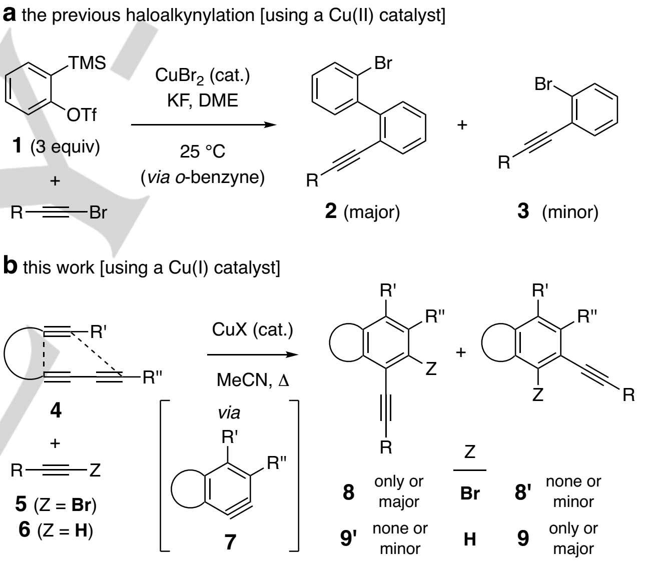
Cu(I)-Mediated Bromoalkynylation and Hydroalkynylation Reactions of Unsymmetrical Benzynes: Complementary Modes of Addition

Xiao Xiao,[a] Tao Wang,[a] Feng Xu,[a] and Thomas R. Hoye*[a]

Abstract: Benzynes formed by heating a suitable triyne (or tetrayne) substrate are shown to react with in situ-generated alkynyl copper species. The latter are compatible with the polyyne substrates and two types of chemistries have been achieved: (i) 1-bromo-1-alkynes efficiently undergo net bromoalkynylation of the (unsymmetrical) benzynes and (ii) in situ-generated alkynylcopper species give rise to hydroalkynylation products. The regiochemical preferences of these two modes of reaction are complementary to one another with respect to the position of alkynyl substituent in the final products.

1,2-Haloalkynylation of arynes is a potentially valuable way to install a considerable degree of complexity into the aryne family of reactive intermediates. We are aware of only one report describing such a transformation (Figure 1a). In 2010 Yoshida[1] and coworkers showed that (symmetrical) benzynes generated by the Kobayashi protocol[2] from 2-trimethylsilylaryl triflates (**1**) could engage bromoalkynes in the presence substoichiometric amounts of $CuBr_2$. The major products **2** arose from the (presumably sequential) introduction of two molecules[3] of benzyne; these were sometimes accompanied by lesser amounts of the 1:1 adducts **3**, depending upon reaction conditions. We report here that benzynes **7**, generated by the hexadehydro-Diels-Alder (HDDA) cycloisomerization reaction,[4] efficiently undergo bromo- and hydro-alkynylation in the presence of copper (I) catalysts (Figure 1b). A hallmark of the HDDA reaction is that the reactive benzyne intermediates are generated in the absence of any external reagent, rendering a pristine environment for the trapping event. The hydroalkynylation of benzynes has been studied more extensively and, again, the (mostly symmetric) benzynes have been generated by the Kobayashi protocol of fluoride treatment of *o*-trimethylsilylaryl triflates.[5] Here, we not only show the generality of this reaction under essentially neutral conditions, but also provide mechanistic insights that can be inferred from the products arising from the, necessarily, unsymmetrical HDDA-benzynes. In addition, the regiochemical preferences for the hydroalkynylation and the bromoalkynylation are complementary to one another (cf. **8/8'** vs. **9/9'**)—C–C bond formation occurs preferentially at different carbon atoms of the benzynes **7**.

More generally,[6] metal-catalyzed functionalization of an aryne is inherently challenging because the steady state concentration of both the aryne and the active organometallic must be sufficiently high to allow for their mutual capture. We have found that bromoalkynylation occurs smoothly in the presence of CuBr in MeCN solvent. For example (Figure 2a), the tetrayne benzyne precursor **10**, is trapped by 1-bromo-2-phenylethyne (**5a**) in excellent yield when heated (80 °C) in the presence of 10 mol% of CuBr (structural assignment discussed below). Benzyne **11** is known to preferentially undergo nucleophilic attack at C6, which is consistent with both the easier steric access of the nucleophilic atom to C6 vs. C7 as well as with the larger internal bond angle[7] at C6 computed for (the N-methanesulfonyl analog of)[8] the N-toluenesulfonylbenzyne **11**.


a the previous haloalkynylation [using a Cu(II) catalyst]

b this work [using a Cu(I) catalyst]

Figure 1. [a] Previous reports by Yoshida et al. [b] This work.

The scope of the bromoalkynylation reaction is quite broad (Figure 2a). Aliphatic and aromatic bromoalkynes with a variety of functionalities are tolerated (cf. **12a**–**12k**). We have also examined several polyyne substrates that incorporate different tethers; these led to the bromoalkynylation products **13**–**17**. It is noteworthy that we have never observed a product indicating premature reaction of the HDDA polyyne precursor with any of the active organometallic species involved in this chemistry.[9] Moreover, we observed no desired product formation in the absence of the copper catalyst.[10]

We envision the reaction proceeding through a mechanism such as that depicted in Figure 2b. The initial thermal cycloisomerization is the rate-determining step in the overall cycle, because the reaction rate is similar for triyne **10** regardless of the trapping agent used.[11] We propose that benzyne **11** initially undergoes nucleophilic addition with CuBr to

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produce the aryl copper(I) species **18**, which then reacts with a molecule of the bromoalkyne to generate the Cu(III) adduct **19**.

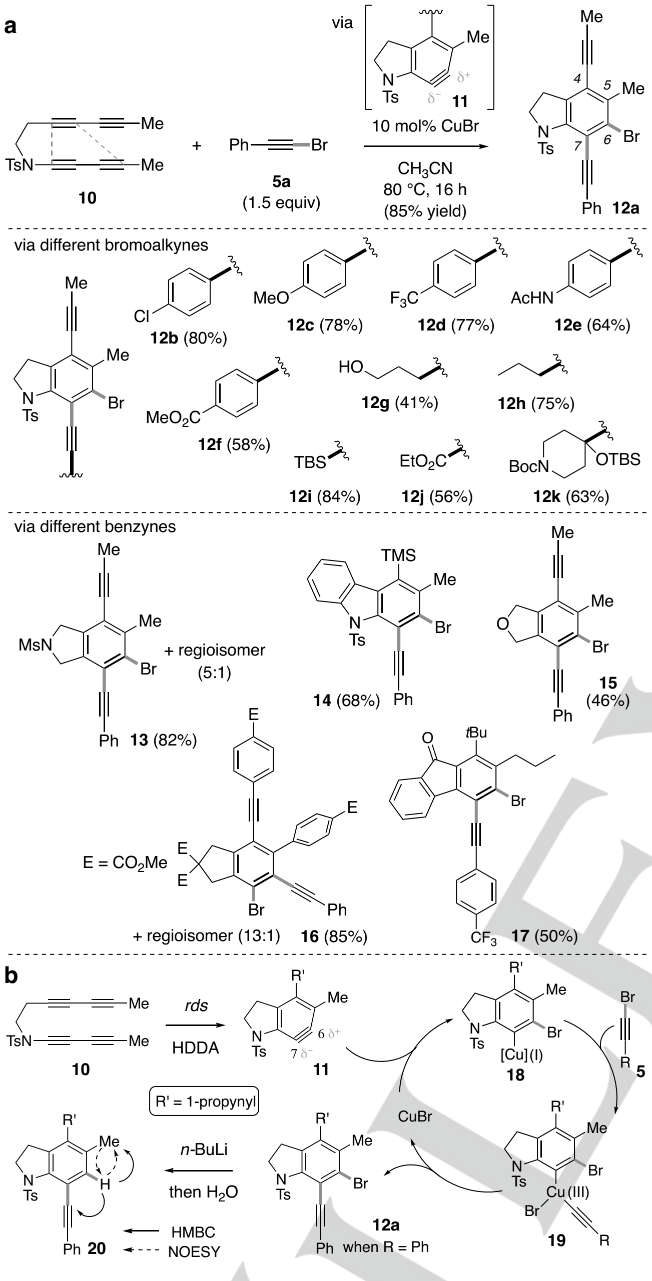

Figure 2. [a] Scope of the bromoalkynylation reaction. [b] Proposed catalytic cycle and basis for assignment of the constitution of **12a** (cf. **20**).

This view is consistent with the fact that trace amounts of chloro- or iodo-alkynylation products were observed (GC-MS) when CuCl or CuI was used as the catalyst instead of CuBr. Reductive elimination of the alkyne and arene ligands produces product **12**. Two minor byproducts often detected were those corresponding to net hydrobromination and/or dibromination of the benzyne. These can be accounted for by hydrolytic capture of the ArCu species **18** by adventitious water or competitive (and, fortunately, less facile) reductive elimination of bromo and arene ligands from **19**. It is noteworthy that when iodoalkynes was used, efficient diiodination rather than iodoalkynylation of the benzyne was observed. Presumably, the reductive elimination of iodo and arene ligands from the ArCuI$_2$ species (analogous to **19**) became the dominate pathway (for more details, see Supporting Information, page S19).[12] Purposely adding water into the reaction mixture at the outset led to decreased overall yield of **12** with concomitant formation of the net hydrobromination adduct. The structure of **12** was confirmed by its conversion to the reductively debrominated derivative **20**. The site of the aromatic proton was definitively identified based on the indicated nOe and HMBC analyses. This mode of regioselectivity supported the above mechanistic view—namely, that the initial bromination by CuBr had occurred at the more electrophilic site in benzyne **11**.

We briefly explored several potential synthetic applications of the bromoalkynylation products (Figure 3). One-pot halogen exchange and global deprotections of, for example, bromocarbazole **14** gave rise to alkynylcarbazole **21**, whereas heating compound **14** with sodium sulfide efficiently provided the deprotected thienocarbazole **22**.[13] Palladium-catalyzed cross-couplings of the bromobenzene moiety were also tested.[14] For example, Sonogashira and Suzuki reactions of the bromoalkyne **15** efficiently afforded the trialkynylbenzene **23** and the biaryl **24**, respectively.

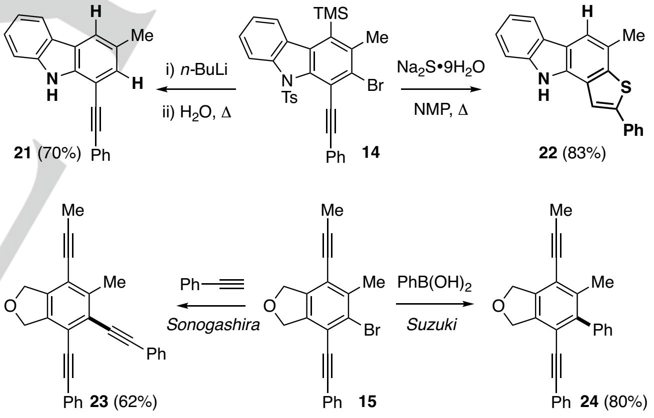

Figure 3. Potential synthetic applications [see Supporting Information (SI) for more experimental details].

Many alkyne cross-coupling reactions rely on the robustness of copper acetylides.[15] We envisioned that when formed *in situ*, these could serve as nucleophiles to arynes and that a net hydroalkynylation process could ensue. This had the potential to be complementary to the bromoalkynylation reaction with respect to the point of attachment of the alkyne in the product arene. However, an organic amine is often required to promote Cu-acetylide formation, but (even tertiary) amines are excellent nucleophilic trapping agents for benzynes.[16] Cu-acetylides can be formed and trapped in situ by the action of a fluoride base under conditions where arynes are being co-produced.[5] We were pleased to see that in the absence of any added base, copper chloride alone (5 mol%), in acetonitrile solution, induces the addition of terminal alkynes (e.g., **6a**) to HDDA benzyne intermediates (e.g., **11** from **10**) to give net hydroalkynylation products (e.g., **25a**; see SI for the reaction optimization studies leading to the choice of conditions shown in the top of Figure 4a).

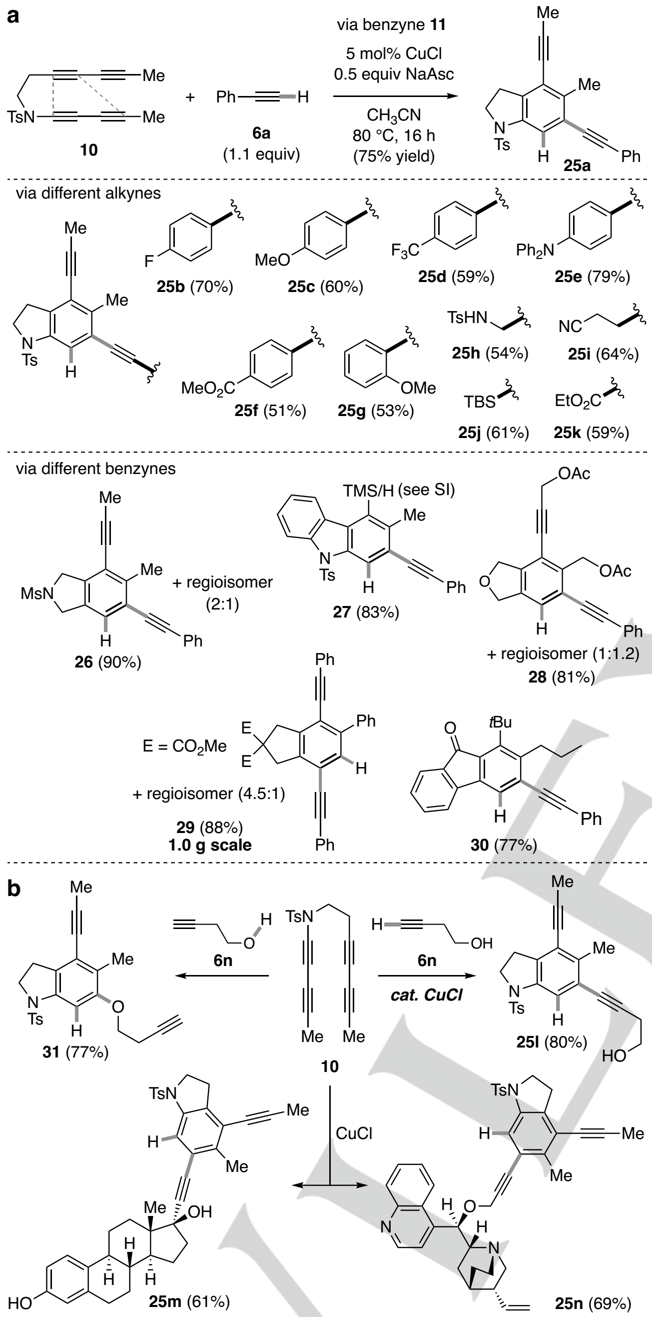

Figure 4. [a] Scope of the hydroalkynylation reaction revealed by outcomes with various alkynes and benzyne precursors. [b] Cu-catalyzed hydroalkynylation occurs faster than other potential aryne trapping reactions; in the absence of catalyst, aryl ether **31** is the major product.

Notably, only a slight excess (1.1 equiv) of alkyne needs to be used because its oxidative dimerization can be mitigated either by careful deoxygenation of the reaction solution or, more conveniently, using sodium ascorbate, even under an ambient atmosphere, to prevent formation of Cu(II) species. Presumably these conditions allow for the Cu-acetylide to be relatively long-lived; the use of just 5 mol% of copper loading gave high enough steady-state concentration to effectively trap the reactive benzyne. The structure of **25a** is the complement to that of **20** (Figure 2b) and is consistent with the proposal that Cu-acetylide addition is involved in this transformation. Namely, the distorted nature of the HDDA-benzyne **11** (Figure 2a) is consistent with an initial alkynyl-cupration of the benzyne.

Given the quite good isolated yield, mild reaction conditions, and the easy experimental setup, we were encouraged to explore the generality of this hydroalkynylation reaction. Products of both aromatic (**25a**–**25g**) and aliphatic (**25h**–**25k**) alkyne addition are readily formed. For aromatic alkynes, the impact of electronic effects from substituents was minimal and *ortho*-substitution (**25g**) was tolerated.[17] As with the bromoalkynylation, we also tested the behavior of several HDDA-benzyne precursors containing different tethers in the hydroalkynylation. These gave products **26**–**30** in high overall yield. The level of regioselectivity was uniformly lower for the hydroalkynylation. The reaction leading to **29** was performed on a relatively large scale and showed no erosion in efficiency (88% yield). The flanking aryl substituent in the intermediate benzyne substantially inhibits approach of the nucleophile to the proximal sp-carbon, leading to a reversal in the location of the alkyne in **29** vs. **30** (cf., also, **16**).

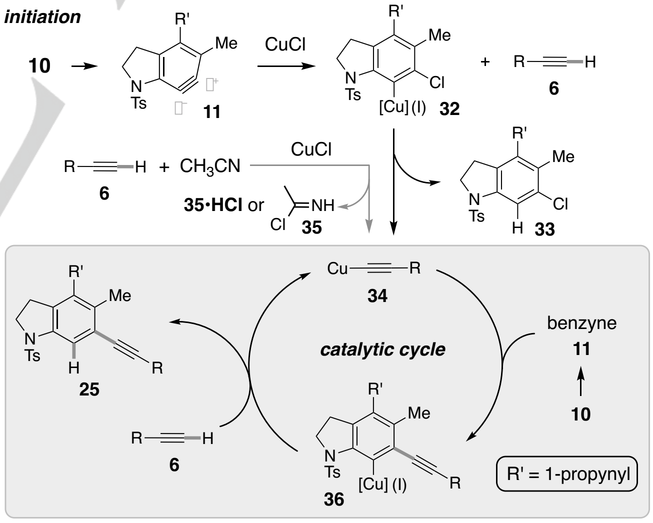

Figure 5. Proposed initiation event(s) and catalytic cycle for the hydroalkynylation reaction.

Orthogonal chemoselectivity can be achieved simply by performing the reaction in the presence or absence of the Cu catalyst. For example (Figure 4b), the hydroxy group in alkynol 6n traps benzyne **11** (from **10**) to give the ether **31** when no CuCl is used.[18] In contrast, under the copper catalysis conditions described here, the complementary alkyne **25l** was formed highly selectively, indicating that the copper acetylide trapping event of benzynes is much faster than that by OH. In neither reaction was any of the product of the alternative constitution observed by NMR analysis of the crude product mixture. Additional selectivity was seen when natural product derivatives were used as trapping agents.[19] Namely, the hydroalkynylation products **25m** and **25n** were efficiently produced in the presence of CuCl when terminal alkynes derived from estradiol and cinchonidine (see SI for details) were used as the trapping agents. This is especially notable because these molecules contain additional potentially competing reactive moieties that include phenol,[8] alcohol,[18] tertiary amine,[19] ether,[20] alkene,[21] cyclic alkane,[22] and quinoline sites[23].[24]

A mechanistic proposal for the hydroalkynylation reaction is shown in Figure 5. At the top are possible ways by which an initial copy of the requisite Cu-acetylide (**34**) could be formed. Sacrificial reaction of one benzyne with CuCl would give the arylcopper species **32**, which could then engage in proton exchange with the terminal alkyne **6**.; indeed, we have detected low levels of the benzyne + HCl adduct **33** by GCMS analysis of a crude reaction mixture. Alternatively, acetonitrile could function as a base to deprotonate a CuCl•**6** complex, leading to the HCl adduct **35**[25] or its iminium hydrochloride salt **35•HCl**.[26] Indeed, we have observed that the choice of acetonitrile as solvent is critical for success of the hydroalkynylation reaction. Once produced, **34** could then enter the cycle highlighted by the gray box. Alkynyl-cupration of benzyne **11** would give **36** and proton exchange with **6** would lead to **25** and close the cycle.

In conclusion, we have developed an efficient copper-catalyzed protocol for installation of an alkynyl substituent onto a HDDA-generated benzyne. 1-Bromoalkynes lead to products of bromoalkynylation in which the bromide has preferentially engaged the more electrophilic carbon of the (necessarily) unsymmetrical benzyne (Figure 2a). The hydroalkynylation reaction of terminal alkynes occurs in complementary fashion; namely, the alkyne carbon is now attached to the more electrophilic carbon (Figure 4). Catalytic cycles for each of these two reaction processes are proposed (Figures 2b and 5). The potential utility of the *ortho*-alkynylbromobenzene products as substrates in further transformations of interest is also demonstrated (Figure 3).

Acknowledgements

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Keywords: metal-catalyzed aryne trapping • copper catalysis • alkynylations

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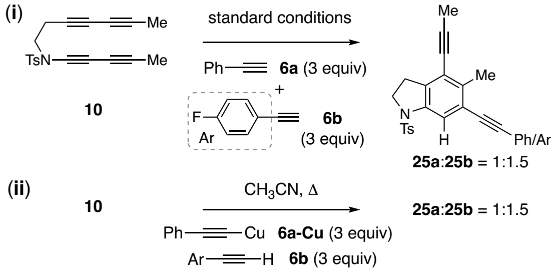

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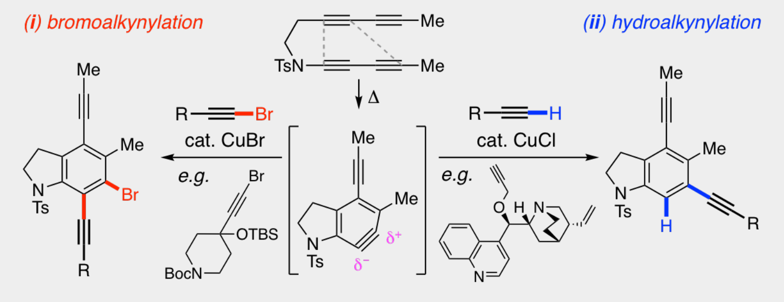

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Cu-catalyzed bromo- and hydro-alkynylations of unsymmetrical arynes was described. These two mechanistically distinct modes of reaction are efficient, broad in scope, and giving complementary alkynylation products. Mechanisms are proposed and potential for synthetic elaboration is demonstrated.