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

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Supporting Information

ABSTRACT: We report the synthesis of a series of aryl- or alkyl-substituted 2-mercaptobenzoxazoles 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 Na2CO3. 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, 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’-thiobenzothiazole (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 benzoazole 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 activation6 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 benzoazoles 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 alkyl 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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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 (L1) that can stabilize the Cu(I) species in solutions are marked effect on the reaction yield (Table 2, entry 14). The entry has been done without the bipy ligand. Yield of the isolated product is in parentheses. Bipy = 2,2′-bipyridine.

2. Ligand Influence on Direct Thiolation of Benzothiazole. To investigate the ligand effect on the 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,N,N′,N′-tetramethylethane-1,2-diamine (L3) and N,N,N,N′,N′-tetramethylthiophene-1,2-diamine (L4) were much less effective for the alkylthiol substrate. In the case of using N2-(2-(dimethylamino)ethyl)-N,N,N,N′′-trimethylthiophene-1,2-diamine (L5), ethane-1,2-diamine (L6), and pentane-2,4-dione (L7), satisfactory results were not obtained for both aryl and alkyl 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 alkyl 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-aminothiophenol (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

### Table 1. Optimization of the C–S Coupling of Benzothiazole with 4-Methoxythiophenol

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

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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.

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 (1a)\textsuperscript{9−12} or the Cu-thiolate complex...
Table 3. Scope of Heteroarene Coupling Partners

<table>
<thead>
<tr>
<th>Z = S, NMe, NH</th>
<th>X = N, C</th>
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<tr>
<td>C=S=O</td>
<td>H</td>
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</table>

Scheme 3. Proposed Reaction Pathways

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. 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).

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 sp² carbon of the benzothiazole moiety to form the Cu-mercaptopbenzothiazole complex IV via transition state TS-III. The occurrence of β-hydride elimination process from IV via transition state TS-Vb to the Cu²⁺-hydrido intermediate VIIib 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/functionlization by Cu²⁺-superoxido complexes in biological enzymes such as dopamine hydroxylase and peptidylglycine α-hydroxylating monooxygenases prompted us to construct models for probing the reactivity of V₃., which is believed to form through dioxygen binding to IV. The geometry of the optimized triplet state intermediate 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). The distance of 2.23 Å between the terminal O and the C₂ hydrogen suggests that it is well positioned for the subsequent hydrogen abstraction step. Through transition state TS-VI(3), the hydperoxo complex VII(3) is located but at +18.0 kcal/mol relative to the singlet hydperoxo complex VII(1). By computing the potential energy surfaces of V for both singlet and triplet states in the abstraction of the C₂ hydrogen, it was observed that the two profiles intersect before TS-VI(3) at the hypothetical point termed as the minimum-energy crossing point (MECP) (Figure 3). 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, the MECP geometry and its corresponding energy was estimated to be 2.0 kcal/mol lower than TS-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 hydperoxo VII(1) O–O bond length of 1.49 Å. Complex VII(1) will dissociate to the desired product and the Cu²⁺-hydperoxo complex. We believe that the Cu²⁺-hydperoxo complex will be subsequently oxidized to the Cu³⁺ species and no longer participate in the reaction.

To elucidate the critical role of molecular oxygen in mediating the coupling reaction, we also conducted a series of experiments delineated from two parallel experiments. The reaction of benzothiazole with Cu, 2,2′-bipyridine, and Na₂CO₃ 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 ¹H 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.
of experiments by varying the concentration of oxygen. As summarized in Table 4, the reaction between benzothiazole 1a and 1-octanethiol (2e) conducted under N2 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-mercapto-benzothiazoles, 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. 1H NMR and 13C 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. To an ice-cold mixture of concd aq NH3 (25 mL) and water (100 mL) was added CuSO4·5H2O (6.26 g, 25.1 mmol), forming a blue-colored solution. Then, a solid form of NH2OH·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(NH3)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; 1H NMR (500 MHz, D6-DMSO): δ 7.51 (d, J = 10 Hz, 2H), 7.37 (t, J = 10 Hz, 2H), 7.28 (t, J = 5 Hz, 1H).

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

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.

**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**

**Path A**

![Path A](image)

**Path B**

![Path B](image)
added CuI (95.2 mg, 0.5 mmol), 2,2′-bipyridyl (78 mg, 0.5 mmol), and Na2CO3 (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 ethyl acetate (3 × 15 mL). The organic layers were combined, dried over anhydrous Na2SO4, 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). White solid; 1H NMR (500 MHz, CDCl3) 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); 13C NMR (125 MHz, CDCl3) 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 C14H11ONS2: 273.0282).

2-(Propylthio)benzo[d]thiazole (3b). Yellow liquid; 1H NMR (300 MHz, CDCl3): δ 7.88−7.85 (d, 1H), 7.76−7.73 (t, 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); 13C NMR (125 MHz, CDCl3): δ 167.4,
1.26 (m, 16H), 0.89 − 3.33 (t, 2H), 1.85 − 2.18 (m, 2H, 1.82−1.78 (m, 2H), 1.67−1.29 (m, 6H); 13C NMR (125 MHz, CDCl3): δ 166.6, 153.3, 139.7, 135.3, 128.7, 126.8, 126.5, 124.2, 121.5, 121, 35.6, 34.8; HR EIMS: 271.0484 m/z (calc for C13H12N3S2: 271.0489).

2-(Cyclohexylthio)benzof[thiazole (3h). Yellow liquid; 1H NMR (500 MHz, CDCl3): 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); 13C NMR (125 MHz, CDCl3): δ 166.6, 153.4, 135.3, 129.4, 121.6, 121.0, 120.8, 47.3, 33.3, 25.8, 25.6; HR EIMS: 249.0636 m/z (calc for C12H11NS2: 249.0646).

2-(Phenylthio)benzof[thiazole (3l). Yellow liquid; 1H NMR (500 MHz, CDCl3): 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); 13C NMR (75 MHz, CDCl3): δ 169.6, 153.9, 153.5, 133.4, 130.4, 129.4, 129.9, 126.1, 124.3, 121.9, 120.7; HR EIMS: 243.0157 m/z (calc for C10H10N2S2: 243.0176).

2-(p-Tolythio)benzof[thiazole (3j). White solid; 1H NMR (300 MHz, CDCl3): δ 7.87−7.84 (d, 1H), 7.63−7.67 (d, 4H), 7.4−7.35 (t, 1H), 7.29−7.21 (m, 3H), 2.42 (s, 3H); 13C NMR (75 MHz, CDCl3): δ 170.5, 153.5, 139.7, 139.7, 135.5, 135.4, 130.7, 126.2, 126.4, 121.8, 121.7, 21.4; HR EIMS: 271.0472 m/z (calc for C13H12N2S2: 271.0489).

2-(3,5-Dimethylphenylthio)benzof[thiazole (3l). Light yellow liquid; 1H NMR (300 MHz, CDCl3): 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); 13C NMR (125 MHz, CDCl3): δ 170.5, 153.8, 139.7, 139.7, 135.5, 135.4, 133.8, 133.7, 131.1, 129.7, 128.1, 127.9, 127.7, 127.6, 122.4, 121.9, 120.8; HR EIMS: 293.0315 m/z (calc for C13H13N2S2: 293.0333).

2-(4-Bromophenylthio)benzof[thiazole (3m). Yellowish white solid; 1H NMR (300 MHz, CDCl3): δ 7.9−7.89 (d, 1H), 7.7−7.67 (d, 1H), 7.63−7.57 (m, 4H), 7.45−7.39 (t, 1H), 7.32−7.26 (m, 2H, 1.81−1.78 (m, 2H). 13C NMR (125 MHz, CDCl3): δ 168.1, 153.7, 136.5, 135.5, 135.3, 129.1, 126.3, 125.1, 124.5, 121.2, 121.0; HR EIMS: 320.2965 m/z (calc for C13H12BrN2S2: 320.2982).

2-(4-Chlorophenylthio)benzof[thiazole (3n). Yellow liquid; 1H NMR (500 MHz, CDCl3): 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); 13C NMR (125 MHz, CDCl3): δ 168.4, 153.7, 136.4, 135.5, 130.1, 128.4, 126.3, 124.6, 122, 120.8; HR EIMS: 276.9780 m/z (calc for C13H12ClN2S: 276.9787).

4-(Benzo[1,2-b:4,5-b']dithiophenol)benzo[b]thiazole (3e). Brown solid; 1H NMR (500 MHz, CDCl3): δ 7.88−7.83 (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); 13C NMR (125 MHz, CDCl3): 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 (calc for C13H11ClN2S2: 258.0285).

N-(4-(Benzo[b]thiophenol)phenyl)-3,5-dichloro-2-hydroxybenzamide (3p). Off-white solid; 1H NMR (500 MHz, CDCl3 DMSO): δ 12.12 (br s, 1H), 10.86 (br s, 1H), 8.07−8.02 (m, 7H), 7.47−7.44 (t, 1H), 7.36−7.32 (t, 1H); 13C NMR (125 MHz, CDCl3 DMSO): δ 169.5, 166.4, 154.1, 154.3, 140.1, 136.1, 134.7, 132.9, 126.6, 124.5, 123.7, 122, 122.4, 122.1, 121.7, 121.3, 119.7; HR EIMS: 445.9725 m/z (calc for C13H13Cl2N2O2S: 445.9717).

2-(4-Methoxyphenylthio)thiazole (3g). Yellow liquid; 1H NMR (500 MHz, CDCl3): 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); 13C NMR.

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

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<tr>
<td>5</td>
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</table>

Reaction conditions: 1a (1.0 mmol), 2e (1.5 mmol), DMF (3.0 mL), Cu (1.0 equiv), 2,2′-bipyridine (1.0 equiv), Na2CO3 (2.5 equiv), 140 °C, 24 h. GC analysis.

Figure 4. Optimized geometries of selected transition states and intermediates showing key bond lengths.
3-(Phenyl-1H-indole) (3i). Brown solid; 1H NMR (300 MHz, CDCl3): δ 8.31 (s, 1H), 7.60–7.61 (m, 4H), 7.44–7.45 (m, 2H), 7.08–7.10 (m, 2H), 6.70–6.74 (m, 2H), 2.43 (s, 3H); 13C NMR (125 MHz, CDCl3): δ 139.5, 134.8, 130.8, 130.4, 129.4, 128.7, 125.9, 124.8, 123, 121.1, 120.7, 117.4, 103.4, 16.4; HR EIMS: 329.0769 m/z (calc for C19H19N3: 329.0769).

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 C 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/6-31+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 Fortran-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.

REFERENCES


(17) For reviews on studies of the reactivity of organometallic complexes with multiple spin states, see: (a) Harvey, J. N.; Poli, R.; Smith, K. M. Coord. Chem. Rev. 2003, 238–239, 347. For an example of a computational study of organometallic complexes with dioxygen, see: (b) Yu, H.; Fu, Y.; Guo, Q.; Liu, Z. Organometallics 2009, 28, 4443.


