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Cu(I)-Catalyzed Aerobic Cross-Dehydrogenative Coupling of Terminal Alkynes with Thiols for Construction of Alkynyl Sulfides

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Highly active and selective aerobic cross-dehydrogenative coupling of terminal alkynes with thiols to construct alkynyl sulfides catalyzed by Cu(I) using molecular oxygen as the oxidant has been developed under mild reaction conditions. The process is applicable to a wide range of alkynes and various thiols and is compatible with a variety of functional groups on both alkyne and thiols coupling partners.

10 Introduction

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Alkynyl sulfides are extremely versatile and essential building blocks in organic synthesis and intermediates for sulfur-rich functional polymers.¹⁻⁶ The vast majority have commonly used metal-acetylides and sulfuryl halides or disulfides for synthesis of ¹⁵ alkynyl sulfides up to date.⁷⁻⁹ However, these methods require a prefunctionalization process of terminal alkynes or sulfur nucleophiles coupling partner, resulting in inevitable formation of large amounts of side-products during the preactivation steps. In addition, these methods lack generality, suffer from the forcing ²⁰ reaction conditions, low chemoselectivity, and/or limited substrate scopes making these methods less attractive and

practical. It is therefore of considerable importance to develop a direct, efficient, and practical catalytic procedure for synthesis of alkynyl sulfides without preactivation of terminal alkynes and ²⁵ thiols.

Metal-catalyzed direct functionalization of C-H bonds has gained enormous attention as a powerful and straightforward method to construct new C-X bonds (X = heteroatom) over the past decades,^{10, 11} providing a toolbox of tunable reaction ³⁰ conditions for a large range of substrates. In particular, oxidative cross-dehydrogenative coupling reactions catalyzed by metals provides an elegant protocol for creation such compounds through direct activation of C-H and/or X-H bonds, which is now emerging as an important reaction in organic synthesis.¹² Despite

- ³⁵ considerable progress, the activation of C(sp)-H bond of terminal alkynes for the incorporation with heteroatom into organic molecules still remains a significant challenge because of the undesired diyne formation through Glaser coupling.¹³ Another major concern is the predominant use of stoichiometric oxidants
- ⁴⁰ for the coupling such as metal salts (Cu^{II} or Ag^I), organohalide, PhI(OAc)₂, or benzoquinone which are not either environmental or economical viable. Replacement of these oxidants by molecular oxygen is highly desirable from the standpoint of green chemistry. A few known examples of the direct oxidative cross-
- ⁴⁵ dehydrogenative coupling of terminal alkynes with nitrogen nucleophiles and H-phosphonates using air or O₂ as the sole

 Table 1. Optimization results for Cu(I)-catalyzed aerobic crossdehydrogenative coupling of 4-methylphenylacetylene and thiophenol.^a



| Entry | Base | Conv. | Yield (%) ^c | | | |
|-----------------|---------------------------------|------------------|------------------------|--|----|----|
| _ | | (%) ^b | 3a | 4a (<i>Z</i> / <i>E</i>) ^d | 5a | 6a |
| 1 | K ₂ CO ₃ | 100 | 96 | 2 (100/0) | 0 | 0 |
| 2 | Na ₂ CO ₃ | 100 | 85 | 11 (89/11) | 0 | 0 |
| 3 | Cs_2CO_3 | 98 | 90 | 5 (92/8) | 0 | 0 |
| 4 | N(Et) ₃ | 94 | 0 | 3 (100/0) | 87 | 0 |
| 5 | Pyridine | 89 | 0 | 5 (100/0) | 78 | 0 |
| 6 | TBD | 100 | 25 | <2 | 0 | 70 |
| 7 | DBU | 100 | 45 | <2 | 50 | 0 |
| 8 | TMG | 100 | 87 | <2 | 9 | 0 |
| 9 ^e | - | 65 | 0 | 40 (77/23) | 21 | 0 |
| $10^{\rm f}$ | K_2CO_3 | 82 | 49 | 32 (80/20) | 0 | 0 |
| 11 ^g | K_2CO_3 | 90 | 0 | 14 (80/20) | 72 | 0 |
| 12 ^h | K ₂ CO ₃ | 88 | 0 | 63 (59/41) | 22 | 0 |
| 13 ⁱ | K ₂ CO ₃ | 98 | 91 | 3 (100/0) | 0 | 0 |
| 14 ^j | K ₂ CO ₃ | 100 | 90 | 5 (90/10) | 0 | 0 |

^a Reaction conditions: 5 mol% Cu^ICl with respect to 1a, 10 mol% base with respect to 1a, 0.5 mmol 1a, 0.55 mmol 2a, 2 mL DMSO, 70°C, 1 atm O₂, 1 h. ^b Conversion was determined by ¹H NMR of the reaction mixture, based on 1a. ^c NMR yield based on 1a using CH₂Br₂ as an internal standard. ^d Stereoselecivity was determined by ¹H NMR. ^c In the absence of base. ^f 5 mol% of K₂CO₃. ^g In the absence of Cu^ICl, 2 h. ^h Under argon atmosphere, 2 h. ⁱ In open air, 1.5 h. ^j At room temperature, 3 h.

oxidant to form C-N and C-P acetylenes have been developed recently by Stahl,¹⁴, Bolm¹⁵, Evano,¹⁶ Han^{17a} and Wang,^{17b} respectively. In terms of the incorporation of S atom into ⁵⁰ acetylenes to form alkynyl sulfides using direct oxidative crossdehydrogenative coupling method, there is still no precedent using O2 or air as a terminal oxidant.

Recent considerable advances in the broad array of copper-catalyzed oxidative C-H functionalization highlight the potential to 5 construct sulfur-incorporated functional acetylenes.18 Herein, we report the successful application of Cu^ICl as an efficient catalyst for the direct oxidative cross-dehydrogenative coupling of a wide scope of terminal alkynes 10 with variant thiols to afford the corresponding alkynyl sulfides in moderate to high yield and excellent selectivity in the presence of base using molecular oxygen as the sole oxidant under mild conditions.

Results and discussion

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We initiated our studies by examining the oxidative cross-dehydrogenative coupling of 4methyl phenylacetylene (1a) with thiophenol (2a) 20 as a model reaction in the presence of CuCl as a catalyst and K₂CO₃ as а base in dimethylsulfoxide (DMSO) at 70°C under 1 atm of oxygen. The reaction took place efficiently to produce the desired 4-methylphenyl alkynyl 25 benzonic sulfide (3a) in 96% yield with excellent selectivity (Table 1, entry 1). Only a trace amount of (E + Z) vinyl sulfide (4a) (Z/E)100/0) due to the occurrence of anti-Markovnikov addition was detected without the 30 observation of the undesirable dinye resulting from homocoupling dimerization. Based on this finding, we then tried to optimize the reaction conditions starting with a screen of bases. Na₂CO₃, or Cs₂CO₃ as an inorganic base worked

- ³⁵ well albeit with slightly lower yield to 3a, respectively, under otherwise identical reaction conditions (entries 2 and 3). No formation of 3a was observed when triethylamine or pyridine was employed as the base, which showed good yield to diphenyldisulfide (5a) due to dimerization of thiophenol along ⁴⁰ with a small amount of *anti*-Markovnikov adducts (entries 4 and 5). Other organic bases, such as 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5,7-trizazbicyclo[4.4.0]dec-5-ene (TBD), and 1,1,3,3-tetramethylguanidine (TMG), however, exhibited poor to good yield to 3a (entries 6-8). Notably, when TBD was used as a
- 45 base, the reaction showed considerably high selectivity to the unwanted alkyne homocoupling by-product (**6a**) (entry 6), which stands apart from the results with other bases. However, in the absence of any base, 40% and 21% yield to **4a** (Z/E = 77/23) and **5a** were produced without the formation of **3a** (entry 9).
- ⁵⁰ Decreasing the amount of K_2CO_3 (5 mol%, equal molar to Cu) led to lower activity and selectivity (entry 10). Apparently, base plays a critical role for the reaction and K_2CO_3 proved to be the best choice among all bases investigated. The solvent also had a considerable influence on the reaction (Table S1, see the
- 55 Supporting Information for details). Among the solvents investigated, DMSO gave the best results for activity and selectivity.



^a Reaction conditions: 5 mol% Cu¹Cl, 10 mol% K₂CO₃, 0.5 mmol alkyne, 0.55 mmol thiol, 2 mL DMSO, 70°C, 1 atm O₂. Yields of the isolated product are given based on the terminal alkyne. ^b 4 h. ^c 0.5 mmol 1,3-diethynylbenzene, 1.1 mmol thiophenol, 2 h. ^d 1.0 mmol phenylacetylene, 0.55 mmol benzene-1,3-dithiol, 2 h.

Next, the copper sources were investigated and we found that Cu¹Br, Cu¹I, or even CuCl₂ and Cu(NO₃)₂ also worked efficiently 60 and selectively to afford 3a in high yield under otherwise identical reaction conditions (Table S2 in the Supporting Information). In the absence of any copper sources, no 3a was produced at all (entry 11). O₂ as an oxidant is necessary for the highly selective cross-dehydrogenative coupling reaction to 65 produce the alkynyl sulfide. In the presence of an argon atmosphere, the reaction readily switched to the anti-Markovnikov addition to yield 4a as major product along with the formation of 5a, no 3a was formed under these conditions (entry 12). The reaction proceeded efficiently to afford **3a** in high yield 70 even in open air (entry 13) or at room temperature with relatively longer reaction time (entry 14). Impressively, the selectivity for either 3a or 4a could be tuned by a slight modification of reaction conditions e.g. reaction atmosphere.

With the optimized conditions in hand, we subsequently ⁷⁵ investigated the scope of the direct oxidative crossdehydrogenative coupling of various alkynes with thiophenol (Table 2). A set of alkynes including aromatic and aliphatic could efficiently couple with thiophenol to selectively deliver the desired alkynyl sulfides in moderate to high yields. Electron-⁸⁰ donating and electron-withdrawing substituents at the *m*-, *o*-, and *p*- positions on the phenyl ring of aromatic alkynes all gave high Published on 22 August 2013. Downloaded by Monash University on 23/08/2013 12:44:26.



Figure 1. Plot of concentration change as a function of reaction time for oxidative cross-coupling of phenylacetylene (\circ) with thiophenol (\bullet) and the produced product methylphenyl alkynl benzonic sulfide 3d (\triangle). Reaction conditions: 5 mol% Cu¹Cl, 10 mol% K₂CO₃, 0.5 mmol (0.25 M in solution) phenylacetylene, 0.55 (0.275 M in solution) mmol thiophenol, 2 mL DMSO, 70°C, 1 atm O₂.

yields to their corresponding alkynyl sulfides. Reactions of *m*-, *o*, and *p*-ethynyltoluenes (**1a**, **1b**, and **1c**) or *o*-, *p*-ethynylanisole (**1e** and **1f**) proceeded well, and almost equal yields were achieved, suggesting the steric effect of substituents on aromatic rings is ⁵ negligible. Importantly, in the case of halo-substituted aromatic alkynes (**1g** and **1h**), excellent chemoselectivities were observed and afforded the desired **3g** and **3h** in high yields without the occurrence of dehalogenation. The electron-donating substituted aromatic alkynes showed superior reaction efficiency to that of the electron-withdrawing ones. The sulfur-containing alkyne, 3-

ethynylthiophene (1j), coupled with thiophenol efficiently to afford the corresponding 3j in 84% yield, while the presence of a pyridyl moiety in the alkyne, 2-ethynylpyridine (1i), significantly decreased the reaction selectivity and only

- ¹⁵ 14% isolated yield of **3i** was obtained. In this case, the selectivity to *anti*-Markovnikov addition became the predominant reaction, affording the Z-vinyl sulfide in 63% yield. Notably, the conjugated terminal enyne, 1-ethynylhexene (1k), readily reacted with thiophenol to
- ²⁰ convert **3k** in 91% yield; the conjugated C-C double bond did not cause any influence on the selectivity and remained intact during the reaction. In addition, aliphatic alkynes could act as good coupling partners. The reaction proceeded efficiently to afford their ²⁵ corresponding alkynyl sulfides in good to high yields, even for the aliphatic alkynes bearing functional groups such as hydroxyl and chloro (**1n** and **10**).

Along this line, both aromatic and aliphatic thiols coupled with phenylacetylene in moderate to high yields.

- ³⁰ In the cases for the coupling reaction of aromatic thiols bearing electron-donating and electron-withdrawing substituents (2p-s), the electron-withdrawing substituted thiophenols (2r and 2s) displayed superior reaction efficiency to the electron-donating ones (2p and 2q)
- ³⁵ under otherwise identical reaction conditions. Longer reaction times are required to achieve a satisfactory yield for the coupling of aliphatic thiols with phenylacetylene

(2t and 2u). Aliphatic thiol (2v) readily coupled with the aliphatic alkyne (1l) to afford 3v in moderate yield (34%) with prolonged ⁴⁰ reaction time.

Finally, the coupling reactions of the terminal diynes with thiol or dithiol with terminal alkyne also operated efficiently to give the corresponding sulfides. For example, 1,6-heptadiyne (1w) or 1,3-diethynlbenzene (1x) could couple with 2 equivalents of 45 thiophenol to form the corresponding 3w and 3x in 88 and 93% yields, respectively. Similarly, the reaction between benzene-1,3dithiol (2y) and 2 equivalents of phenylacetylene proceeded efficiently to afford 3y in 87% yield. These results highlight the power of this procedure for preparation of sulfur-rich π -⁵⁰ conjugated polymers, which have unique properties for materials applications.^{1, 19}

In an attempt to determine the reaction mechanism, some control experiments were carried out. When the coupling reaction of phenylacetylene and thiophenol was performed in the presence 55 of an equimolar amount galvinoxyl with respect to Cu¹Cl, as a radical scavenger, methylphenyl alkynyl benzonic sulfide (3d) was obtained in 92% yield with roughly equal activity with its absence under otherwise identical reaction conditions. This result indicates that the involvement of a free radical pathway for this 60 transformation might be ruled out. The kinetic study of tracing the concentration changes as a function of reaction time for the coupling partners, e.g. phenylacetylene, thiophenol, and the produced product 3d demonstrates (Figure 1): 1) thiophenol is consumed more quickly via the reaction with Cu^ICl compared to 65 phenylacetylene in the same reaction vessel. Especially in the first 10 minutes of the reaction, almost no consumption of phenylacetylene was found, meanwhile the formation of the desired product 3d was marginally observed during this period; 2) phenylacetylene starts to be consumed and its concentration 70 gradually decreases after 10 min accompanied with a linear increase of the formation of 3d. It was well-documented that



Figure 2. X-band EPR spectra acquired from monitoring the reaction at variable reaction time (a) 0 min; (b) 10 min; (c) 12 min;(d) 15 min; (e) 20 min; (f) 30 min; (g) 40 min; (h) 50 min; and (i) 60 min. (left) Experimental and simulated EPR spectra of the active Cu^{II} species for the reaction at 30 min (right). Reaction conditions: 5 mol% Cu^ICl, 10 mol% K₂CO₃, 0.5 mmol phenylacetylene, 0.55 mmol thiophenol, 2 mL DMSO, 70°C, 1 atm O₂.

phenylacetylene could react with Cu^ICl to form copper phenylacetylide in the presence of K_2CO_3 in DMSO or DMF.²⁰ Considering this result and in combination with our observation, we believe that an initial deprotonation of a S-H bond of 5 thiophenol in the presence of K_2CO_3 followed by further reaction with CuCl to form copper phenylthiolate is more reactive and favorable rather than the formation of copper phenylacetylide as previously proposed in most Cu-catalyzed oxidative processes.¹⁴⁻ 16, 21

EPR spectroscopic studies were further performed to gain 10 insight into copper species that might be relevant to the reaction, as shown in Figure 2. No EPR signal was observed for the reaction mixture in the first 10 minutes of the reaction, indicating that only EPR silent Cu¹ species is present (Figure 2a and b). The 15 observation is consistent with the result of kinetic studies that only Cu^I phenolthiolate was formed in the first 10 minutes of the reaction. After 10 minutes, a weak EPR signal was observed at g = 2 region and its intensity considerably increased with elapsed reaction times without any change in the signal pattern (Figure 20 2c-f); while a gradual decrease of such EPR signal (Figure 2g-i) was observed after 40 min. At the completion of the reaction, most of EPR signal disappeared. This EPR signal is originated from $S = \frac{1}{2}$ species, it can be simulated as a single species with nearly axial g values (($g_x = 2.03, g_y = 2.04, g_z = 2.16$), and the ²⁵ presence of an I = 3/2 nucleus having axial nuclear hyperfine constants ($A_x = 110$ MHz, $A_y = 110$ MHz, $A_z = 550$ MHz). The larger A_z value together with $\Delta g_z \sim 4 \Delta g_{x,y}$ are typical parameters from type 2 Cu^{II} centers.^{22, 23} The relative low g_z value suggests the presence of sulfur coordination to the cooper center.²²⁻²⁴ The

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- ³⁰ decrease of this Cu^{II} signal after 40 minutes of the reaction indicates the regeneration of the Cu^I species after the completion of the catalytic cycle. EPR spectroscopic data strongly reflected and supported the control experiment results described above and also further reveal that no radical signal is present in the reaction.
- ³⁵ More interestingly, a similar observation in EPR study was found when CuCl₂ was chosen as a catalyst instead of Cu^ICl for the reaction (Figure S2, see the Supporting Information for details). We failed to isolate the intermediate Cu^{II} species from the reaction at this point.
- On the basis of the observed results, a plausible mechanism for the present process is proposed as shown in Scheme 1. Firstly, an initial deprotonation of a S-H bond of thiol in the presence of a base to form Cu¹ thiolate (A). At this stage, a possible dimerization pathway of copper thiolate is operative to give rise





⁴⁵ to disulfide in the presence of O₂ atmosphere,²⁵ which could also react with alkyne to form the desired alkynyl sulfide.^{8a} Secondly, a Cu^{II} intermediate (B) possibly formed albeit with no direct evidence by subsequent transmetalation of alkyne into copper thiolate via activation of terminal alkynes with assistance of O₂. 50 Finally, the desired alkynyl sulfide was reductively eliminated and regenerated the Cu^I thiolate (A) in the excess of thiol. Molecular oxygen plays an essential role on facilitating the formation of the Cu^{II} intermediate (B) via activation of C-H bond. When the reaction was performed under argon atmosphere, the 55 entire process operated in completely different way to give anti-Markovnikov addition product with a mixture of stereoselective isomers. However, an intermediacy of radicals associated to Cu or dinuclear Cu species^{18a} involves in the reaction could not be totally ruled out at this point. Further studies for understanding of 60 reaction mechanism are necessary and are currently underway in our lab.

Conclusions

In summary, we demonstrated that inexpensive copper catalyze the oxidative cross-dehydrogenativecoupling of terminal alkynes with thiols to selectively construct alkynyl sulfides with the aid of K_2CO_3 under an atmosphere of O_2 . This simple straightforward and atom-economical procedure is applicable to a wide range of alkynes and various thiols and is compatible with a variety of functional groups on both alkyne and thiols reaction partners. The process represents a new methodology for selective synthesis of alkynyl sulfides and highlights the feasibility for preparations of sulfur-rich π -conjugated polymers.

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Notes and references

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- 24 Both ⁶³Cu and ⁶⁵Cu isotopes in natural abundance (69% for ⁶³Cu, and 31% for ⁶⁵Cu) were accounted for in the simulation. Both isotopes have nuclear spin I = 3/2, but the nuclear magnetic moment is 7.1% larger for ⁶⁵Cu. The A values of ⁶³Cu are reported. See Figure S1 for ⁶³Cu and ⁶⁵Cu simulations.
- 25 Indeed, a separate experiment for the reaction of sole coupling partner of thiophenol catalyzed by CuCl with K₂CO₃ under O₂ atmosphere produced exclusively disulfide in 90% isolated yield after 1 h; while only insoluble copper phenylthiolate was obtained in the presence of an argon atmosphere under otherwise identical reaction conditions.

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Highly active and selective aerobic cross-dehydrogenative coupling of terminal alkynes with thiols to construct alkynyl sulfides catalyzed by Cu(I) using molecular oxygen as the oxidant has been developed under mild reaction conditions.