Copper-Catalyzed Carboarylation of Alkynes via Vinyl Cations

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**S** *Supporting Information*

ABSTRACT: Copper-catalyzed arylation of electron rich alkynes reveals stabilized trisubstituted vinyl cation equivalents that react with pendant arene nucleophiles to form all carbon tetrasubstituted alkenes. The new process streamlines the synthesis of important medicinally relevant molecules.

The hydroarylation of alkynes is an important synthetic process as it provides general access to substituted styrene derivatives, molecules that display significant utility as building blocks for chemical synthesis, medicines, and functionalized materials. In the simplest case, an alkyne is protonated by a strong acid and the resulting vinyl cation intermediate is intercepted by an arene nucleophile.[1] Many transition metal salts are also capable of catalyzing hydroarylation, and this continues to inspire the development of new general catalytic methods for the preparation of highly substituted styrenes.[2] Most metal-catalyzed hydroarylation processes involve carbon–carbon triple bond activation by the π-Lewis acidity of the metal salt. This promotes an anti-addition of the nucleophilic aryl group to the π-complex followed by protonation of the resulting vinyl-metal bond. Despite its broad use, the hydroarylation of alkynes is limited to the formation of mono-, di-, or trisubstituted alkenes. The development of catalytic methods that lead to the carboarylation of disubstituted alkynes remains a challenge to synthetic chemists, and while the overall transformation can be achieved in a stepwise fashion,[3] catalytic processes to form all-carbon tetrasubstituted alkenes are still rare.[4]

Inspired by the simplicity of acid mediated hydroarylation, we questioned whether a related process could be initiated through the reaction of a carbon electrophile with an alkyne (eqs 1,2).[5] On the basis of recent reports from our laboratory,[6] we proposed that a catalytically generated aromatic electrophile equivalent (eq 3), formed via activation of a diaryliodonium triflate with a Cu(I) salt,[7] would react with an electron rich carbon–carbon triple bond to form a putative stabilized trisubstituted vinyl cation-type intermediate.[8]

This reactive species could then be intercepted by a latent aromatic nucleophile via a Friedel–Crafts-type process to form the all-carbon tetrasubstituted substituted alkene. Here we report the development of a copper-catalyzed intramolecular carboarylation process that forms cyclic tetrasubstituted alkenes. The new process is operationally simple, works with a range of alkynes and diaryliodonium salts, and can accommodate a variety of electronically distinct arenes as the nucleophilic component of the reaction. This alkyne carboarylation can also be used to streamline the synthesis of
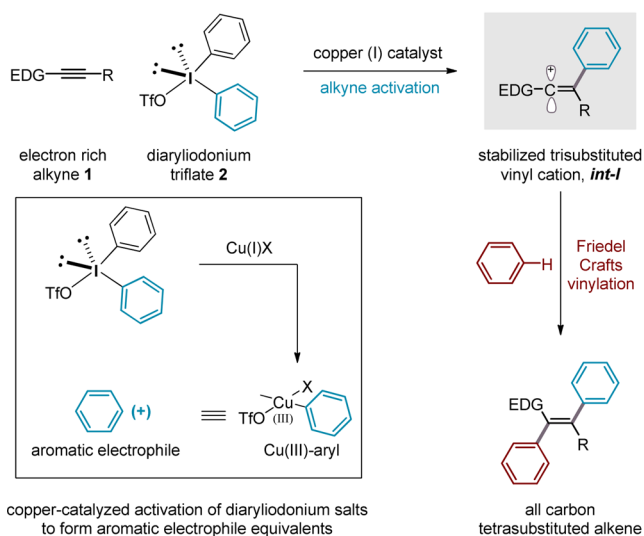
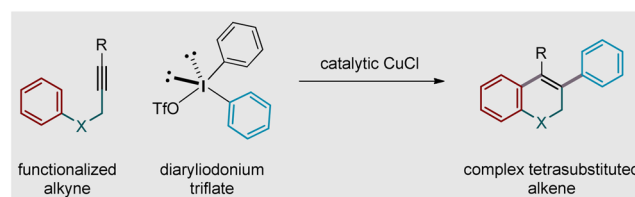**Hydroarylation of alkynes (Eq 1)**
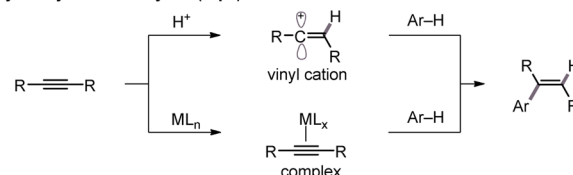
Electrophile induced di-carbofunctionalization of alkynes (Eq 2)
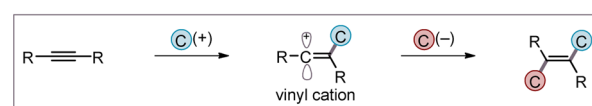
Proposed mechanism to exploit highly substituted vinyl carbocation (Eq 3)

This work – Copper-catalyzed carboarylation of alkynes (Eq 4)


important anticancer therapeutics and has great potential for the synthesis of complex alkenes.

Our initial studies were guided by an observation made during our work on the copper-catalyzed carbotriflation of alkynes using diaryliodonium salts.[6b] Reactions on alkynes

bearing one alkyl group and one phenyl group resulted in an *E*-selective reaction, whereas alkynes with two alkyl groups displayed *Z*-selectivity under the same conditions. We reasoned that the *E*-selectivity observed in the phenyl-substituted system could arise from the intermediacy of the vinyl cation; aromatic substituents appended directly to the carbenium atom are known to stabilize vinyl cations (eq 5).

Electrophilic carbotriflation of alkynes – substrate controlled selectivity (Eq 5)
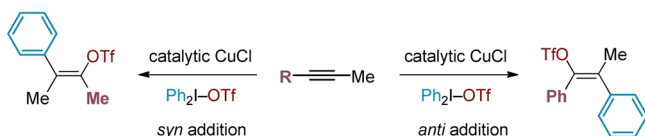
The feasibility of the carboarylation hypothesis was first examined using alkyne **1a**, an alkyne displaying an electron rich aryl group that should stabilize the vinyl cation species formed in the proposed mechanistic pathway. A survey of reaction parameters is shown in Table 1 and revealed that optimal

**Table 1. Selected Optimization of Carboarylation**

entry	catalyst	solvent	DTBP, equiv	2a, equiv	temp, °C	yield 3a, %[a]
1	Cu(OTf)$_2$	DCE	1.0	1.0	70	0
2	CuCl	DCE	1.0	1.0	70	50
3	CuTC	DCE	1.0	1.0	70	42
4	CuI + AgOTf	DCE	1.0	1.0	70	51
5	CuCl	dioxane	1.0	1.0	70	18
6	CuCl	C$_6$H$_5$Cl	1.0	1.0	70	58
7	CuCl	toluene	1.0	1.0	70	62
8	CuCl	Me$_2$CO	1.0	1.0	70	13
9	CuCl	DCE	2 × 1.0	2 × 1.0	70	94[b]
10	CuCl	DCE	2.0	2.0	50	95
11	CuCl[c]	DCE	2.0	2.0	50	93[d]
12	none	DCE	2.0	2.0	50	0
13	none	DCE	2.0	2.0	90	0
14	none	DCE	2.0	2.0	110	0

[a]Reactions performed with 0.1 mmol of **1a** and yield of **3a** are presented as an average of two runs determined by ^{1}H NMR with Ph$_3$CH as the internal standard. [b]Portionwise addition of 2.0 equiv of **2a** and DTBP. [c]2.5 mol % CuCl. [d]Yield of isolated product.

conditions could be achieved by treating **1a** with 2.5 mol % CuCl as the catalyst and 2.0 equiv of diaryliodonium triflate (**2a**) and 2,6-di-*tert*-butyl pyridine (DTBP)[9a] with 1,2-dichloro-ethane as the solvent at 50 °C.[9b] No reaction was observed in the absence of the copper salt, even at higher temperatures.

With an optimized set of reaction conditions in hand we next turned our attention to assessing the scope of the alkyne carboarylation. We first explored the electrophilic aryl coupling partner by testing a variety of unsymmetrical aryl(mesityl)-iodonium triflates (Table 2).[10a,b] We found that aryl groups displaying halogen substituents and electronic withdrawing groups could be transferred giving excellent yields of the desired dihydronaphthalene products (**3b–f**). Surprisingly, a

Table 2. Scope of Electrophilic Component
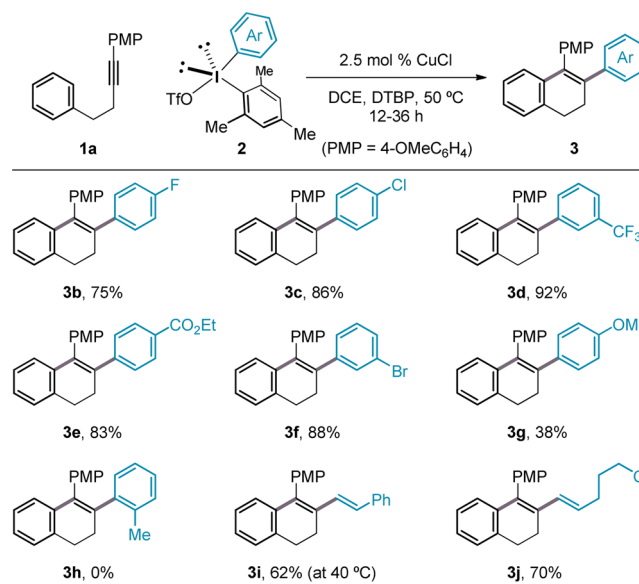
lower yield was obtained for the transfer of a 4-methoxyphenyl group (**3g**), and no reaction was observed for the transfer of ortho-substituted aryl groups, most likely due to the low reactivity of salt **2h**. However, we were pleased to find that this process was amenable to the use of vinyl(aryl)iodonium salts,[10c] with styrenyl and functionalized vinyl groups transferred in good yields (**3i–j**).

The electronic requirements for the substituent on the carbon–carbon triple bond were more rigid, and we observed that it is essential to have a group capable of adequately stabilizing a cation intermediate (Table 3).[11] In addition to the

**Table 3. Scope of Alkyne Substituent and Linking Unit**
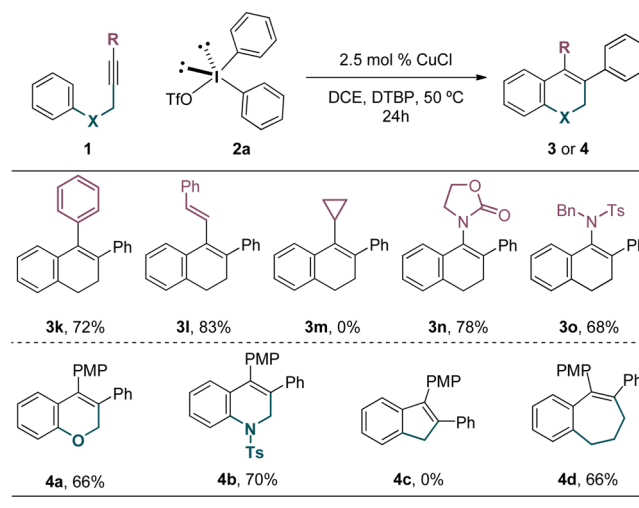
anisyl group, a simple phenyl group was sufficiently reactive, providing a good yield of the corresponding product **3k** after 48 h. We were pleased to find that a styrenyl substituent on the alkyne also worked well, further reflecting the similarities with established vinyl carbocation stability (**3l**).[8] While alkynes with alkyl substituents undergo the aryltriflation reaction, a substrate with a cyclopropyl substituent (a group that is capable of stabilizing an adjacent positive charge) led to an intractable mixture of products. Heteroatom functional groups directly

appended to the alkyne also worked well and provided a route in more complex dihydronaphthalene derived systems (**3n,o**).

We next investigated substrates displaying a selection of linkers between the alkyne and the arene nucleophile (Table 3). In addition to the ethylene linkage, oxygen and nitrogen substituents could also be incorporated to provide the substituted chromene and dihydroquinoline ring systems (**4a,b**). Complex mixtures were observed when we tried to form the corresponding indene derivative **4c**. However, we were delighted to find that a seven-membered ring could be formed in good yield, further extending the efficacy of this process (**4d**).

The final aspect of our scope studies focused on the arene used to intercept the proposed vinyl cation intermediate (Table 4). We found that the arene nucleophile could accommodate

Table 4. Scope of Arene Nucleophile

3p, 91%   3q, 91%   3r, 97%   3s, 83%

3t, 93%   3u, 88% (2.2:1*)   3v, 95%   3w, 86%

3x, 83%   3y, 76%   3z, 78%
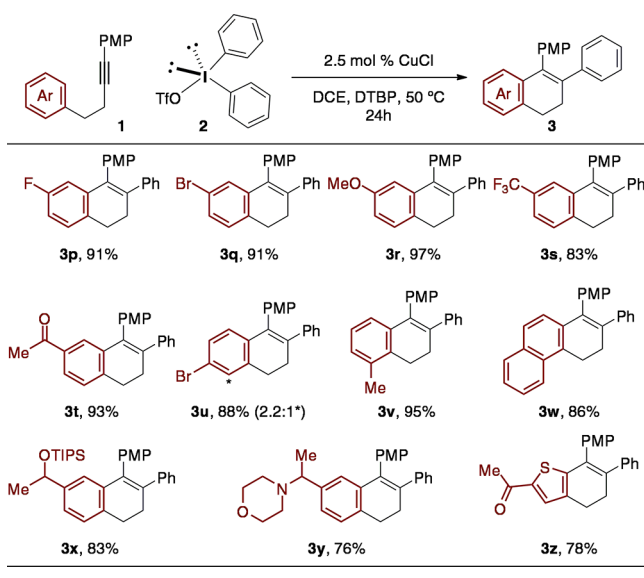
substituents at the ortho or para positions with respect to the alkyne containing appendage and in all cases gave rise to excellent yields of the products; meta substituents led to isomeric mixtures of products (**3u**). Electron donating, electron withdrawing, and naphthalene groups, heterocycles, and a wide range of useful functionality could be introduced as the nucleophilic component of the carboarylation.[12]

To demonstrate the utility of this new copper-catalyzed carboarylation we showed that the dihydronaphalene products can be oxidized to the polyaromatic naphthalenes **5**.[13] We also developed a short route toward the anticancer agent nafoxidine (Scheme 1).[14] Subjecting the alkyne **6** to the standard reaction conditions produced a 73% yield of the desired dihydro-naphthalene (not shown) on gram scale. Treatment with pyrrolidine at 100 °C in ethanol provided nafoxidine **7** in excellent yield.

Finally, we showed that external nucleophiles can be accommodated as part of the carboarylation process (Scheme 2). Our preliminary experiments revealed that a three component carboarylation reaction between alkyne **8**, diphe-nyliodonium triflate (**2a**), and anisole (**9**) as the nucleophilic component is also possible, forming the all carbon tetrasub-stituted alkene **10** in 67% yield. This is a promising result that opens potential new strategies for the synthesis of complex

Scheme 1. Applications of the Carboarylation
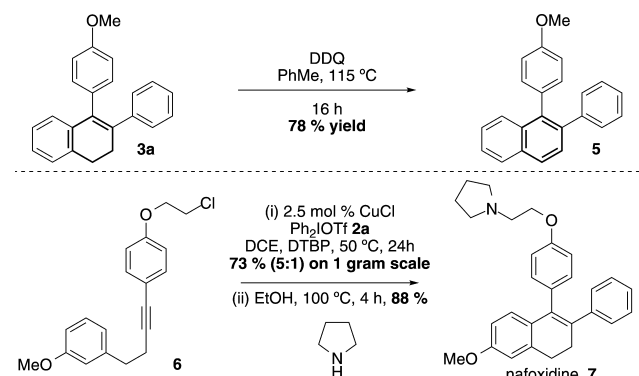
Scheme 2. Intermolecular Carboarylation
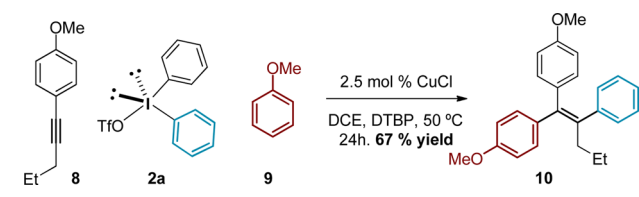
unsaturated systems using a simple multicomponent ap-proach.[6b,c]

In summary, we have developed a Cu-catalyzed alkyne carboarylation process that generates highly functionalized all carbon tetrasubstituted alkenes as part of a dihydronaphthalene framework. We believe the process exploits a catalytically generated aromatic electrophile that reacts with an alkyne to form a trisubstituted vinyl cation intermediate, which is intercepted by a tethered arene nucleophile. The carboarylation proceeds under mild conditions, produces the products in high yields, and can be used to streamline the synthesis of complex molecules. Current studies are focused on the synthesis of naphthoquinone and chromenone derived natural products[15] and on exploiting the vinyl cation reactivity that underpins this novel transformation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectral data are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(9) (a) In the absence of the DTBP we observe complete consumption of **1a** and **2a** but no formation of **3a**. (b) At 70 °C we observe a rapid decomposition of **2a**. Equivalent yields of **3a** could be achieved by portion wise addition of 2 × 1 equivalents of **2a** at 70 °C (c.f. Table 1, entry 11.)

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(11) We attempted to prepare vinyl triflate **12** from the corresponding enolate. The only product formed was **3a** and no vinyl triflate was observed. This suggests **12** undergoes the Friedel−Crafts cyclization under mild conditions implicating it and the corresponding vinyl cation in the Cu-catalyzed carboarylation.

(12) A competition experiment between a substrate containing a phenyl ring and one displaying an electron deficient aromatic ring (CF₃) showed a 1:1 mixture of products (**3a**:**3s**), suggesting that the rate determining step is prior to the Friedel−Crafts stage of the reaction pathway.

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