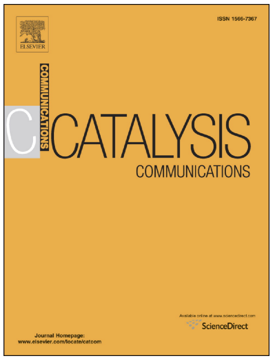

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PII: S1566-7367(18)30360-1
DOI: https://doi.org/10.1016/j.catcom.2019.01.015
Reference: CATCOM 5599

To appear in: *Catalysis Communications*

Received date: 21 August 2018
Revised date: 17 January 2019
Accepted date: 20 January 2019

Please cite this article as: X. Ge, L. Cheng, F. Sun, et al., Mechanistic and experimental study on copper-catalyzed C3-sulfenylation of indoles with sulfur powder and aryl iodides, Catalysis Communications, https://doi.org/10.1016/j.catcom.2019.01.015

Mechanistic and experimental study on copper-catalyzed C3-sulfenylation of indoles with sulfur powder and aryl iodides

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Abstract: The copper-catalyzed sulfenylation of indoles with aryl iodide and sulfur powder has been investigated both experimentally and theoretically. This protocol provides a direct and facile approach to prepare 3-sulfenylindoles with moderate to excellent yields and good functional-group tolerance. The *in-situ* IR analysis provided evidence for that NaOAc could promote the synthesis of diphenyl disulfide by the coupling of aryl iodide and sulfur powder. According to DFT calculations, the coupling pathway involving the intermediate *N*-methyl-3-iodoindole is more favored than the direct coupling by the C-H activation of indole. The *N*-methyl-3-iodoindole was identified as a crucial intermediate in the catalytic cycle.

Keywords: sulfur powder; indole; sulfenylation; copper; mechanism

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Introduction

Organosulfur compounds play important role in the production of pharmaceuticals, agrochemicals and functional materials.[1] Up till now, numerous methods for the construction of C-S bonds to prepare organosulfur compounds have been developed and continue to attract much attention.[2, 3] Classified by sulfur sources, there are two general approaches to form the C-S bonds, using organosulfur substrates and inorganic sulfur reagents, respectively. The first approach relied on organosulfur substrates is so prevalent that various organosulfur reagents, e.g. thiols[4], disulfides[5], sulfonyl hydrazides[6], and arylsulfonyl chlorides[7] have been employed; direct coupling of these reagents with organic halides can be promoted by a transition metal or metal-free catalysts. However, most organic sulfur agents suffer from repulsive odors and instability. Thus, the second approach based on “clean” inorganic sulfur reagents like metal sulfides[8, 9], $Na_2S_2O_3$[10], and sodium sulfonates[11, 12], have been exploited. Recently, as a cheap and abundant sulfur source, sulfur powder (S_8) is attracting more and more interest for its high atom economy in C-S bond formation.[13-19] In general, the substrates with easy leaving groups, such as Br, I or $B(OH)_2$, could be coupled with elemental sulfur catalyzed by transition metals. The strategy combing C-H activation and elemental sulfur is a more atom-economic method to construct a C-S bond whereby great progress has been achieved. However, the associated mechanism remains a mystery and there are only a few reports on the coupling of the activated substrates and elemental sulfur[20].

The indole scaffold is a ubiquitous structural motif that exists in bioactive natural and pharmacological compounds.[21-24] Among them, 3-thioindole exhibits a broad range of bioactivities for treating bacterial infection, cancer, and HIV.[25] However, there are rare efficient methods for the synthesis of 3-thioindole via direct C-H functionalization of indole and elemental sulfur. Li and Deng[26] found that a double C-H sulfuration by employing sulfur powder, indoles, and cyclohexanones was catalyzed by Pd to prepare the benzothieno[2,3-b]indole. Wu and Jiang[27] reported Pd-catalyzed oxidative sulfenylation of indoles and heteroarenes with aryl boronic acids and elemental sulfur. In addition, the construction of C-Se bond via direct C-H functionalization of indole and Se powder has received considerable attention and copper-catalyzed three-component reactions for arylselenation of aromatic heterocyclic using Se powder have been reported.[18, 28-31] Thus, it is always challenging and interesting to probe a green and efficient approach for constructing the 3-sulfenylindole motif. In this work, we report an eco-friendly and efficient protocol for the synthesis of copper-catalyzed 3-sulfenylindoles using iodobenzene and sulfur powder. The mechanistic aspects for the C-S bond formation via three-component reaction will be revealed upon the comparison of several conceivable pathways.

Results and Discussion

The reaction of 1-methyl-1*H*-indole (1a), iodobenzene (2a) and sulfur powder (S_8) was employed as the model reaction to optimize the reaction conditions, and the detailed results are shown in Table 1. Initially, several bases including Na_2CO_3, K_2CO_3, Et_3N, NaOAc, and KOAc were tested and NaOAc outperformed all the other bases (Table 1, entries 1-5). Moreover, the base is crucial for this reaction (Table 1, entry 6). Next, different solvents were screened and DMF was proven to be the most favorable to this C3-sulfenylation (Table 1, entries 4, 7-10). In comparison of different copper sources, *i.e.* CuI, CuBr, CuCl, $CuBr_2$, $CuCl_2$, $Cu(OTf)_2$, $CuSO_4$, $Cu(OAc)_2$ and CuOAc, $Cu(OAc)_2$ gave the best performance (Table 1, entries 4, 11-18). Without 1,10-phenanthroline or additive KI, this reaction could not occur at all. The presence of OAc was demonstrated to be crucial, while the addition of the 1,10-phenanthroline ligand, as well as the additive KI, was indispensable (Table 1, entries 20-25). Moreover, when the reaction was carried out under a nitrogen atmosphere, the yield was poor (Table 1, entry 27). Therefore, it indicates that the air is essential for this model reaction. In contrast, no significant changes were found on the final reaction yield by changing oxidizers, such as oxygen and $Na_2S_2O_8$ (Table 1, entries 28 and 29). A little of water was added into reaction system and it is not moisture sensitive (Table 1, entry 30). Thus, the optimum conditions are obtained: 1,10-phen as the ligand, KI as an additive, DMF as the solvent, under air atmosphere, the yield of 3-phenylthioindole is up to 95%. When we found this reaction protocol, the reaction of 1-methyl-1*H*-indole (1a), iodobenzene (2a) with Se powder instead was immediately attempted. To our disappointment, the reaction with Se powder failed (Table 1, entry 26).

Furthermore, an extensive study was performed to examine the applicable scope of substrates. Detailed results were summarized in Table 2. Aryl iodides with electron-donating groups like Me, Et, OMe, OEt, and OCF_3, on the para-position of benzene ring can be converted to the corresponding products in excellent yields. When aryl iodide possessed 4-Cl, 4-NO_2 or 3-NO_2 groups, the yield of desired product decreased to 74%, 55%, and 46%, respectively. Unfortunately, aryl iodide with 4-Ac failed to obtain the final product. Remarkably, the electronic properties of the substituents on the aryl iodides have a significant influence on the reaction efficiency. Moreover, the structure of product 3h was further confirmed by single-crystal X-ray diffraction. By contrast, aryl iodide with F group in the para-position was well tolerated and the desired product was obtained in 98%. And the electron-withdrawing groups, e.g. Cl, NO_2, substituted on indole resulted in excellent yield. On the other hand, indoles possessing methyl group in C2, C5, C6, and C7 position, only gave moderate yields. It may be caused by that the strong electron donor capacity of methyl group makes the density of aromatic ring electron cloud large, since it is not beneficial to the formation of iodide intermediates. Finally, the copper-catalyzed sulfenylation of different *N*-substituted indoles was studied, demonstrating the high tolerance of this reaction. *N*-substituted indoles with methyl, isopropyl, phenyl and benzyl groups can afford the corresponding products in moderate to excellent yields. Unfortunately, indole failed to obtain the targeted product. It is suspected to be caused by that the C-N coupling reaction of indole with iodobenzene is more likely to occur in this optimized condition. Moreover, when the substrates have both bromo and iodo groups, they will be incompatible with this catalytic protocol. The existing of too many byproducts in this complicated reaction lead to the difficulty for the product purification.

To reveal the mechanism of the above C3-sulfenylation, several controlled experiments have been carried out (Scheme 1). For example, without iodobenzene (**2a**) and sulfur powder (S_8), *N*-methyl-3-iodoindole was detected with 50% yield, which is due to copper-catalyzed aerobic C-H oxidation of indole under air (Scheme 1a).[11, 32] Subsequently, when iodobenzene (**2a**) reacted with sulfur powder (S_8) catalyzed by $Cu(OAc)_2$ and NaOAc, diphenyl disulfide was obtained with excellent yield (Scheme 1b). However, without NaOAc, the yield of diphenyl disulfide was only 45% (Scheme 1c). This result suggested that NaOAc played a crucial role to control the selectivity of diphenyl disulfide and phenyl sulfide, which is consistent with Chen's report[20]. Furthermore, the desired product can be obtained by copper-catalyzed Ullmann type C-S coupling reaction of *N*-methyl-3-iodoindole and diphenyl disulfide and 1,10-phen (Scheme 1d). In addition, the reaction equivalent of iodobenzene (2a) and sulfur powder (S_8) must be twice as much as that of 1-methyl-1H-indole(1a) (Table 1, entries 17, 19). It revealed that only one sulfanyl group of diphenyl disulfide participated in this reaction. Moreover, under the condition without air, the reaction resulted in poor performance (Scheme 1e), indicating that aerial oxygen served as an oxidizing agent for this reaction. The desired reaction processes were not affected when it happened in the presence of radical inhibitor TEMPO

(Scheme 1f). This result refutes the radical pathway in this reaction pathway.

Subsequently, we used *in-situ* IR to monitor the stoichiometric reaction of iodobenzene (**2a**) and sulfur powder (S_8), catalyzed by copper. Initially, sulfur powder and $Cu(OAc)_2$ were added into DMF at 110 ^oC. When adding iodobenzene into the solvent, the peak concerning Ar-I stretch vibration shifted from 731 cm^{-1} to 742 cm^{-1} [33] (Figure S1, ESI) and diminishing of the 1062 cm^{-1} peak is probably due to cleavage of the C_6H_5-I bond.[34] After that, a stoichiometric amount of NaOAc was added to the mixture. As shown in Figure 1, a new peak (1140 cm^{-1}) that belongs to phenylthiol compound[35] appeared immediately. Based on the controlled experiments as well as *in-situ* IR study, it can be concluded that the OAc group is crucial to the formation of diphenyl disulfide intermediates. Note that the route for generating **C** was proposed previously in Scheme 2a.[13, 20]

However, it remains to be uncovered whether or not the formation of *N*-methyl-3-iodoindole is dispensable. Thus, two possible mechanisms have been proposed, as shown in Scheme 2b and Scheme 2c. The reaction mechanisms were further interrogated by quantum mechanical calculations. The potential energy surfaces (PESs) and selected structural information for the two possible reaction routes are shown in Figure 2. As shown in Figure 2a, the intermediate **IM1** is formed when *N*-methyl-3-iodoindole approaches $LCu^ISC_6H_5$ (L = 1,10-Phenanthroline). Insertion of the metal center into the C-I bond via **TS1** generates **IM2**, oxidizing Cu^I to Cu^{III}. Next, upon liberating an iodide anion in the reductive elimination, the C_6H_5S group spontaneously couples with the *N*-methylindole-3-yl ligand to form an intact 3-

phenylthioindole ligand; the final product was obtained. On the other hand, the alternative direct coupling pathway (in Figure 2b), however, is not only energetically but also entropically much less favored. The transformation starts from an encounter complex **IM4**, in which the C_6H_5S, OAc and 1,10-Phenanthroline ligands are bound to the Cu^{II} center. The C3-H bond of indole is activated by transferring the hydrogen to an oxygen atom of the OAc ligand via **TS2**, generating **IM5**. Subsequently, coupling of the *N*-methylindole-3-yl and the C_6H_5S ligands achieves by surmounting **TS3** and **TS4**. While **TS2** and **TS4** possess higher barrier as compared to **TS1**, the barrier to generate *N*-methyl-3-iodoindole is comparative to **TS4** as demonstrated in our previous study.[11] In the process of direct coupling, the OAc group serves as a hydrogen acceptor. Therefore, compared with the direct coupling pathway, the coupling reaction involving intermediate *N*-methyl-3-iodoindole is more favored, which is consistent with the experimental results that *N*-methyl-3-iodoindole could be detected as an intermediate. Finally, by substituting the 1,10-Phenanthroline ligand to 2,2'-Bipyridine, we obtained almost the same PESs as the ones shown in Figure 2 (Figure S2, ESI). Thus, it is not the kinetic hindrance leading to the poor yield (in Entry 13, Table 1) but most likely due to the lower solubility of Cu^I(2,2'-Bipyridine) as compared to Cu^I(1,10-Phenanthroline).

Conclusion

In summary, we have presented a combined experimental and theoretical study on C3-sulfenylation of indoles with sulfur powder; this reaction is promoted by 1,10-phen and $Cu(OAc)_2$. The addition of KI is crucial for the formation of the key intermediate *N*-methyl-3-iodoindole, and the *in-situ* IR analysis proved that NaOAc can promote the coupling of aryl iodide and sulfur powder to form diphenyl disulfide. According to DFT calculations, the coupling pathway involving the intermediate *N*-methyl-3-iodoindole is energetically more favorable than the direct coupling route. These findings provide insight into the course of the reaction and give experimental & theoretical evidence for the existence of the key intermediate *N*-methyl-3-iodoindole.

Acknowledgements

The authors are grateful for the financial support from the Natural Science Foundation of China (21476194, 21606104) and the National Key Research and Development Program of China (2016YFB0301800).

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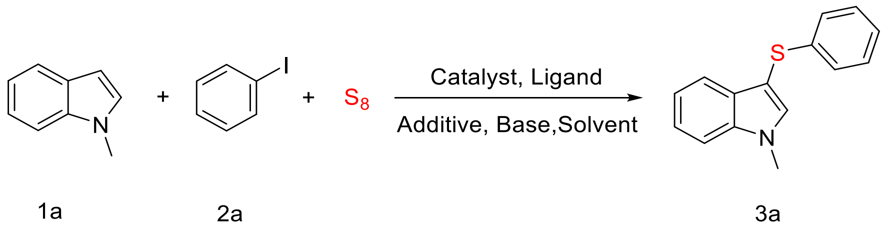
Table 1. Screening of Reaction Conditions [a]

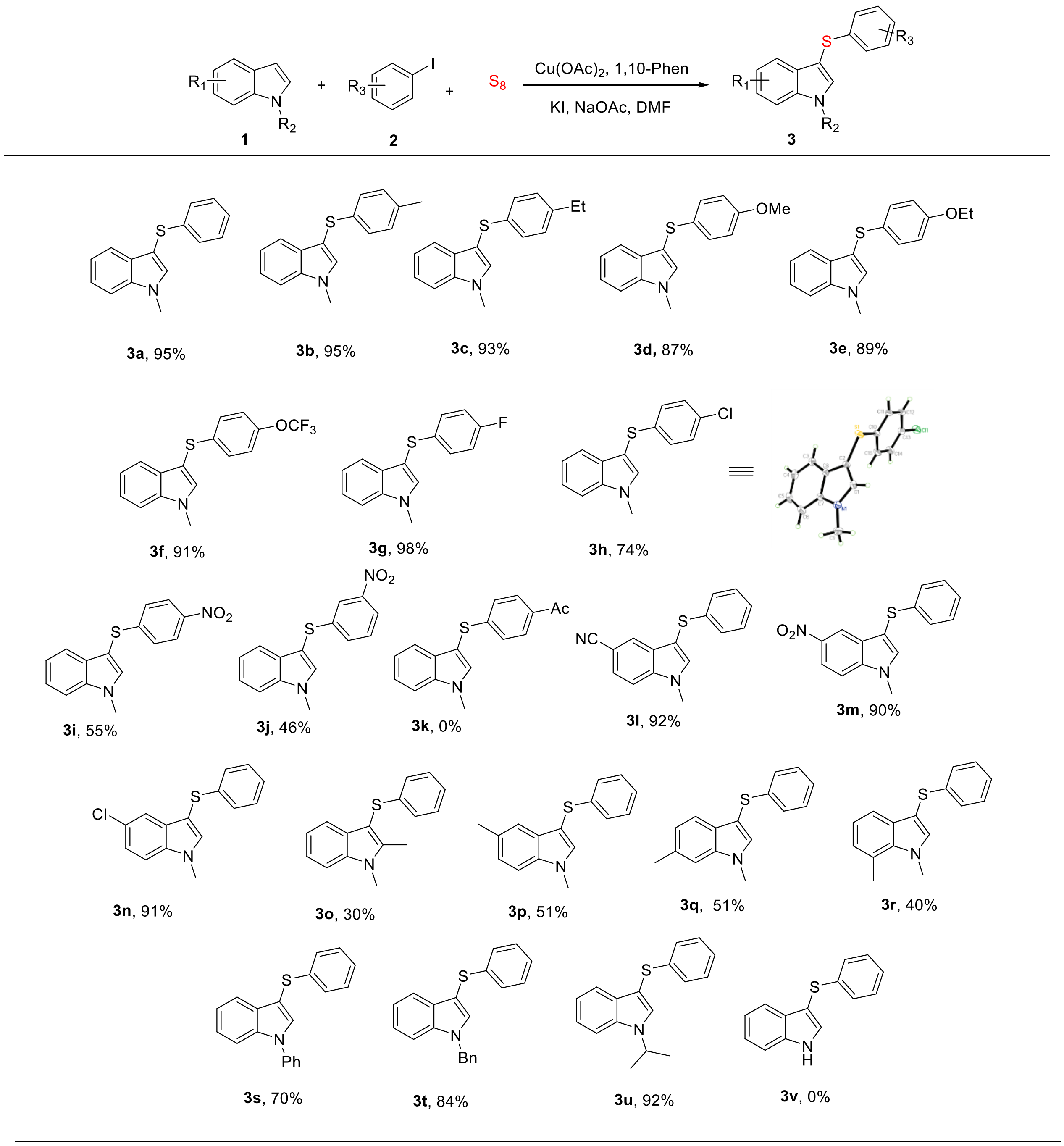


entry	catalyst	ligand	additive	base	solvent	yield [b]
1	CuI	1,10-phen	KI	Na_2CO_3	DMF	30
2	CuI	1,10-phen	KI	K_2CO_3	DMF	8
3	CuI	1,10-phen	KI	Et_3N	DMF	10
4	CuI	1,10-phen	KI	NaOAc	DMF	60
5	CuI	1,10-phen	KI	KOAc	DMF	55
6	CuI	1,10-phen	KI	-	DMF	trace
7	CuI	1,10-phen	KI	NaOAc	DMSO	42
8	CuI	1,10-phen	KI	NaOAc	1,4-dioxane	25
9	CuI	1,10-phen	KI	NaOAc	NMP	30
10	CuI	1,10-phen	KI	NaOAc	Xylene	trace
11	CuBr	1,10-phen	KI	NaOAc	DMF	48
12	CuCl	1,10-phen	KI	NaOAc	DMF	46
13	$CuBr_2$	1,10-phen	KI	NaOAc	DMF	49
14	$CuCl_2$	1,10-phen	KI	NaOAc	DMF	51
15	$Cu(OTf)_2$	1,10-phen	KI	NaOAc	DMF	46
16	$CuSO_4$	1,10-phen	KI	NaOAc	DMF	34

17	$Cu(OAc)_2$	1,10-phen	KI	NaOAc	DMF	95
18	CuOAc	1,10-phen	KI	NaOAc	DMF	91
19[c]	$Cu(OAc)_2$	1,10-phen	KI	NaOAc	DMF	41
20	$Cu(OAc)_2$	-	KI	NaOAc	DMF	trace
21	$Cu(OAc)_2$	2,2'-dipyridyl	KI	NaOAc	DMF	trace
22	$Cu(OAc)_2$	1,10-phen	-	NaOAc	DMF	trace
23	$Cu(OAc)_2$	1,10-phen	CuI	NaOAc	DMF	trace
24	$Cu(OAc)_2$	1,10-phen	NH_4I	NaOAc	DMF	trace
25	$Cu(OAc)_2$	1,10-phen	I_2	NaOAc	DMF	trace
26[d]	$Cu(OAc)_2$	1,10-phen	KI	NaOAc	DMF	-
27[e]	$Cu(OAc)_2$	1,10-phen	KI	NaOAc	DMF	5
28[f]	$Cu(OAc)_2$	1,10-phen	KI	NaOAc	DMF	94
29[g]	$Cu(OAc)_2$	1,10-phen	KI	NaOAc	DMF	95
30[h]	$Cu(OAc)_2$	1,10-phen	KI	NaOAc	DMF	95

[a] Reaction conditions: 1a (1 mmol), 2a (2 mmol), sulfur powder (2 mmol), catalyst (10 mol%), ligand (10 mol%), additive (1 mmol), base (1 mmol), solvent (5 mL), 110 °C, air, 12 h. [b] Isolated yield. [c] 2a (1 mmol) and sulfur powder (1 mmol). [d] Se powder (2 mmol) is instead of sulfur powder. [e] Under nitrogen atmosphere. [f] Under oxygen atmosphere. [g] Using $Na_2S_2O_8$ as oxidizer. [h] Adding water (0.1 ml) into the reaction.

Table 2. Scope for Three-Component Coupling Reactions



3a, 95%

3b, 95%

3c, 93%

3d, 87%

3e, 89%

3f, 91%

3g, 98%

3h, 74%

3i, 55%

3j, 46%

3k, 0%

3l, 92%

3m, 90%

3n, 91%

3o, 30%

3p, 51%

3q, 51%

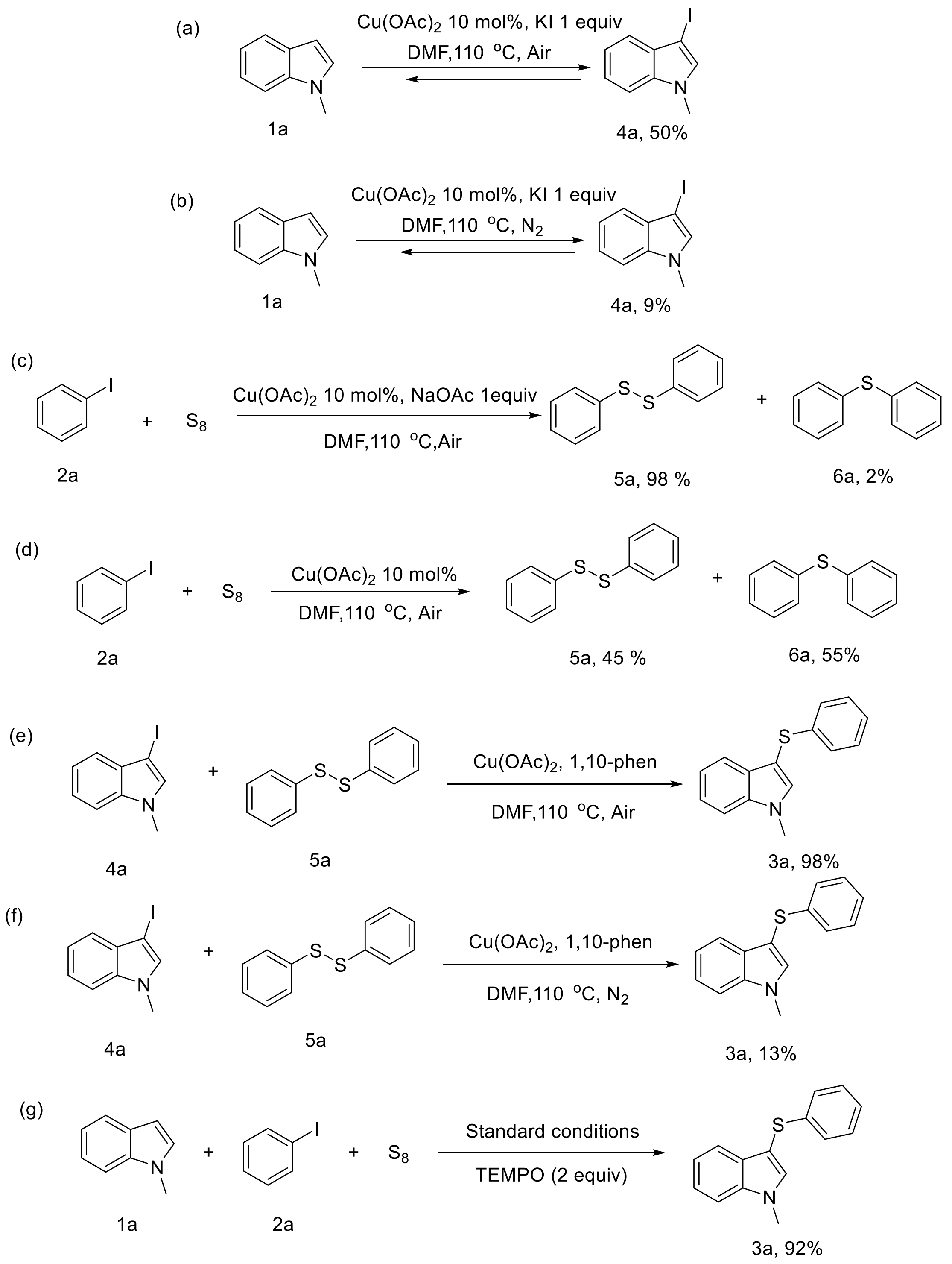
3r, 40%

3s, 70%

3t, 84%

3u, 92%

3v, 0%



Scheme 1. Control experiments

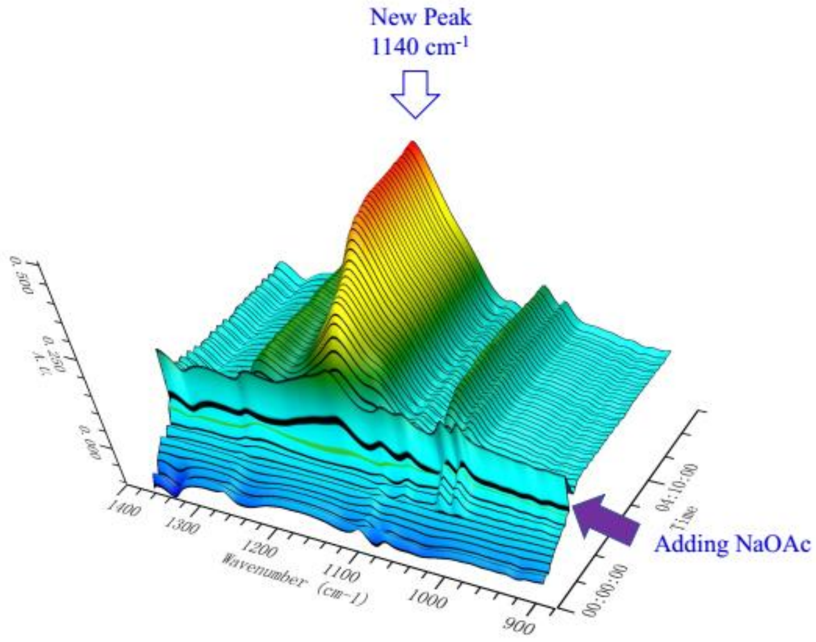
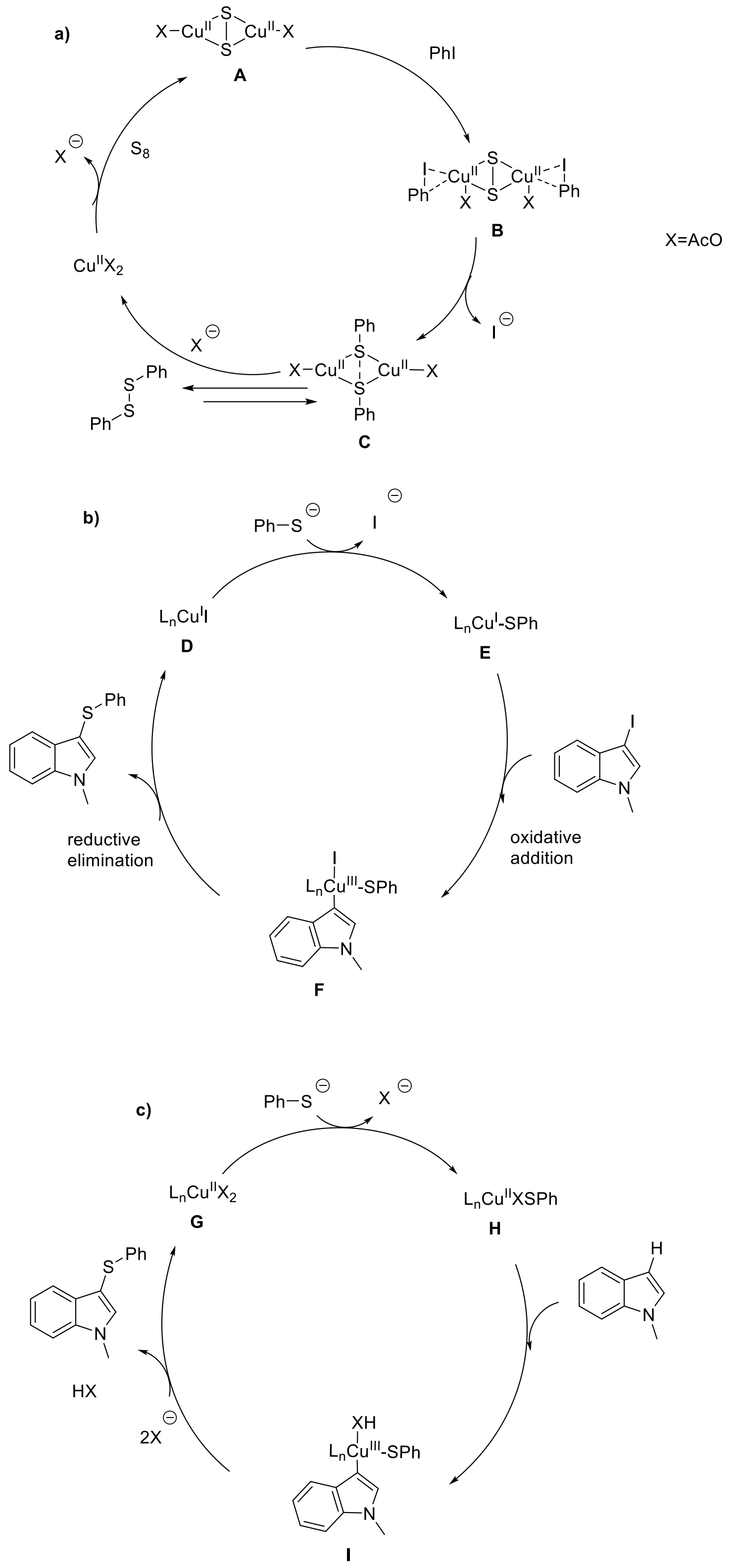


Figure 1. Overall three-dimensional Fourier transform IR (3D-FTIR) profile after adding NaOAc.



Scheme 2. Proposed mechanism, **a):** the route for generating diphenyldisulfide, **b):** the *N*-methyl-3-iodoindole involved route, **c):** the direct coupling by the C-H activation of indole

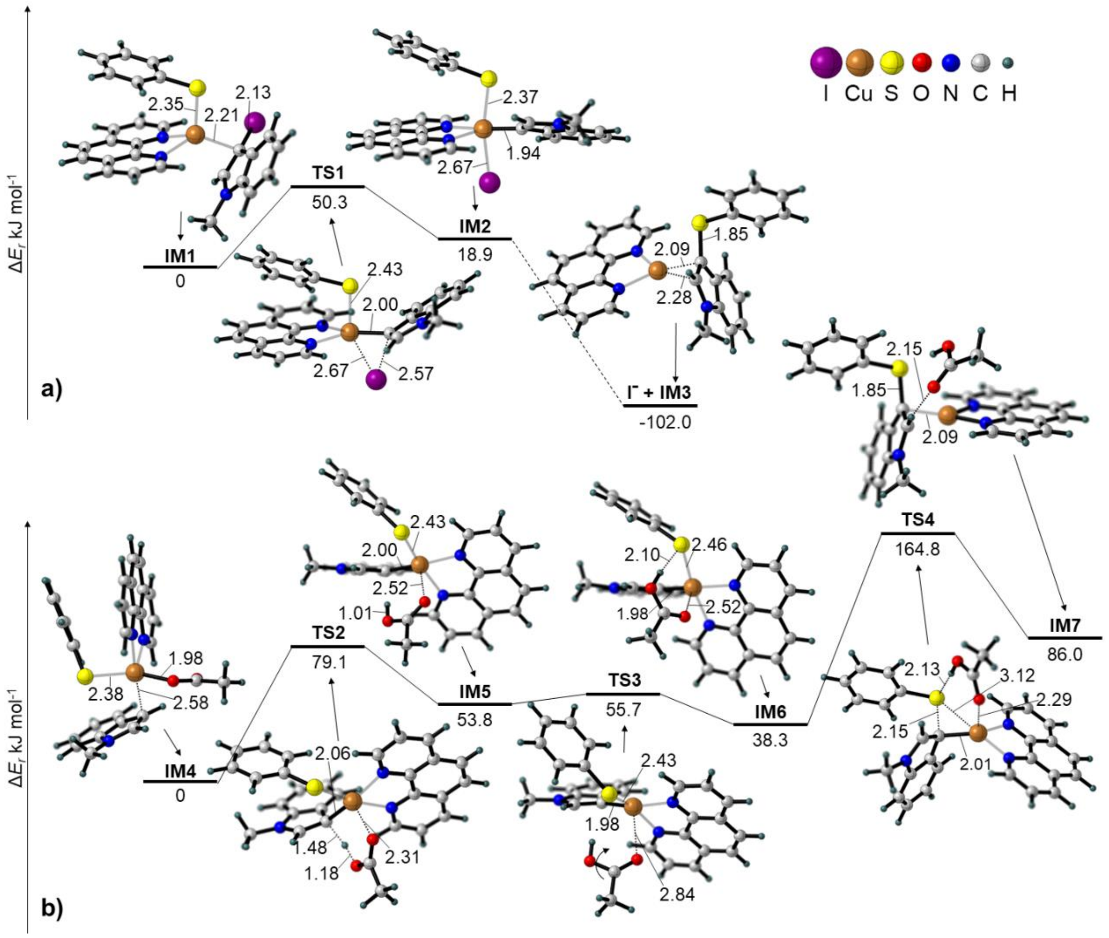


Figure 2. Simplified PESs and selected structural information for **a**: the pathway involving *N*-methyl-3-iodoindole and **b**: the direct coupling pathway as calculated at the B97-1/BSII//B97-1/BSI level of theory. Zero-point corrected, relative energies are given in kJ mol^{-1} and bond lengths in Å. Charges are omitted for the sake of clarity.

Graphical Abstract