

Intermediacy of Copper(I) under Oxidative Conditions in the Aerobic Copper-Catalyzed Decarboxylative Thiolation of Benzoic Acids

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ABSTRACT: An experimental mechanistic study of the aerobic copper-catalyzed decarboxylative thiolation of benzoic acids with aryl thiols is reported. For the model reaction, the findings support the corresponding disulfide (PhSSPh) of the aryl thiol (PhSH) as the active thiolating source under reaction conditions. Synthesis and reactivity studies along with kinetic measurements support the chemical and kinetic competence of catalytically active well-defined Cu-complexes; (phen)Cu^I(O₂CC₆H₄-o-NO₂) (2), (phen)Cu^I(C₆H₄-o-NO₂) (4), [(phen)Cu^I(μ-SC₆H₅)₂] (3) and (phen)Cu^{II}(O₂CC₆H₄-o-NO₂)₂ (5), (phen = 1,10-phenanthroline). The presence of an induction period in the stoichiometric reaction of copper(II) complex (phen)Cu^{II}(O₂CC₆H₄-o-NO₂)₂ (5) with PhSSPh, and the absence of an induction period in the analogous stoichiometric reaction of copper(I) complex (phen)Cu^I(O₂CC₆H₄-o-NO₂) (2), suggests a copper(I) carboxylate is a more likely intermediate than a copper(II) carboxylate. The observation of in situ reduction of Cu^{II} to Cu^I further supports Cu^I as the primary active catalytic species and spectroscopic studies also indicate the catalyst resting state to be a Cu^I species. The catalytic reaction exhibits a first order dependence on [Cu^I] and [2-nitrobenzoic acid] and a zero order dependence on [PhSSPh] and *p*O₂, suggestive of turn-over-limiting decarboxylation of a copper(I) carboxylate. Oxygen was found to promote the essential oxidative cleavage of the copper(I)-thiolate intermediate [(phen)Cu(μ-SC₆H₅)₂] (3) to regenerate a catalytically active [(phen)Cu^{II}] (Cu_{ox}) species with concomitant formation of PhSSPh. On the basis of these findings, a reaction pathway is proposed for the C-S coupling reaction that includes the key Cu^I-based intermediates, (phen)Cu(O₂CC₆H₄-o-NO₂) (2), and (phen)Cu(C₆H₄-o-NO₂) (4). The pathway accounts for the role of O₂ in generating the active thiolating source, PhSSPh, as well as enabling catalytic turnover of in situ generated [(phen)Cu(μ-SC₆H₅)₂] (3).

INTRODUCTION

Copper-catalyzed cross-coupling reactions are powerful tools for the construction of new C-C and C-heteroatom bonds.¹ Transition metal-catalyzed decarboxylative cross-coupling reactions offer the advantage of providing high levels of regioselectivity using stable, readily available, simple carboxylic acid substrates.^{2,3} These strategies have been applied extensively to C-C^{4,5} and C-N^{6,7} bond forming reactions. The corresponding C-S coupling reactions, however, are less developed and not well understood mechanistically,⁸ despite the importance of the aryl sulfide motif in pharmaceutically and biologically relevant compounds and as intermediates in organic synthesis.⁹

We recently reported the aerobic copper-catalyzed decarboxylative thiolation of benzoic acids with aryl thiols.¹⁰ Not only is this system one of the few copper catalysts developed for decarboxylative thiolation

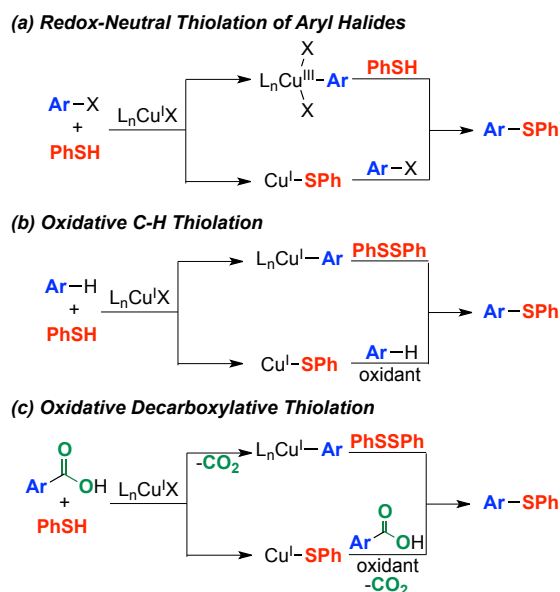
reactions,¹¹ but it is also one of only a handful of oxidative decarboxylative cross-coupling (ODC) reactions capable of employing O₂ as the terminal oxidant.^{3a,4b-d,6,12} Cu-mediated aerobic coupling transformations are particularly attractive because of the ubiquitous, cheap and environmentally benign nature of oxygen as oxidant,¹³⁻¹⁷ yet the majority of ODC reactions are plagued by the need for superstoichiometric silver-based oxidants which are known to facilitate the decarboxylation step in many cases.^{2a,18-20} An improved understanding of this copper-catalyzed decarboxylative thiolation and related reaction mechanisms could enable the development of more efficient aerobic catalytic copper systems.

Copper-promoted redox-neutral decarboxylative coupling reactions have been studied mechanistically, and the generally accepted pathway for these reactions involves initial decarboxylation of a Cu^I-carboxylate to form a Cu^I-aryl species, followed by activation of the aryl halide or proton-containing coupling partner.^{5c,21-24}

In contrast, the oxidative variants are less well understood, in part due to the various oxidation states accessible to copper. Typical mechanisms proposed for these reactions include decarboxylation from in situ generated Cu^{I} - or Cu^{II} -carboxylates to form the corresponding Cu^{I} - or Cu^{II} -aryl species and subsequent reaction with the nucleophilic coupling partner. Although mechanistic proposals are posited in the literature,^{4d,6a,11a} experimental studies to probe these pathways are limited.

In the case of decarboxylative thiolation reactions, mechanistic proposals are further complicated by the multitude of reaction pathways available to thiols and disulfides under copper-mediated conditions.^{11a,25-28} For example, the redox-neutral thiolation of aryl halides has been shown by Hartwig and coworkers²⁹ to proceed through activation of the aryl halide by copper(I)-thiolate species, while Ribas and others³⁰ have shown an aryl copper(III) pathway to be plausible for the same reaction type (Scheme 1a). Similarly, the $\text{C}(\text{sp}^2)\text{-H}$ thiolation reactions could proceed through either initial C-H activation followed by reaction with thiol or disulfide, or initial formation of a copper(I)-thiolate which then cleaves the C-H bond to form the coupled product (Scheme 1b).³¹ Thus, for the oxidative decarboxylative thiolation reactions (Scheme 1c), a number of pathways are possible and many mechanistic questions remain.

Scheme 1. Simplified Mechanistic Pathways for Copper-Catalyzed Thiolation Reactions.



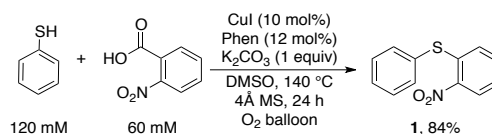
Herein, we report an experimental mechanistic study of the aerobic copper-catalyzed decarboxylative coupling reaction of benzoic acids and aryl thiols to elucidate the nature of the key reactive Cu-based

intermediates, identify the active thiolating source and establish the role(s) played by O_2 . Our findings demonstrate the importance of the disulfide as oxidant and thiolating source; a reactivity pattern that has been acknowledged or observed in related Cu-mediated thiolations.^{32,33} Synthesis and reactivity studies, along with kinetic measurements and spectroscopic studies, support well-defined $(\text{phen})\text{Cu}^{\text{I}}$ species as key intermediates and indicate a Cu^{I} resting state. A significant role of molecular oxygen is the oxidative dissociation of the in situ generated copper(I)-thiolate dimer to provide disulfide and regenerate a catalytically active Cu species. These findings of the catalytic relevance of well-defined Cu^{I} species under oxidative conditions may have implications for related systems as researchers seek to expand the scope and utility of aerobic Cu-mediated coupling transformations.

RESULTS AND DISCUSSION

Overview of the Catalytic System. For this mechanistic study, we chose the model reaction of 2-nitrobenzoic acid and thiophenol (PhSH), which generates (2-nitrophenyl)(phenyl)sulfane (**1**) in 84% yield (Scheme 2). Under the standard catalytic conditions 2-nitrobenzoic acid (60 mM), PhSH (120 mM) and potassium carbonate are treated with 10 mol% of CuI and 12 mol% of 1,10-phenanthroline (phen) in DMSO at 140°C , under an aerobic atmosphere maintained with an O_2 balloon.¹⁰ The reaction time course can be monitored using an aliquot method with ^1H NMR spectroscopic analysis, which shows sharp signals for the sulfide product (**1**). Monitoring the standard catalytic reaction in this fashion reveals a time course with an approximate 12 min induction period, followed by exponential formation of the product. A linear fit to the early time points following the induction period provides an initial rate of $12.7 \pm 0.6 \text{ mM h}^{-1}$ (Figure S6).

Scheme 2. Model Reaction for Mechanistic Study.



PhSSH in Catalytic Reactions. The copper-mediated oxidation of thiols (RSH) to the corresponding disulfides (RSSR) under aerobic conditions is well established.^{32,34} Furthermore, the intermediacy of RSSR in related oxidative Cu-catalyzed thiolation reactions has been supported by the

observed formation and demonstrated reactivity of RSSR under typical reaction conditions.^{32,35}

Under the standard catalytic decarboxylative thiolation conditions, we observed the nearly quantitative consumption of PhSH to form PhSSPh as the only reaction product (84% yield) within the first 4 min of the reaction. Similarly, the CuI/phen-catalyzed aerobic oxidation of PhSH proceeds rapidly in the absence of 2-nitrobenzoic acid, both with and without K₂CO₃. Monitoring this catalytic PhSH oxidation by ¹H NMR spectroscopy provides an estimate of the rate of formation of PhSSPh in the absence of K₂CO₃ as 516 ± 49 mM h⁻¹ at [PhSH]₀ = 97 mM (Figure S7). Furthermore, when PhSSPh was employed in place of PhSH under otherwise standard catalytic decarboxylative thiolation conditions, (2-nitrophenyl)(phenyl)sulfane (**1**) was successfully generated in 82% yield.¹⁰ The time course for this reaction in which [PhSSPh]₀ = 60 mM and [2-nitrobenzoic acid]₀ = 60 mM shows an initial rate of 13.7 ± 3.7 mM h⁻¹ (Figures 1 and S9). This reaction rate is within error of that involving PhSH (12.7 ± 0.6 mM h⁻¹, at [PhSH]₀ = 120 mM, *vide supra*), supporting the chemical and kinetic competence of PhSSPh as the active thiolating source under standard conditions.

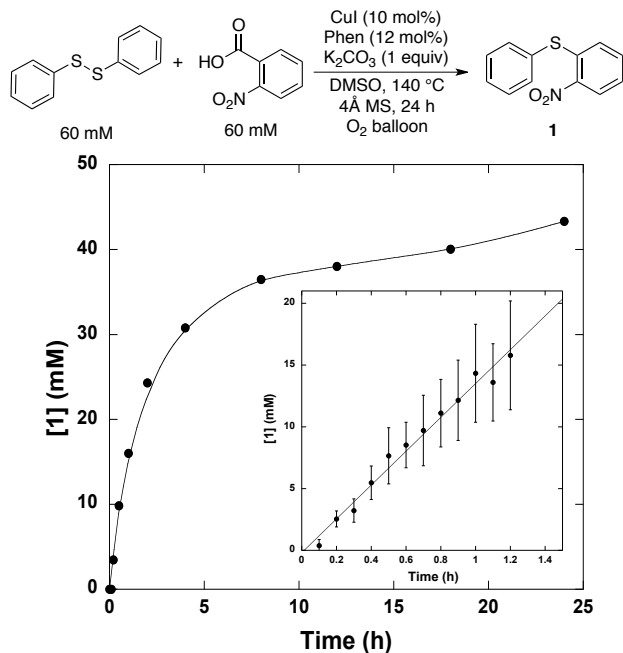


Figure 1. Formation of [(2-nitrophenyl)(phenyl)sulfane] (**1**) over time for the standard catalytic reaction of 2-nitrobenzoic acid with PhSSPh under O₂. The trace of the full time course is not a fit and is included to guide the eye. The inset shows the linear fit to early reaction times; data points are an average of four runs and error bars shown are one standard deviation of the mean.

Identification of a Copper(I) Resting State. The standard catalytic reaction of 2-nitrobenzoic acid with PhSSPh undergoes characteristic color changes as the reaction progresses. Prior to heating, the reaction mixture is a deep brown color. Upon heating, the mixture turns green initially, followed by a gradual change to yellow-green, and finally a persistent orange-brown color. Because of the observed color changes during the catalytic reactions and the characteristic spectral features in the absorption spectra for Cu^I and Cu^{II} species, UV-visible spectroscopic studies were performed to gain insight into the catalyst resting state.

The UV-visible spectroscopic features of phenanthroline-ligated copper complexes are well established. The low valent (phen)Cu^I and (phen)₂Cu^I species exist in equilibrium³⁶ and give rise to metal-to-ligand charge transfer absorptions at 364 and 445 nm, respectively.³⁷ In contrast, the corresponding (phen)₂Cu^{II} displays a broad d-d transition band of weak intensity around 700 nm.³⁸ Because the ~364 nm absorption range is obscured by the sulfane product **1** (λ_{max} = 375 nm) under our reaction conditions, and given the rapid ligand-exchange equilibria common with phenanthroline-ligated copper(I) species, we will use “(phen)Cu^I” to refer to both the mono- and bis-phenanthroline ligated copper(I) species throughout this study.

The reaction mixture of CuI, phen, K₂CO₃, 2-nitrobenzoic acid and PhSSPh was prepared in a septum-sealed cuvette equipped with a stir bar and an O₂ balloon, then heated in a pre-heated aluminum block. The reaction mixture has an initial brown color and a strong absorption at 440 nm characteristic of a (phen)Cu^I species (Figure 2, black trace)³⁷ and a broad band of weak intensity around 699 nm attributed to Cu^{II}.³⁸ The presence of copper(II) in the initial reaction mixture results from background oxidation of copper(I) under these aerobic conditions. The band at 440 nm is suggestive of the formation of (phen)Cu^I. Upon heating at 140 °C, the spectral band at 440 nm is quenched (Figure 2, blue trace) followed by the gradual appearance of a new band at 443 nm (Figure 2, red trace). The appearance of this band was accompanied by the loss of the Cu^{II} feature at 699 nm. The behavior observed in the visible region of the spectrum supports a phenanthroline-ligated copper(I), (phen)Cu^I, species as the catalyst resting state, and suggests the initial formation and consumption of a copper(II) species.

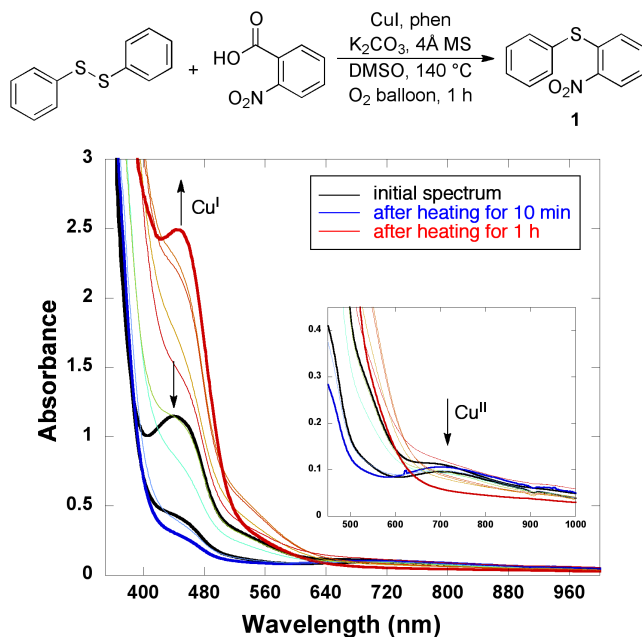


Figure 2. Selected UV-visible spectra measured for the standard catalytic reaction over 1 h. Reaction conditions: 2-nitrobenzoic acid (9.3 mM), PhSSPh (9.7 mM), CuI (1.1 mM), phen (1.0 mM), K_2CO_3 (1.2 equiv), DMSO (2.5 mL), O_2 balloon, 140 °C. Final spectrum: from a 3-fold dilution of the mixture after 1 h.

Determination of Kinetic Reaction Orders. The kinetic dependence of reaction components were measured using an aliquot method. Initial rate measurements reveal a first order dependence on both [CuI/phen] ($[Cu]_0 = 3\text{--}60$ mM, Figure 3a) and [2-nitrobenzoic acid] ($[2\text{-nitrobenzoic acid}]_0 = 30\text{--}120$ mM, Figure 3b), and a zero order dependence on [PhSSPh] ($[PhSSPh]_0 = 10\text{--}120$ mM, Figure 3c). The observed dependence are suggestive of a turn-over-limiting step that involves a copper carboxylate species. Given the high temperatures and forcing reaction conditions often required for the decarboxylation of copper carboxylates,^{2b,23,39-41} it is plausible that decarboxylation from such a species could be turn-over-limiting, however formation of a copper(I)-carboxylate, or oxidation of such a species may also be turn-over-limiting.

The possibility of turn-over-limiting oxidation by O_2 was explored by measuring the rate of the standard catalytic reaction conducted under air ($\sim 21\%$ O_2) used in place of O_2 (14.9 ± 1.8 mM h^{-1} , Figure S13). The data show no dependence on pO_2 and instead, indicate a turn-over-limiting-step that is either formation of or decarboxylation from a copper(I)-carboxylate.

Given the observed kinetic dependence, the rate constant for the standard catalytic reaction is determined to be $k = 0.038 \pm 0.010$ mM $^{-1}$ h $^{-1}$. An induction period is observed under some conditions,

that appears to correlate with steps that generate an active Cu^I -benzoate species. Although there is no significant induction period under standard catalytic conditions (Figure 1), an induction period of ~ 12 min is observed at low $[CuI/phen]$, consistent with the formation of an active copper species during the induction period. The events occurring during this time include copper oxidation and reduction events (*vide infra*), as well as formation of the copper-benzoate species from copper, the benzoic acid, and base. Thus, to gain further insight into the product forming steps from copper carboxylate species, we sought to explore the reactivity of well-defined copper complexes as described below.

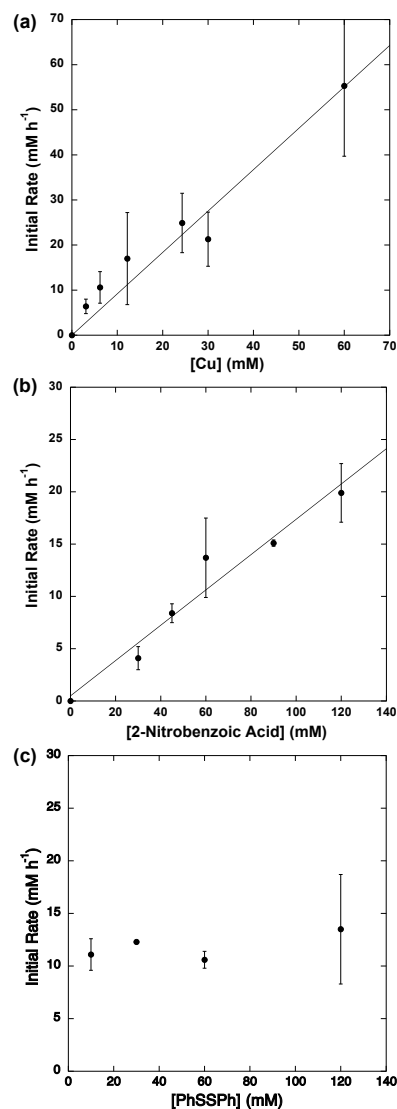
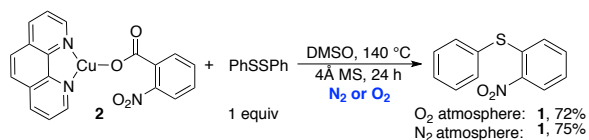


Figure 3. Plot of initial rate (mM h^{-1}) versus (a) $[Cu^I]$ (mM), (b) [2-nitrobenzoic acid] (mM), and (c) [PhSSPh] (mM) for the standard catalytic reaction of 2-nitrobenzoic acid with PhSSPh under O_2 . Data points are an average of two runs and error bars shown are one standard deviation of the mean.

Intermediacy of Copper(I) Benzoate. Copper(I) benzoate species have been proposed by us and others as key intermediates in decarboxylative coupling reactions^{4a,11a,21,40,42} and we envisioned (phen)Cu(O₂CC₆H₄-o-NO₂) (**2**), as a likely species to be generated under our reaction conditions. Therefore, we sought to probe the formation of such a species under typical reaction conditions. The stoichiometric reaction of CuI, phen, 2-nitrobenzoic acid and K₂CO₃ in DMSO-*d*₆ under N₂ at 80 °C was monitored by in situ ¹H NMR analysis (Figure S2). Under these conditions, we observed the formation of **2** in approximately 57% yield after 6 h. The reaction was conducted at 80 °C, because complex **2** is reactive at the typical 140 °C reaction temperature (*vide infra*). The identity of **2** was verified by comparison with an authentic sample synthesized according to a literature procedure.^{4a} This result provides support for the likely generation of **2** under the standard reaction conditions. Furthermore, the relatively slow formation of **2** under these conditions is consistent with the generation of this species contributing to the induction period under catalytic conditions (*vide supra*).

Complex **2** is also catalytically competent. The reaction of 2-nitrobenzoic acid and PhSH with 10 mol% of complex **2** provided (2-nitrophenyl)(phenyl)sulfane (**1**) in 89% yield. Similarly, the stoichiometric reaction of **2** and PhSSPh in DMSO performed under oxygen furnished **1** in 72% yield, while the analogous reaction performed under nitrogen provided **1** in 75% yield (Scheme 3).

Scheme 3. Stoichiometric Reactions of Complex **2** with PhSSPh under O₂ and N₂ Atmospheres.



¹H NMR analysis of the stoichiometric reaction of **2** with PhSSPh in DMSO-*d*₆ under N₂ shows the copper(I)-thiolate dimer [(phen)Cu(μ-SC₆H₅)₂] (**3**) to be the sole copper-containing product in 84% yield (Figure 4a). The identity of **3** was verified following the independent synthesis of this complex from a literature protocol.²⁹ The initial rate of this stoichiometric reaction under N₂ was determined to be 350.0 ± 30 mM h⁻¹ (at [2]₀ = 60 mM and [PhSSPh]₀ = 60 mM, Figures 4b and S15), slightly faster but of the same order of magnitude as the rate predicted based on the catalytic reaction rate (13.7 mM h⁻¹ at 6 mM Cu) and the measured first order dependence on [CuI/phen]. In addition, no induction period was observed for this

reaction, and the mixture maintained an intense brown to red-brown color throughout, indicative of (phen)Cu^I. These data combined suggest that **2** is kinetically competent under reaction conditions and is likely a key reaction intermediate.

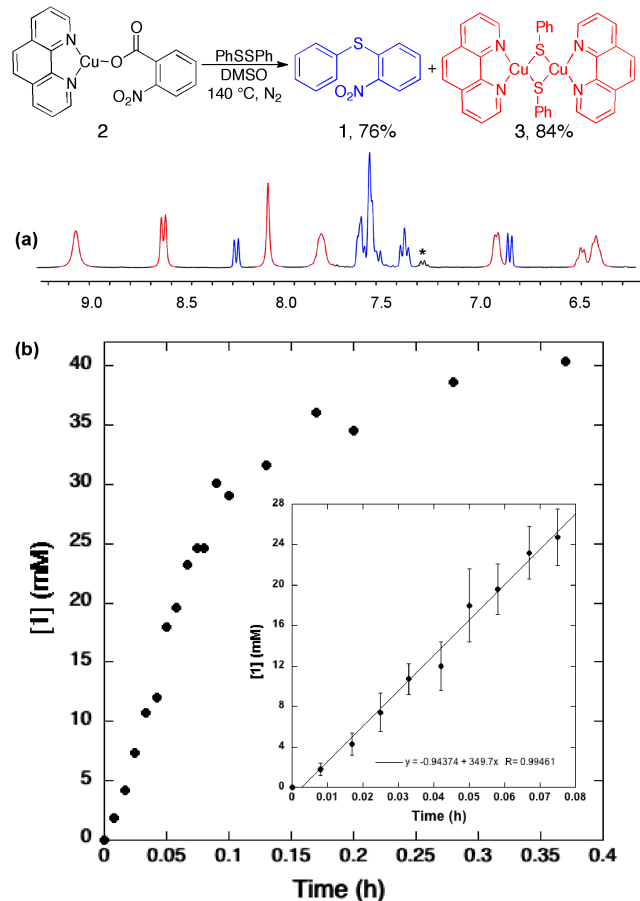
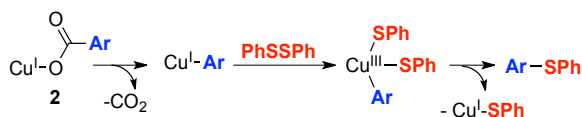


Figure 4. (a) Final ¹H NMR spectrum of the reaction of (phen)Cu(O₂CC₆H₄-o-NO₂) (**2**) (12.7 μmol, 25.4 mM) and PhSSPh (12.4 μmol, 24.8 mM) under N₂ after heating at 140 °C for 55 min in DMSO-*d*₆. Residual PhSSPh is indicated by *. (b) Plot of [(2-nitrophenyl)(phenyl)sulfane] (**1**) (mM) versus time for the reaction of complex **2** (60 mM) and PhSSPh (60 mM) in DMSO under N₂. Inset: Early reaction times indicating the linear fit used to calculate the initial rate. Data points are an average of four runs and error bars shown are one standard deviation of the mean.

Intermediacy of Copper(I) Aryl. The efficient generation of **1** from **2** and PhSSPh described above likely involves a decarboxylation step paired with oxidative addition of Cu^I to the disulfide.^{11a} Sulfide ligands are known to stabilize high-valent Cu^{III} and there are instances wherein disulfides oxidize Cu^I to Cu^{III}.^{43,44} Consequently, discrete organocopper(III) thiolate species have also been proposed as intermediates in oxidative Cu-catalyzed thiolation reactions.^{11a,45} Thus we imagined a product-forming pathway involving initial decarboxylation of **2** to

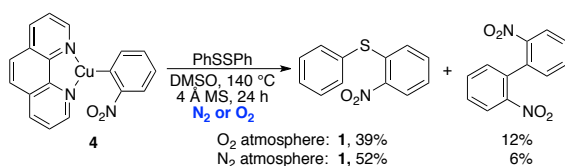
generate a copper(I)-aryl species capable of undergoing oxidative addition with PhSSPh (Scheme 4).

Scheme 4. Plausible Pathway for Product Formation from Complex 2.



We therefore explored the reactivity of the Cu^I-(aryl) complex (phen)Cu(C₆H₄-o-NO₂) (**4**)^{4a} as a possible reaction intermediate. When a mixture of 2-nitrobenzoic acid and PhSH was treated with 10 mol% of **4** under standard catalytic conditions, the (2-nitrophenyl)(phenyl)sulfane product (**1**) was obtained in 75% yield. On treatment of **4** with a stoichiometric amount of PhSSPh (1 equiv) under O₂ 39% yield of **1** was obtained along with the 2,2'-dinitrobyproduct in 12% (Scheme 5). Both an improved yield

Scheme 5. Stoichiometric Reactions of Complex 4 with PhSSPh.



of **1** (52%) and a reduction in byproduct formation (6%) resulted when the same reaction was conducted under nitrogen. The moderate yields of **1** formed from these stoichiometric reactions of **4** at 140 °C are attributed to the competitive decomposition of **4** at elevated temperatures. In a control experiment at 140 °C in DMSO-*d*₆ under N₂, **4** was observed to decompose to a mixture containing nitrobenzene and 2,2'-dinitrobyphenyl (see SI for details). Therefore, we also explored the stoichiometric reaction of **4** with PhSSPh under milder room temperature conditions.

The reaction of **4** with PhSSPh was conducted under N₂ at room temperature in a J. Young NMR tube. ¹H NMR analysis reveals the rapid formation of **1** in 82% and [(phen)Cu(μ-SC₆H₅)₂] (**3**) in 90% within approximately 7 min of mixing (Figure 5). No other reaction products were observed. Because the reaction is nearly complete within 7 min at room temperature, we were unable to measure the initial rate for this reaction. Nevertheless, these observations confirm the facile formation of **1** from **4** and are consistent with the formation of a reactive organocopper(III) dithiolate complex via oxidative addition of PhSSPh to **4** (Scheme 4).

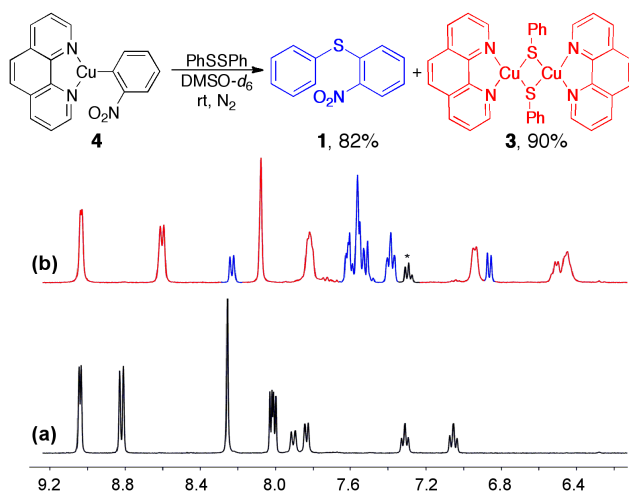
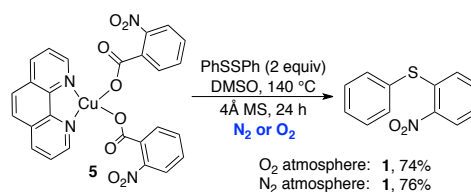


Figure 5. ¹H NMR spectra of (a) **4** in DMSO-*d*₆ at rt, and (b) a mixture of **4** (12.6 μmol, 25.2 mM) and PhSSPh (12.8 μmol, 25.6 mM) in DMSO-*d*₆ (0.5 mL) under N₂ after 7 min at rt. Products: (2-nitrophenyl)(phenyl)sulfane (**1**) and **3**. Residual PhSSPh is indicated by *.

Synthesis and Reactivity of Copper(II) Benzoate.

The observed formation of Cu^{II} species at early reaction times by UV-visible spectroscopy (*vide supra*) suggests that divalent copper species could also be relevant intermediates in these oxidative decarboxylative thiolation reactions. The oxidation of a Cu^{II}(aryl) species by a sulfenyl radical (•SR) to generate the corresponding Cu^{III}(aryl)(SR) species has been proposed in related systems and is a possible pathway under our reaction conditions.⁴⁶ Additionally, we and others have shown Cu^{II} benzoate species to be likely intermediates in decarboxylative arylation^{4a} and selenation reactions.⁴⁷ Consequently, the copper(II) complex (phen)Cu(O₂CC₆H₄-o-NO₂)₂ (**5**) was prepared,^{4a} and its reactivity probed. Complex **5** was catalytically competent for the model reaction of 2-nitrobenzoic acid with PhSH and generated (2-nitrophenyl)(phenyl)sulfane (**1**) in 98% yield. We also probed the stoichiometric reaction of **5** with PhSSPh and observed the successful generation of **1** in 74% yield under oxygen, and 76% under nitrogen (based on carboxylate, Scheme 6).

Scheme 6. Stoichiometric Reactions of Complex 5 with PhSSPh



When this stoichiometric reaction was conducted under an air atmosphere in DMSO-*d*₆ no copper-

containing species could be observed by ^1H NMR spectroscopy at the end of the reaction. In contrast, when the same stoichiometric reaction was conducted under N_2 , $[(\text{phen})\text{Cu}(\mu\text{-SC}_6\text{H}_5)]_2$ (**3**) was formed quantitatively as the only copper-containing product (Figure 6). In addition, the (2-nitrophenyl)(phenyl)sulfane (**1**) is formed quantitatively and exclusively. Two equivalents of **1** are formed for each equivalent of **5** indicating that both carboxylates of **5** are consumed to generate product with the reduction of Cu^{II} to Cu^{I} .

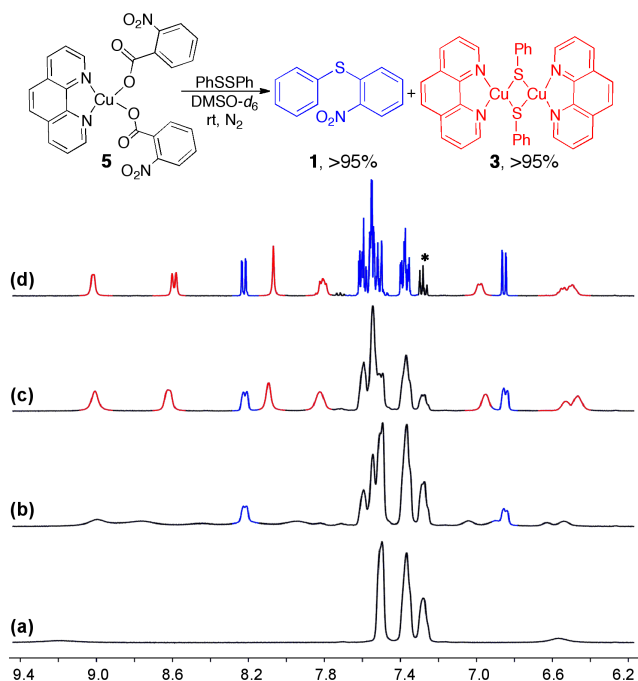


Figure 6. ^1H NMR spectra of the reaction of $(\text{phen})\text{Cu}(\text{O}_2\text{CC}_6\text{H}_4\text{-o-NO}_2)_2$ (**5**) (6.1 μmol , 10.2 mM) and PhSSPh (12.4 μmol , 20.7 mM) in $\text{DMSO-}d_6$ (0.6 mL) under N_2 . (a) mixture of **5** and PhSSPh in $\text{DMSO-}d_6$ at rt (b) mixture heated at 140°C for 9 min (c) mixture heated at 140°C for 40 min (d) mixture heated at 140°C for 3 h 40 min. Residual PhSSPh is indicated by *.

The reduction of Cu^{II} to Cu^{I} in the stoichiometric reaction of **5** with PhSSPh is supported by UV-visible spectroscopic experiments. Upon heating complex **5** and PhSSPh in DMSO at 140°C under N_2 the absorbances at ~ 438 nm and 535 nm grow in over time, diagnostic of $(\text{phen})\text{Cu}^{\text{I}}$ (Figure 7). Concurrently, there is a loss of the broad band at ~ 695 nm, typical of **5**. These observations indicate the generation of Cu^{I} during this reaction and support its relevance under reaction conditions.

Finally, monitoring the stoichiometric reaction under N_2 by ^1H NMR spectroscopy of reaction aliquots allows us to probe the kinetic behavior of the reaction. For the reaction in which $[\text{5}]_0 = 30$ mM and $[\text{PhSSPh}]_0 = 60$ mM the formation of product **1** produces an

apparent sigmoidal curve with an approximate 3 min induction period (Figure 8, red points). Qualitative observations of the reaction of **5** with PhSSPh also support the reduction of copper(II) to copper(I) during the initial lag phase. Visual observation reveals that upon heating, the blue color characteristic of **5** dissipates and the mixture becomes green. After the approximate 3 minute induction period, the mixture becomes yellow-green, followed by a rapid change to a final persistent orange-brown color indicative of Cu^{I} .

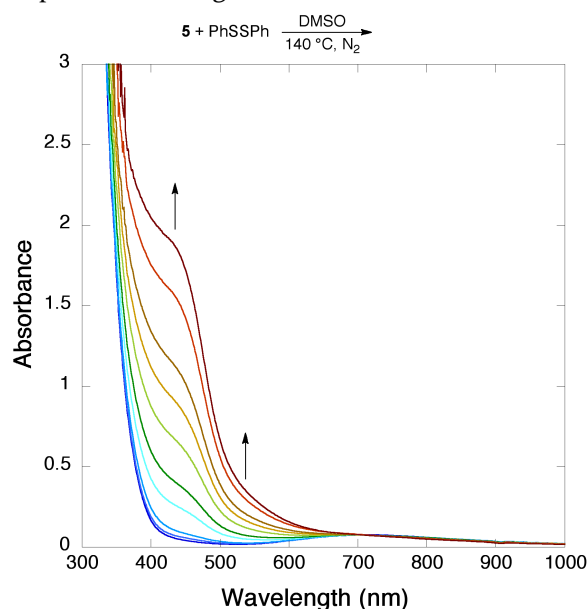


Figure 7. UV-visible spectra for the stoichiometric reaction of **5** and PhSSPh under N_2 at 140°C in DMSO. Reaction conditions: $(\text{phen})\text{Cu}(\text{O}_2\text{CC}_6\text{H}_4\text{-o-NO}_2)_2$ (**5**) (0.83 mM), PhSSPh (1.6 mM), DMSO (2.5 mL), N_2 balloon, 140°C .

The presence of an induction period and sigmoidal time course for the reaction of complex **5** with PhSSPh is in contrast to the observations for the copper(I) complex **2**, for which no induction period was observed (*vide supra*). A comparison of the reaction time courses for the stoichiometric reactions of complexes **2** and **5** with PhSSPh under N_2 at 140°C , obtained by ^1H NMR analysis of reaction aliquots is represented in Figure 8. Despite the difference in appearance of the two time courses, both reactions form **1** and complex **3** in high yields and as the sole reaction products.

The empirical observations combined with the lack of an induction period in the case of **2** and the presence of a ~ 3 min induction period in the case of **5** serve to corroborate the intermediacy of the Cu^{I} species and suggest reduction of Cu^{II} to Cu^{I} during the initial slow phase. Additionally, the observed similarity in reaction products for the reactions of **2** and **5** with PhSSPh is consistent with Cu^{I} and Cu^{II} complexes generating product via a common pathway. Thus, these data indicate that direct decarboxylation from a

copper(II) benzoate intermediate is unlikely, and instead reduction to copper(I) and subsequent decarboxylative coupling from a copper(I) carboxylate is more plausible.

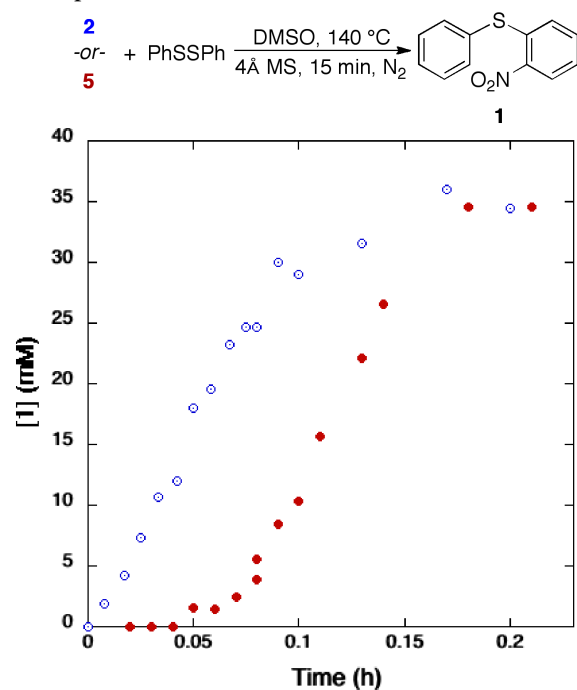
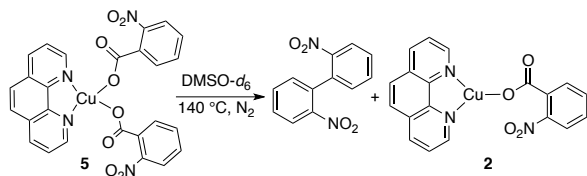


Figure 8. Comparison of reaction profiles for the reaction of (phen)Cu(O₂CC₆H₄-o-NO₂) (**2**) (60 mM) \circ , and (phen)Cu(O₂CC₆H₄-o-NO₂)₂ (**5**) (30 mM) \bullet , with PhSSPh (60 mM) under N₂ at 140 °C. Product concentrations were determined by quantitative ¹H NMR analysis.

Decarboxylation of Copper(II) Benzoate. In the absence of PhSSPh, the reduction of Cu^{II} complex **5** occurs via a distinct, decarboxylation-based pathway to generate **2** and 2,2'-dinitrobiphenyl as the oxidation product (Scheme 7). The ¹H NMR spectrum of complex **5** in DMSO-*d*₆ at rt under N₂ is broad and almost featureless. Upon heating at 140 °C, a gradual sharpening of the signals occurs along with the formation of nitrobenzene and 2,2'-dinitrobiphenyl. These changes in the ¹H NMR spectra are accompanied by a change in the color of the initially blue solution of **5** to a final orange-brown color indicative of Cu^I formation.

Scheme 7. Proposed pathway for the reduction of **5 under N₂ in the absence of PhSSPh.**



Probing the same decarboxylation of **5** by UV-visible spectroscopy, reveals the loss of the initial band at 695

nm characteristic of **5** with the formation of a new band at 444 nm and an additional increase in absorption at ~543 nm. This final spectrum is identical to the spectrum of **2** (Figure S26). The spectroscopic data suggest that a decarboxylation pathway could be responsible for the initial reduction of Cu^{II} to Cu^I.

Reduction of Cu^{II} to Cu^I prior to decarboxylation is consistent with work by Cohen *et al.*³⁹ who showed Cu^I to be the active catalyst in the decarboxylation of cupric aromatic carboxylates in quinoline solvent. Evidence for the reduction of Cu^{II} to Cu^I in this prior work was provided by the loss of the ESR signal within a few minutes, prior to decarboxylation. In addition, the observed Cu^{II}-(2-nitrobenzoate) was found to decarboxylate 100 times slower than its Cu^I counterpart.²² In these cases, the reduction of Cu^{II} to Cu^I was attributed to the capability of the quinoline to facilitate the conversion, via the possible formation of 2-oxygenated quinolines.³⁹

The reduction of Cu^{II} to Cu^I in the absence of an explicit reductant has been observed throughout the realm of copper-mediated transformations.^{48,49} For example, in the related Ullmann-type coupling to form C-O and C-N bonds,^{50,51} Paine^{48a} and Weingarten⁵¹ observed that in the presence of coordinating nucleophiles, Cu^{II} reduces to active Cu^I species prior to catalysis, with the concomitant oxidation of the phenoxide and amine nucleophiles.^{ib} More recently, Jutand and coworkers^{37a} reported on the reduction of phenanthroline-ligated Cu^{II} precursors by alcohols or amines to generate the active Cu^I catalyst in the presence of Cs₂CO₃. Peñeñory and coworkers^{37b} later made a similar observation with a sulfur-based nucleophile. Yi and coworkers,^{48b} further reported on the role of the tert-butoxide anion as base and as single electron donor in promoting the reduction of Cu^{II} precursors via the homolytic cleavage of an O-Cu^{II} bond. Thus, many pathways have been established for the in situ reduction of Cu^{II} to Cu^I, however a unique decarboxylation step appears to be responsible for the reduction of these copper(II)-carboxylate species.

Based on the data above, we expected the reaction shown in Scheme 7 to be responsible for the initial uncatalyzed formation of **2** from **5** in the stoichiometric reaction of **5** with PhSSPh. Alternatively, **2** could also result from an initial step involving the reaction of **5** with PhSSPh (Scheme 8, step 1). Thus, we monitored the stoichiometric reaction of **5** with PhSSPh by ¹H NMR spectroscopy at two different initial concentrations of PhSSPh to help distinguish between these two possible pathways (Figure 9). Under these conditions, there is a clear dependence of the initial lag phase on [PhSSPh]₀ indicating a key role for disulfide in the initial reaction of complex **5**.

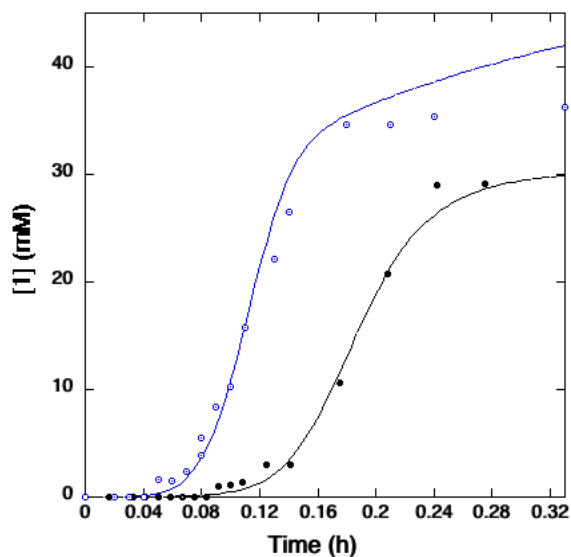


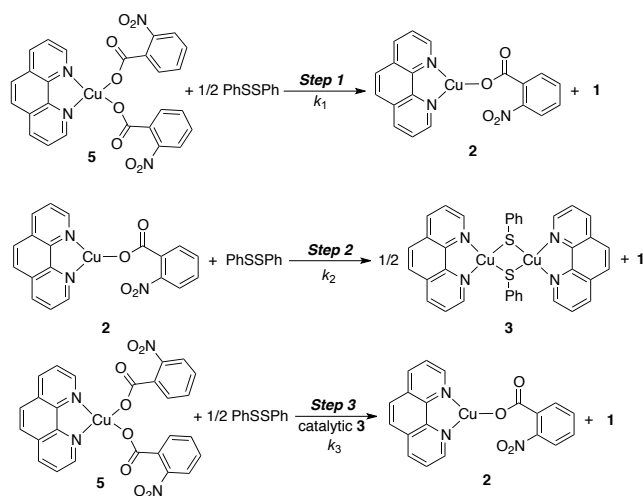
Figure 9. Comparison of reaction profiles for the reaction of (phen)Cu(O₂CC₆H₄-o-NO₂)₂ (**5**) (30 mM) with PhSSPh at 30 mM (●) and 60 mM (⊙) under N₂ at 140 °C. Product concentrations were determined by quantitative ¹H NMR analysis.

Loss of Induction Period with Complex 3. The time course profiles for the stoichiometric reactions of complex **5** all feature a distinctive sigmoidal shape. Sigmoidal time course traces characterized by this type of three-phase kinetic profile, i.e. a lag, exponential and saturation phase, are common under conditions of autocatalysis, in which a reaction product catalyzes its own formation.^{52,53} Because the stoichiometric reaction of complex **5** with PhSSPh generates the copper(I)-thiolate complex **3**, we suspected that complex **3** may catalyze the conversion of **5** to product **1** with the concomitant formation of complex **2** (Scheme 9). The resulting copper(I)-carboxylate **2** also generates copper(I) upon reaction with PhSSPh as shown in Scheme 3 above, leading to the three step sequence shown in Scheme 8. In this sequence, Steps 1 and 3 are identical, with the exception that Step 3 is catalyzed by complex **3**.

In this model, Step 2 corresponds to the stoichiometric reaction of complex **2** with PhSSPh, discussed above ($k_2 = 0.097 \pm 0.008 \text{ mM}^{-1} \text{ h}^{-1}$). The time course data for the reaction of **5** with PhSSPh (30 mM) was fit to this model using the reaction fitting and data simulation software COPASI.⁵⁴ The time course data are shown in Figure 9 and the black trace shown is obtained from fitting the experimental data to the model described above. This fit provides rate constants of $k_1 = 0.0010 \pm 0.00045$, $k_3 = 6.20 \pm 0.63$. This same model and rate constants were then used to predict the time course for the reaction of **2** with PhSSPh (60 mM, blue trace). Both data sets are well described by the same model. It is worth noting that this and all stoi-

chiometric reactions of **5** feature increased scatter in the data at later reactions times, likely due to competing side reactions and decomposition pathways (Figures S16 and S17).

Scheme 8. Proposed Pathway for the Reaction of 5 with PhSSPh under N₂.



To directly probe the possible catalysis by **3**, the inclusion of a small amount of **3** (0.05 or 0.1 equiv) at the beginning of the reaction of **5** with PhSSPh led to the disappearance of the induction period (Figure 10). Variable time normalization analysis (VTNA) of these time course data with the graphical evaluation method developed by Burés and coworkers⁵⁵ (Figure S18b) indicates a 0.5 order dependence on [**3**], indicative of dissociation of this dimeric complex to access the reactive monomeric form, (phen)Cu(SPh). These time course

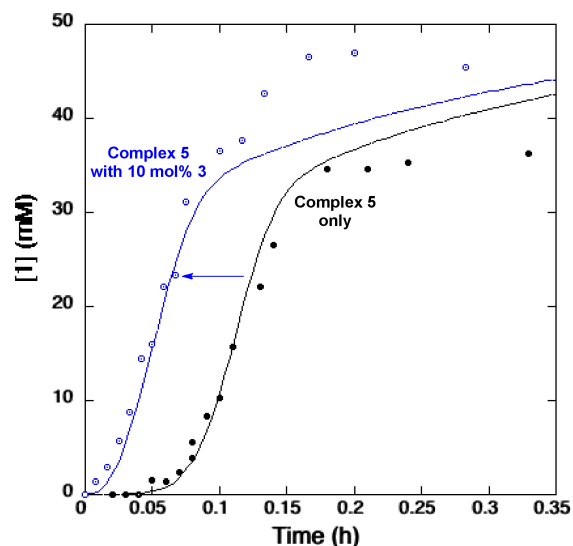


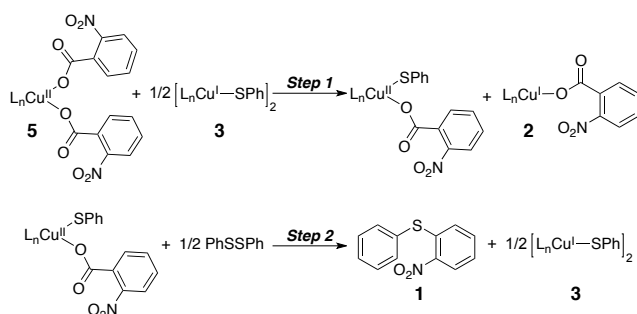
Figure 10. Comparison of the reaction profiles for the reaction of (phen)Cu(O₂CC₆H₄-o-NO₂)₂ (**5**) (30 mM) with PhSSPh (60 mM) under N₂ at 140 °C with (⊙) and without (●) complex **3** (3 mM). Product concentrations were determined by quantitative ¹H NMR analysis.

data can also be fit using the same three-step model shown in Scheme 8, with the inclusion of a fourth step to describe the dissociation of **3** (Scheme S3). This fit is shown in Figure 10 and provides a rate constant for dissociation of $k_4 = 2.64 \pm 0.48$.

There are several examples of copper-catalyzed reactions that exhibit autocatalytic behavior such as polymerization,⁵⁶ coupling^{57,58} and cycloaddition^{52,59} reactions. Lei *et al.*⁵⁷ elegantly described Cu^{II}-Cu^I cooperativity in the homocoupling of terminal alkynes with Cu^{II}. Biphenylacetylene, generated in situ, mediates the reduction of CuCl₂(TMEDA) with an accompanying induction period and autoacceleration curve. Cu^I was confirmed as an autocatalyst, serving to reduce the induction period and enhance the reaction rate. Hartwig and coworkers have described the autocatalytic behavior of in situ generated Cu^I in the reaction of well-defined Cu^I-amido complexes with iodoarenes.⁵⁸ Finally, Whitesides *et al.*⁵² have reported on the autocatalytic behavior of the triazolyl product in the copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction between tripropargylamine and 2-azidoethanol. In this example, the initial reduction of Cu^{II} to catalytically active Cu^I is attributed to the terminal alkyne serving as a reducing agent, another well-accepted reactivity pattern throughout the literature.^{52,61}

We imagined that under our conditions, the catalysis by **3** (Scheme 8, Step 3) could occur by ligand exchange between complexes **3** and **5** to form the heteroleptic complex (phen)Cu^{II}(O₂CC₆H₄-o-NO₂)(SPh) (Scheme 9, Step 1). This intermediate could react productively with PhSSPh to form product **1** and regenerate complex **3** (Scheme 9, Step 2). Thus, the overall reaction would be the formation of product **1** and complex **2** from **5** and PhSSPh, catalyzed by complex **3** as shown in Scheme 8 (Step 3).

Scheme 9. Proposed Pathway for the Reaction of **5** with PhSSPh catalyzed by **3**.^a



^a L_n = 1,10-phenanthroline

To explore the possible ligand exchange between complexes **3** and **5**, we conducted the stoichiometric reaction of these two species under N₂ at 140 °C. Under

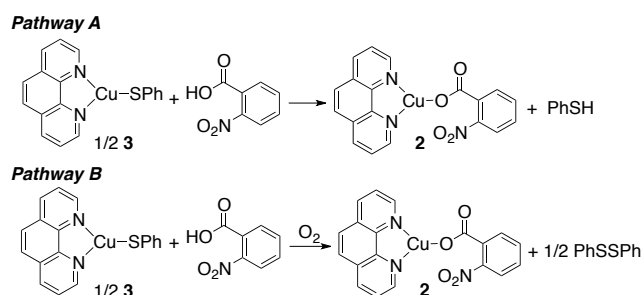
these conditions, both product **1** and the 2,2'-dinitrobiphenyl byproduct were formed in 35% and 26% yields respectively. When the same reaction was performed under an O₂ atmosphere, **1** was formed in 75% with no 2,2'-dinitrobiphenyl detected. The formation of **1** from complexes **3** and **5** indicate facile ligand exchange under these conditions and support a ligand exchange step en route to product formation in the stoichiometric reactions of **5**.

From the data described above, it is apparent that copper(II)-carboxylates can generate product **1** through a pathway that involves initial reduction to copper(I). More broadly, under our reaction conditions decarboxylation occurs from a Cu^I species, and product formation occurs from subsequent reaction of the resulting Cu^I-(aryl) with PhSSPh as shown above. Cu^{II}-(carboxylate) species are not the catalytically relevant species but can access the same pathway either via decarboxylation (Scheme 7) or by ligand exchange in the presence of **3** (Scheme 9).

Aerobic Oxidation of Copper(I)-Thiolate. Owing to the formation of [(phen)Cu(μ-SC₆H₅)₂] (**3**) in the stoichiometric reactions of complexes **2**, **4**, and **5** with PhSSPh under nitrogen, we decided to explore the reactivity of independently prepared **3** under catalytic conditions. For the reaction of 2-nitrobenzoic acid and PhSH with **3** as catalyst, in a sealed Schlenk tube equipped with an O₂ balloon, **1** was obtained in 88% yield, demonstrating the catalytic competence of **3**.

We considered two likely pathways for the turnover of complex **3**. First, we considered ligand exchange of **3** with benzoic acid or potassium 2-nitrobenzoate to generate complex **2** directly (Scheme 10, Pathway A). Alternatively, we considered a pathway in which O₂ is required to facilitate the turnover of **3** (Scheme 10, Pathway B).

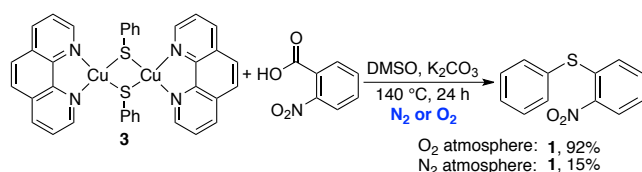
Scheme 10. Possible pathways for the turnover of **3**



In pathway A, complex **3** would be expected to form product upon treatment with 2-nitrobenzoic acid under N₂. In addition, the sole role of O₂ in this manifold would be to generate PhSSPh from PhSH, and catalytic turnover with PhSSPh would be expected to be efficient under anaerobic conditions. Such a pathway was

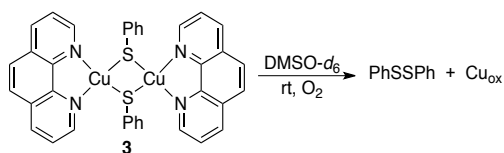
ruled out based on a series of control experiments. The stoichiometric reaction of **3** and 2-nitrobenzoic acid was conducted under both N₂ and O₂ atmospheres. In the presence of O₂, the sulfane product **1** is formed in 92% yield, while under N₂ only 15% is obtained (Scheme 11). In addition, when the standard catalytic reaction of 2-nitrobenzoic acid and PhSSPh was conducted under N₂, only a 15% yield of (2-nitrophenyl)(phenyl)sulfane (**1**) was obtained, indicating an additional role for O₂ in catalysis. These results are consistent with the quantitative formation of **3** in all stoichiometric reactions conducted under nitrogen, but its absence under aerobic conditions (*vide supra*). We suspected that this species may be inert to turnover in the absence of O₂ and thus requires O₂ for catalysis. These data indicate a clear role for O₂ in the activation of the copper(I)-thiolate dimer **3** as an entryway into catalysis, and are consistent with pathway B.

Scheme 11. Stoichiometric Reaction of Complex **3** with 2-Nitrobenzoic Acid



We therefore investigated the interaction of **3** with O₂ by monitoring a solution of **3** in DMSO-*d*₆ under an O₂ headspace at room temperature, by ¹H NMR spectroscopy. Complex **3** was observed to gradually generate PhSSPh in 71% conversion at room temperature after 2 h (Scheme 12). No diamagnetic copper species were observed, indicating the oxidation of Cu^I. Similarly, the color change from a deep-brown to a final green color accompanies this oxidation, consistent with the formation of a new oxidized copper(II) species, Cu_{ox}.

Scheme 12. Aerobic oxidation of [(phen)Cu(μ-SC₆H₅)₂] (**3**) in DMSO-*d*₆



This aerobic oxidation of [(phen)Cu(μ-SC₆H₅)₂] (**3**) at 140 °C was also monitored by UV-visible spectroscopy. Complex **3** has characteristic bands at 441 nm attributed to a (phen)Cu^I species and a shoulder at ~538 nm. A solution of **3** in DMSO was prepared in a septum-sealed cuvette equipped with a stir bar, in a N₂ filled glovebox. On removal from the glovebox, an initial spectrum was taken after which an O₂ balloon

was inserted via the septum. The solution was heated with stirring at 140 °C in an aluminum block and the oxidation of Cu^I was followed by monitoring the loss of the intense band shifted to ~429 nm upon heating. The appearance of a new band of weak intensity between 711-722 nm attributed to (phen)₂Cu^{II} was also observed (Figure 11). An estimate of the rate of oxidation for an initial concentration of [(phen)Cu(μ-SC₆H₅)₂] = 0.17 mM was 0.23 mM h⁻¹.

Thus, we envisioned that under catalytic conditions, the aerobic oxidation of in situ generated **3** to liberate PhSSPh and catalytically relevant oxidized copper species, Cu_{ox}, is a key step in the process. The resulting Cu_{ox} regenerates **2** in the presence of carboxylate, as a path for re-entry into the cycle. We therefore explored the reactivity of in situ generated Cu_{ox} in a series of NMR tube experiments. When a solution of **3** in DMSO-*d*₆ in a septum-sealed NMR tube was bubbled with O₂ for several minutes and the resulting solution subsequently treated with 2-nitrobenzoic acid (**3** equiv) in the presence of K₂CO₃ with heating at 140 °C, (2-nitrophenyl)(phenyl)sulfane (**1**) was observed in 98% yield, after 4 h. These results are indicative of the chemical competence of the Cu_{ox} species resulting from the aerobic oxidation of **3**.

The importance of O₂ for product formation has been observed in related aerobic Cu-catalyzed thiolation reactions. Some of the more commonly proposed roles of O₂ in these reactions include facilitating the conversion of thiol to disulfide, promoting the formation of organocopper thiolates, mediating H-atom abstraction in C-H substrates, oxidation of Cu(I)-thiolates, suppressing undesired side reactions and facilitating the regeneration of catalytically active species.^{23,31,35} Based on our findings, however, in addition to facilitating the generation of RSSR from RSH, a key role of O₂ in this system is to enable catalytic turnover via oxidative dissociation of an otherwise tightly bound thiolate ligand in [(phen)Cu(μ-SC₆H₅)₂] (**3**). This observation is consistent with findings of related aerobic copper-catalyzed thiolation reactions wherein dramatically reduced yields are observed in the absence of O₂ thereby validating the importance of O₂ in generating relevant competent species including catalytically active Cu species.^{11a,25-27}

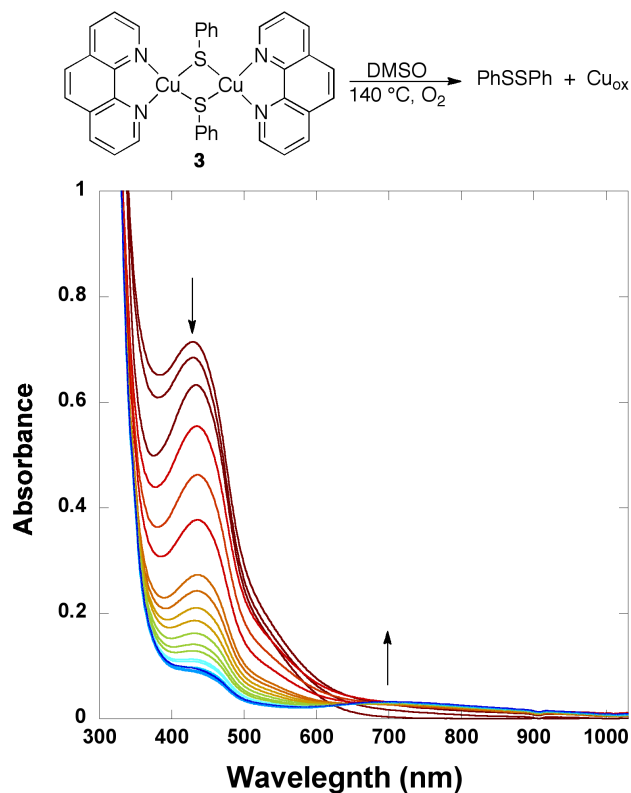


Figure 11. UV-visible spectra for the aerobic oxidation of $[(\text{phen})\text{Cu}(\mu\text{-SC}_6\text{H}_5)]_2$ (**3**) in DMSO at 140°C . Reaction conditions: $[(\text{phen})\text{Cu}(\mu\text{-SC}_6\text{H}_5)]_2$ (**3**) (0.2 mM), DMSO (2.5 mL), O_2 balloon, 140°C .

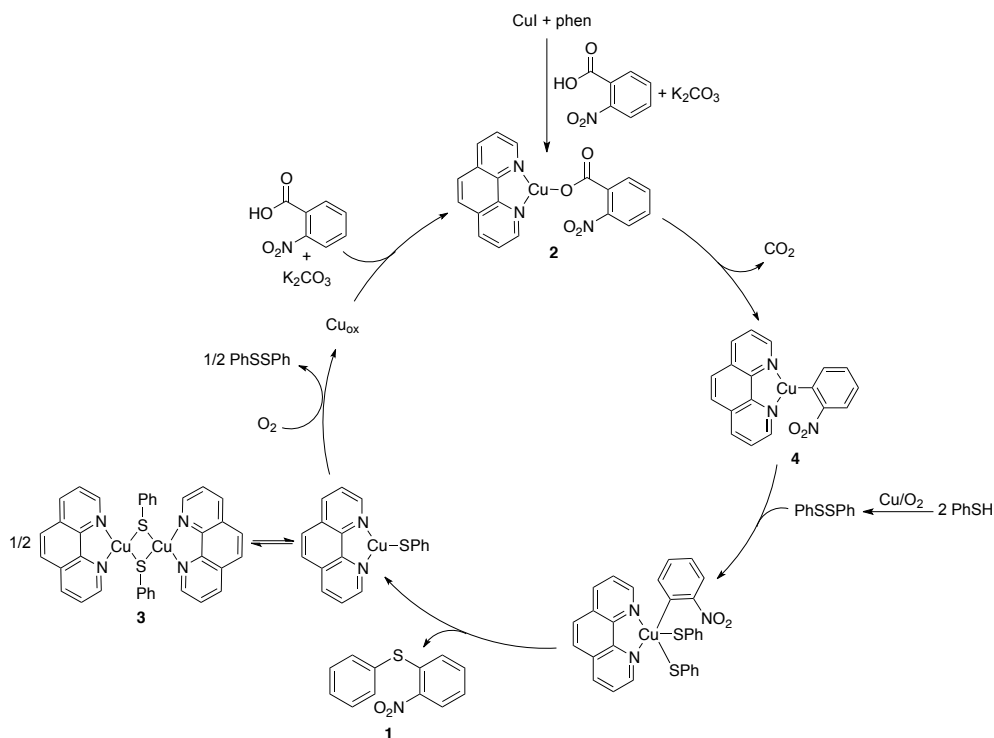
Mechanistic Model. The above results reveal some key features of the mechanism of this aerobic copper catalyzed decarboxylative thiolation of benzoic acids. First, the rapid conversion of PhSH to PhSSPh under reaction conditions and the demonstrated chemical and kinetic competence of PhSSPh suggest PhSSPh is the active thiolating source. Secondly, all of the copper complexes synthesized in this study are competent catalysts for the reaction of 2-nitrobenzoic acid with PhSH, and the observed generation of $(\text{phen})\text{Cu}(\text{O}_2\text{CC}_6\text{H}_4\text{-o-NO}_2)$ (**2**) under N_2 from reaction components strongly supports the intermediacy of this species under reaction conditions. Additionally, the spectroscopic data indicate a copper(I) resting state and the measured reaction orders exclude a turn-over-limiting step that is oxidation by O_2 or reaction with PhSSPh. Instead, decarboxylation of a copper(I)-carboxylate is the most likely turn-over-limiting step of this reaction.

Mechanistic studies of copper-mediated redox-neutral decarboxylation reactions have shown these reactions to proceed through a pathway involving decarboxylation of a copper(I)-carboxylate. Under oxidative conditions, however, we expected that decarboxylation from a copper(II)-carboxylate

intermediate may be plausible. Instead, our data indicate two pathways for the possible reduction of a copper(II)-carboxylate species to copper(I). In the absence of disulfide, a decarboxylative pathway enables reduction of copper with concomitant formation of the biaryl, while in the presence of disulfide, decarboxylative coupling forms **1** and copper(I). This pathway is evidenced by the dramatic difference in reaction profiles of the stoichiometric reactions of well-defined copper(I) and copper(II) carboxylate complexes. In particular, the reaction of copper(II) features an induction period and sigmoidal kinetics. This reaction behavior arises from the slow initial reaction of **5** with PhSSPh, suggesting decarboxylation from a copper(I)-carboxylate to be operative under catalytic conditions.

O_2 is essential for efficient product formation owing to the poor yields of the diarylsulfide (**1**) obtained in its absence. Although the oxidation of copper(I) species has been observed to be turn-over-limiting in a number of other copper-catalyzed aerobic reactions,⁶⁴⁻⁶⁶ we believe that under our conditions the oxidation step is required in order to release a tightly bound thiolate ligand from **3**, regenerating the active catalyst **2** in the presence of 2-nitrobenzoic acid and base. This was evidenced by the generation of PhSSPh upon the exposure of a solution of $[(\text{phen})\text{Cu}(\mu\text{-SC}_6\text{H}_5)]_2$ (**3**) in DMSO to O_2 (Figure S5). The resultant in situ generated Cu_{ox} species was also chemically competent in producing (2-nitrophenyl)(phenyl)sulfane (**1**).

Inhibition of copper catalysis by a sulfur-based ligand has been observed in other systems, via the formation of the thermodynamically stable Cu-SR bond. Liebeskind and coworkers^{65,66} have introduced a chelation-based dissociation strategy to re-activate the Cu catalyst in their C-C coupling reactions. The generation of an active Cu-oxygenate species from Cu-SR under aerobic conditions was believed to be a significant step in providing catalytic Cu for turnover. We believe that related oxidative dissociation pathways may be operative in a variety of Cu-catalyzed aerobic thiolation reactions.²⁵



Scheme 13. Proposed mechanism of the aerobic Cu-catalyzed oxidative decarboxylative thiolation of benzoic acids.

Based on our findings we propose a reaction pathway (Scheme 13), that involves the generation and subsequent decarboxylation of **2** to form **4**. This decarboxylation precedes oxidative addition of the PhSSPh to the Cu^I-(aryl) **4**, to generate a highly reactive organocopper(III)-dithiolate species that is well-poised for rapid reductive elimination to generate the diaryl sulfide product **1** and [(phen)Cu(μ -SC₆H₅)₂] (3). This latter step is supported by literature precedent involving well-defined macrocyclic organocopper(III) species and sulfur-based nucleophiles.³⁰ The oxidative dissociation of **3** with O₂ liberates PhSSPh and Cu_{ox} which regenerates **2** in the presence of 2-nitrobenzoic acid and K₂CO₃.

CONCLUSIONS

In summary, this work describes an experimental mechanistic study of the aerobic copper-catalyzed decarboxylative thiolation of benzoic acids. PhSSPh was found to be the active thiolating source under reaction conditions. Spectroscopic and kinetic studies suggest catalytically-relevant discrete (phen)Cu^I complexes are chemically and kinetically competent in mediating product formation supporting their intermediacy. UV-visible studies strongly support a Cu^I resting state. These findings provide valuable insight into key mechanistic steps for a phenanthroline-ligated Cu^I catalyst system involved in the aerobic copper

catalyzed C-S coupling reactions. Overall, the identification of the catalytic intermediates will allow for a more rational approach to the catalyst design and development process targeting catalytic systems capable of exploiting this observed mode of reactivity. The findings may also have implications for the improvement of related aerobic Cu-mediated C-heteroatom bond formation reactions.^{6a,6c}

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge

Experimental procedures, kinetic data, spectral data (PDF)

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SYNOPSIS TOC

