

Copper-Catalyzed Electrophilic Carbofunctionalization of Alkynes to Highly Functionalized Tetrasubstituted Alkenes

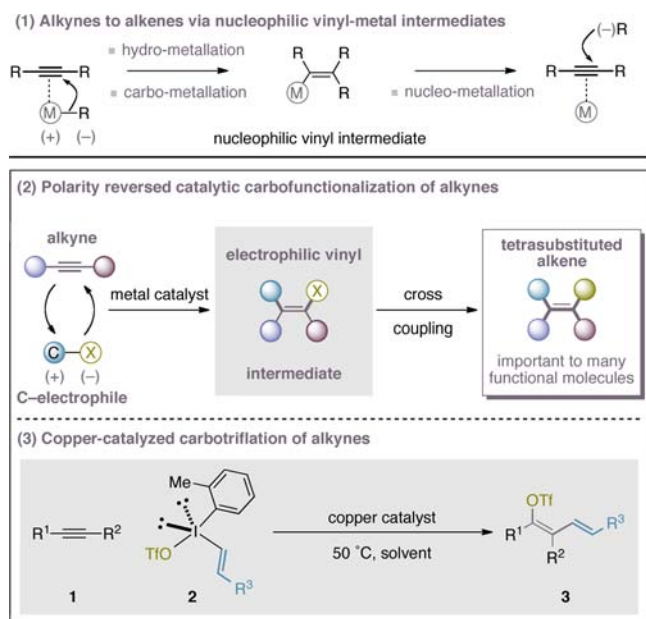
Marcos G. Suero, Elliott D. Bayle, Beatrice S. L. Collins, and Matthew J. Gaunt*

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, United Kingdom

S Supporting Information

ABSTRACT: Copper catalysts enable the electrophilic carbofunctionalization of alkynes with vinyl- and diaryliodonium triflates. The new process forms highly substituted alkenyl triflates from a range of alkynes via a pathway that is opposite to classical carbometallation. The alkenyl triflate products can be elaborated through cross-coupling reactions to generate synthetically useful tetrasubstituted alkenes

The invention of processes that use transition metals to exploit the inherent reactivity of carbon–carbon triple bonds has captured the imagination of chemists.¹ These reactions have become cornerstone methodologies for the synthesis of many important chemical products in both academic and industrial laboratories. Arguably, the most prevalent class of alkyne reactions are π -insertion processes to the triple bond, forming alkenes. It is, however, surprising that the majority of these processes stem from a small number of related activation pathways. A metal catalyst binds to the π -orbitals of the alkyne and transfers a group via an external nucleophilic attack (nucleometalation) or via the metal (hydrometalation).^{1a} The resulting nucleophilic vinyl-metal species can undergo a range of further reactions to form substituted alkenes (eq 1).



The formation of tetrasubstituted alkenes by these catalytic methods is difficult due to steric hindrance around the unsaturated core and is restricted to specific examples.² Despite this, their useful properties mean they find many important applications as medicines, biological probes, functional materials, and building blocks for synthesis. The most reliable method to form tetrasubstituted alkenes is alkyne carbometallation (eq 1),³ although there is still a paucity of general catalytic methods available.⁴ Surprisingly, methods based on intermolecular carbopalladation have not become a mainstay for tetrasubstituted alkene synthesis, despite notable recent advances.⁵

Given the inherent reactivity within the carbon–carbon triple bond, we were surprised that little consideration has been afforded to a “polarity-reversed” alkyne carbofunctionalization strategy to form tetrasubstituted alkenes (eq 2). The catalyzed union of a carbon electrophile with an alkyne would preclude the use of reactive organometallics and, more importantly, generate a highly substituted electrophilic vinyl intermediate whose reactivity would contrast to the vinyl-nucleophile species formed in classical carbometallation. The scarcity of such catalytic processes is striking considering that the addition of acids and halogen-derived reagents to alkynes is well documented via electrophilic pathways.⁶

Here we report the development of a Cu-catalyzed electrophilic carbofunctionalization of alkynes with vinyl- and diaryliodonium triflates (eq 3). The new process forms highly functionalized tetrasubstituted alkenyl triflates, is operationally simple, and works with a range of alkynes and electrophile coupling partners. The alkenyl triflate products can be further elaborated through well-established cross-coupling reactions to generate synthetically useful tetrasubstituted alkenes, difficult to make by other methods.

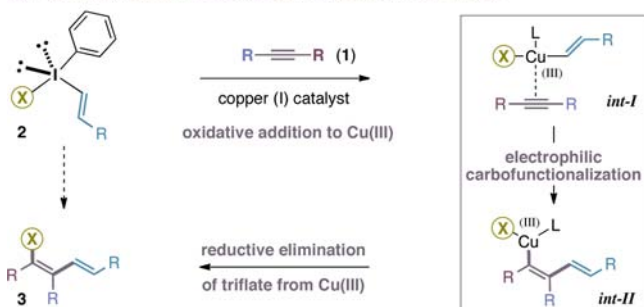
We reasoned diaryl- and vinyl(aryl)iodonium salts could function as suitable carbon electrophiles,⁷ acknowledging two important features relating to their reactivity. First, Beringer et al.⁸ had shown that treatment of diphenyliodonium chloride with Cu(I) salts forms chlorobenzene; we⁹ (and subsequently others)¹⁰ have demonstrated that the combination of diaryliodonium salts and copper catalysts produces aromatic electrophile equivalents which react with π -rich nucleophiles. We believe the mechanism involves a high oxidation state Cu(III)-aryl intermediate, where both the aryl group and the counteranion have been assembled on the Cu(III) center.¹¹ As part of our polarity reversal hypothesis, this intermediate could

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engage the alkyne (*int-I*), facilitating the insertion of the aryl-Cu(III) species to the carbon–carbon triple bond (*int-II*, eq 4).

(4) Working hypothesis for electrophilic carbofunctionalization



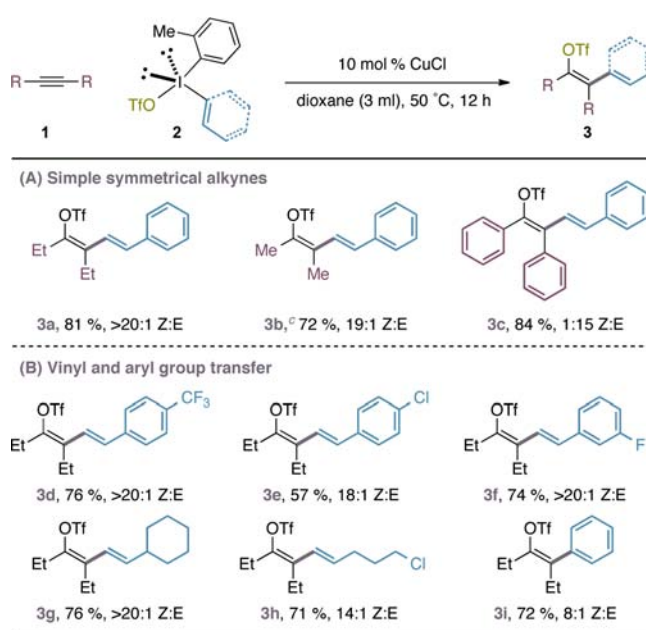
Taken together with Berenger's observation,⁹ the resulting Cu(III) species, which displays a vinyl group and the counteranion from the diaryliodonium salt, could undergo reductive elimination, producing the alkene product bearing a versatile functional group 3.¹²

Initially, we selected styryl(*o*-tolyl)iodonium salts displaying different halide counteranions with which to test our hypothesis (Table 1). After screening a range of conditions for the reaction between 3-hexyne 1a and styryl(*o*-tolyl)iodonium salts 2 (X = Cl, I), with CuCl as catalyst and dichloromethane as solvent, we were disappointed to find that none of these reactions produced the desired tetrasubstituted alkene, and instead we observed the formation of the corresponding styryl chloride (entry 1), or no reaction (entry 2). Speculating that a more electron-withdrawing counteranion might afford a more reactive Cu(III)-styryl intermediate, we were pleased to find that changing the counteranion to triflate (2c) had a dramatic effect on the outcome, and the desired tetrasubstituted vinyl triflate 3a was formed as a 6:1 ratio of Z:E isomers (entry 3). This result is particularly notable as the vinyl triflate product may result from a rare example of the reductive elimination of a triflate group from a metal center.¹² Following this breakthrough, an optimization screen revealed that the nature of the solvent also had an important influence on the reaction (entries

4–8), and when the reaction was conducted using 10 mol % copper(I) chloride in dioxane at 50 °C, 81% yield of the highly functionalized and synthetically useful 3a was obtained selectively as the Z-isomer (>20:1 Z:E, entry 8).^{13–17}

The scope of this new electrophilic carbofunctionalization process was first explored by varying the substituents on the alkyne. We found that a selection of symmetrical dialkyl and diaryl alkynes worked well in the process and delivered the alkene products in excellent yield and selectivity for the Z-isomer (Table 2A, 3a–c). We also found that the reaction can

Table 2. Vinyl Triflation of Symmetrical Alkynes^{a,b}



^aReactions performed with 2.0 mmol of 1, 0.5 mmol of 2; yields are of isolated product. ^bRatio of isomers determined by ¹⁹F NMR. ^c12 g scale with 1 mol % CuCl.

Table 1. Selected Optimization Results^a

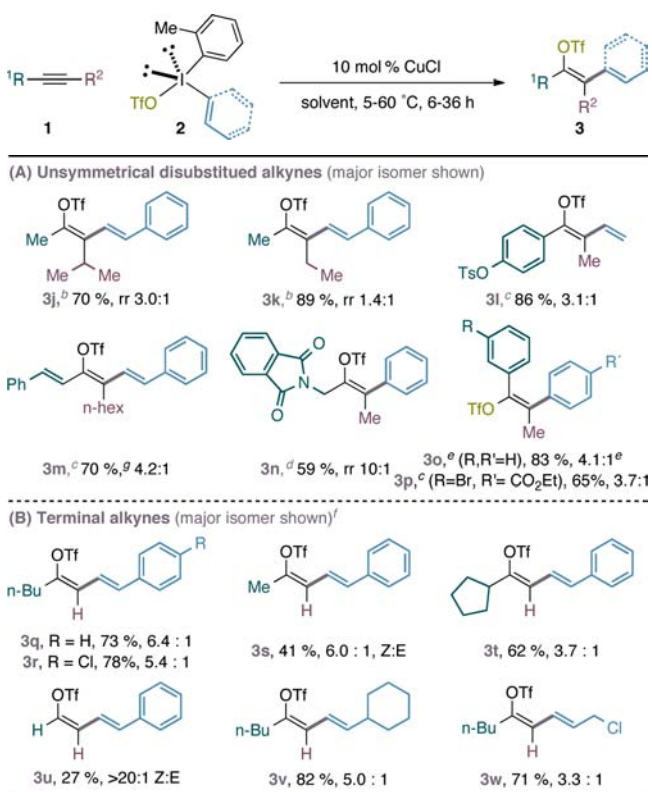
entry	catalyst	X	solvent	temp, °C	yield 3a, % ^b	ratio Z:E ^c
1	CuCl	Cl	CH ₂ Cl ₂	50	–	–
2	CuCl	I	CH ₂ Cl ₂	50	–	–
3	CuCl	OTf	CH ₂ Cl ₂	50	66	6:1
4	CuCl	OTf	dichloroethane	50	61	7:1
5	CuCl	OTf	PhMe	50	50	13:1
6	CuCl	OTf	EtOAc	50	67	16:1
7	CuCl	OTf	Et ₂ O	50	71	16:1
8	CuCl	OTf	dioxane	50	81 ^d	>20:1
9	CuI	OTf	dioxane	50	65	>20:1
10	CuTC	OTf	dioxane	50	46	>20:1
11	none	OTf	dioxane	50	–	–
12	none	OTf	dioxane	90, 110	–	–

^aReactions performed with 0.4 mmol of 1a, 0.1 mmol of 2. ^b¹H NMR yields, calculated using trimethyl 1,3,5-benzenetricarboxylate as internal standard. ^cDetermined by ¹⁹F NMR. ^dYield of isolated product.

be performed on multigram scale and with lower catalyst loading, without compromising the outcome of the reaction (3b). A range of substituted vinylidonium triflates can be successfully applied in this reaction, maintaining good yields and excellent selectivities (Table 2B, 3d–h). Furthermore, the corresponding arylation reaction using diphenyliodonium triflate also works well, producing 72% yield of a fully substituted styryl triflate, 3i (8:1, Z:E), further enhancing the potential synthetic utility of this process.

A significant selectivity challenge is presented by carbon–carbon triple bonds with two different substituents; however, this Cu-catalyzed process can still distinguish between both steric and electronically differentiated alkynes (Table 3A). For

Table 3. Scope of Alkyne Carbofunctionalization^a



^aRatio of isomers determined by ¹⁹F NMR; yields are of isolated products; ratios shown are of major isomer to the sum of all other isomers, unless otherwise stated; rr = regioselectivity ratio. ^bIn dioxane. ^cIn CH₂Cl₂. ^dIn dichloroethane. ^eIn toluene. ^fIn cyclopentyl methyl ether. ^gYield of major product based on ¹H NMR using 1,2-dimethoxyethane as standard.

example, substrates displaying isopropyl and methyl groups result in 3j, where the vinyl group is added to the more sterically hindered position with a regioselectivity ratio (rr) of 3:1, exclusively as the Z-isomer. Interestingly, this regioselectivity is opposite to that observed in conventional alkyne carbometalation.³ We also observed a 1.4:1 rr in the reaction of 2-pentyne (Et vs Me, 3k). A simple ethylene unit can be transferred in the reaction of arylpropynes (3l); enynes react selectively to form conjugated trienes, molecules that may have interesting applications in the synthesis of functionalized materials (3m).

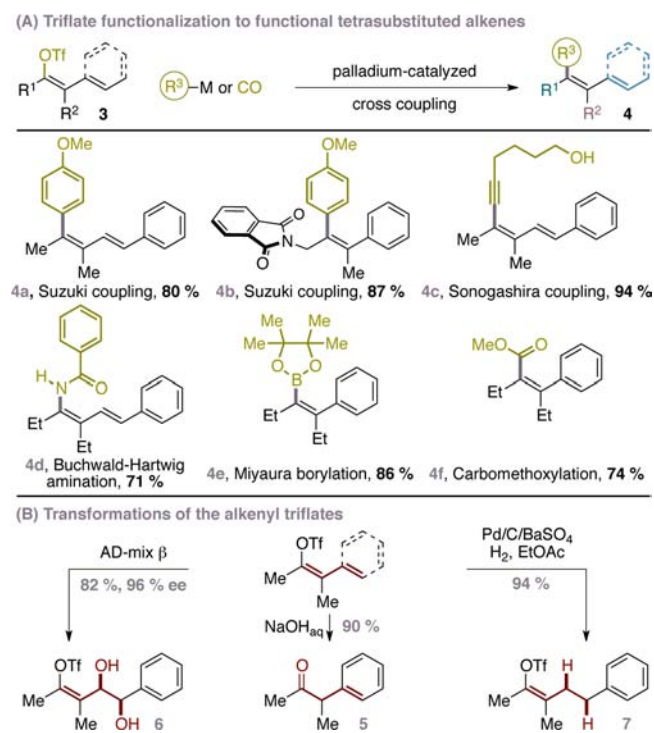
We see excellent regio- and stereoselectivity in the arylation process of propargylic amides, providing highly functionalized vinyl triflates in good yield (3n). We were surprised to find

that, while arylpropynes gave predominantly Z-isomers in the vinylation reactions, the corresponding arylation processes resulted in the selective formation of the E-isomers. While this represents a useful extension to the reaction, we cannot yet explain this unusual result (3o,p).

We next investigated the reaction of terminal alkynes as a means of extending our reaction to the formation of trisubstituted dienyl triflates. The combination of terminal alkynes with Cu(I) catalysts presents a potential problem in the way of oxidative dimerization reactions. Furthermore, Kang et al. reported a Cu-catalyzed Sonogashira-type coupling of alkynes and diaryliodonium salts in the presence of base.¹⁸ However, when we tested the reaction of terminal alkynes under our standard conditions, we were delighted to observe the formation of the desired trisubstituted dienyltriflates, predominantly as the Z-isomer and in favor of the Markovnikov-type regioisomer (Table 3B). We did not observe the alkyne homodimerization or the Sonogashira product. A range of simple terminal alkynes worked well in this reaction (3q–w), and even the feedstock alkyne, acetylene, can be transformed with excellent selectivity to the corresponding dienyl triflate (3u). This example underlines the efficacy of this new process in converting inexpensive starting materials into versatile building blocks. The ratios for 3l,m,o–r,t,v,w are expressions of the major product (shown) to the sum of all other isomers, which comprises the E-isomer of the major product and a regioisomer.^{16,19}

Finally, we demonstrated the utility of the alkenyl triflate products by further transformation into synthetically versatile tetrasubstituted alkenes. A series of Pd-catalyzed cross-coupling methods diversify the vinyl triflates to a range of useful products in high yields without the loss of isomeric purity (Scheme 1, 4a–f).^{16,20} The alkenyl triflates can also be hydrolyzed to form α -aryl ketones (5), chemo- and stereo-selectively dihydroxylated (6), and hydrogenated (7).

Scheme 1. Reactions of Tetrasubstituted Vinyl Triflates



In summary, we have developed a Cu-catalyzed synthesis of highly functionalized tri- and tetrasubstituted alkenyl triflates from alkynes and vinyl(aryl)- and diaryliodonium salts. We believe that this method operates through an electrophilic carbofunctionalization pathway involving a high oxidation state Cu(III) species. Notable features of this process are the Z-selectivity, an apparent reductive elimination of a triflate group to form an electrophilic vinyl product, and compatibility with both disubstituted and terminal alkynes. Well-established catalytic reactions transform the products into synthetically useful tetrasubstituted alkenes. This Cu-catalyzed alkyne activation pathway employs a reactivity principle that is opposite to classical carbometalation and could provide a series of strategic bond-forming processes that will have broad appeal in synthesis.

■ ASSOCIATED CONTENT

Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

mjg32@cam.ac.uk

Notes

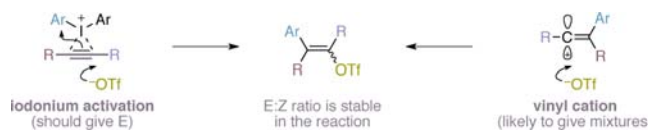
The authors declare no competing financial interest.

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