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Copper-Mediated Nucleophilic Addition/Cascade Cyclization of Aryl Diynes

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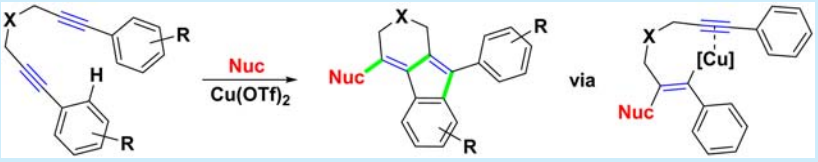
Supporting Information

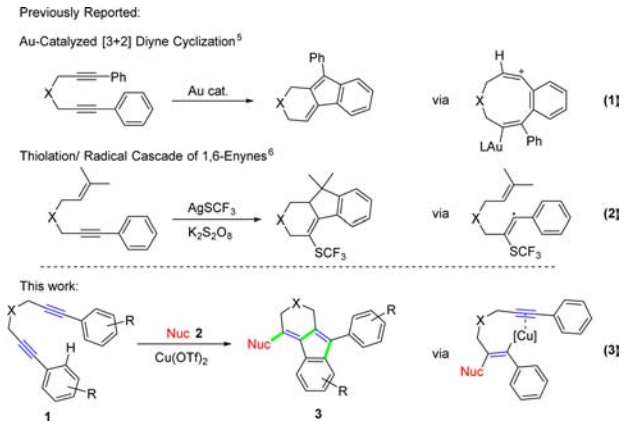


ABSTRACT: Treatment of diyne substrates with sulfinate salts under the action of copper(II) triflate results in a cascade cyclization reaction. The reaction involves nucleophilic addition of the sulfinate and formation of two new C−C bonds with concomitant cleavage of an aryl C−H bond. The reaction proceeds in good yields with a range of diyne precursors and sulfinate salts. Preliminary mechanistic analysis reveals a rare example of an operative ionic mechanism in contrast to other related cyclizations.

Rapid and efficient construction of complex molecular structures has become an increasingly important goal in organic chemistry. This ever-demanding need stems from the desire to limit the number of synthetic steps and hence reduce the costs associated with a synthesis.[1] A typical class of reactions that fit these needs are tandem or domino reactions. With these methods, a significant increase in molecular complexity can be afforded through multiple steps occurring in a cascade solely due to the reactivity installed in the initial steps.[2] In more recent years, the functionalization of carbon−hydrogen bonds by transition metals has become a linchpin in the development of efficient synthetic pathways.[3] The associated efficiency is gained by activating and functionalizing previously nonfunctionalized components of organic substrates. Therefore, approaches that combine C−H functionalization with tandem reactions are highly desired because they allow for increased efficiency in the elaboration of molecular architectures. Additionally, exploring mechanistically distinct pathways opens the door to developing new, increasingly efficient methods.

While C−H functionalization and tandem reactions have been studied in detail, instances of their combination are rare.[4] In a seminal example, Liu and co-workers report the formal [3 + 2] cyclization of aryl diynes where C−H functionalization is coupled with the tandem formation of an additional C−C bond to yield a tricylic ring product (Scheme 1, eq 1).[5] The cyclization mechanism is suggested to proceed through the formation of a nine-membered cationic ring that is closed by a 5-*exo*-*dig* cyclization and the catalytic cycle turned over by a proto-demetalation event. More recently, Liang and co-workers have demonstrated the ability to also install new functionality such as radical thiol incorporation during the formation of formal [3 + 2] cyclization products (Scheme 1, eq 2).[6] These noteworthy examples, while enlightening, have limitations in scope and functionality due the mechanistic pathway they proceed through such as the turnover-requisite proto-demetalation and thiol radical-producing silver salt precursors. As such, there is currently a paucity of synthetic methods that can enable incorporation of additional functionality, such as nucleophiles.

Scheme 1. Cyclization of Aryl Diynes



Herein, we describe a novel synthetic method in which an ionic nucleophilic addition occurs in tandem with a cyclization. This method is technically simple and proceeds via a mechanistically distinct pathway where the incorporation of the nucleophile facilitates transition-metal mediated C−C bond formation and C−H bond functionalization (Scheme 1, eq 3).

The copper-mediated tandem reaction was first discovered using aryl 1,6-diyne **1a** with Cu(II) triflate and nucleophilic sulfinate salt **2a**, which yielded a mixture of products **3a** and **4**

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after a reaction time of 16 h (Table 1). The product **3a** was identified and characterized by single-crystal X-ray crystallography. We then continued with a series of reactions to optimize conditions to maximize the yield of product **3a** while eliminating the unwanted side product **4**. An initial solvent screen revealed that chlorinated solvents such as dichloromethane (DCM) (Table 1, entry 1) produced the target compound, while nonchlorinated solvents showed no sign of product formation.[7]

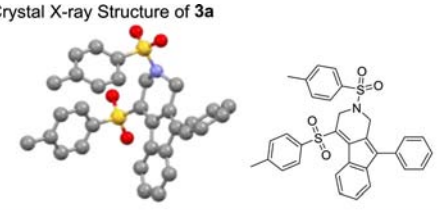
Switching the solvent to 1,2-dichloroethane (DCE) (Table 1, entry 2) gave slightly better results while also allowing higher reaction temperatures to be examined. Increasing the reaction temperature from room temperature to 100 °C afforded a rise in yield of product **3a** while eliminating side product **4** (Table 1, entry 3), although further temperature increases resulted in starting material decomposition. While a diverse range of copper(II) reagents were shown to be capable of producing product **3a**, the most effective reagent in facilitating this reaction was $Cu(OTf)_2$ (Table 1, entry 4–6). Finally, applying 2 equiv of $Cu(OTf)_2$ to the reaction mixture offered a significant increase to 83% yield of desired product (Table 1, entry 7) and led us to establish the optimal conditions.

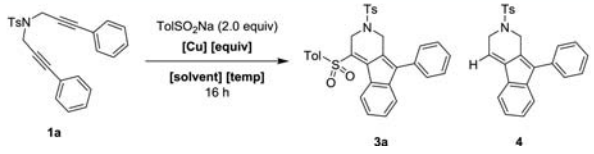
With optimized conditions in hand, we proceeded to explore the substrate scope of the reaction, the results of which are outlined in Figure 1. After identifying the reaction with a nitrogen-based tether (**1a**), carbon- (**1b,c**) and oxygen-based (**1d**) tethers were synthesized and employed as substrates to deliver products **3b–d**. The dimethyl malonate substrate gave an isolated yield of 85% of product **3b**. A range of substrates with electron-withdrawing group substituted aromatics (**1e–o**) were also synthesized and tested. These include trifluoromethyl- (**3e** and **3n**), chloro- (**3f**), nitro- (**3g**), nitrile- (**3h**), fluoro- (**3i,m,o**), and acetyl- (**3j**) groups where yields ranging from 41% to 90% were obtained. Diynes **1b** and **1o** were further applied to investigate the scope of various nucleophiles which include the methyl (**2b**) as well as phenyl (**2c**) sulfinate salts. The yields of products obtained for these reactions (**3p,q**) were lower than with the comparable *p*-tolyl sodium sulfinate salt. However, halogen substitution on the sulfinate salt (**2d,e**) was also tolerated, giving chloro- and bromo-substituted products **3r** and **3s** in 62% and 65%, respectively. In addition, electron-rich aromatics (**1k,l**) as well as asymmetric substrates containing a single alkylated or terminal alkyne only provided trace amounts of cyclized product.

Specifically for diyne substrates with electron-donating substituents on the aromatic ring (**1k,l**), it is possible to attribute these diminished yields to either the low activity of electron rich aromatics or, alternatively, poisoning of the copper(II) reagent. To test this hypothesis, a poisoning experiment was carried out in which two reactions were performed on substrate **1h**, one containing an additive of 1 equiv of **1k** and the other with no additive (Scheme 2). The

Table 1. Optimization of Conditions[a]

Single-Crystal X-ray Structure of **3a**





entry[a]	solvent	temp (°C)	copper (equiv)	% yield of **3a**/**4**
1	DCM	rt	$Cu(OTf)_2$ (1.0)	16:15[b]
2	DCE	rt	$Cu(OTf)_2$ (1.0)	20:10[b]
3	DCE	100	$Cu(OTf)_2$ (1.0)	42:0[b]
4	DCE	100	$Cu(OAc)_2$[e] (1.0)	33:0[b]
5	DCE	100	$CuSO_4$[e] (1.0)	36:0[b]
6	DCE	100	$Cu(BF_4)_2$[e] (1.0)	28:0[b]
7[c]	**DCE**	**100**	**$Cu(OTf)_2$ (2.0)**	**83:0**[d]

[a]Conditions: sodium *p*-toluenesulfinate hydrate (2 equiv), aryl diyne (1 equiv), and Cu(II) reagent in solvent (0.025 M) with stirring at the indicated temperature for 16 h. [b]^{1}H NMR yield of the major product using 1,3,5-trimethoxybenzene as an internal standard. [c]Anhydrous sodium *p*-toluenesulfinate (2.0 equiv) is applied. [d]Separated yield. [e]Hydrous copper reagent.

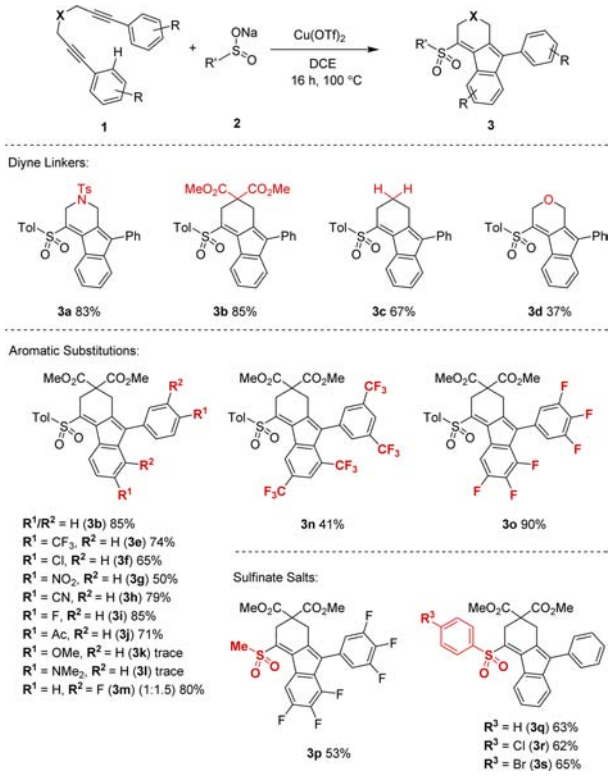
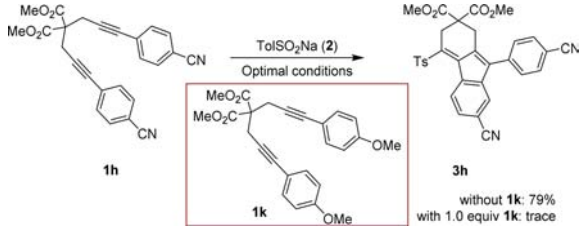


Figure 1. Scope of copper-mediated C–S bond formation via cascade cyclization. Conditions: aryl diyne (1 equiv), sulfinate salt (2 equiv), $Cu(OTf)_2$ (2 equiv), in DCE (0.025 M) at 100 °C for 16 h. Isolated yields.

Scheme 2. Poisoning Experiment



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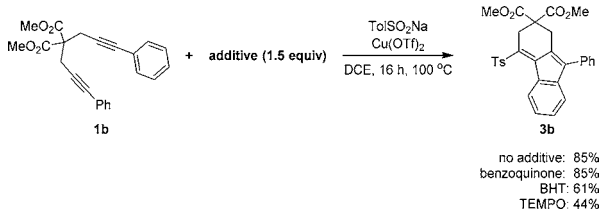
reaction without additive resulted in a 79% yield of the desired product, while the reaction with **1k** as additive resulted in only trace amounts of product **3h**. This indicated that it was, in fact, a poisoning of the copper reagent that was responsible for the diminished yields obtained by electron-rich aromatic substrates, as the reaction of substrate **1h** to product **3h** was also inhibited by the presence of **1k**.

To understand the observed reactivity, we began our investigation into the reaction mechanism with radical-inhibition experiments to determine if the reaction proceeded by a radical mechanism (Scheme 3). The reaction on substrate

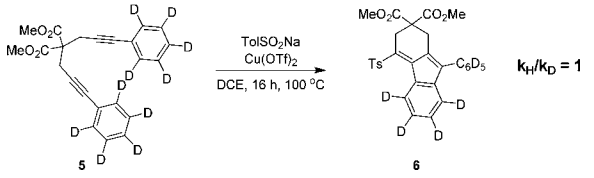
Scheme 3. Radical-Trapping Experiments



1b was performed with either no additive or with 1.5 equiv of radical-trapping reagents such as benzoquinone, dibutylhydroxytoluene (BHT),[8] or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO).[9] In all cases, product **3b** was observed in equivalent or slightly diminished yields when compared to no additive. If the mechanism proceeded by a radical pathway, we would expect only trace amounts of product to be observed. This indicates that the reaction mechanism likely does not generate radical intermediates, and it is, therefore, likely to proceed by an ionic mechanistic pathway.

Given that the mechanism proceeds via an ionic pathway, it is likely that the copper center is intimately involved in the C−H bond-cleavage step. We hypothesized that the C−H bond-cleavage step could be proceeding through one of two pathways: concerted metalation−deprotonation (CMD)[10] or electrophilic aromatic substitution (S_EAr).[11] In the case of CMD, we would expect a significant deuterium isotope effect.[10a,b,12] Conversely, for S_EAr, we would likely see a lack of any deuterium isotope effect.[13] Therefore, we devised a kinetic isotope experiment to shed light on the nature of the C−H bond-cleavage step as well as to help determine the rate-limiting step. First, the relative rate of product formation for deuterated substrate **5** was compared to the nondeuterated substrate (**3b**, Scheme 4) in separate parallel reactions. The

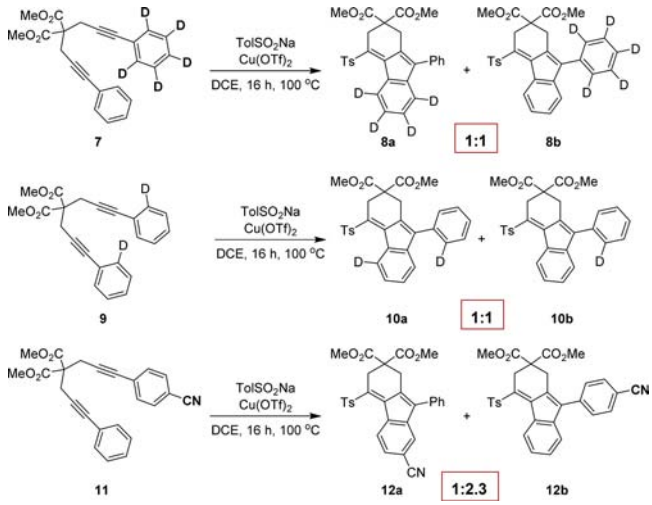
Scheme 4. Kinetic Isotope Effect



K_H/K_D was determined to be 1, which indicates that the C−H bond-cleavage step of the reaction is a non-rate-limiting step. Also, since the C−H bond cleavage is not rate limiting, this experiment or others on substrate **5** would not be effective in revealing more information about the C−H bond-cleavage step.

We next turned our attention to asymmetric substrates for use in internal competition experiments (Scheme 5) to further

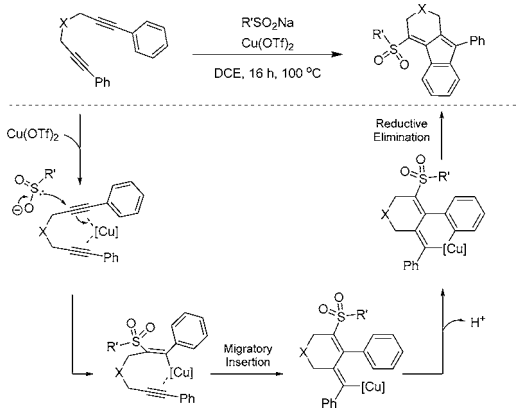
Scheme 5. Internal Competition Experiments



evaluate reaction kinetics and probe the C−H bond cleavage step. Deuterated asymmetric substrate **7** was first synthesized and subjected to the optimal reaction conditions. The two products **8a** and **8b** were produced in a 1:1 ratio,[14] and no significant isotopic effect on the reaction was observed. This may seem to indicate that the reaction proceeds by an S_EAr-type pathway, but these results could also be explained by an irreversible step prior to C−H functionalization.[15] Following this experiment, symmetric substrate **9** was prepared and under optimal conditions yielded products **10a** and **10b** in a 1:1 ratio.[14] Since this experiment showed no sign of kinetic isotope effect, it is probable that the mechanism proceeds though an S_EAr-type pathway. To gain additional evidence, asymmetric substrate **11** was prepared containing an electron-poor ring and a phenyl ring. The results of this reaction under optimal conditions led to a 1:2.3 ratio[14] of products **12a** and **12b**, revealing that the more electron-rich phenyl ring was favored for C−H functionalization, which is also consistent with S_EAr-type reactivity.

Based on these observations, a plausible mechanism consistent with experimental evidence is proposed (Scheme 6). The reaction is initiated by coordination of the copper to the alkyne functional groups, rendering them electrophilic.[16] Nucleophilic attack by the sulfinate salt onto an activated alkyne[17] can be followed by migratory insertion of the remaining alkyne in the carbon−copper bond, which furnishes

Scheme 6. Proposed Reaction Mechanism



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the first C−C bond and forms the six-membered ring. Electrophilic aromatic substitution establishes a bond between the aromatic ring and the electrophilic copper center with concomitant loss of a proton. Finally, reductive elimination forges the final C−C bond and provides the final product.

In conclusion, we have developed a novel pathway for the cyclization of aryl 1,6-diynes which also allows for facile installation of a nucleophile. This pathway is facilitated by relatively inexpensive copper(II) and results in the formation of two new C−C bonds. The reaction is tolerable to a wide range of diynes, aromatic functional groups, and sulfinate nucleophiles, while additional classes of nucleophiles are currently under investigation. This method should prove valuable in the rapid and efficient construction of complex molecular structures. Furthermore, this novel mechanism for the tandem nucleophilic addition/cascade cyclization should have broader implications for the development of related transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03787.

Crystallographic data for **3a** (CIF)
Experimental procedures and characterization data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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