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Carbon Dioxide Mediated Stereoselective Copper-Catalyzed Reductive Coupling of Alkynes and Thiols

Siti Nurhanna Riduan, Jackie Y. Ying,* and Yugen Zhang*

Institute of Bioengineering and Nanotechnology, 31 Biopolis Way, The Nanos, Singapore 138669, Singapore

jyying@ibn.a-star.edu.sg; ygzhang@ibn.a-star.edu.sg

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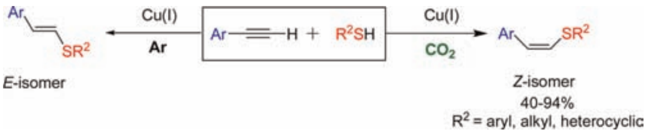
ABSTRACT



A simple protocol for the stereoselective copper-catalyzed hydrothiolation of alkynes under a CO_2 atmosphere has been developed. The stereoselectivity is determined by the presence/absence of a CO_2 atmosphere. The reaction system is robust and utilizes inexpensive, readily available substrates. A cyclic alkene/carboxylate copper complex intermediate is proposed as the key step in determining the stereoselectivity, and an equivalent amount of water is found to play an active role as a proton donor.

Vinyl sulfides are ubiquitous in many natural products and pharmaceuticals and are important synthetic intermediates due to their ease of transformation.[1] The most convenient way to synthesize such analogs includes hydrothiolation of alkynes, commonly through transformations with transition metal catalysts, bases, or free radicals. Both Markovnikov[2−6] and anti-Markovnikov[7−11] selectivity can be realized in transition metal catalyzed processes (Scheme 1). High selectivity for Markonikov products was achieved with nickel,[2] rhodium,[3] organoactinide and organolanthanide,[4] and zirconium complexes as catalysts.[5] Selective formation of *E* and *Z* isomers of anti-Markovnikov products has also been accomplished, whereby the selective synthesis of *E*-vinyl sulfides was first successfully demonstrated by Ogawa et al. using a Wilkinson catalyst, $Rh(PPh_3)_3Cl$,[7] and more recently by Corma et al. using both gold(I) and (III) complexes.[8] The synthesis of *Z*-vinyl sulfides over transition metal catalysts has been limited to neutral and cationic complexes of rhodium and iridium but suffered from a limited substrate scope and low stereoselectivity.[9] Base-mediated hydrothiolations were first reported in 1956 by Truce et al.,[10] and more recently, a cesium carbonate catalyzed process to form *Z*-vinyl sulfides was reported.[11] However, such a process required the

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use of a radical inhibitor, and the substrate scope was limited to alkyl thiols. Alkyne hydrothiolation via a radical mechanism was first reported in 1970, whereby a free radical process yielded anti-Markovnikov products with typically low E/Z selectivity.[12,13] Thus, a general and simple method for the synthesis of Z-vinyl sulfides from alkynes remains a challenge to be addressed.

Scheme 1. Transition Metal Catalyzed Hydrothiolation of Alkynes

In the past decade, immense efforts in research have been dedicated to utilizing CO_2 in organic synthesis.[14,15] Recently, we reported a room-temperature conversion of terminal alkynes to propiolic acids with 1 atm of CO_2 in the presence of a Cu(I) catalyst.[16,17] With this result, we envisioned the use of CO_2 as a mediator[18] to achieve the stereoselective coupling of alkynes and thiols to form Z-vinyl sulfides via a propiolic acid intermediate.[19] Herein we reported a simple procedure for the synthesis of Z-vinyl sulfides by hydrothiolation of terminal alkynes under a CO_2 atmosphere. The stereoselectivity of this reaction was controlled by CO_2, and the mechanism of this stereoselectivity controlling process was also investigated.

The study was initiated with phenylacetylene and thiophenol as model substrates for the reaction. The proof of concept was conducted with phenylacetylene (0.5 mmol), thiol (0.75 mmol), K_2CO_3 (0.6 mmol), and 5 mol % CuI catalyst in 3 mL of N,N'-dimethylformamide (DMF) with a CO_2 balloon. After a 16-h reaction, vinyl sulfide products were obtained at a yield of 85% and an E/Z ratio of 13:87. Control experiments for this reaction under the same conditions, except for the use of argon or air, gave similar products with reverse stereoselectivity (E/Z ratio = 80:20). These results clearly demonstrated that the stereoselectivity of this Cu(I)-catalyzed alkyne hydrothiolation reaction could be controlled with the presence or absence of the CO_2 atmosphere. Further study showed that a trace amount of water also played an important role in this reaction. With 2 equiv of H_2O additive, the reaction rate was remarkably increased (Supporting Information (SI) Table S1). With that, reaction conditions were further screened. Dimethyl sulfoxide (DMSO) proved to be the optimum solvent for the reaction, while a DMSO/H_2O volume ratio of 1:1 was found to be detrimental to the selectivity. The use of ligands, such as tetramethylethylenediamine (TMEDA) and IPr (1,3-bis(2,6-diisopropylphenyl imidazolylidene) did not improve the yields, while the use of organic bases such as TMEDA and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) did not lead to any E/Z selectivity. The use of K_2CO_3, with DMSO as solvent, proved to be the best for the reaction, with the presence of 5 mol % of CuI catalyst, 1 atm of CO_2 atmosphere, and 1.4 equiv (25 μL) of H_2O (SI Table S1).

It was found that a reaction temperature of 90 °C was optimal to the yield and selectivity of this hydrothiolation reaction. The selectivity was kept high with the use of a slight excess of thiol. In addition, allowing the reaction mixture of phenylacetylene and potassium carbonate in DMSO to be stirred in an atmosphere of CO_2 prior to the addition of thiol proved to be beneficial for enhanced stereoselectivity (SI Table S1).

With the optimal reaction conditions, we proceeded to expand the reaction scope for a wide range of thiol substrates (see Figure 1). In general, it was observed that the hydrothiolation of phenylacetylene in the presence of CO_2 mediator generated the anti-Markovnikov products with high Z selectivity, in good-to-excellent yields. Aryl, benzylic, and aliphatic thiols reacted cleanly to furnish the corresponding Z-vinyl sulfides with high selectivity.

It should be noted that the synthesis of aryl Z-vinyl sulfides with base-mediated hydrothiolation reactions have been met with limited success.[11] The current reaction was tolerant toward electron-rich and -deficient aryl thiols and a number of other functional groups, including amines, furan rings, and alcohols. It was also observed that aliphatic thiols were slower to react, and reaction was promoted with an extended reaction time and/or the change of base from potassium carbonate to cesium carbonate (Figure 1, **3n**–**3q**). No reaction was observed with 4-mercaptobenzoic acid.

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To further improve the utility of our reaction, various alkynes were screened in this reaction. No conversion was observed with the use of terminal aliphatic alkynes, even with strong bases such as ^{t}BuOK. In contrast, the use of terminal aryl alkynes yielded vinyl sulfides in good-to-excellent yields. It was also observed that the presence of electron-withdrawing groups on the phenyl ring diminished the selectivity of the reaction toward forming the *Z*-vinyl sulfide. Remarkably, modifying the reaction setup by adding a σ-donor ligand (TMEDA) and leaving the ethynylbenzene to stir in a CO_2 atmosphere for 6 h before the thiol addition improved the selectivity toward *Z*-vinyl sulfides, as exemplified in Figure 2, **3ak** and **3al**.

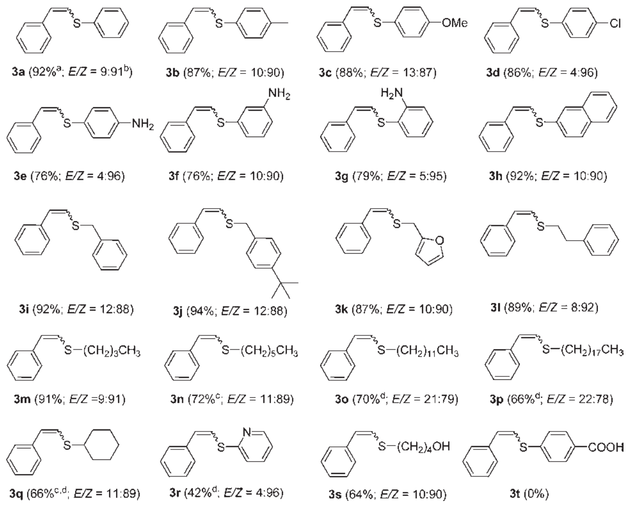


Figure 1. Coupling of phenylacetylene with various thiols. Reaction conditions: phenylacetylene (0.5 mmol), thiol (0.75 mmol), 5 mol % of CuI with respect to alkynes, K_2CO_3 (0.6 mmol), 25 μL of H_2O and 3 mL of DMSO, 16 h, unless otherwise noted. ^{a}Isolated yields were average of 2 separate experiments. ^{b}*E*/*Z* ratio determined by ^{1}H NMR analysis. ^{c}Cs_2CO_3 was used instead of K_2CO_3. ^{d}Reaction time = 40 h.

The reaction was examined in further detail to establish the crucial factor in determining its stereoselectivity. First, we believe that the reaction went through the propiolic acid intermediate, followed by the hydrothiolation decarboxylation process. As previously mentioned, the additional time allowed for the stirring of alkynes and base in a DMSO solution in a CO_2 atmosphere was beneficial for stereoselectivity. This process allowed for propiolic acid formation in the system.[16] Ranjit et al. reported the direct hydrothiolation reaction using propiolic acids as starting materials.[19] Our observations from replication of experiments with Ranjit's protocol,[19] which were performed under air, led us to believe that a small amount of water was beneficial to the reaction. Experiments performed in a closed system or under an argon atmosphere did not yield the same published results.

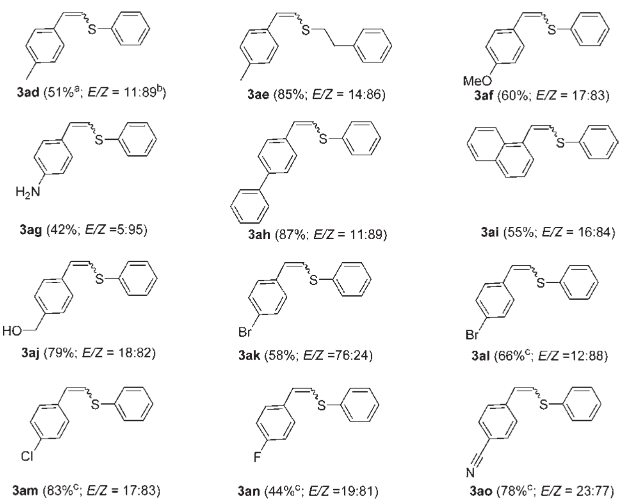
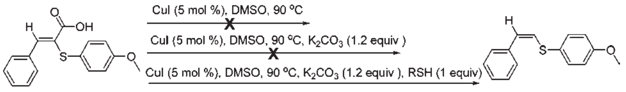
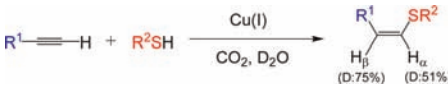


Figure 2. Coupling of terminal alkynes with thiophenols. Reaction conditions: alkyne (0.5 mmol), thiol (0.75 mmol), 5 mol % of CuI with respect to alkynes, K_2CO_3 (0.6 mmol), 25 μL of H_2O and DMSO (3 mL), 16 h, unless otherwise noted. ^{a}Isolated yields, average of 2 separate experiments. ^{b}*E*/*Z* ratio determined by ^{1}H NMR analysis. ^{c}12 mol % of TMEDA was added; the ethynylbenzene was allowed to stir in the reaction mixture at room temperature for 6 h before the thiol was added.

Scheme 2. Conditions for the Decarboxylation of (Phenylthio)phenylpropenoic Acid



Scheme 3. Reaction with D_2O Additive

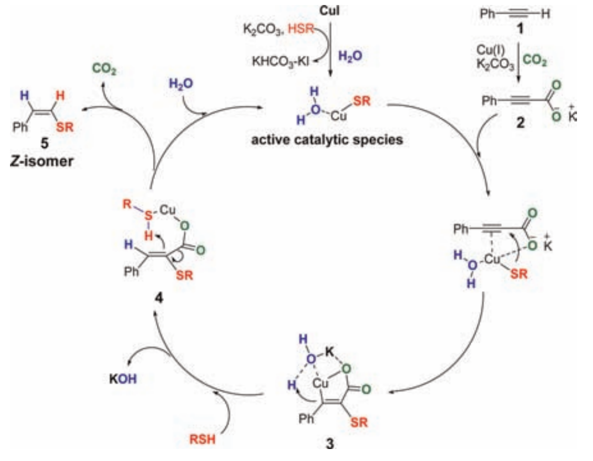


However, when the reaction was conducted in an open system or with trace amounts of water, the decarboxylation hydrothiolation reaction worked well to give high *Z* selectivity. The reductive coupling of propiolic acids and thiols did not occur in the absence of a Cu catalyst. Experiments with different combinations of variables were examined (SI Table S2). From these studies, one could conclude that the CO_2 atmosphere was the determining factor in the stereoselectivity of the desired product, and the terminal alkyne was converted to a propiolic acid in CO_2 before a stereoselective decarboxylative hydrothiolation occurred. However, the reaction mechanism of this decarboxylative hydrothiolation process has not yet been studied.[19] The addition of thiophenols across propiolic esters has been examined and was found to provide the resulting *Z*-selective (phenylthio)phenylpropenoic acid cleanly, after acid workup.[22] The decarboxylation of such acids was investigated further, whereby the as-prepared *Z*-3-phenyl-2-(4-methoxyphenylthio)propenoic acid was subjected to several conditions (Scheme 2). The acid decarboxylated only in the presence of a Cu catalyst, 1.2 equiv of K_2CO_3, and excess thiols in DMSO solvent, similar to the typical reaction conditions in Figures 1 and 2. Attempts to isolate such a propenoic acid intermediate in the reaction of **3a** using equimolar amounts of Cu or the addition of iodomethane were not successful.

The role of water in the reaction was also examined. It is known that water can improve the yield of hydrothiolation of alkynes in the presence of an amine as a solvent and mediator, through H-atom donation to vinyl radical intermediates.[20] The addition of radical inhibitors (TEMPO) to the reaction mixture of the current system did not prove to be detrimental to both the yield and selectivity, indicating that the reaction did not proceed via a radical mechanism. Reactions with diphenyl disulfide did not yield any results.[13,21] To understand the role of water in the reaction mechanism, experiments were performed using deuterated water (D_2O) instead of H_2O. It was found that the proton at the β-position of the vinyl sulfide was mostly replaced by deuterium (D/H = 3/1, see Scheme 3 and SI). Meanwhile, the proton at the α-position was 51% replaced by deuterium. This observation supported the proposed mechanism (Scheme 4) and also corresponded to the result of controlled H/D exchange experiments, in which the different deuterium substitution ratios at both the α- and β-positions were a result of the RSH/D_2O deuterium–hydrogen exchange during the course of the reaction. The acidic proton in 4-methyl thiophenol was found to be partially replaced by deuterium (52%), when 2 equiv of D_2O was mixed with the thiol and base in DMF-D_7. Quenching of a typical reaction mixture with an aliquot of deuterated hydrochloric acid (DCl) in D_2O did not result in the replacement of the protons with deuterium at both the α- and β-positions.

The proposed mechanism included the initial carboxylation of terminal alkyne (**1**) with CO_2 to form propiolic acid (**2**). It is known that the electron density of the C–C triple bond of a propiolic acid is weaker[16] as compared to that of an acetylene, due to the electron-withdrawing nature of the carboxyl group. Thus, as the Cu center of the catalytic species approached the triple bond, the nucleophilic attack of the thiyl anion was induced.[23] The reductive C–S coupling to form a cyclic alkene/carboxylate copper complex intermediate **3** was the key step determining the stereoselectivity. The subsequent proton attack on the cyclic intermediate (**3**) to the β-carbon generated the intermediate **4**. The newly coordinated thiol on intermediate **4** induced decarboxylation under the prescribed conditions (Scheme 4), releasing CO_2 gas and furnishing the *Z*-vinyl sulfide (**5**).[21] The diminished stereoselectivity observed for ethynylbenzenes with electron-withdrawing groups could be attributed to the lower activity for carboxylation with CO_2 under Cu(I)-catalyzed conditions.[16] For **3ak**, the competitive hydrothiolation of the alkynes occurred, instead of hydrothiolation of the propiolic acid intermediate, due to the slower rate of carboxylation of such alkynes. The presence of a σ-donor ligand was beneficial for the carboxylation of such inactive alkynes,[16] and as expected, better selectivities were observed for **3al** when TMEDA was used as a ligand for the reaction.

Scheme 4. Proposed Mechanism for the Hydrothiolation of Alkyne with CO_2



In conclusion, a simple procedure for the stereoselective hydrothiolation of alkynes under a CO_2 atmosphere has been developed. To the best of our knowledge, this is the first instance of stereoselectivity determination with CO_2 as a mediator. A cyclic alkene/carboxylate copper complex intermediate was proposed as the key step in determining the stereoselectivity, and an equivalent amount of water was found to play an active role as a proton donor. The reaction system was robust and utilized inexpensive and readily available substrates. It provided a promising method for stereoselective *Z*-vinyl sulfides synthesis and new insight into carbon dioxide utilization.

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Supporting Information Available. A description of materials and methods for experiments, along with spectroscopic data are included in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.