, DMSO-d_6, 25 °C, δ): 11.73 (br s, 1H), 7.70 (d, J = 7.8 Hz, 2H), 7.45 (t, J = 7.9 Hz, 2H), 7.29–7.19 (m, 4H), 7.15 (d, J = 6.7 Hz, 2H), 3.75 (s, 2H), 1.74 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6, 25 °C, δ): 155.0, 152.0, 138.5, 138.1, 129.0, 128.9, 128.1, 126.7, 125.4, 120.6, 89.4, 11.8.

*Spectroscopic data of 3-methyl-1-p-tolyl-4-(p-tolylthio)-1H-pyrazol-5-ol (**3j**).*[19] Column chromatography (SiO_2, chloroform/methanol = 100/0 to 99/1, v/v) afforded the desired product (169 mg, 91%) as a pale yellow solid. ^1H NMR (500 MHz, DMSO-d_6, 25 °C, δ): 12.01 (br s, 1H), 7.62 (d, J = 8.4

Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.1 Hz, 2H), 6.99 (d, J = 8.0 Hz, 2H), 2.32 (s, 3H), 2.23 (s, 3H), 2.11 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6, 25 °C, δ): 154.9, 151.2, 136.0, 135.0, 134.8, 134.3, 129.6, 129.3, 125.3, 120.9, 86.7, 20.5, 20.4, 12.3.

*Spectroscopic data of 1-(4-chlorophenyl)-3-methyl-4-(p-tolylthio)-1H-pyrazol-5-ol (**3k**).*[19] Column chromatography (SiO_2, chloroform/methanol = 100/0 to 99/1, v/v) afforded the desired product (186 mg, 94%) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C, δ): 12.35 (br s, 1H), 7.79 (d, J = 8.9 Hz, 2H), 7.52 (d, J = 8.9 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 8.1 Hz, 2H), 2.22 (s, 3H), 2.11 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6, 25 °C, δ): 156.4, 152.3, 137.1, 134.6, 134.4, 129.7, 128.9, 128.3, 125.3, 122.0, 87.9, 20.4, 12.3.

*Spectroscopic data of 1,3-dimethyl-4-((1-methyl-1H-tetrazol-5-yl)thio)-1H-pyrazol-5-ol (**3l**).* Column chromatography (SiO_2, chloroform/methanol = 100/0 to 10/1, v/v) afforded the desired product (122 mg, 90%) as a white solid. Mp: 185.6-186.5 ˚C. IR (KBr, cm^{-1}): 3448, 1559, 1057. ^{1}H NMR (500 MHz, DMSO-d_6, 25 ˚C): δ 3.99 (s, 3H), 3.45 (s, 3H), 2.09 (s, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6, 25 °C): δ 155.6, 154.0, 149.4, 80.0, 33.8, 33.0, 12.1. HRMS (ESI+) (m/z): (M + Na^+) calculated for $C_7H_{10}N_6SONa$, 249.0529; found, 249.0527.

*Spectroscopic data of 4-((4-bromophenyl)thio)-1,3-dimethyl-1H-pyrazol-5-ol (**3m**).*[20] Column chromatography (SiO_2, chloroform/methanol = 100/0 to 9/1, v/v) afforded the desired product (159 mg, 89%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C, δ): 11.51 (br s, 1H), 7.43 (d, J = 8.5 Hz, 2H), 6.93 (d, J = 8.5 Hz, 2H), 3.49 (s, 3H), 1.98 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6, 25 °C, δ): 155.0, 149.3, 138.9, 131.7, 126.6, 117.4, 83.4, 33.3, 12.1. HRMS (ESI+) (m/z): (M + Na^+) calculated for $C_{11}H_{11}BrN_2OSNa$, 320.9668; found, 320.9668.

*Spectroscopic data of 3-tert-butyl-1-phenyl-4-(p-tolylthio)-1H-pyrazol-5-ol (**3n**).*[19] Column chromatography (SiO_2, chloroform/methanol = 100/0 to 99/1, v/v) afforded the desired product (200 mg, 98%) as a beige solid. ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C, δ): 11.91 (br s, 1H), 7.78 (d, J = 7.7 Hz, 2H), 7.47 (t, J = 7.9 Hz, 2H), 7.28 (t, J = 7.4 Hz, 1H), 7.08 (d, J = 8.1 Hz, 2H), 6.95 (d, J = 8.1 Hz, 2H), 2.22 (s, 3H), 1.30 (s, 9H). $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6, 25 °C, δ): 160.6, 156.6, 138.6, 135.6, 133.8, 129.5, 128.9, 125.8, 124.6, 121.2, 84.4, 33.6, 28.9, 20.4.

Typical Procedure for Catalytic Sulfenylation of Pyrazoles. A mixture of 1,3,5-trimethylpyrazole (**6b**, 110 mg, 1.0 mmol), **2a** (137 mg, 1.1 mmol), I_2 (25.4 mg, 0.10 mmol), **4·TfO** (44.9 mg, 0.10 mmol), and CH_3CN (1.0 mL) was stirred at 80 °C for 12 h under an O_2 atmosphere (1 atm). Evaporation of the solvent and purification of the residue by column chromatography (SiO_2, hexane/chloroform = 1/10, v/v)

afforded **7b** (201 mg, 87%) as a yellow oil. The results for the sulfenylation of pyrazoles are summarized in Table 3.

*Spectroscopic data of 1,3,5-trimethyl-4-(phenylthio)-1H-pyrazole (**7a**).*[22] Column chromatography (SiO_2, hexane/ethyl acetate = 2/1, v/v) afforded the desired product (112 mg, 85%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, δ): 7.19 (t, *J* = 7.7 Hz, 2H), 7.06 (t, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 7.4 Hz, 2H), 3.80 (s, 3H), 2.25 (s, 3H), 2.20 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, 25 °C, δ): 151.9, 144.0, 138.9, 128.9, 125.3, 124.8, 103.8, 36.8, 12.0, 10.2.

Spectroscopic data of 1,3,5-trimethyl-4-(*p*-tolylthio)-1H-pyrazole (**7b**). Column chromatography (SiO_2, hexane/chloroform = 1/10, v/v) afforded the desired product (201 mg, 87%) as a yellow oil. IR (neat, cm^{-1}): 2922, 1492, 1384, 1084, 805. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, δ): 7.00 (d, *J* = 8.1 Hz, 2H), 6.89 (d, *J* = 8.2 Hz, 2H), 3.78 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H), 2.20 (s, 3H).^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, 25 °C, δ): 151.7, 143.8, 135.2, 134.6, 129.6, 125.6, 104.2, 36.7, 20.9, 12.0, 10.1. HRMS (ESI+) (m/z): ($M + H^+$) calculated for $C_{13}H_{17}N_2S$, 233.1107; found, 233.1111.

Spectroscopic data of 4-(4-chlorophenylthio)-1,3,5-trimethyl-1H-pyrazole (**7c**). Column chromatography (SiO_2, hexane/ethyl acetate = 2/1, v/v) afforded the desired product (134 mg, 88%) as a yellow oil. IR (neat, cm^{-1}): 2925, 1474, 1090, 1010, 815. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, δ): 7.12 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 3.76 (s, 3H), 2.21 (s, 3H), 2.16 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, 25 °C, δ): 151.6, 143.8, 137.5, 130.5, 128.9, 126.4, 103.3, 36.7, 11.9, 10.0. HRMS (ESI+) (m/z): ($M + H^+$) calculated for $C_{12}H_{14}ClN_2S$, 253.0561; found, 253.0566.

*Spectroscopic data of 3,5-dimethyl-1-phenyl-4-(p-tolylthio)-1H-pyrazole (**7d**).*[23] Column chromatography (SiO_2, chloroform/methanol = 100/0 to 99/1, v/v) afforded the desired product (145 mg, 82%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, δ): 7.52-7.45 (m, 4H), 7.42-7.36 (m, 1H), 7.06 (d, *J* = 8.2 Hz, 2H), 7.00 (d, *J* = 8.2 Hz, 2H), 2.36 (s, 3H), 2.32 (s, 3H), 2.30 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, 25 °C, δ): 153.2, 144.0, 139.8, 134.8, 134.7, 129.7, 129.2, 127.8, 125.8, 124.7, 106.8, 20.9, 12.1, 11.6.

*Spectroscopic data of 3,5-dimethyl-4-(p-tolylthio)-1H-pyrazole (**7e**).*[23] Column chromatography (SiO_2, chloroform/methanol = 95/5, v/v) afforded the desired product (107 mg, 82%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, δ): 10.55 (br s, 1H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 2H), 2.33 (s, 6H), 2.29 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, 25 °C, δ): 148.8, 135.0, 134.7, 129.7, 125.7, 104.4, 20.9, 11.2.

*Spectroscopic data of 3,5-dimethyl-4-((1-methyl-1H-tetrazol-5-yl)thio)-1-phenyl-1H-pyrazole (**7f**).* Column chromatography (SiO_2, hexane/ethyl acetate = 2/1, v/v) afforded the desired product (150 mg,

88%) as a yellow oil. IR (neat, cm^{-1}): 2927, 1597, 1505, 1388, 1022. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, δ): 7.47-7.39 (m, 4H), 7.36 (tt, J = 1.7, 7.0 Hz, 1H), 4.00 (s, 3H), 2.37 (s, 3H), 2.31 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$, 25 °C, δ): 153.5, 152.4, 144.8, 139.4, 129.2, 128.2, 124.9, 99.8, 33.8, 12.2, 11.7. HRMS (ESI+) (m/z): ($M + H^+$) calculated for $C_{13}H_{15}N_6S$, 287.1073; found, 287.1074.

*Spectroscopic data of 4-(1-methyl-tetrazol-5-ylthio)-3,5-dimethyl-1H-pyrazole (**7g**).*[24] Column chromatography (SiO_2, hexane/ethyl acetate = 1/5, v/v) afforded the desired product (102 mg, 81%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, δ): 4.01 (s, 3H), 2.25 (s, 6H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$, 25 °C, δ): 154.6, 148.9, 96.7, 33.8, 11.2.

Typical Procedure for Catalytic Sulfenylation of Electron-Rich Benzenes. A mixture of **8a** (202 mg, 1.2 mmol), **2a** (74.9 mg, 0.60 mmol), I_2 (15.2 mg, 0.060 mmol), **4·TfO** (13.4 mg, 0.030 mmol), and pyridine (0.60 mL) was stirred at 100 °C for 24 h under an O_2 atmosphere (1 atm). Evaporation of the solvent and purification of the residue by column chromatography (SiO_2, hexane/ethyl acetate = 8/1 to 4/1, v/v) afforded *p*-tolyl(2,4,6-trimethoxyphenyl)sulfane (**9a**, 160 mg, 91%) as a white solid. The results for the sulfenylation of benzenes are summarized in Scheme S1.

*Spectroscopic data of p-tolyl(2,4,6-trimethoxyphenyl)sulfane (**9a**).*[25] ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, *δ*): 7.00–6.92 (m, 4H), 6.21 (s, 2H), 3.86 (s, 3H), 3.80 (s, 6H), 2.25 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$, 25 °C, *δ*): 162.9, 162.6, 135.2, 134.2, 129.4, 126.1, 99.5, 91.3, 56.4, 55.5, 21.0.

*Spectroscopic data of 4-(methylthio)-2-(p-tolylthio)aniline (**9b**).*[25] Column chromatography (SiO_2, hexane/ethyl acetate = 8/1 to 4/1, v/v) afforded the desired product (135 mg, 86%) as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, *δ*): 7.48 (d, J = 2.3 Hz, 1H), 7.24 (dd, J = 2.3, 8.4 Hz, 1H), 7.09–7.03 (m, 4H), 6.72 (d, J = 8.3 Hz, 1H), 4.27 (s, 2H), 2.43 (s, 3H), 2.30 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$, 25 °C, *δ*): 147.1, 137.7, 135.8, 132.5, 129.9, 127.3, 126.0, 116.3, 116.0, 21.0, 18.7.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Results of Catalytic Sulfenylation and NMR spectra of products (PDF)

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REFERENCES

(1) For the recent reviews, see: (a) Yoshida, H.; Yanai, H.; Namiki, Y.; Fukatsu-Sasaki, K.; Furutani, N.; Tada, N. Neuroprotective Effects Of Edaravone: A Novel Free Radical Scavenger in Cerebrovascular Injury. *Cns Drug Rev*. **2006**, *12*, 9-20. (b) Bekhit, A. A.; Hymete, A.; Bekhit, A. E.-D. A.; Damtew, A.; Aboul-Enein, H. Y. Pyrazoles as Promising Scaffold for the Synthesis of Anti-Inflammatory and/or Antimicrobial Agent: A Review. *Mini-Rev. Med. Chem*. **2010**, *10*, 1014-1033. (c) Kucukguzel, S. G.; Senkardes, S. Recent Advances in Bioactive Pyrazoles. *Eur. J. Med. Chem*. **2015**, *97*, 786-815. (d) Khan, M. F.; Alam, M. M.; Verma, G.; Akhtar, W.; Akhter, M.; Shaquiquzzaman, M. The Therapeutic Voyage of Pyrazole and Its Analogs: A Review. *Eur. J. Med. Chem*. **2016**, *120*, 170-201. (e) Ansari, A.; Ali, A.; Asif, M.; Shamsuzzaman, Review: Biologically Active Pyrazole Derivatives. *New J. Chem*. **2017**, *41*, 16-41. (f) Xu, Z.; Gao, C.; Ren, Q. C.; Song, X. F.; Feng, L. S.; Lv, Z. S. Recent Advances of Pyrazole-Containing Derivatives as Anti-Tubercular Agents. *Eur. J. Med. Chem*. **2017**, *139*, 429-440. (g) Faria, J. V.; Vegi, P. F.; Miguita, A. G. C.; dos Santos, M. S.; Boechat, N.; Bernardino, A. M. R. Recently Reported Biological Activities of Pyrazole Compounds. *Bioorg. Med. Chem*. **2017**, *25*, 5891-5903.

(2) Sun, H.-Y.; Ji, F.-Q. A Molecular Dynamics Investigation on the Crizotinib Resistance Mechanism of C1156Y Mutation in ALK. *Biochem. Biophys. Res. Commun.* **2012**, *423*, 319-324.

(3) Terrett, N. K.; Bell, A. S.; Brown, D.; Ellis, P. Sildenafil (VIAGRATM), A Potent and Selective Inhibitor of Type 5 Cgmp Phosphodiesterase With Utility for the Treatment of Male Erectile Dysfunction. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1819-1824.

(4) Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. Synthesis and Biological Evaluation of the 1,5-Diarylpyrazole Class of Cyclooxygenase-2 Inhibitors: Identification of 4- 5-(4-Methylphenyl)-3-(Trifluoromethyl)-1h-Pyrazol-1-Yl Benzenesulfona Mide (Sc-58635, Celecoxib). *J. Med. Chem.* **1997**, *40*, 1347-1365.

(5) Cravedi, J. P.; Delous, G.; Zalko, D.; Viguié, C.; Debrauwer, L. Disposition of Fipronil in Rats. *Chemosphere* **2013**, *93*, 2276-2283.

(6) For the recent examples, see: (a) Li, D. Y.; Mao, X. F.; Chen, H. J.; Chen, G. R.; Liu, P. N. Rhodium-Catalyzed Addition Cyclization of Hydrazines with Alkynes: Pyrazole Synthesis via Unexpected C-N Bond Cleavage. *Org. Lett.* **2014**, *16*, 3476-3479. (b) Li, H.; Liu, C. J.; Zhang, Y. H.; Sun, Y. D.; Wang, B.; Liu, W. B. Green Method for the Synthesis of Chromeno 2,3-c pyrazol-4(1H)-ones through Ionic Liquid Promoted Directed Annulation of 5-(Aryloxy)-1H-pyrazole-4-carbaldehydes in Aqueous Media. *Org. Lett.* **2015**, *17*, 932-935. (c) Fuse, S.; Morita, T.; Johmoto, K.; Uekusa, H.; Tanaka, H. Directing/Protecting-Group-Free Synthesis of Tetraaryl-Substituted Pyrazoles through Four Direct Arylations on an Unsubstituted Pyrazole Scaffold. *Chem.-Eur. J.* **2015**, *21*, 14370-14375. (d) Yuan, B. X.; Zhang, F. M.; Li, Z. M.; Yang, S. H.; Yan, R. L. $AgNO_2$ as the NO Source for the Synthesis of Substituted Pyrazole N-Oxides from N-Propargylamines. *Org. Lett.* **2016**, *18*, 5928-5931. (e) Cheng, J.; Li, W. P.; Duan, Y. Q.; Cheng, Y. X.; Yu, S. Y.; Zhu, C. J. Relay Visible-Light Photoredox Catalysis: Synthesis of Pyrazole Derivatives via Formal 4+1 Annulation and Aromatization. *Org. Lett.* **2017**, *19*, 214-217. (f) Fricero, P.; Bialy, L.; Brown, A. W.; Czechtizky, W.; Mendez, M.; Harrity, J. P. A. Synthesis

and Modular Reactivity of Pyrazole 5-Trifluoroborates: Intermediates for the Preparation of Fully Functionalized Pyrazoles. *J. Org. Chem.* **2017**, *82*, 1688-1696. (g) Das, P.; Gondo, S.; Tokunaga, E.; Sumii, Y.; Shibata, N. Anionic Triflyldiazomethane: Generation and Its Application for Synthesis of Pyrazole-3-triflones via 3+2 Cycloaddition Reaction. *Org. Lett.*, **2018**, *20*, 558-561. (h) You, G. R.; Wang, K.; Wang, X. D.; Wang, G. D.; Sun, J.; Duan, G. Y.; Xia, C. C. Visible-Light-Mediated Nickel(II)-Catalyzed C-N Cross-Coupling in Water: Green and Regioselective Access for the Synthesis of Pyrazole-Containing Compounds. *Org. Lett.* **2018**, *20*, 4005-4009. (i) Wang, H. Y.; Guo, C. Enantioselective gamma-Addition of Pyrazole and Imidazole Heterocycles to Allenoates Catalyzed by Chiral Phosphine. *Angew. Chem., Int. Ed.*, **2019**, *58*, 2854-2858 and references there in.

(7) For the recent reviews, see: (a) Kumar, V.; Kaur, K.; Gupta, G. K.; Sharma, A. K. Pyrazole Containing Natural Products: Synthetic Preview and Biological Significance. *Eur. J. Med. Chem.* **2013**, *69*, 735-753. (b) Karrouchi, K.; Radi, S.; Ramli, Y.; Taoufik, J.; Mabkhot, Y. N.; Al-aizari, F. A.; Ansar, M. Synthesis and Pharmacological Activities of Pyrazole Derivatives: A Review. *Molecules* **2018**, *23*, 134.

(8) For the reviews, see: (a) Kondo, T.; Mitsudo, T. Metal-Catalyzed Carbon-Sulfur Bond Formation. *Chem. Rev.*, **2000**, *100*, 3205-3220. (b) Beletskaya, I. P.; Ananikov, V. P. Transition-Metal-Catalyzed C-S, C-Se, and C-Te Bond Formation via Cross-Coupling and Atom-Economic Addition Reactions. *Chem. Rev.* **2011**, *111*, 1596-1636. (c) Lee, C.-F.; Liu, Y.-C.; Badsara, S. S. Transition-Metal-Catalyzed C-S Bond Coupling Reaction. *Chem.-Asian J.* **2014**, *9*, 706-722. (d) Shen, C.; Zhang, P. F.; Sun, Q.; Bai, S. Q.; Hor, T. S. A.; Liu, X. G. Recent Advances In C-S Bond Formation Via C-H Bond Functionalization And Decarboxylation. *Chem. Soc. Rev.* **2015**, *44*, 291-314. (e) Dong, D. Q.; Hao, S. H.; Yang, D. S.; Li, L. X.; Wang, Z. L. Sulfenylation of C-H Bonds for C-S Bond Formation under Metal-Free Conditions. *Eur. J. Org. Chem.* **2017**, 6576-6592. (f) Zhu, J.; Yang, W. C.; Wang, X. D.; Wu, L. Photoredox Catalysis in C-S Bond Construction: Recent Progress in Photo-Catalyzed Formation of Sulfones and Sulfoxides. *Adv. Synth. Catal.* **2018**, *360*, 386-400.

(9) (a) Kawakubo, K.; Shindo, M.; Konotsune, T. Mechanism of Chlorosis Caused by 1,3-Dimethyl-4-(2,4-Dichlorobenzoyl)-5-Hydroxypyrazole, A Herbicidal Compound. *Plant Physiol*. **1979**, *64*, 774-779. (b) Watanabe, K.; Morinaka, Y.; Iseki, K.; Watanabe, T.; Yuki, S.; Nishi, H. Structure-Activity Relationship of 3-Methyl-1-Phenyl-2-Pyrazolin-5-One (Edaravone). *Redox Rep*. **2003**, *8*, 151-155. (c) Haydar, S. N.; Yun, H.; Andrae, P. M.; Mattes, J.; Zhang, J.; Kramer, A.; Smith, D. L.; Huselton, C.; Graf, R.; Aschmies, S.; Schechter, L. E.; Comery, T. A.; Robichaud, A. J. 5-Cyclic Amine-3-arylsulfonylindazoles as Novel 5-HT6 Receptor Antagonists. *J. Med. Chem*. **2010**, *53*, 2521-2527. (d) Abdel-Aziz, H. A.; Al-Rashood, K. A.; ElTahir, K. E. H.; Suddek, G. M. Synthesis of N-Benzenesulfonamide-1H-Pyrazoles Bearing Arylsulfonyl Moiety: Novel Celecoxib Analogs as Potent Anti-Inflammatory Agents. *Eur. J. Med. Chem*. **2014**, *80*, 416-422. (e) Wang, B.-L.; Li, Q.-N.; Zhan, Y.-Z.; Xiong, L.-X.; Yu, S.-J.; Li, Z.-M. The Synthesis and Biological Activities of 5-(4-Substituted Phenylsulfinyl/Sulfonyl)-1,3-Dimethyl-1h-Pyrazol-4-Yl -Arylmethanones. *Phosphorus Sulfur Silicon Relat. Elem*. **2014**, 189, 483-491.

(10) For the recent examples, see: (a) Bao, Y.; Yang, X.; Zhou, Q.; Yang, F. Iodine-Promoted Deoxygenative Iodization/Olefination/Sulfenylation of Ketones with Sulfonyl Hydrazides: Access to β-Iodoalkenyl Sulfides. *Org. Lett*. **2018**, *20*, 1966-1969. (b) Yang, X.; Bao, Y.; Dai, Z.; Zhou, Q.; Yang, F. Catalyst-Free Sulfenylation of Indoles with Sulfinic Esters in Ethanol. *Green Chem*. **2018**, *20*, 3727-3731. (c) Li, D. D.; Li, S. B.; Peng, C.; Lu, L. J.; Wang, S. C.; Wang, P.; Chen, Y. H.; Cong, H. J.; Lei, A. W. Electrochemical Oxidative C-H/S-H Cross-Coupling between Enamines and Thiophenols with H-2 Evolution. *Chem. Sci*. **2019**, *10*, 2791-2795. (d) Wang, X.; Yi, X.; Xu, H.; Dai, H. X. Cu-Mediated C-H Thioetherification of Arenes at Room Temperature. *Org. Lett*. **2019**, *21*, 5981-5985. (e) Kang, Y. S.; Zhang, P.; Li, M. Y.; Chen, Y. K.; Xu, H. J.; Zhao, J.; Sun, W. Y.; Yu, J. Q.; Lu, Y. Ligand-Promoted Rh-III-Catalyzed Thiolation of Benzamides with a Broad Disulfide Scope. *Angew. Chem. Int. Ed*. **2019**, *58*, 9099-9103. (f) Bogonda, G.; Patil, D. V.; Kim, H. Y.; Oh, K. Visible-Light-Promoted Thiyl Radical Generation from Sodium Sulfinates: A Radical-Radical Coupling to Thioesters. *Org. Lett*. **2019**, *21*, 3774-3779. (g) Gao, W. C.; Shang, Y. Z.; Chang, H. H.; Li, X.; Wei, W. L.; Yu, X. Z.; Zhou, R. N-Alkynylthio

Phthalimide: A Shelf-Stable Alkynylthio Transfer Reagent for the Synthesis of Alkynyl Thioethers. *Org. Lett.* **2019**, *21*, 6021-6024.

(11) (a) Purohit, V. B.; Karad, S. C.; Patel K. H.; Raval, D. K. Palladium N-Heterocyclic Carbene Catalyzed Regioselective Thiolation of 1-Aryl-3-Methyl-1H-Pyrazol-5(4H)-Ones Using Aryl Thiols. *Tetrahedron* **2016**, *72*, 1114-1119. (b) Liu, X.; Cui, H.; Yang, D.; Dai, S.; Zhang, T.; Sun, J.; Wei, W.; Wang, H. Metal-Free Direct Construction of Sulfenylated Pyrazoles via The Naoh Promoted Sulfenylation of Pyrazolones with Aryl Thiols. *Rsc Adv.* **2016**, *6*, 51830-51833. (c) Wang, D.; Guo, S.; Zhang, R.; Lin, S.; Yan, Z. TBAI-Hbr System Mediated Generation of Various Thioethers with Benzenesulfonyl Chlorides in PEG(400). *RSC Adv.* **2016**, *6*, 54377-54381. (d) Zhao, X.; Lu, X.; Wei, A.; Jia, X.; Chen, J.; Lu, K. Potassium Iodide Promoted Thiolation of Pyrazolones and Benzofurans using Aryl Sulfonyl Chlorides as Sulfenylation Reagents. *Tetrahedron Lett.* **2016**, *57*, 5330-5333. (e) Siddaraju, Y.; Prabhu, K. R. Iodine-Catalyzed Sulfenylation of Pyrazolones Using Dimethyl Sulfoxide as An Oxidant. *Org. Biomol. Chem.* **2017**, *15*, 5191-5196. (f) Sun, P.; Yang, D.; Wei, W.; Jiang, L.; Wang, Y.; Dai, T.; Wang, H. DMSO-Promoted Regioselective Synthesis of Sulfenylated Pyrazoles via A Radical Pathway. *Org. Chem. Front.* **2017**, *4*, 1367-1371.

(12) Yang, D.; Sun, P.; Wei, W.; Meng, L.; He, L.; Fang, B.; Jiang, W.; Wang, H. Metal-Free Iodine-Catalyzed Direct Cross-Dehydrogenative Coupling (CDC) Between Pyrazoles and Thiols. *Org. Chem. Front.* **2016**, *3*, 1457-1461.

(13) (a) Hill, C. L. Homogeneous Catalysis - Controlled Green Oxidation. *Nature*, **1999**, *401*, 436-437. (b) Bäckvall, J.-E. *Modern Oxidation Methods*, Wiley-VCH, Weinheim, **2004**. (c) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. Recent Advances in Transition-Metal Catalyzed Reactions Using Molecular Oxygen as the Oxidant. *Chem. Soc. Rev.* **2012**, *41*, 3381-3430. (d) Campbell, A. N.; Stahl, S. S. Overcoming the "Oxidant Problem": Strategies to Use O_2 as the Oxidant in Organometallic C-H Oxidation Reactions Catalyzed by Pd (and Cu). *Acc. Chem. Res.*, **2012**, *45*, 851-863. (e) Bryliakov, K. P. Catalytic Asymmetric Oxygenations with the Environmentally Benign Oxidants H_2O_2 and O_2. *Chem. Rev.* **2017**, *117*, 11406-11459 (f) Tang, X. D.; Wu, W. Q.; Zeng, W.; Jiang, H. F. Copper-Catalyzed Oxidative Carbon-Carbon

and/or Carbon-Heteroatom Bond Formation with O_2 or Internal Oxidants. *Acc. Chem. Res.* **2018**, *51*, 1092-1105.

(14) (a) Ishikawa, T.; Kimura, M.; Kumoi, T.; Iida, H. Coupled Flavin-Iodine Redox Organocatalysts: Aerobic Oxidative Transformation from N-Tosylhydrazones to 1,2,3-Thiadiazoles. *ACS Catal.* **2017**, *7*, 4986-4989. (b) Ohkado, R.; Ishikawa, T.; Iida, H. Flavin–Iodine Coupled Organocatalysis for the Aerobic Oxidative Direct Sulfenylation of Indoles with Thiols under Mild Conditions. *Green Chem.* **2018**, *20*, 984-988. (c) Iida, H.; Demizu, R.; Ohkado, R. Tandem Flavin-Iodine-Catalyzed Aerobic Oxidative Sulfenylation of Imidazo 1,2-a Pyridines with Thiols. *J. Org. Chem.* **2018**, *83*, 12291-12296.

(15) For the selected examples, see: (a) Imada, Y.; Iida, H.; Ono, S.; Murahashi, S. I. Flavin Catalyzed Oxidations of Sulfides and Amines with Molecular Oxygen. *J. Am. Chem. Soc.* **2003**, *125*, 2868-2869. (b) Imada, Y.; Iida, H.; Murahashi, S.-I.; Naota, T. An Aerobic, Organocatalytic, and Chemoselective Method for Baeyer-Villiger Oxidation. *Angew. Chem., Int. Ed.*, 2005, **44**, 1704-1706. (c) Imada, Y.; Iida, H.; Naota, T. Flavin-Catalyzed Generation of Diimide: An Environmentally Friendly Method for the Aerobic Hydrogenation of Olefins. *J. Am. Chem. Soc.* **2005**, *127*, 14544-14545. (d) Chen, S.; Foss, Jr, F. W. Aerobic Organocatalytic Oxidation of Aryl Aldehydes: Flavin Catalyst Turnover by Hantzsch's Ester. *Org. Lett.* **2012**, *14*, 5150-5153. (e) Chen, S.; Hossain, M. S.; Foss, Jr, F. W. Bioinspired Oxidative Aromatizations: One-Pot Syntheses of 2-Substituted Benzothiazoles and Pyridines by Aerobic Organocatalysis. *ACS Sustain. Chem. Eng.* **2013**, *1*, 1045-1051. (f) Muhldorf, B.; Wolf, R. C-H Photooxygenation of Alkyl Benzenes Catalyzed by Riboflavin Tetraacetate and a Non-Heme Iron Catalyst. *Angew. Chem., Int. Ed.* **2016**, *55*, 427-430. (g) Hering, T.; Muhldorf, B.; Wolf, R.; König, B. Halogenase-Inspired Oxidative Chlorination Using Flavin Photocatalysis. *Angew. Chem., Int. Ed.*, **2016**, *55*, 5342-5345. (h) Zelenka, J.; Svobodova, E.; Tarabek, J.; Hoskovcova, I.; Boguschova, V.; Bailly, S.; Sikorski, M.; Roithova, J.; Cibulka, R. Combining Flavin Photocatalysis and Organocatalysis: Metal-Free Aerobic Oxidation of Unactivated Benzylic Substrates. *Org. Lett.* **2019**, *21*, 114-119.

(16) For the recent reviews of flavin catalysts, see: (a) Gelalcha, F. G. Heterocyclic Hydroperoxides in Selective Oxidations. *Chem. Rev.* **2007**, *107*, 3338-3361. (b) de Gonzalo, G.; Fraaije, M. W. Recent

Developments in Flavin-based Catalysis. *ChemCatChem* **2013**, *5*, 403-415. (c) Cibulka, R. Artificial Flavin Systems for Chemoselective and Stereoselective Oxidations. *Eur. J. Org. Chem.*, **2015**, *2015*, 915-932. (d) Iida, H.; Imada, Y.; Murahashi, S.-I. Biomimetic Flavin-Catalysed Reactions for Organic Synthesis. *Org. Biomol. Chem.* **2015**, *13*, 7599–7613. (e) König, B.; Kümmel, S.; Svobodová, E.; Cibulka, R. Flavin Photocatalysis. *Phys. Sci. Rev.* **2018**, *3*, DOI: 10.1515/psr-2017-0168.

(17) Sakai, T.; Kumoi, T.; Ishikawa, T.; Nitta, T.; Iida, H. Comparison of Riboflavin-Derived Flavinium Salts Applied to Catalytic H_2O_2 Oxidations. *Org. Biomol. Chem.* **2018**, *16*, 3999-4007.

(18) Siddaraju, Y.; Prabhu, K. R. Iodine-Catalyzed Sulfenylation of Pyrazolones Using Dimethyl Sulfoxide as An Oxidant. *Org. Biomol. Chem.* **2017**, *15*, 5191-5196.

(19) Sun, P.; Yang, D.; Wei, W.; Sun, X.; Zhang, W.; Zhang, H.; Wang, Y.; Wang, H. Metal- and Solvent-Free, Iodine-Catalyzed Cyclocondensation And C-H Bond Sulphenylation: A Facile Access to C4 Sulfenylated Pyrazoles via A Domino Multicomponent Reaction. *Tetrahedron* **2017**, *73*, 2022-2029.

(20) Zhao, X.; Zhang, L.; Li, T.; Liu, G.; Wang, H.; Lu, K. P-Toluenesulphonic Acid-Promoted, I-2-Catalysed Sulphenylation of Pyrazolones with Aryl Sulphonyl Hydrazides. *Chem. Commun.* **2014**, *50*, 13121-13123.

(21) Liu, X.; Cui, H.; Yang, D.; Dai, S.; Zhang, T.; Sun, J.; Wei, W.; Wang, H. Metal-Free Direct Construction of Sulfenylated Pyrazoles via The NaOH Promoted Sulfenylation of Pyrazolones with Aryl Thiols. *RSC Adv.* **2016**, *6*, 51830-51833.

(22) Sayah, M.; Organ, M. G. Carbon-Sulfur Bond Formation of Challenging Substrates at Low Temperature by Using Pd-PEPPSI-IPent. *Chem. Eur. J.* **2011**, *17*, 11719-11722.

(23) Yang, D.; Sun, P.; Wei, W.; Meng, L.; He, L.; Fang, B.; Jiang, W.; Wang, H. Metal-Free Iodine-Catalyzed Direct Cross-Dehydrogenative Coupling (CDC) between Pyrazoles and Thiols. *Org. Chem. Front.,* **2016**, *3*, 1457-1461.

(24) Zhan, S. Z.; Jiang, X.; Zheng, J.; Huang, X. D.; Chen, G. H.; Li, D. A Luminescent Supramolecular $Cu_2I_2(NH_3)_2$-Sandwiched Cu_3(Pyrazolate)$_3$ Adduct as A Temperature Sensor. *Dalton Trans.* **2018**, *47*, 3679-3683.

(25) Yan, K.; Yang, D.; Sun, P.; Wei, W.; Liu, Y.; Li, G.; Lu, S.; Wang, H. Direct Thiolation of Methoxybenzenes with Thiols under Metal-Free Conditions by Iodine Catalysis. *Tetrahedron* **2015**, *56*, 4792-4795.