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Copper-Mediated C−H Activation/C−S Cross-Coupling of Heterocycles with Thiols

Sadananda Ranjit,[†] Richmond Lee,[‡] Dodi Heryadi,[‡] Chao Shen,[⊥] Ji'En Wu,[†] Pengfei Zhang,[⊥] Kuo-Wei Huang,*[,‡] and Xiaogang Liu*[,†,§]

[†]Department of Chemistry, National University of Singapore, Singapore 117543

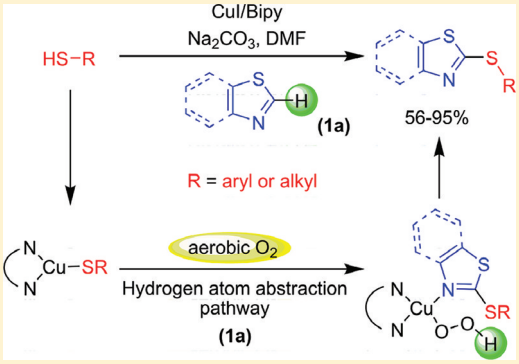
[§]Institute of Materials Research and Engineering, A*STAR, 3 Research Link, Singapore 117602

[‡]KAUST Catalysis Center and Division of Chemical and Life Sciences and Engineering, King Abdullah University of Science and Technology, Thuwal 23955-6900, Kingdom of Saudi Arabia

[⊥]College of Material, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 310036, China

Supporting Information

ABSTRACT: We report the synthesis of a series of aryl- or alkyl-substituted 2-mercaptobenzothiazoles by direct thiolation of benzothiazoles with aryl or alkyl thiols via copper-mediated aerobic C−H bond activation in the presence of stoichiometric CuI, 2,2′-bipyridine and Na_2CO_3. We also show that the approach can be extended to thiazole, benzimidazole, and indole substrates. In addition, we present detailed mechanistic investigations on the Cu(I)-mediated direct thiolation reactions. Both computational studies and experimental results reveal that the copper−thiolate complex [(L)Cu(SR)] (L: nitrogen-based bidentate ligand such as 2,2′-bipyridine; R: aryl or alkyl group) is the first reactive intermediate responsible for the observed organic transformation. Furthermore, our computational studies suggest a stepwise reaction mechanism based on a hydrogen atom abstraction pathway, which is more energetically feasible than many other possible pathways including β-hydride elimination, single electron transfer, hydrogen atom transfer, oxidative addition/reductive elimination, and σ-bond metathesis.



INTRODUCTION

The formation of C−S bonds, fundamental to the art of organic synthesis, represents a key step to the synthesis of a broad range of biologically important molecules and functional materials.[1] In particular, 2-thio-substituted-1,3-benzothiazoles are essential building blocks found in a large number of pharmaceutically active molecules. These molecules include Cathepsin-D inhibitor (**A**), potent heat shock protein-90 inhibitor (**B**), avarol-3′-thiobenzothizole (**C**), 2-(thiocyanatomethylthio)-1,3-benzothiazole (TCMBT; **D**), and dual antagonist for the human CCR1 and CCR3 receptors (**E**) (Figure 1).[1] Additionally, 2-thio-substituted-1,3-benzothiazoles have also been found in advanced materials used as corrosion inhibitors, vulcanization catalysts in the rubber industry, as well as reagents for metal-catalyzed cross-coupling reactions.[2a−c]

The most straightforward method for the synthesis of 2-(arylthio)benzothiazoles involves either cross-coupling of mercapto-benzothiazole with aryl halides (Scheme 1, route **a**)[2] or a nucleophilic attack of arylthiols by preformed 2-halobenzothiazoles (Scheme 1, route **b**).[3] Alternatively, the 2-(arylthio)benzothiazole can be prepared through intramolecular S-arylation of a dithiocarbamate.[4] Despite the promise of these methods, there are significant limitations typically associated with the need of mercapto-benzothiazole or organohalide precursors and multistep procedures. Recently, Fukuzawa and Daugulis have independently reported the direct thiolation of benzoxazole and benzothiazole substrates with aryl thiols or aryl disulfides.[5] However, their methods have shown limitation in reaction scope with access only to aryl thiols or aryl disulfides, and the reaction mechanisms have not been thoroughly investigated. Therefore, a general synthetic method that allows direct thiolation of benzothiazole and its analogues with alkyl or aryl thiols via C−H bond activation[6] would be highly desirable due to the simplified one-step procedure and the elimination of halocarbon precursors.

As part of our longstanding interest in developing novel C−S cross-coupling reactions, we recently developed a convenient strategy for the synthesis of aryl-substituted benzothiazoles and benzoxazoles through use of arylboronic acids by metal-catalyzed direct arylation reactions.[7] Herein, we report a new route to 2-thio-substituted-1,3-benzothiazoles by direct C−H bond functionalization with alky or aryl thiols in the presence of copper. We also present mechanistic investigations that suggest a stepwise reaction mechanism involving a hydrogen atom abstraction pathway.

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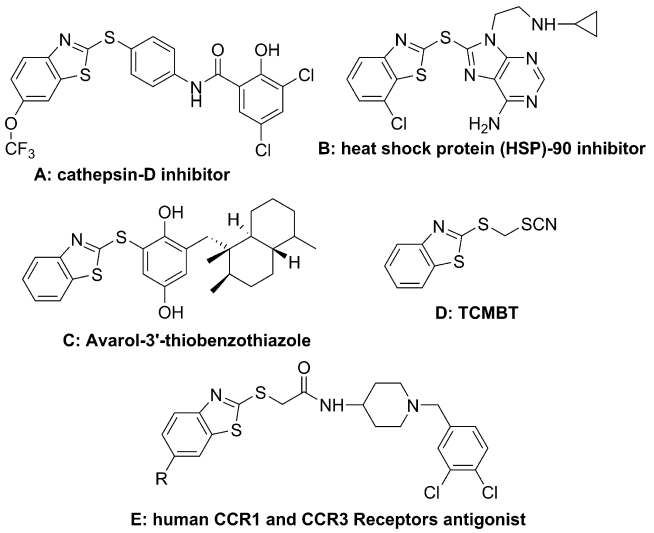
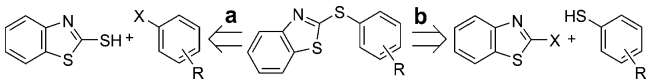


Figure 1. Molecular examples illustrating the incorporation of the 2-thio-1,3-benzothiazole scaffold.

Scheme 1. Classical routes for the synthesis of 2-(arylthio)benzothiazoles

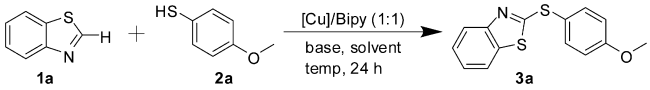


RESULTS AND DISCUSSION

1. Development of Direct Thiolation of Benzothiazole. The coupling of benzothiazole (**1a**) with electron-rich 4-methoxythiophenol (**2a**) was chosen as a model system to determine the optimum reaction conditions, and the selected results are summarized in the Table 1. In the absence of a metal salt or ligand, only trace amounts of desired products (**3a**) were obtained after 24 h (Table 1, entries 1 and 2). However, to our surprise, upon adding a combination of CuI (20 mol %) and 2,2′-bipyridine ligand (**L-1**) in the presence of K_3PO_4 in DMSO at 100 °C, the desired product **3a** was obtained in 15% yield (Table 1, entry 3). The yield of **3a** could be improved with an increased amount of CuI/**L-1** (Table 1, entries 4 and 5) or at an increased reaction temperature (Table 1, entries 6 and 7). Further experimentations revealed that this C−S cross-coupling reaction was effective in a range of polar aprotic solvents such as DMSO, DMF, and NMP (Table 1, entries 8 and 9). In stark contrast, the coupling reaction proceeded less efficiently in polar protic solvents (PEG, EG) or nonpolar solvent (dioxane). In all cases studied, the conversion is less than 10% (Table 1, entries 10−12). Notably, the reactions through use of strong bases, including NaO*t*Bu, KO*t*Bu, KOH, and Cs_2CO_3, occurred with low reaction conversions (Table 1, entries 13−16). The reaction with K_2CO_3 or Na_2CO_3 as the base resulted in the formation of **3a** in 54 and 99% yield, respectively (Table 1, entries 17 and 18). From subsequent examinations of various copper sources (Table 1, entries 19−22), CuI was proven to be the best (Table 1, entry 18).

2. Ligand Influence on Direct Thiolation of Benzothiazole. To investigate the ligand effect on the C−S cross-coupling, a series of Cu(I)-mediated reactions between **1a** and arylthiol **2a** or alkylthiol (1-octanethiol; **2e**) in the presence of different ligands were carried out under the standard reaction conditions (see Figure 2). Nitrogen-based bidentate or tridentate ligands (**L1** to **L6**) and oxygen-based bidentate

Table 1. Optimization of the C−S Coupling of Benzothiazole with 4-Methoxythiophenol[a]



1a 2a 3a

entry	additive (equiv)	base	temp (°C)	solvent	conversion (%)[b]
1		K_3PO_4	100	DMSO	<3
2[c]	CuI (0.2)	K_3PO_4	100	DMSO	<3
3	CuI (0.2)	K_3PO_4	100	DMSO	15
4	CuI (0.5)	K_3PO_4	100	DMSO	22
5	CuI (1.0)	K_3PO_4	100	DMSO	30
6	CuI (1.0)	K_3PO_4	120	DMSO	48
7	CuI (1.0)	K_3PO_4	140	DMSO	60
8	CuI (1.0)	K_3PO_4	140	DMF	75
9	CuI (1.0)	K_3PO_4	140	NMP	68
10	CuI (1.0)	K_3PO_4	140	PEG	<3
11	CuI (1.0)	K_3PO_4	140	EG	<3
12	CuI (1.0)	K_3PO_4	140	dioxane	8
13	CuI (1.0)	NaO*t*Bu	140	DMF	<5
14	CuI (1.0)	KO*t*Bu	140	DMF	<5
15	CuI (1.0)	KOH	140	DMF	<1
16	CuI (1.0)	Cs_2CO_3	140	DMF	10
17	CuI (1.0)	K_2CO_3	140	DMF	54
18	**CuI (1.0)**	**Na_2CO_3**	**140**	**DMF**	**99 (95)[d]**
19	CuBr (1.0)	Na_2CO_3	140	DMF	92
20	CuCN (1.0)	Na_2CO_3	140	DMF	95
21	CuCl (1.0)	Na_2CO_3	140	DMF	83
22	$CuCO_3$ (1.0)	Na_2CO_3	140	DMF	10

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.5 mmol), solvent (3.0 mL), base (2.5 equiv), 140 °C, 24 h. [b]GC analysis. [c]The entry has been done without the bipy ligand. [d]Yield of the isolated product is in parentheses. Bipy = 2,2′-bipyridine.

ligand (**L7**) that can stabilize the Cu(I) species in solutions are well studied for C−S cross-coupling reactions.[4a,8] In our studies, the reaction with added **L1** gave high reaction yields for both aryl and alkyl thiol substrates. By comparison, 1,10-phenanthroline (**L2**), *N*,*N*″-dimethylethane-1,2-diamine (**L3**) and *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (**L4**) were much less effective for the alkythiol substrate. In the case of using N^1-(2-(dimethylamino)ethyl)-N^1,N^2,N^2-trimethylethane-1,2-diamine (**L5**), ethane-1,2-diamine (**L6**), and pentane-2,4-dione (**L7**), satisfactory results were not obtained for both aryl and alky thiol substrates.

3. Scope of the Reaction. In a further set of experiments, we examined the scope and generality of the approach for the direct sulfurization of benzothiazole **1a** with a series of alky and aryl thiols (**2b−o**) under the optimum reaction conditions. Our results showed that both alkyl and aryl thiols can be efficiently converted to the corresponding cross-coupling products (Table 2). Importantly, good chemoselectivity was observed in the coupling of **1a** with 4-bromothiophenol (**2m**) or 4-chlorothiophenol (**2n**). In both cases, the benzothiazole underwent direct thiolation with the halogenated arylthiol substrates to give the desired bromo- or chloro-substituted 2-(arylthio)benzothiazoles (**3m** and **3n**) in relatively high yield (Table 2, entries 12 and 13). Functional group tolerance was also tested in the reaction of benzothiazole and 4-aminothiolphenol (**2o**). We found that the amine substituent had no marked effect on the reaction yield (Table 2, entry 14). The GC/MS analysis of the reaction mixture revealed that no C−N

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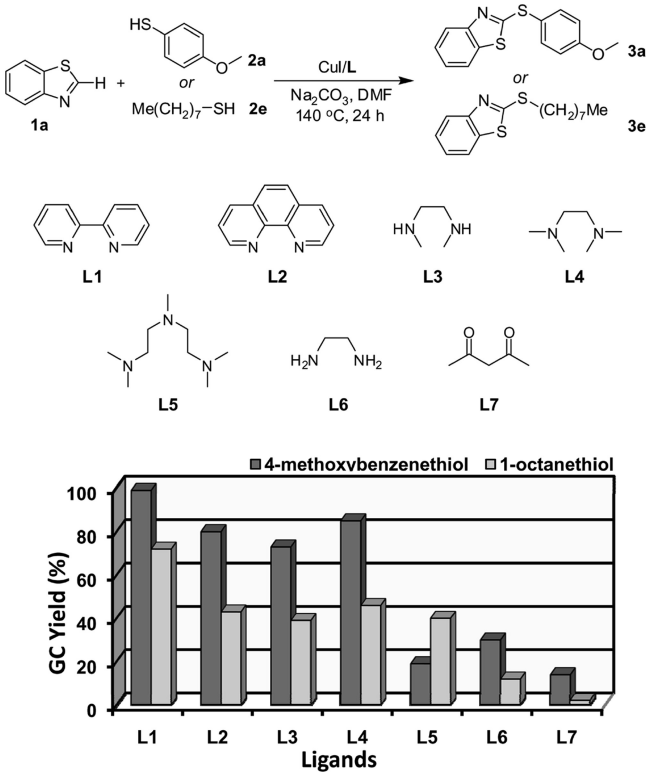


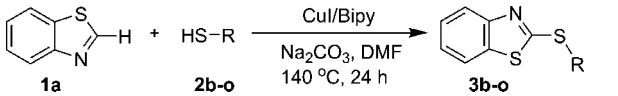
Figure 2. Effect of ligand on the cross-coupling of benzothiazoles with thiols. Reaction condition: **1a** (1.0 mmol), **2a** (1.5 mmol), CuI/ligand (1.0 equiv/1.0 equiv), and Na_2CO_3 (2.5 equiv) in DMF (3.0 mL) at 140 °C for 24 h.

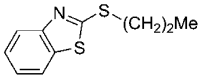
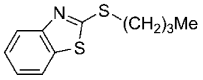
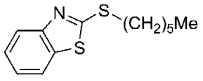
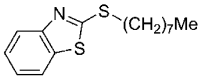
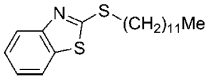
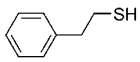
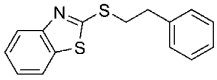
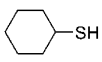
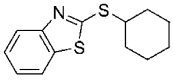
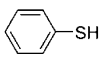
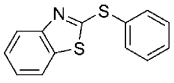
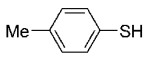
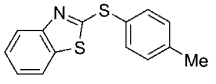
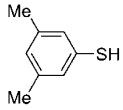
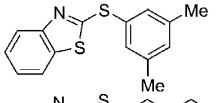
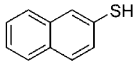
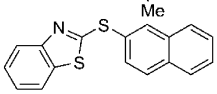
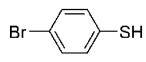
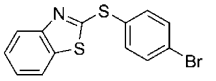
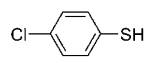
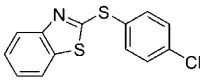
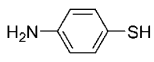
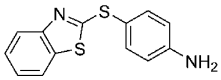
coupling product is formed. Importantly, the amine-substituted benzothiazole (**3o**) enables direct derivatization by reacting with 3,5-dichloro-2-hydroxybenzoic acid in the presence of *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) to give the Cathepsin-D inhibitor analogue (**3p**), demonstrating a potential utility of our simplified strategy for accessing a broad range of biologically important molecules (Scheme 2).

In addition to the benzothiazole substrate **1a**, other substituted heterocycles can react with arylthiols to furnish the corresponding aryl sulfides. For example, under the standard reaction conditions 1,3-thiazole is selectively monothiolated at the 2 position by 4-methoxythiophenol **2a** to generate the cross-coupling product (**3q**) in 79% yield (Table 3). Similarly, 4,5-dimethylthiazole and 1-methylbenzimidazole can be directly thiolated by **2a** to afford the cross-coupling thiazole and imidazole products (**3r** and **3s**) in 86 and 96% yields, respectively (Table 3). Interestingly, indole and its methylated derivatives can be selectively monothiolated at the 3 position in good yields (**3t**−**v**) by reacting with phenylthiol (**2i**) under the optimized reaction condition (Table 3). The preferential electrophilic substitution of the indole substrate at the 3 position is largely due to its more nucleophilic nature than that at the 2 position.[6e]

4. Mechanistic Considerations. *4.1. First Reactive Intermediate.* In an effort to gain a better understanding of the reaction mechanism, we carried out density functional theory (DFT) studies and concurrently conducted control experiments to verify our hypothesis. The first active intermediate formed may be either the C−H activated Cu-benzothiazole complex (**Ia**)[9−12] or the Cu-thiolate complex

Table 2. CuI/Bipy-Mediated Direct Sulfurization of Benzothiazole with Thiols[a]



entry	thiols		product **3**		yield (%)[b]
1	$Me(CH_2)_2$−SH	**2b**		**3b**	85
2	$Me(CH_2)_3$−SH	**2c**		**3c**	93
3	$Me(CH_2)_5$−SH	**2d**		**3d**	80
4	$Me(CH_2)_7$−SH	**2e**		**3e**	66
5	$Me(CH_2)_{11}$−SH	**2f**		**3f**	75
6		**2g**		**3g**	62
7		**2h**		**3h**	93
8		**2i**		**3i**	90
9		**2j**		**3j**	80
10		**2k**		**3k**	95
11		**2l**		**3l**	68
12		**2m**		**3m**	56
13		**2n**		**3n**	66
14		**2o**		**3o**	74

[a]Reaction conditions: **1a** (1.0 mmol), **2b**−**o** (1.5 mmol each), DMF (3.0 mL), CuI (1.0 equiv), 2,2′-bipyridine (1.0 equiv), Na_2CO_3 (2.5 equiv), 140 °C, 24 h. [b]Yields of the products are the average of at least two experiments.

Scheme 2. Synthesis of Cathepsin-D Inhibitor Analogue

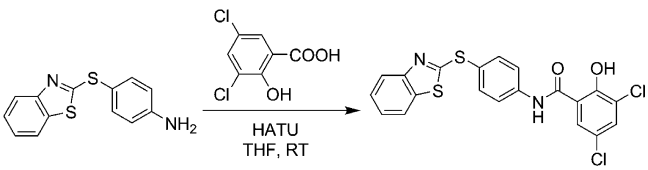


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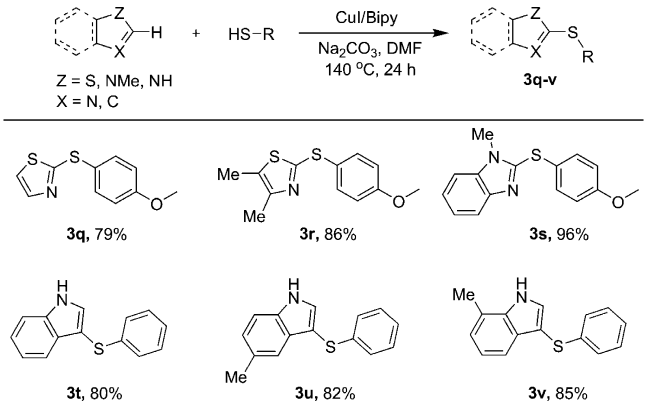
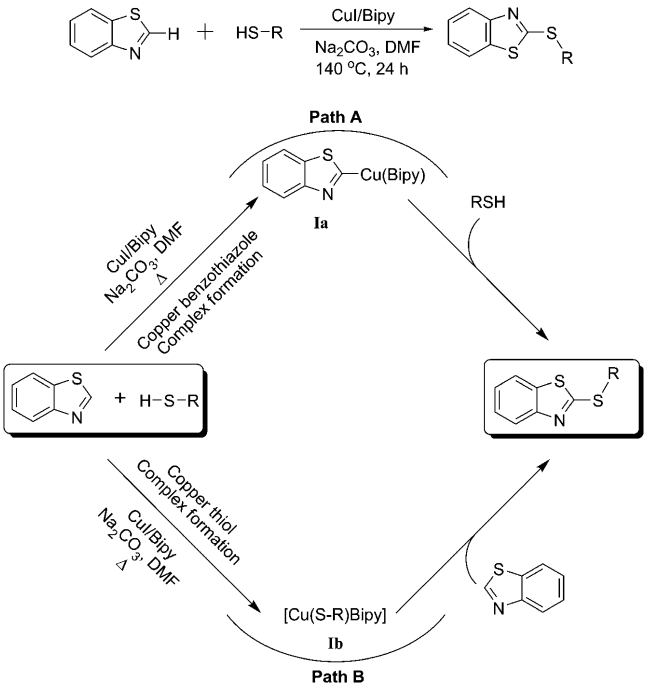
Table 3. Scope of Heteroarene Coupling Partners[a]



[a]Reaction conditions: heterocycles (1.0 mmol), thiols (1.5 mmol), DMF (3.0 mL), CuI (1.0 equiv), 2,2′-bipyridyl (1.0 equiv), Na_2CO_3 (2.5 equiv), 140 °C, 24 h. Yields of the products are the average of at least two experiments.

(**Ib**) (Scheme 3). Results from our modeling suggested that the formation of the Cu-thiolate complex **Ib** is thermodynamically

Scheme 3. Proposed Reaction Pathways



more favored than the Cu-benzothiazolate complex **Ia** by 19.8 kcal/mol (Figure 3). Further experimental evidence was delineated from two parallel experiments. The reaction of benzothiazole with CuI, 2,2′-bipyridine, and Na_2CO_3 dissolved in deuterated dimethylformamide showed no formation of the perceived C−H activated product **Ia** upon heating at 140 °C for 4 h based on in situ ^{1}H NMR analysis (Scheme 4, path A). In sharp contrast, the second control experiment involving a two-step procedure and the formation of a CuSPh complex gave rise to the cross-coupling product, **3i**, in 90% yield (Scheme 4, path B). These data provide strong support that the reaction between the benzothiazole and thiol substrates under our standard reaction conditions may operate via the formation of the Cu-thiolate complex intermediate.

4.2. β-Hydride Elimination (BHE) versus Hydrogen Atom Abstraction (HAA). Mechanistic scenarios into Cu-catalyzed Ullmann-type coupling reactions have been proposed and explored.[13] Single electron transfer (SET), hydrogen atom transfer (HAT), σ-bond metathesis, and oxidative addition/reductive elimination (OA/RE) pathways were evaluated in order to search for the most plausible pathway (Scheme 5). The SET and HAT pathways were first ruled out due to significantly increased energies of intermediates relative to **I** by 136.0 and 88.4 kcal/mol, respectively. The other two pathways were also excluded as the OA/RE Cu^{III} intermediate optimization failed with the thiazolate breaking off and nonconvergence for the σ-bond metathesis transition-state structures. It was observed that the formation of the proposed cuprous hydride species resulting from all above-mentioned processes is unlikely (+39.5 kcal/mol relative to **I**), suggesting that the preceding TS minima, even if located, would be of considerably higher energy and unattainable under our reaction conditions. Alternative pathways, independent of the Ullmann type, were therefore proposed and examined (Scheme 6).

Starting from Cu-thiolate intermediate **I**, a benzothiazole-coordinated intermediate **II** was proposed and located. The phenylthiolate group was then found to migrate onto the electrophilic sp^2 carbon of the benzothiazole moiety to form the Cu-mercaptobenzothiazole complex **IV** via transition state **TS-III**. The occurrence of β-hydride elimination process from **IV** via transition state **TS-Vb** to the Cu^I-hydrido intermediate **VIb** and the product was ruled out due to the high overall transition state energy of 57.5 kcal/mol (Figures 3 and 4). These observations urged us to consider the involvement of oxygen in these processes (Scheme 6).

Reports on C−H bond activation/functionalization by Cu^{II}-superoxo complexes in biological enzymes such as dopamine hydroxylase and peptidylglycine α-hydroxylating monooxygenases prompted us to construct models for probing the reactivity of $\mathbf{V}^{(3)}$, which is believed to form through dioxygen binding to **IV**.[14] The geometry of the optimized triplet state intermediate $\mathbf{V}^{(3)}$ shows a characteristic superoxo O−O bond length of 1.26 Å and a Cu−O−O bond angle of 119.0° (Figure 4).[15] The distance of 2.23 Å between the terminal O and the C-2 hydrogen suggests that it is well positioned for the subsequent hydrogen abstraction step. Through transition state $\mathbf{TS\text{-}VI}^{(3)}$, the hydroperoxo complex $\mathbf{VII}^{(3)}$ is located but at +18.0 kcal/mol relative to the singlet hydroperoxo complex $\mathbf{VII}^{(1)}$. By computing the potential energy surfaces of **V** for both singlet and triplet states in the abstraction of the C-2 hydrogen, it was observed that the two profiles intersect before $\mathbf{TS\text{-}VI}^{(3)}$ at the hypothetical point termed as the minimum-energy crossing point (MECP) (Figure 3),[16,17] which serves to rationalize the transitioning of the triplet energy surface to the singlet energy surface. Utilizing a code developed by Harvey and co-workers,[18] the MECP geometry and its corresponding energy was estimated to be 2.0 kcal/mol lower than $\mathbf{TS\text{-}VI}^{(3)}$ (Figure 4). It is portrayed that the bond length of the dioxygen elongates as it reaches to abstract the hydrogen, beginning with the O−O bond length of 1.26−1.33 Å of MECP and finally to the hydroperoxo $\mathbf{VII}^{(1)}$ O−O bond length of 1.49 Å.[19] Complex $\mathbf{VII}^{(1)}$ will dissociate to the desired product and the Cu^I-hydroperoxo complex. We believe that the Cu^I-hydroperoxo complex will be subsequently oxidized to the Cu^{II} species and no longer participate in the reaction.[20]

To elucidate the critical role of molecular oxygen in mediating the coupling reaction, we also conducted a series

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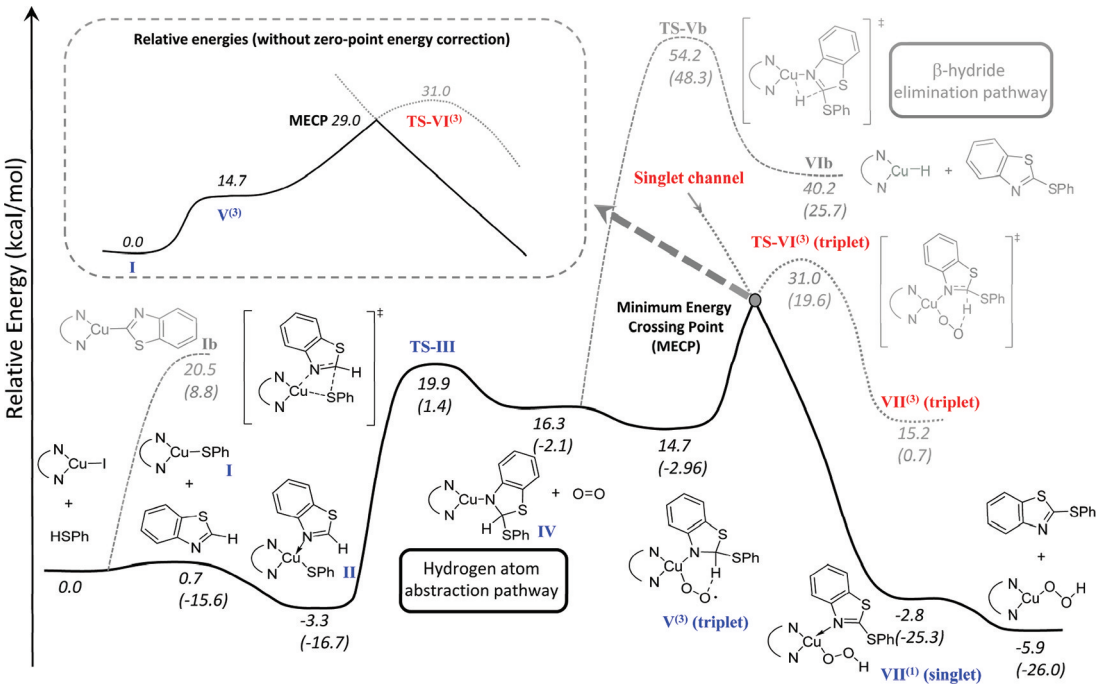
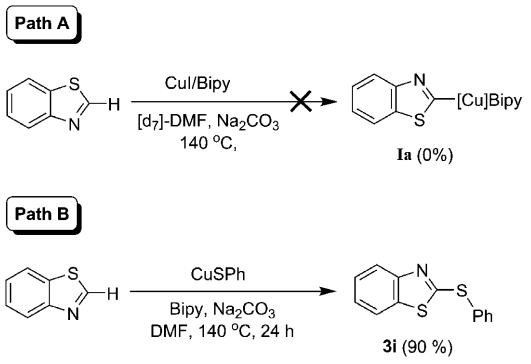


Figure 3. Schematic representation (energy versus reaction coordinate) of the Cu(I)-mediated C−S cross-coupling reaction. Inset: selected energies of intermediates and the transition state compared with the energy of the optimized MECP structure. Relative energies are reported in kcal/mol. Single-point energies in DMF on gas-phase optimized stationary points are styled italics and in parentheses.

Scheme 4. Control Experiments Supporting the Formation of Thio-Substituted Benzothiazole via Path B



of experiments by varying the concentration of oxygen. As summarized in Table 4, the reaction between benzothiazole **1a** and 1-octanethiol (**2e**) conducted under N_2 did not proceed (entry 1). Intriguingly, the yield of coupling product **3e** increases with higher oxygen concentration and reaches 72% in air (entries 2−4). However, the reaction yield decreased significantly to 30% when the reaction was conducted under a pure oxygen atmosphere. The suppressed production is likely due to the facile formation of disulfide byproducts generated by oxidation of 1-octanethiol at elevated oxygen concentrations.

CONCLUSION

In summary, we have presented a general and highly efficient method for C−S cross-coupling through direct functionalization of a heterocyclic C−H bond with aryl or alky thiols in the presence of a stoichiometric amount of copper(I) reagent. By using this synthetic strategy, various substituted 2-mercaptobenzothiazoles, imidazoles, and indoles were conveniently synthesized in good yields under aerobic reaction conditions. The copper-mediated protocol is palladium free, tolerates a variety of functional groups, and eliminates the need for an organohalide species. Mechanistic investigations of this organic transformation revealed that the generation of the first reactive intermediate as a Cu-thiol complex occurs instead of the generally accepted Cu-thiazole complex, as corroborated by DFT calculations. We postulated that molecular oxygen participates in the reaction by abstracting the hydrogen from the C-2 carbon of the thiazole to form the Cu-hydroperoxo compound. Further work is underway to expand the scope of this direct C−S bond functionalization reaction.

EXPERIMENTAL SECTION

General. Unless otherwise noted, all operations were performed without taking precautions to exclude air and moisture, and all solvents and chemicals were used as received. ^{1}H NMR and ^{13}C NMR spectra were recorded on 300 and 75 MHz FT-NMR spectrometers as well as 500 and 125 MHz FT-NMR spectrometers and referenced to solvent peaks. Coupling reactions of benzothiazole with 4-methoxybenzenethiol shown in Tables 1 and 4 were monitored by GCMS analysis.

Synthesis of the CuSPh Complex. The copper complex was prepared according to a previously reported method.[6t] To an ice-cold mixture of concd aq NH_3 (25 mL) and water (100 mL) was added $CuSO_4 \cdot 5H_2O$ (6.26 g, 25.1 mmol), forming a blue-colored solution. Then, a solid form of $NH_2OH \cdot HCl$ (3.89 g, 56.0 mmol) was added to the resulting mixture and stirred overnight at 25 °C under a nitrogen purge to produce a colorless solution of $[Cu(NH_3)_2]^+$. A solution of PhSH (2.84 g, 25.8 mmol) in 125 mL of ethanol was added dropwise, resulting in formation of a pale yellow solid. The solid product was collected via filtration, washed several times with water, ethanol, and ether, and vacuum-dried. Yellowish solid; ^{1}H NMR (500 MHz, D_6-DMSO): δ 7.51 (d, J = 10 Hz, 2H), 7.37 (t, J = 10 Hz, 2H), 7.28 (t, J = 5 Hz, 1H).

Copper(I)-Mediated C−S Cross-Coupling. Typical Procedure for the Reaction of Benzothizole (1a) and 4-Methoxybenzenethiol (2a) (Table 1, Entry 18). To a solution of *N*,*N*-dimethylformamide (DMF) (3.0 mL) charged with benzothizole (**1a**, 0.5 mmol) and 4-methoxybenzenethiol (**2a**, 0.75 mmol) was

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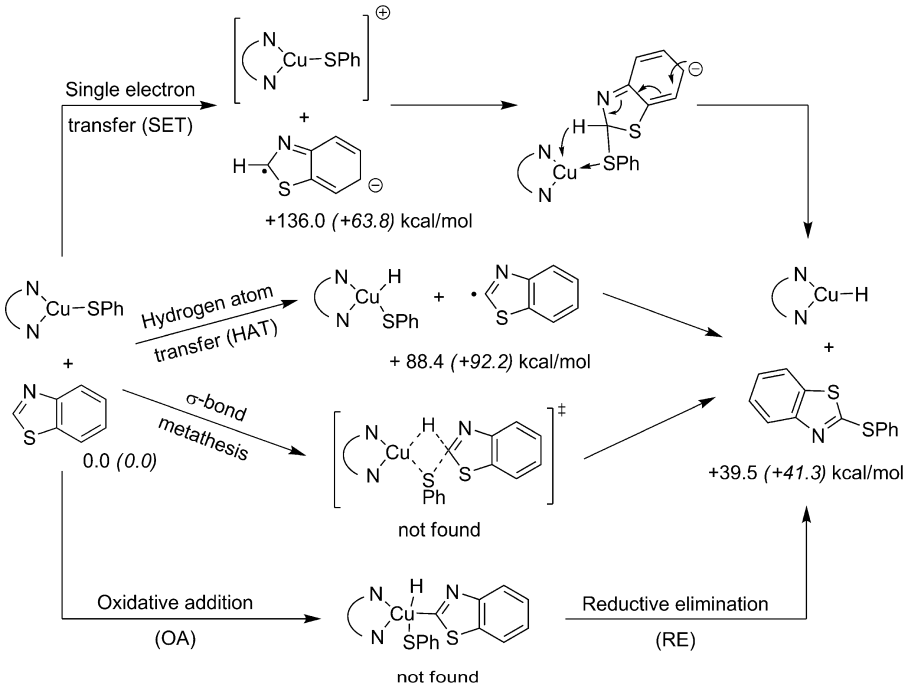
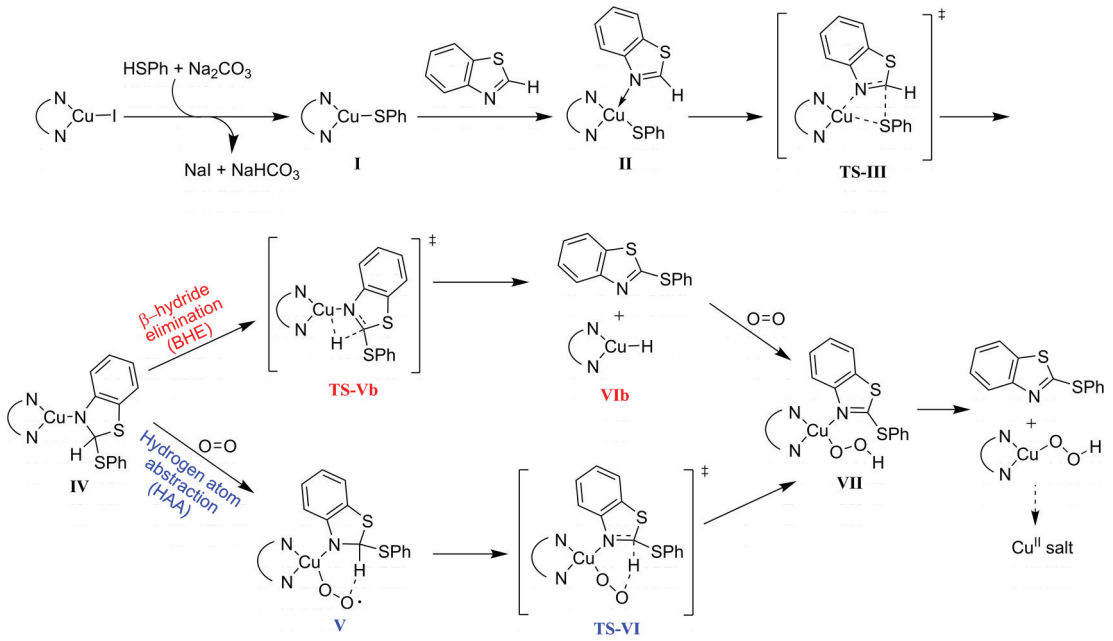
Scheme 5. Plausible Ullmann-Type Reaction Pathways[a]



[a]Single electron transfer (SET), hydrogen atom transfer (HAT), σ-bond metathesis, and oxidative addition/reductive elimination (OA/RE). Relative energies are reported in kcal/mol. Single-point energies in DMF on gas-phase optimized stationary points are styled italics and in parentheses.

Scheme 6. Proposed Reaction Mechanism



added CuI (95.2 mg, 0.5 mmol), 2,2′-bipyridyl (78 mg, 0.5 mmol), and Na_2CO_3 (2.5 equiv). The resulting mixture was stirred at 140 °C and monitored by TLC. Upon completion of the reaction (approximately 24 h), the mixture was cooled to room temperature and mixed with water (15.0 mL). The product was then extracted with ethylacetate (3 × 15 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified over a column of silica gel (EtOAc/hexane as eluents) to give product **3a** in 95% yield. The identity and purity of the products were confirmed by spectroscopic analysis.

2-(4-Methoxyphenylthio)benzo[*d*]thiazole (3a).[4b] White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86–7.85 (d, 1H), 7.68–7.62 (m, 3H), 7.4–7.37 (t, 1H), 7.26–7.22 (t, 1H), 7.02–6.99 (d, 2H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 161.7, 154.2, 137.5, 135.4, 126, 124, 121.8, 120.7, 120.2, 115.5, 55.4; HR EIMS 273.0264 m/z (calcd for $C_{14}H_{11}ONS_2$: 273.0282).

2-(Propylthio)benzo[*d*]thiazole (3b).[4d] Yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88–7.85 (d, 1H), 7.76–7.73 (d, 1H), 7.43–7.38 (t, 1H), 7.31–7.26 (t, 1H), 3.35–3.31 (t, 2H), 1.92–1.80 (m, 2H), 1.11–1.06 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.4,

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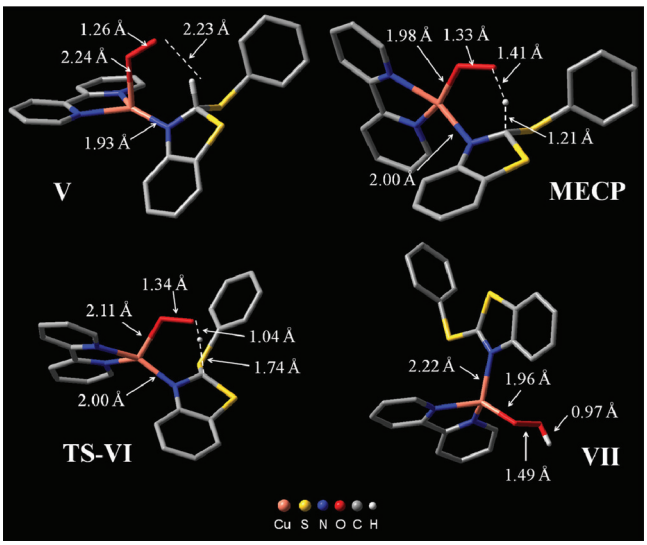
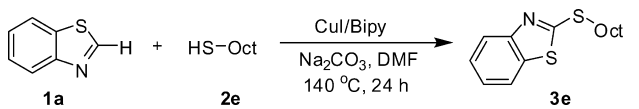


Figure 4. Optimized geometries of selected transition states and intermediates showing key bond lengths.

Table 4. Effect of Atmosphere on the Cross-Coupling Reactions[a]



1a 2e 3e

entry	O_2/N_2	conversion (%)[b]
1	0:100	<1
2	~(1:50)	5
3	~(4:50)	15
4	air (21% O_2)	72
5	100:0	30

[a]Reaction conditions: **1a** (1.0 mmol), **2e** (1.5 mmol), DMF (3.0 mL), CuI (1.0 equiv), 2,2′-bipyridine (1.0 equiv), Na_2CO_3 (2.5 equiv), 140 °C, 24 h. [b]GC analysis.

153.2, 135.1, 126, 124.1, 121.4, 120.9, 35.5, 22.7, 13.4; HR EIMS: 209.0329 *m/z* (calcd for $C_{10}H_{11}NS_2$: 209.0333).

2-(Butylthio)benzo[*d*]thiazole (3c). Yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87–7.86 (d, 1H), 7.75–7.74 (d, 1H), 7.42–7.39 (t, 1H), 7.30–7.27 (t, 1H), 3.36–3.34 (t, 2H), 1.84–1.78 (m, 2H), 1.5–1.47 (m, 2H), 0.98–0.95 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 153.4, 135.1, 126, 124.1, 121.4, 120.9, 33.3, 31.2, 21.9, 13.6; HR EIMS: 223.0489 *m/z* (calcd for $C_{11}H_{13}NS_2$: 223.0489).

2-(Hexylthio)benzo[*d*]thiazole (3d). Yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92–7.89 (d, 1H), 7.80–7.77 (d, 1H), 7.47–7.42 (t, 1H), 7.35–7.30 (t, 1H), 3.41–3.36 (t, 2H), 1.91–1.81 (quint, 2H), 1.57–1.47 (quint, 2H), 1.41–1.29 (m, 4H), 0.96–0.91 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.4, 153.4, 135.1, 126, 124.1, 121.4, 120.8, 33.6, 31.2, 29.1, 28.4, 22.4, 14; HR EIMS: 251.0791 *m/z* (calcd for $C_{13}H_{17}NS_2$: 251.0802).

2-(Octylthio)benzo[*d*]thiazole (3e). Yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87–7.85 (d, 1H), 7.75–7.74 (d, 1H), 7.42–7.39 (t, 1H), 7.30–7.25 (t, 1H), 3.35–3.34 (t, 2H), 1.85–1.79 (quint, 2H), 1.5–1.45 (quint, 2H), 1.35–1.26 (m, 8H), 0.90–0.87 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.4, 153.3, 135.1, 126, 124.1, 121.4, 120.8, 33.7, 31.7, 29.2, 29.1, 29, 28.7, 22.6, 14; HR EIMS: 279.1112 *m/z* (calcd for $C_{15}H_{21}NS_2$: 279.1115).

2-(Dodecylthio)benzo[*d*]thiazole (3f).[4e] Yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87–7.86 (d, 1H), 7.75–7.74 (d, 1H), 7.42–7.39 (t, 1H), 7.30–7.27 (t, 1H), 3.36–3.33 (t, 2H), 1.85–1.80 (quint, 2H), 1.50–1.45 (m, 2H), 1.35–1.26 (m, 16H), 0.89–0.87 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.4, 153.3, 135.1, 125.9, 124.1, 121.4, 120.9, 33.6, 31.9, 29.63, 29.61, 29.5, 29.4, 29.3, 29.2, 29, 28.7, 22.6, 14.1; HR EIMS: 335.1741 *m/z* (calcd for $C_{19}H_{29}NS_2$: 335.1741).

2-(Phenethylthio)benzo[*d*]thiazole (3g).[4d] Light yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89–7.88 (d, 1H), 7.76–7.74 (d, 1H), 7.43–7.40 (t, 1H), 7.34–7.22 (m, 6H), 3.61–3.57 (t, 2H), 3.15–3.12 (t, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.6, 153.3, 139.7, 135.3, 128.7, 128.6, 126.7, 126, 124.2, 121.5, 121, 35.6, 34.8; HR EIMS: 271.0484 *m/z* (calcd for $C_{15}H_{13}NS_2$: 271.0489).

2-(Cyclohexylthio)benzo[*d*]thiazole (3h). Yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88–7.87 (d, 1H), 7.75–7.74 (d, 1H), 7.42–7.39 (t, 1H), 7.30–7.27 (t, 1H), 3.93–3.87 (m, 1H), 2.22–2.18 (m, 2H), 1.82–1.78 (m, 2H), 1.67–1.29 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.4, 153.4, 135.3, 125.9, 124.1, 121.6, 120.8, 47.3, 33.3, 25.8, 25.6; HR EIMS: 249.0636 *m/z* (calcd for $C_{13}H_{15}NS_2$: 249.0646).

2-(Phenylthio)benzo[*d*]thiazole (3i).[4b] Light yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89–7.86 (d, 1H), 7.75–7.72 (d, 2H), 7.66–7.63 (d, 1H), 7.51–7.37 (m, 4H), 7.28–7.23 (t, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 153.9, 135.5, 135.3, 130.4, 129.94, 129.9, 126.1, 124.3, 121.9, 120.7; HR EIMS: 243.0157 *m/z* (calcd for $C_{13}H_9NS_2$: 243.0176).

2-(*p*-Tolylthio)benzo[*d*]thiazole (3j).[4b] White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87–7.84 (d, 1H), 7.63–7.6 (d, 3H), 7.4–7.35 (t, 1H), 7.29–7.21 (m, 3H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 154, 141.1, 135.5, 135.4, 130.7, 126.2, 126, 124.1, 121.8, 120.7, 21.4; HR EIMS: 257.0314 *m/z* (calcd for $C_{14}H_{11}NS_2$: 257.0333).

2-(3,5-Dimethylphenylthio)benzo[*d*]thiazole (3k). Light yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88–7.87 (d, 1H), 7.65–7.64 (d, 1H), 7.41–7.38 (t, 1H), 7.35 (s, 2H), 7.27–7.24 (t, 1H), 7.13 (s, 1H), 2.35 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 153.8, 139.7, 135.5, 132.9, 132.2, 129.2, 126.1, 124.2, 121.8, 120.7, 21.2; HR EIMS: 271.0472 *m/z* (calcd for $C_{15}H_{13}NS_2$: 271.0489).

2-(Naphthalen-2-ylthio)benzo[*d*]thiazole (3l). Brown solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.93–7.86 (m, 4H), 7.73–7.71 (dd, 1H), 7.62–7.55 (m, 3H), 7.41–7.38 (t, 1H), 7.27–7.23 (t, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 153.7, 135.5, 135.4, 133.8, 133.7, 131.1, 129.7, 128.1, 127.9, 127.7, 127, 126.2, 124.4, 121.9, 120.8; HR EIMS: 293.0315 *m/z* (calcd for $C_{17}H_{11}NS_2$: 293.0333).

2-(4-Bromophenylthio)benzo[*d*]thiazole (3m). Yellowish white solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.9–7.87 (d, 1H), 7.7–7.67 (d, 1H), 7.63–7.57 (m, 4H), 7.45–7.39 (t, 1H), 7.32–7.26 (t, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.1, 153.7, 136.5, 135.5, 133.1, 129, 126.3, 125.1, 124.6, 122.1, 120.9; HR EIMS: 320.9265 *m/z* (calcd for $C_{13}H_8BrNS_2$: 320.9282).

2-(4-Chlorophenylthio)benzo[*d*]thiazole (3n). Yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.9–7.89 (d, 1H), 7.69–7.65 (m, 3H), 7.47–7.39 (m, 3H), 7.32–7.27 (t, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.4, 153.7, 137, 136.4, 135.5, 130.1, 128.4, 126.3, 124.6, 122, 120.8; HR EIMS: 276.9780 *m/z* (calcd for $C_{13}H_8ClNS_2$: 276.9787).

4-(Benzo[*d*]thiazol-2-ylthio)aniline (3o). Brown solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85–7.83 (d, 1H), 7.63–7.62 (d, 1H), 7.52–7.49 (d, 2H), 7.39–7.36 (t, 1H), 7.24–7.21 (t, 1H), 6.77–6.74 (d, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.3, 154.3, 148.8, 137.6, 135.4, 126, 123.9, 121.6, 120.7, 116.8, 115.9; HR EIMS: 258.0274 *m/z* (calcd for $C_{13}H_{10}N_2S_2$: 258.0285).

***N*-(4-(Benzo[*d*]thiazol-2-ylthio)phenyl)-3,5-dichloro-2-hydroxybenzamide (3p).** Off-white solid; ^{1}H NMR (500 MHz, [D_6] DMSO): δ 12.25 (br s, 1H), 10.86 (br s, 1H), 8.07 (s, 1H), 8.06–7.82 (m, 7H), 7.47–7.44 (t, 1H), 7.36–7.32 (t, 1H); ^{13}C NMR (125 MHz, [D_6] DMSO): δ 169.5, 166.4, 154.1, 153.4, 140.1, 136.1, 134.7, 132.9, 126.6, 126.4, 124.4, 123.7, 122.6, 122.45, 122.4, 121.7, 121.3, 119.7; HR EIMS: 445.9725 *m/z* (calcd for $C_{20}H_{12}Cl_2N_2O_2S_2$: 445.9717).

2-(4-Methoxyphenylthio)thiazole (3q). Yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65–7.64 (d, 1H), 7.62–7.59 (d, 2H), 7.14–7.13 (d, 1H), 6.97–6.94 (d, 2H), 3.85 (s, 3H); ^{13}C NMR

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(125 MHz, $CDCl_3$): δ 169, 161.2, 143.2, 136.7, 121.6, 119.3, 115.4, 55.4; HR EIMS: 223.0117 *m/z* (calcd for $C_{10}H_9NOS_2$: 223.0120).

2-(4-Methoxyphenylthio)-4,5-dimethylthiazole (3r). Red liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57−7.54 (d, 2H), 6.93−6.90 (d, 2H), 3.83 (s, 3H), 2.26 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.6, 160.9, 148.8, 136.2, 127.4, 122.5, 115.1, 55.3, 14.6, 11.2; HR EIMS: 251.0433 *m/z* (calcd for $C_{12}H_{13}ONS_2$: 251.0439).

2-(4-Methoxyphenylthio)-1-methyl-1*H*-benzo[*d*]imidazole (3s). Brown solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71−7.69 (d, 1H), 7.44−7.41 (d, 2H), 7.25−7.19 (m, 3H), 6.87−6.84 (d, 2H), 3.76 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.9, 149.6, 143, 136.5, 133.9, 122.7, 122.1, 121.1, 119.5, 115.1, 109, 55.3, 30.6; HR EIMS: 270.0817 *m/z* (calcd for $C_{15}H_{14}N_2OS$: 270.0827).

3-(Phenylthio)-1*H*-indole (3t). White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41 (br s, 1H), 7.64−7.61 (d, 1H), 7.49−7.43 (m, 2H), 7.3−7.03 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.2, 136.5, 130.6, 129.1, 128.7, 126, 125.9, 124.8, 123, 120.9, 119.7, 111.5; HR EIMS: 225.0607 *m/z* (calcd for $C_{14}H_{11}NS$: 225.0612).

5-Methyl-3-(phenylthio)-1*H*-indole (3u). White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (br s, 1H), 7.44−7.43 (m, 2H), 7.34−7.31 (d, 1H), 7.26−7.04 (m, 6H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.5, 134.8, 130.8, 130.4, 129.4, 128.7, 125.7, 124.7, 124.6, 119.2, 111.2, 102.1, 21.4; HR EIMS: 239.0767 *m/z* (calcd for $C_{15}H_{13}NS$: 239.0769).

7-Methyl-3-(phenylthio)-1*H*-indole (3v). Brown-colored gel; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (br s, 1H), 7.50−7.46 (m, 2H), 7.20−7.03 (m, 7H), 2.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.3, 136.1, 130.3, 128.8, 128.7, 125.9, 124.8, 123.6, 121.1, 120.7, 117.4, 103.4, 16.4; HR EIMS: 239.0769 *m/z* (calcd for $C_{15}H_{13}NS$: 239.0766).

Computational Details. All DFT gas-phase calculations were performed with the Gaussian 09 computational suite.[21] Becke's three-parameter hybrid exchange functional and the nonlocal correlation functional of Lee, Yang, and Parr (B3LYP) was applied for optimizations of all compounds, and frequency analyses were done to verify minimum structures showing positive eigenvalues of the Hessian matrix or transition-state structures exhibiting only a single negative eigenvalue.[22] The LANL2DZ effective core potential of Hay and Wadt was applied for I and Cu atoms,[23] and the all-electron split-valence Pople basis set 6-31+G(d,p) containing polarization functions on both heavy atoms and hydrogens and diffuse functions on heavy atoms was used.[24] Single-point energies in DMF were computed at the B3LYP/6-311+G(d,p) level of theory on the gas-phase optimized structures with the default integral equation formalism variant IEFPCM implemented in Gaussian 09.[25,26] MECP was determined and optimized with the code designed by Harvey and co-workers at the same level of theory.[18] This Fortan-based code together with shell scripts extracts calculated Gaussian output energies and gradients of two input structures with different spin states to generate an effective gradient toward the MECP. All energies reported are a sum of electronic energy with ZPE corrections except for the estimation of the MECP energy.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Mechanistic studies and ^{1}H NMR and ^{13}C NMR spectra of all compounds and details of DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: chmlx@nus.edu.sg (X.L.); hkw@kaust.edu.sa (K.-W.H.)

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