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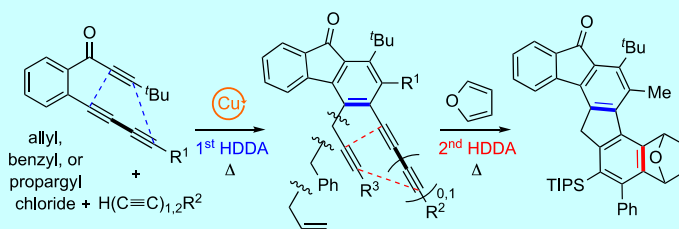
Cu(I)-Catalyzed 1,2-Alkynyl-propargylation and -benzylation of Benzyne Derivatives

Qile Wang and Thomas R. Hoye*

Department of Chemistry, University of Minnesota, 207 Pleasant St. SE, Minneapolis, MN 55455.

Supporting Information Placeholder

ABSTRACT: We report here a three-component, Cu(I)-catalyzed HDDA benzyne 1,2-difunctionalization reaction. This protocol allowed the introduction of two different carbon-based substituents onto the in-situ generated benzyne. These substituents were terminal monoynes or diynes partnered with propargylic, benzylic, or allylic chlorides. An example of a sequential HDDA reaction is demonstrated using the product of a 1,3-diyne and a propargylic halide, itself a newly created HDDA precursor.

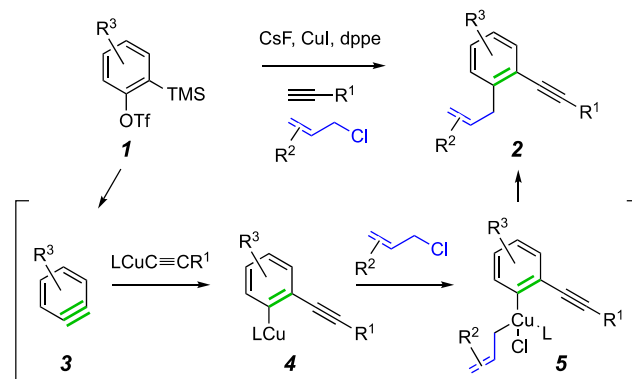


Aryne difunctionalizations that introduce two separate carbon substituents are rare. While cycloaddition reactions, of either the [4+2] or [2+2] type is common,¹ forming two separate C–C bonds at the strained alkyne carbons of the aryne is inherently challenging. To do so requires a pairing of the nucleophilic and electrophilic partners so as to avoid their self-consuming side reactions. One solution to this constraint can be seen in the alkynyl-allylation reaction reported by Zhang and coworkers in 2008 (**1** to **2**, Figure 1a).^{2,3} They devised a copper(I)-mediated, three-component reaction⁴ of terminal alkynes and allylic chlorides with benzyne generated by the Kobayashi method⁵ [fluoride induced fragmentation of o-(trimethylsilyl)aryl triflates]. This bis-carbofunctionalization process was envisioned to proceed through initial alkynyl-cupration of the benzyne **3** to generate **4**, oxidative insertion to the C–Cl bond, and reductive elimination from the copper(III) intermediate **5**. Although direct reaction between alkynyl copper and allylic halide species is known,⁶ it is noteworthy that this process can be out-competed by the rapid interception of these reactants by the benzyne. Consistent with this need to match the relevant competing reactions, when these researchers examined the more reactive, analogous allylic bromides, the efficiency of the benzyne alkynyl-allylation reaction was diminished.

We were interested to learn i) whether this type of process could be extended to include propargylation and benzylation and ii) whether it would be amendable in the setting of the higher temperatures often required for hexadehydro-Diels-Alder (HDDA) benzyne generation (**6** to **8** via **7**, Figure 1b). We have previously shown that Cu(I) catalysis of HDDA-

generated benzyne **7** can function in hydroalkynylation and haloalkynylation reactions.⁷ Other metal-catalyzed reactions of arynes have recently been reviewed.⁸

a Previous: alkynyl-allylation of (“Kobayashi”) benzyne (Zhang et al., 2008)



b Here: alkynyl-propargylation and -benzylation of (HDDA) benzyne

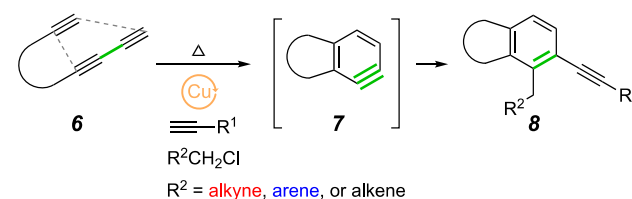


Figure 1. a) Copper (I) catalyzed alkynyl-allylation of classical benzyne. b) Expansion of this difunctionalization reaction to include i) HDDA-generated benzyne and ii) alkynyl-propargylation and -benzylation reactions.

We began the study by examining the alkynyl propargylation reactions of triyne **9** (Figure 2). After an initial brief screening of conditions, CuI and dppp were identified as a suitable catalyst and ligand for this transformation. It is worth noting that having small loadings of catalyst and ligand (0.5 mol%) were beneficial, presumably by minimizing the consumption of terminal alkyne via direct propargylation. That is, if the steady state concentration of benzyne is below that of the alkynylcopper species ($\text{RC}\equiv\text{CCu}$), there is a significantly greater opportunity to produce the undesired skipped diyne $\text{RC}\equiv\text{CCH}_2\text{alkyne}$ by propargylation of $\text{RC}\equiv\text{CCu}$. The presence of a base such as K_2CO_3 , minimized the formation of unwanted benzyne hydroalkynylation products. Presumably sequestration of the equivalent of HCl that is necessarily formed in the reaction minimizes premature protonation of a species analogous to **4**.

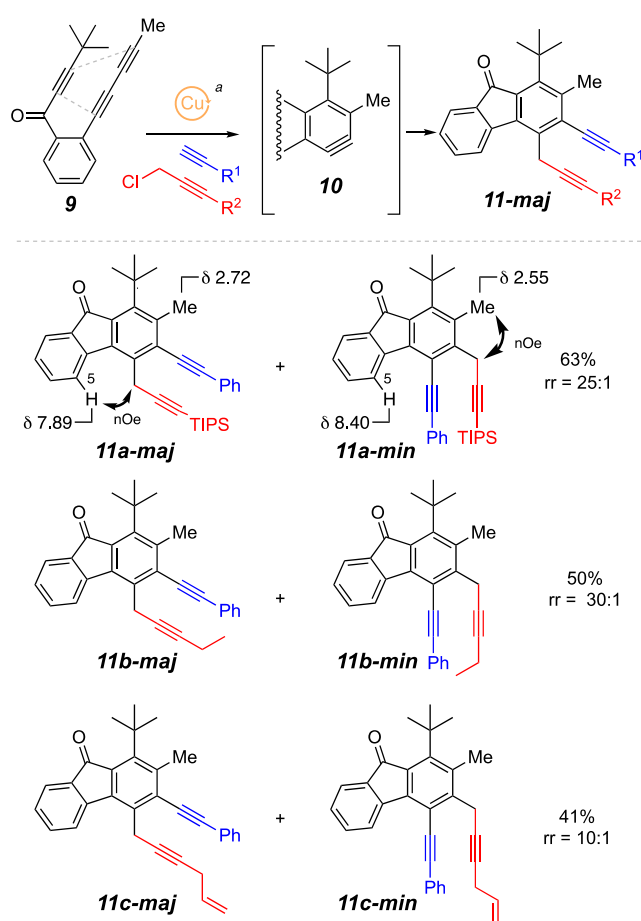


Figure 2. Alkynyl-propargylation reactions of triyne **9**.^a

^a CuI (0.5 mol%), dppp (0.5 mol%), K_2CO_3 (2 equiv) in MeCN ($[\mathbf{9}]_0 = 0.1 \text{ M}$) at 135°C for 18 h.

Phenylacetylene was used as the terminal alkyne partner in these examples. Propargylic halides containing TIPS (to **11a**), ethyl (to **11b**), 2-propenyl (to **11c**) all proceeded with good selectivity for the indicated major isomer; accompanied by small amounts of the minor isomer. The isolated yields of products were ranged from 41–63%. Although the reaction mixture was heated at 135°C for 18 h under the basic conditions, no desilylated product was observed in the case of

11a. It is notable that the skipped enyne moiety in **11c** could be installed without isomerization to the more conjugated isomer; however the slightly diminished efficiency (41%) could be the result of a propargylic ene event available to these products.

The assignment of structure to the two constitutional, major and minor isomers rests on interpretation of their ^1H NMR data. Large chemical shift differences of the protons in the aromatic methyl group and at C5 of the fluorenone ring in the two isomers of **11a-maj** and **11a-min** shown in Figure 2 were diagnostic. We interpreted these differences to reflect the anisotropic deshielding effect of the adjacent phenylalkynyl substituent. This was validated by the observation of the indicated nOe interactions, even for the minor isomer. This chemical shift trend was routinely seen for all of the isomeric mixtures seen throughout this study.

With an established protocol successfully applied to alkynyl propargylation of an HDDA aryne, we turned our attention to alkynyl-benylation and -allylation reactions. When benzyl chloride and phenyl acetylene were employed as the coupling partners, the alkynyl-benylation product **11d-maj** was produced in 63% yield and with a regioselectivity of 5:1 (Figure 3a). Attempts to utilize the secondary benzylic chloride (1-chloroethyl)benzene were not successful.

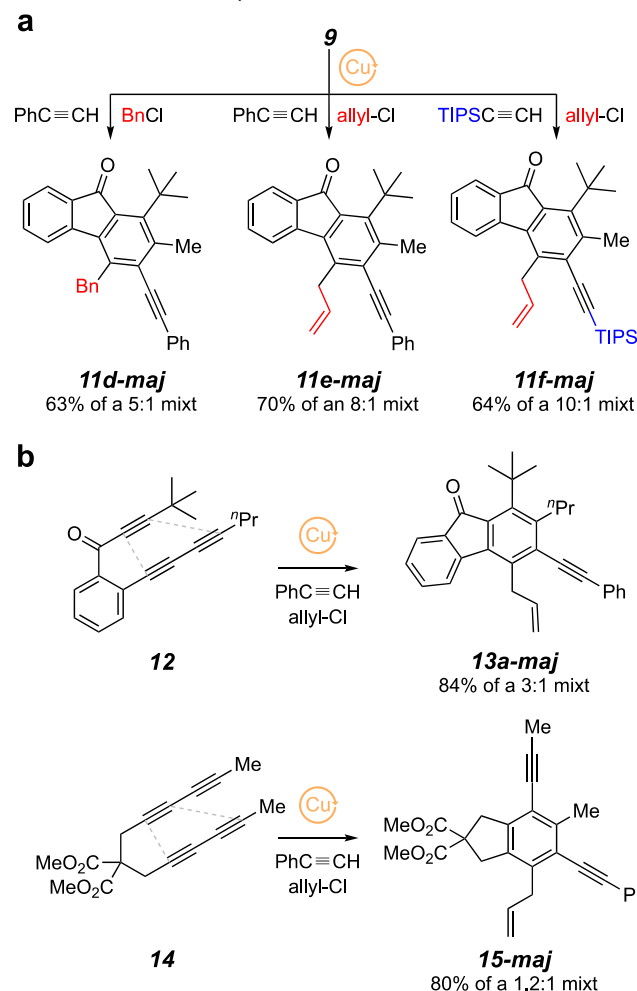


Figure 3.^a Alkynyl-benylation and -allylation reactions of triynes **9**, **12** (135°C), and tetrayne **14** (110°C).^b

^a only the structure of the major isomer is shown for each of these examples. ^b CuI (0.5 mol%), dppp (0.5 mol%), K₂CO₃ (2 equiv) in MeCN ([**9**]₀ or [**12**]₀ or [**14**]₀ = 0.1 M).

Alkynyl-allylation was also possible with benzyne precursor **9**, as demonstrated by the formation of products **11e** and **11f** (70%, rr = 8:1; 64%, rr = 10:1, respectively). For **11f**, the TIPS-acetylene delivered the alkyne moiety without desilylation. When more base sensitive TMS-acetylene was used instead, the desilylation product was detected (MS, NMR) as a component of a complex product mixture (not shown).

The somewhat unexpected difference in the levels of regioselectivity for the formation **11c**, **11d**, and **11e** suggests the possibility that the Cu(III) species alkynylCu(R)Cl could be the intermediate that engages the benzyne. In this scenario, the R group (propargylic vs. allylic vs. benzylic) would be present in the elementary step in which the alkyne–benzyne C–C bond is formed.

The compatibility of several common functional groups was briefly studied by additive-based robustness screening.⁹ We used the reaction of **9** with phenylacetylene and allyl chloride as a test case (see the SI for the protocol). The results showed a negligible impact on the formation of products **11e-maj**/**11e-min** caused by the presence of one equivalent of *N,N*-dimethylaniline, benzaldehyde, iodobenzene, nitrobenzene, acetophenone, naphthalene, and *n*-hexyloxirane, implying those classes of functionalities would be well tolerated. The cleanliness of formation of **11e** was compromised somewhat by the presence of benzoic acid (which also produced allyl benzoate) and glycidol (which have a more complex array of products). Using phenol as an additive resulted in the formation of only a minimal amount of **11e** and a large amount of allyl phenyl ether.

Triyne **12**, a *n*-propyl analog of **9**, could also be used as benzyne precursor, giving the product **13a** in 84% yield and a 3:1 rr (Figure 3b). The difference in the isomer ratio for **13a** compared to **11e** presumably reflects the increased steric hindrance adjacent to the aryne (Me vs ⁿPr). The malonate-derived tetrayne **14** also underwent a successful alkynyl-allylation to give **15** in 80% yield and a 1.2:1 rr. Here the product ratio is also influenced by the known lower site-selectivity for nucleophilic attack of the benzyne derived from **14** relative to that from triynes such as **12**.¹⁰

We next explored whether a terminal 1,3-diyne moiety could be installed via these processes. In addition, it would be convenient if that diyne could be revealed in situ under the reaction conditions by removal of an appropriate protecting group. This proved feasible, as can be seen from the information shown in Figure 4a. Specifically, the acetone adduct of conjugated diyne (e.g., **16a**) can be readily accessed through cross-coupling of 2-methylbut-3-yn-2-ol with another terminal alkyne, either by oxidative coupling (e.g., Glaser-Hay reaction) or by using one of these alkyne partners as it haloalkyne derivative (Cadiot-Chodkiewicz). We envisioned that deacetonation under the basic reaction

conditions (K₂CO₃) could release the terminal 1,3-diyne in situ.¹¹ This could prove advantageous both in avoiding the handling of the often-sensitive 1,3-diyne as well as mitigating potential competing side-reactions of the diyne if present in stoichiometric amount from the outset of the reaction. Indeed, under the standard conditions, K₂CO₃ was able to in-situ deprotect the internal diyne **16a** to generate terminal diyne and acetone and in the presence of the HDDA substrate **12** and allyl chloride, the three component adducts **13b** were produced (43% yield and 1.2:1 rr).

We then speculated that a product containing a newly installed HDDA-substrate triyne moiety could potentially be made by trapping with a propargylic chloride. We were pleased to see product **11g** (61% yield as a single isomer) arise from the reaction of **9**, diyne **16b**, and TIPS-propargyl chloride (Figure 4b). That is, the benzyne precursor **9** was transformed directly into a new HDDA-precursor, the triyne **11g**. Upon being heated at 210 °C in the presence of furan, a second HDDA reaction occurred to form product **17** via the benzyne intermediate **11g***.

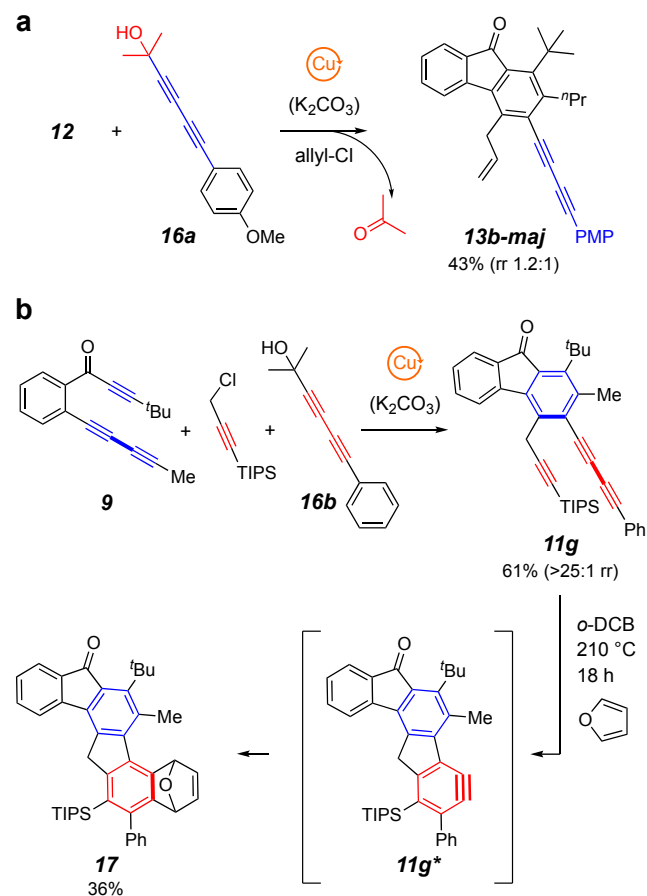


Figure 4. a) In situ deprotection of diynes **16a** provide terminal 1,3-diynes as trapping agents. b) Partnering with a propargylic chloride provides a triyne substrate for second, sequential HDDA reaction.

In summary, a Cu(I)-catalyzed difunctionalization of HDDA benzyne was developed. A propargylic, benzylic, or allylic moiety can be incorporated into benzyne in tandem

with a terminal monoyne or diyne partner in a three-component reaction. A final example involving difunctionalization of the benzyne by a terminal diyne and a propargyl chloride yielded a new triyne product, itself a viable HDDA substrate.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information (SI) is available free of charge on the ACS Publications website.

The SI contains preparative details and spectroscopic characterization data (including copies of ^1H and ^{13}C NMR spectra) for all new compounds.

FAIR Data (in a .zip file) of the raw data for each type of NMR spectrum for compounds **11a-maj**, **11a-min**, **11b-maj**, **11b-min**, **11c-maj**, **11c-min**, **11d-maj**, **11d-min**, **11e-maj**, **11e-min**, **11f-maj**, **11f-min**, **13a-maj**, **13a-min**, **15-maj**, **15-min**, **13b-maj**, **13b-min**, **11g**, **17**.

AUTHOR INFORMATION

Corresponding Author

*hoye@umn.edu

Notes

The authors have no competing financial interests to declare.

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