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COMMUNICATION

Aerobic Cu-Catalyzed Oxidative 1:2 Coupling of Benzynes with Terminal Alkynes

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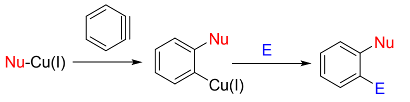
Described herein is the Cu-catalyzed oxidative 1:2 coupling of arynes with nucleophilic terminal alkynes under aerobic conditions. Mechanistic investigation revealed a plausible generation of aryl-Cu(III) pathway from arynes. By this method, ubiquitous arenediynes can be efficiently assembled in a single step under mild conditions.

Arynes are highly reactive and versatile synthetic intermediates have found wide application in the synthesis of many biologically active natural products[1] and functional materials[2]. Among various reaction modes of arynes,[3-4] transition metals catalyzed reactions have attracted wide attention and been widely used in assembly of many important structures.[5] Traditionally, transition metals proven to be catalytically competent for arynes were mainly limited to palladium[6-7] and nickel[8]. The exploration on interaction of arynes with other transition metals, especially those earth-abundant and environmentally benign, is thereafer of much significance and deserving investigation.

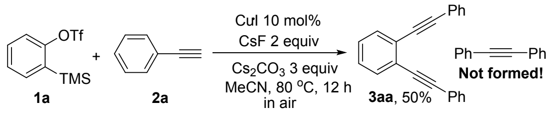
As a kind of cost-effective, environmental-friendly and earth-abundant transition metal, copper has been widely used in organic catalysis for years.[9] In 2008, we reported for the first time Cu(I) could catalyze aryne-terminal alkyne and terminal alkyne-aryne-allylic chloride couplings.[10] Since then, a series of subsequent reports appeared, verifing Cu(I) was an efficient catalyst for arynes.[11] From the viewpoint of mechanism, these reactions probably acted through one unified reaction mode, namely the electrophilic capture of aryl-Cu(I) generated from insertion of aryne into nucleophilic organo-Cu(I) species (Scheme 1). Although has enabled a variety of novel transformations, this reaction mode still suffers from limited substrate space and/or severe side reactions (eg. the undesirable and always yield-reducing protonation of as-formed strongly basic aryl-Cu(I) intermediates[10,11g,i-l]). Thereafter, the development of novel reaction modes between aryne and copper is of much importance and worthy studying.



Nu = alkynyl, CF_3, B(pin), Br-, $P(O)R_2$, CN, 2-(benz)oxazolyl *etc.*
E = H^+, allyl halides, alkenyl epoxides, alkenyl aziridines, $PhSO_2SAr$, CO_2, alkynyl bromide, acrylates, Bu_3SnF, R_2NOBz *ect.*

Scheme 1. Reaction Mode of Cu(I)-catalyzed Aryne Reactions.

During our studies on Cu-catalyzed aryne reactions,[10, 12] we found performing the reaction of benzyne precursor **1a** and ethynylbenzene **2a** using CuI as a catalyst under aerobic conditions, an arenediyne **3aa** could be afforded (Scheme 2). This result was quite intriguing since compared to the above-mentioned nucleophile-aryne-electrophile couplings, this was a scarce example of Cu(I)-catalyzed intermolecular aryne insertion into two molar of nucleophiles.[13] Moreover, it was noteworthy in this reaction, the above-mentioned protonation of aryl-Cu(I), which had proven to be a yield-reducing side-reaction always accompanied Cu(I)-catalyzed aryne reactions, was completely inhibited under the aerobic condition. Regarding that arenediynes were ubiquitous structures in many biologically active substances[14], functional materials[15], complex ligands[16], and synthetic intermediates[17], as well as the significant mechanistic value of this transformation on both aryne chemistry and copper catalysis, we decided to study this reaction in detail and the results are summarized below.



Scheme 2. Initial experiment.

After establishing the optimal reaction conditions by a detailed optimization (see SI, Table S1), we studied the reaction scope and the results were summarized in Table 1. First, we tested benzynes with different substitution and found that besides **1a**, benzynes with both symmetric (**1b**) and

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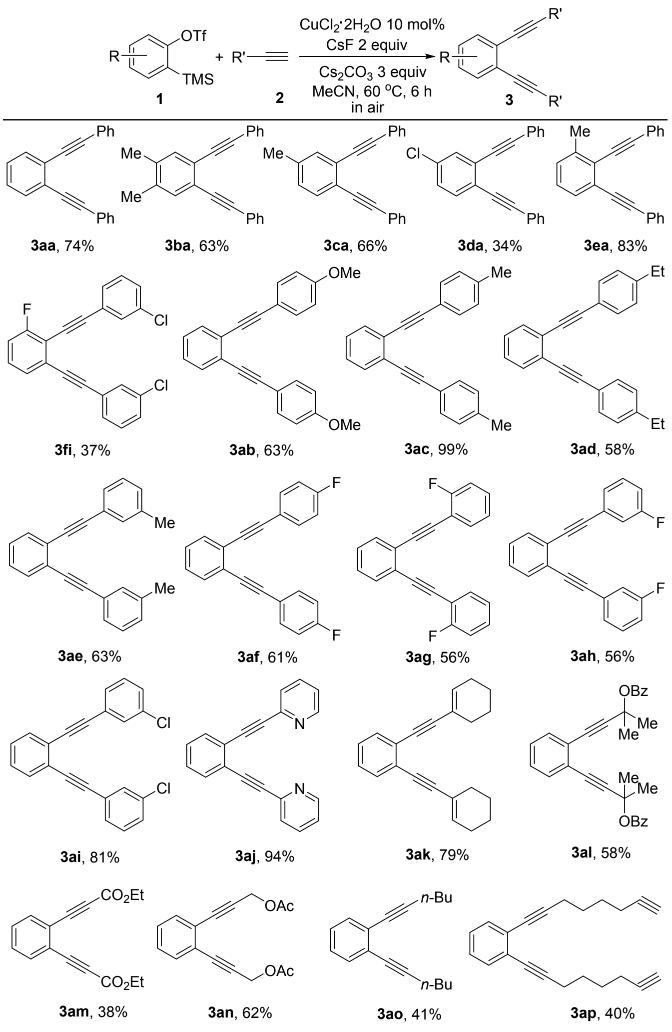
† Electronic Supplementary Information (ESI) available: The experimental details, spectroscopic data (^1H NMR, ^{13}C NMR, and HRMS) for the products. See DOI: 10.1039/x0xx00000x

unsymmetric (**1c**-**f**) substitution could react smoothly with **2a**, giving substituted arenediynes **3ba**-**3fa** in moderate to good yields. In general, electron-rich benzynes such as **1b**, **1c** and **1e** afforded higher yields than electron-poor benzynes (**1d** and **1f**). Steric hindrance showed little impact as both C3 (**1e** and **1f**) and C4 (**1c** and **1d**) substituted benzynes gave similar reaction yields.

In addition, this reaction also showed wide applicability to a variety of terminal alkynes. Besides aryl alkynes having substitution on their *para*-position (**2b**-**2d** and **2f**), those bearing functionalities at their *meta* (**2e**, **2h** and **2i**) and *ortho* (**2g**) positions, could likewise efficiently participate in the reaction, giving desired products **3ab**-**3ai** in good to high yields. Both sterical and eletronic properties of these functional groups seemed having little influence on the reaction, indicating this reaction might be controlled by multiple factors.

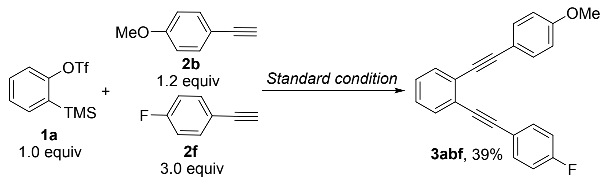
Besides these, heteroaryl alkynes **2j**, 1,3-Enyne **2k** and 2-methylbut-3-yn-2-yl benzoate **2l** also proved to be good reaction partners with **1a**, furnishing arenediyne **3aj**-**3al** in 94%, 79% and 58% yields respectively. Propiolates such as **2m** could also well participate in the reaction with a slightly lower yield (38%) being delivered. Apart from these, aliphatic terminal alkynes such as **2n** and **2o** were also proven to be reliable reactants in the reaction, providing corresponding arenediynes **3an** and **3ao** in moderate yields. 1,7-Diyne **2p** could likewise react with **1a** giving the 1,2-dialkynylbenzene **3ap** in a 40% yield. Ring-closing product formed by the insertion of benzyne into the two terminal alkyne parts of **2p** was not observed even when the reaction was performed under a dilute condition (c(**1a**) = 0.005 M).

Table 1. Scope of the Reaction [a]



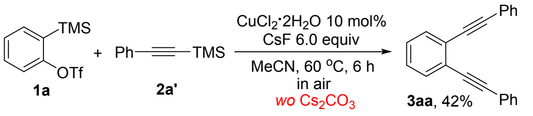
[a] Reaction conditions: **1** (0.5 mmol), **2** (2.0 mmol), $CuCl_2$•$2H_2O$ (0.05 mmol), CsF (1.0 mmol), Cs_2CO_3 (1.5 mmol), MeCN (2.5 mL), 60 °C, 6 h. [b] Isolated yields. [c] **2** (0.24 mmol).

To test the feasibility of benzyne insertion into two different terminal alkynes, we performed the three-component reaction of **1a**, 1-ethynyl-4-methoxybenzene **2b** and 1-ethynyl-4-fluorobenzene **2f** under the standard condition, finding that the target product **3abf** could be obtained in a 39% yield (Scheme 3).



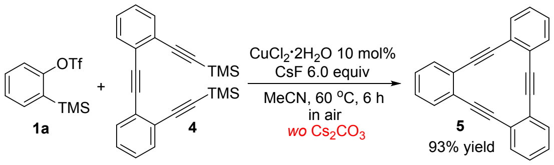
Scheme 3. Insertion of benzyne into two different terminal alkynes.

Apart from these, we also tested the reaction between benzyne **1a** and trimethyl(phenylethynyl)silane **2a'**. We found the reaction could successfully happen, giving the 1,2-bis(phenylethynyl)benzene **3aa** in a 42% yield in the absense of Cs_2CO_3 (Scheme 4). As we know, alkynylsilanes are often the intermediates for the preparation of many terminal alkynes.[18] So the fact that this Cu-catalyzed 1:2 coupling of **1a** and **2a'** could smoothly occur was quite intriguing since it offered a straight way to arenediyne products from alkynylsilanes without desilication.



Scheme4. Reaction of benzyne and alkynylsilane.

Based on this finding, we next conducted the reaction between benzyne precursor **1a** and 1,2-bis(2-((trimethylsilyl)ethynyl)phenyl)ethyne **4** under the Cs_2CO_3 free condition (Scheme 5). To out delight, the intramolecular bisalkynylation of benzyne efficiently took place, providing the dehydrobenzo[12]annulene ([12]DBA) **5**, which had proven to be a core structure in the field of organic functional materials,[19] in a high yield (93%).



Scheme 5. Intramolecular bisalkynylation of benzyne.

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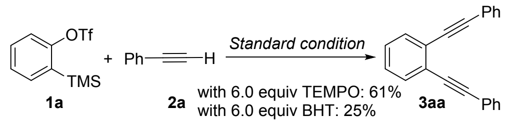
To probe the reaction mechanism, we conducted the reaction between **1a** and **2a** with the addition of a radical trapping reagent TEMPO. It was found that little influence on the reaction was exerted with a slightly lower yield (61%) of **3aa** being dilivered (Scheme 6). Additionally, when performing this reaction in the presence of a radical scavenger BHT, the reaction could still happen in spite of that its yield decreased to 25%. These results implied a radical mechanism might be unlikely for this Cu-catalyzed benzyne insertion reaction.

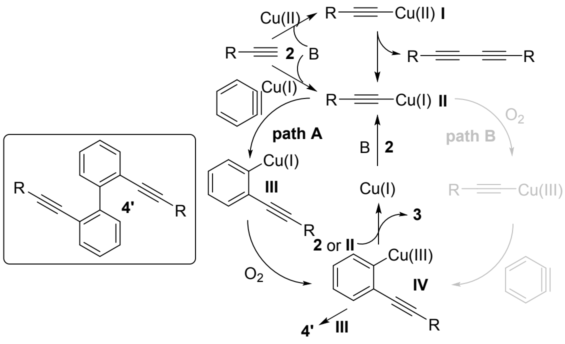


Scheme 6. Radical inhibition experiments.

Subsequently, we used electron paramagnetic resonance (EPR) to analyze several systems relevant to the reaction (Figure S1). From the results we found in both systems, with and without benzyne precursors, the reactions were EPR-active at the very beginning but turned EPR-silent after a few minutes. These characteristics were quite similar to those observed by Lei and his co-workers in their mechanistic investigation on Cu-catalyzed aerobic homocoupling of terminal alkynes,[20] implying the mechanistic relevance of these two reactions. Moreover, the disappearance of EPR signal indicated that EPR-active Cu(II) species might not be the resting-states of the active catalyst in the reaction.

During the past few years, Cu-catalyzed oxidative couplings of two nucleophiles had received wide attention from both academic and industrial community.[21] Among these, much work had been performed on the mechanistic explanation of Cu-mediated oxidative homocouplings of two terminal alkynes.[22] In general, these reactions could be divided into two categories: the aerobic Cu-catalyzed homocouplings (Glaser-Hay type reactions), and the stoichiometric Cu salts promoted homocouplings (Eglinton type reactions). Mechanistically, the former were believed to proceed through O-bridged dinuclear Cu(III) included mechemisms,[22a] whereas the latter pointed to binuclear Cu(II) involved pathways.[22b,c]

Based on these literature precedents and our observations above, possible catalytic cycles could be outlined for our Cu catalyzed aerobic 1:2 coupling of arynes and terminal alkynes (Scheme 7). First, depending on the catalyst precursors employed, alkynyl-Cu(I) **II** could be generated from terminal alkynes **2** under the promotion of bases.[23] Then, two pathways (**A** and **B**) might be involved to give the aryl-Cu(III) intermediates **IV**: the first was the production of aryl-Cu(I) **III** by insertion of benzynes into the alkynyl-Cu(I) **II** and subsequent *in situ* oxidation of the as-formed aryl-Cu(I) **III** by oxygen in air to form the aryl-Cu(III) **IV** (path A); however, another possibility was that alkynyl-Cu(I) **II** were oxidized first by atmospheric oxygen to produce the alkynyl-Cu(III) **III'** followed by insertion of arynes to provide the aryl-Cu(III) - **IV** (path B). For these two possibilities, we inferred **A** was preferred since we had successfully isolated a biphenyl byproduct **4'** in one case (see SI for details). Obviously, biphenyl **4'** might be produced by the reaction of electrophilic aryl-Cu(III) **IV** with nucleophilic aryl-Cu(I) **III**. So this result indicated that aryl-Cu(I) **III** might be indeed generated and verified the reasonability of the path **A**. After the generation of aryl-Cu(III) **IV**, alkynyl-Cu(I) **II** might react with them giving the 1,2-dialkynylated arenes **3** and regenerating active Cu(I) species. The active Cu(I) might subsequently react with terminal alkynes **2** with the aid of bases, producing alkynyl-Cu(I) **II** to enter into next catalytic cycle.[24]



Scheme 7. Possible catalytic cycle of the reaction.

Conclusions

In summary, we reported under areobic conditions, Cu could catalyze oxidative 1:2 couling of arynes and nucleophilic terminal alkynes, giving 1,2-dialkynylated arenes in a single step. Studies on the reaction scope revealed the reaction could tolerate a wide selection of functional groups. Mechanistic analysis indicated generation of aryl-Cu(III) from arynes might be involved. Due to aryl-Cu(III) has proven to be competent electrophiles that can intermediate in many Cu-catalyzed reactions,[25] we believe this novel reaction mode can offer a starting point for developing novel Cu-catalyzed transformations of arynes. Currently, further researches on detailed mechanism of this reaction, novel oxidative insertion of arynes into nucleophiles, as well as Cu catalyzed novel transformations of arynes, are vigorously undertaken in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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13 In reference 11l, Xiao and co-workers had isolated arenediyne product **3aa** as a byproduct in their Cu-catalyzed carboamination of arynes. However, only one example with the highest yield of 31% had been reported.

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23 When using Cu(I) catalyst precursors, the alkynyl-Cu(I) **II** might be directly generated by base-promoted transmetallation of alkynyl to Cu(I). However, when using Cu(II) complexes as catalyst precursors, the reduction of Cu(II) to Cu(I) by alkynes might first happen, giving alkynyl-Cu(I) **II** with the aid of bases. Details of similar processes can be found in reference 20.

24 Possible detailed catalytic cycles can be found in supporting information (Scheme S1).

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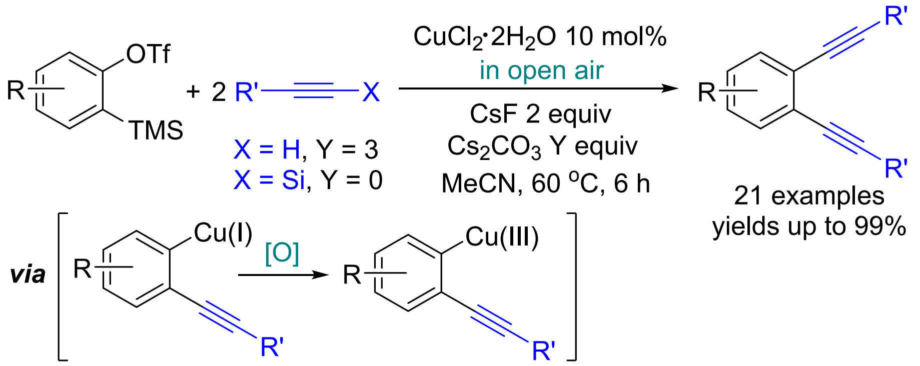

Aryl-Cu(III) may intermediate in Cu-catalyzed aerobic 1:2 coupling of arynes with terminal alkynes, leading to one-step assembly of arenediynes.