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Cu-Catalyzed Three-Component Carboamination of Alkenes

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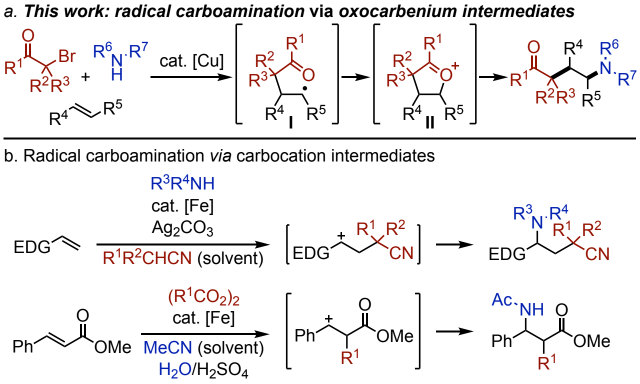
Supporting Information Placeholder

ABSTRACT: The copper-catalyzed intermolecular carboamination of alkenes with α-halocarbonyls and amines is presented with 42 examples. Electron rich, electron poor, and internal styrenes, as well as α-olefins, are readily functionalized with a variety of α-halocarbonyls and aryl or aliphatic amines. Preliminary mechanistic investigations suggest that the reaction is proceeding through the addition of a carbon-centered radical across an olefin followed by oxidation to form a 5-membered oxocarbenium intermediate and subsequent nucleophilic ring opening to forge the C–N bond.

The invention of new methods for the streamlined construction of small organic molecules is essential to the advancement of organic chemistry. Given the ubiquity of C–N bonds in biologically active molecules, devising improved methods for the synthesis of amines is a particularly important challenge.[1] The difunctionalization of olefins provides direct access to complex molecular frameworks that otherwise require multiple synthetic operations to assemble. The carboamination of alkenes is an important subset of such reactions, resulting in the concurrent introduction of carbon and nitrogen functionalities into readily accessible alkene frameworks.[2]

To date, most carboamination methodologies have exploited a two-component approach, delivering cyclic products from preassembled starting materials.[2a-g] As a consequence of their two-component natures, these methods are innately limited in their modularities. To address this, we envisioned that a three-component alkene carboamination could be realized by harnessing the reactivities and selectivities of radical intermediates.[3] Toward this end, we became interested in the proclivity of copper salts to generate electrophilic alkyl radicals from functionalized tertiary alkyl halides, such as α-halocarbonyl compounds.[4] We reasoned that the combination of such electrophiles with nucleophilic amines in the presence of an olefin could deliver the carboamination product in a regio- and chemo- selective fashion (Scheme 1a). These electrophiles are resistant to undesirable S_N1/S_N2 reactivity, therefore reducing the tendency to couple this electrophilic component directly with the amine nucleophile. Furthermore, the addition of these radicals to olefins is well-documented in related methodologies and in the field of atom transfer radical polymerization (ATRP).[5,6]

Scheme 1. Three-component carboamination reactions

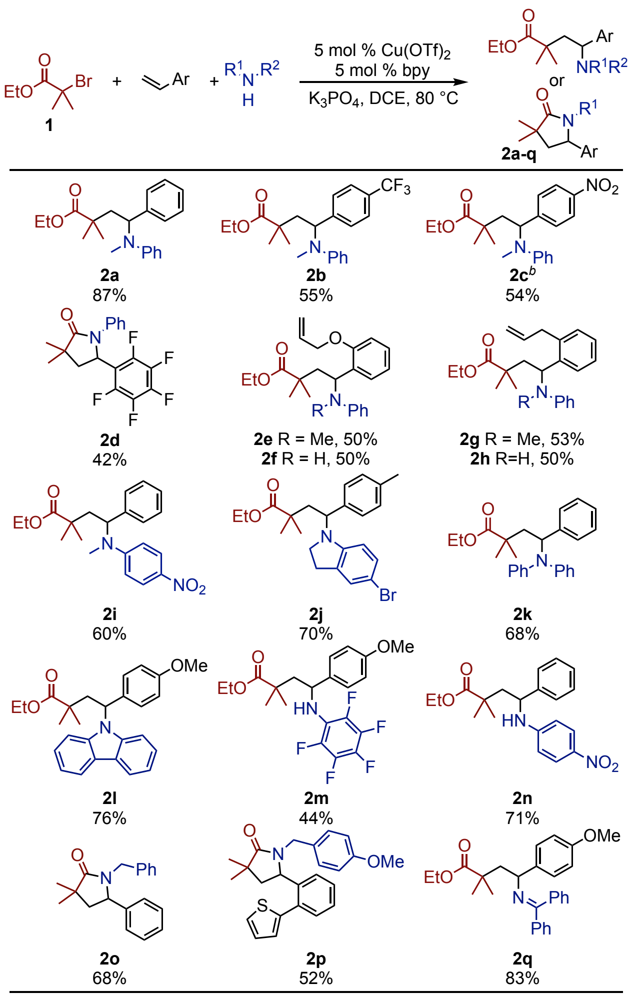


Concurrent with our investigations, two radical couplings utilizing alkyl nitriles[2h] and dialkyl peroxides,[2i-j] were reported (Scheme 1b). The philicities of the radicals generated in these reactions significantly influence the overall scope of the transformations, wherein favorable matching of the alkene and alkyl radical polarities is essential.[7] Efficient reactivity is therefore accomplished by employing electronically activated alkenes and further enhanced with super-stoichiometric loadings of the other coupling partners and of strong oxidants. An alternative approach to the three-component carboamination of alkenes *via* Pd-catalysis was also recently reported.[2k] A pre-installed bidentate directing group is utilized to avoid β-hydride elimination and promote oxidation, thereby enabling the difunctionalization.

In the context of our mechanistic hypothesis, the oxidation of a radical addition intermediate (**I**) would afford a cationic species. Typically such oxidations require electronically activated alkenes, which facilitate the oxidation of the resultant radical addition intermediate.[2h-j] Although this tactic enables the desired transformation, it imposes significant limitations on the substrate scope. We reasoned that the use of an α-halocarbonyl compound as the electrophilic source of carbon would reveal access to a particular geometric relationship between the incident carbonyl group with the newly formed alkyl radical that could assist with the oxidation of this intermediate.[8] Such an oxidation event would afford an oxocarbenium ion intermediate (**II**), which could undergo opening *via* nucleophilic attack by the amine to furnish the carboamination product.[9] Through this assisted oxidation, we envisioned a general platform for olefin carboamination. Indeed, we report herein a carboamination reaction of unprecedented generality.

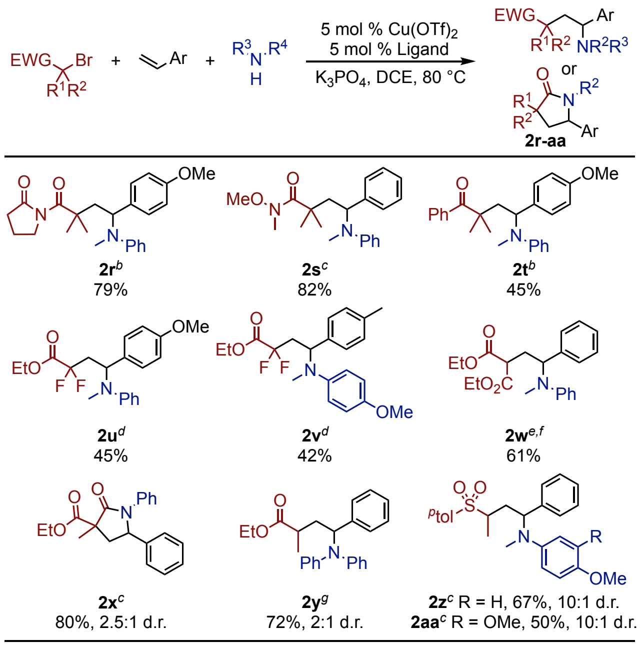
Experimentation began by exploring the reactivity of ethyl α-bromo isobutyrate (**1**), styrene, and *N*-methylaniline as model reaction components in the presence of various Cu catalysts. Gratifyingly, it was found that product **2a** could be formed under a variety of conditions, with the optimized parameters as follows: 5.0 mol % $Cu(OTf)_2$, 5.0 mol % 2,2'-bipyridine (bpy), 1.1 equiv K_3PO_4, 2.0 equiv **1**, 1.0 equiv styrene, 1.0 equiv *N*-methylaniline in DCE (0.50 M) at 80 °C for 24 h under N_2. Product **2a** can be obtained in an 87% isolated yield on 0.20 mmol scale (See Supporting Information, SI, Tables S1-S10 for optimization studies). Importantly, the reaction is scalable, providing 86% and 95% yields on 1.0 and 10 mmol scales, respectively.

Table 1. Scope of Vinylarenes and Amines[a]



[a] **1** (2.0 equiv), alkene (1.0 equiv), amine (1.0 equiv), K_3PO_4 (1.1 equiv), $Cu(OTf)_2$ (5 mol %), bpy (5 mol %), DCE (0.50 M), 80 °C. [b] 3.0 equiv alkene was used.

Table 2. Scope of Electrophiles[a]



[a] Bromide (2.0 equiv), alkene (1.0 equiv), amine (1.0 equiv), K_3PO_4 (1.1 equiv), $Cu(OTf)_2$ (5 mol %), ligand (5-10 mol %), DCE (0.50 M), 80 °C. [b] With TPEN as ligand. [c] With PMDTA as ligand. [d] With DPEPA as ligand. [e] With PEPA as ligand. [f] With 1.0 equiv bromide and 5.0 equiv alkene. [g] With BPY as ligand. See SI for ligand structures.

Under the optimized conditions, the carboamination of a variety of vinylarenes with **1** and various amines can be accomplished (Table 1). Table S11 in the SI provides a concise summary of conditions for all substrate combinations. Depending on the degree of substitution of the nucleophile and of the alkene substrate employed, either acyclic or cyclic products can be obtained. Notably, electron poor styrenes, which are unreactive in related carboamination methods,[2h-j] are suitable substrates for this reaction (**2b-d**). Electron neutral and rich alkenes are also excellent substrates, providing the carboaminated products in good to excellent yields (**2a**, **2e-h**, **2l**). Steric hindrance proximal to the alkene does not significantly affect reactivity (**2e-h**). In cases where reactivity of the alkene substrate is low, it was generally found that use of a mild excess leads to improved yields, such as with **2c**.

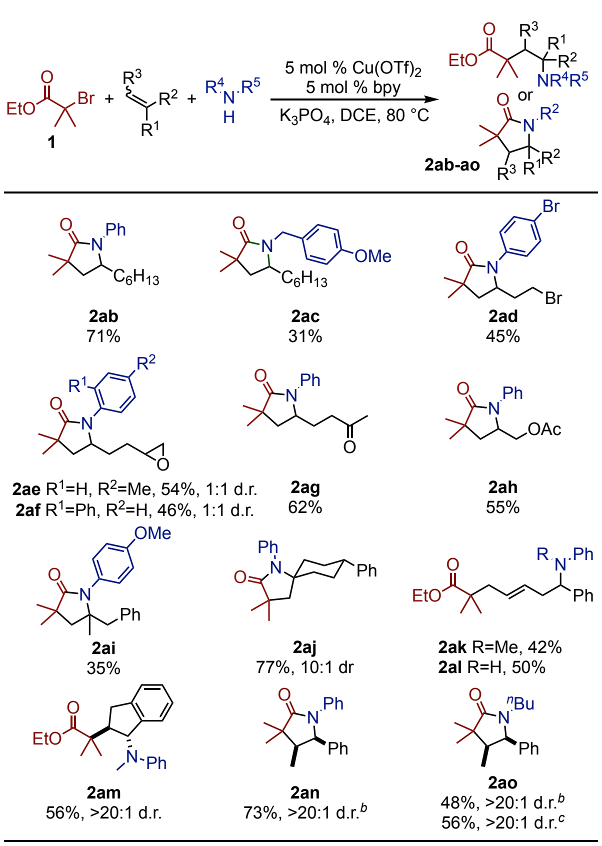
This carboamination reaction tolerates a wide range of functionalities on both the alkene and amine substrates, retaining handles for further functionalizations of the products. Vinylarenes bearing pendant aliphatic alkenes undergo carboamination in a site-selective manner, leaving the aliphatic olefin intact (**2e-h**). Functionalities such as trifluoromethyl groups (**2b**), nitro groups (**2c, 2i, 2n**), halides (**2d, 2j, 2m**), ethers (**2e-f**, **2l**, **2p-q**), and heterocycles (**2j, 2l, 2p**) are also tolerated under the reaction conditions.

Several classes of functionalized bromides can be used in addition to esters (Table 2): imides (**2r**), amides (**2s**), ketones (**2t**), malonates (**2w**), and sulfones (**2z-aa**) all provide modest to good yields of the products. It is noteworthy that the Weinreb amide-type electrophile produces **2s** in good yield, retaining the amide moiety for facile elaboration of the carbonyl group. In addition to methyl-bearing esters, those substituted with fluorine atoms (**2u-v**) are effective for this transformation, providing access to products of pharmacokinetic value given the unique properties of the difluoromethyl moiety.[10] A differentially substituted electrophile was also reactive (**2x**), providing the product in good yield with moderate diastereoselectivity.

Importantly, secondary electrophiles are also amenable in the three-component coupling (**2w, 2y-aa**) including a malonate (**2w**), which provides access to products containing a free methylene unit, following mono-decarboxylation.[11] Given this generality, products with any degree of substitution at the α-carbon can be accessed. The diastereoselectivity with secondary α-bromoesters is moderate (**2y**, 2:1), but the analogous secondary sulfone affords the product in high d.r. (**2z-aa**, 10:1). The additional steric encumbrance in the corresponding sulfoxonium intermediate may be responsible for the enhanced diastereoselectivity.[12] Interestingly, each electrophile class requires a different polyamine ligand to achieve significant reactivity. At present, we attribute this phenomenon to the unique range of reduction potentials of each electrophile class and oxidation potentials of the corresponding radical addition intermediates. Although more reducing catalysts may rapidly activate an electrophile, they may be slow to oxidize the radical intermediate. Thus, a common Cu catalyst of fixed redox reactivity does not achieve high reactivity across all electrophile classes.[6a] Ongoing work in our laboratory aims to understand the ligand effects and to identify a general Cu catalyst for this transformation.

The scope of the amine component in this carboamination reaction is also broad. In addition to *N*-methylaniline, secondary arylamine nucleophiles bearing electron -withdrawing (**2i, 2m, 2n**) and -donating (**2v**, **2z-aa**) groups perform well in the reaction. It was observed that products derived from electron -neutral and -rich primary nucleophiles generally close *in situ* to form γ-lactams (**2d, 2o-p**, **2x**), whereas those derived from electron withdrawn primary nucleophiles

Table 3. Scope of Aliphatic and Internal Alkenes[a]



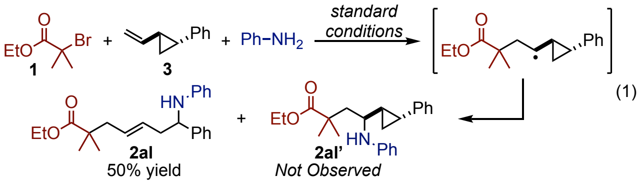
[a] **1** (2.0-5.0 equiv), alkene (1.0-5.0 equiv), amine (1.0 equiv), K$_3$PO$_4$ (1.1 equiv), Cu(OTf)$_2$ (5 mol %), bpy (5 mol %), DCE (0.50 M), 80-100 °C. [b] From *(Z)* alkene. [c] From *(E)* alkene.

remain acyclic (**2m-n**). Products **2f** and **2h** indicate that the steric properties of the alkene may also influence whether *in situ* closure occurs. Diaryl and heterocyclic amines (**2j-l**) also react smoothly to give the corresponding products in good yield. Generally, arylamines are excellent substrates in the reaction, however primary alkylamines perform well (**2o-p**). Benzophenone imine is also reactive, providing access to the corresponding N–H γ-lactam following acidic deprotection (**2q**, see SI for details).[13]

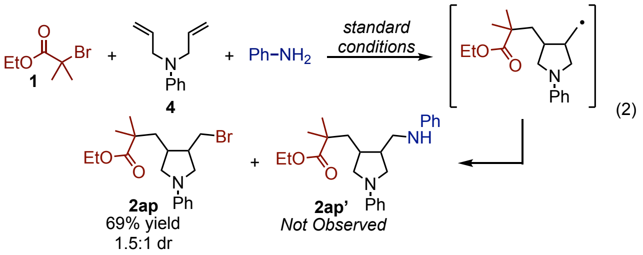
In the interest of expanding the reaction scope, we focused on enabling the use of internal and aliphatic alkenes as substrates. These represent challenging substrate classes, as the radical additions are significantly slower compared to terminal vinylarenes.[7] Aliphatic alkenes are particularly challenging, as the subsequent oxidation is less favorable. However, we hypothesized that the oxocarbenium intermediate could promote this key step. Indeed, only slightly modified reaction conditions elicit reactivity from these olefin classes (Table 3). Typically, higher temperatures and loadings of the alkene are required to consume the amine nucleophile. Under these reaction conditions, unfunctionalized α-olefins can be employed with aryl- and alkyl- amine nucleophiles (**2ab-ac**). Functional groups sensitive to basic conditions are tolerated, including primary alkyl bromides (**2ad**), terminal epoxides (**2ae-af**), ketones (**2ag**), and acetoxy groups (**2ah**). 1,1-Disubstituted alkenes are also viable components, enabling the formation of highly hindered C–N bonds (**2ai-aj**). Notably, an exocyclic 1,1-disubstituted olefin produced the corresponding spirocyclic lactam with good yield and d.r. (**2aj**, 77%, 10:1 d.r.). Finally, cyclopropyl substituted aliphatic alkenes can be used to form the ζ-amino carbonyl products in moderate yields (**2ak-al**).

In addition to terminal alkenes, more hindered internal alkenes readily participate in the reaction, providing highly substituted products in good yields and with excellent d.r. (**2am-ao**). Cyclic internal alkenes afford the *trans* carboamination product in >20:1 d.r. (**2am**), whereas acyclic internal alkenes provide the *cis* product in >20:1 d.r. (**2an-ao**). In the case of the latter, the reactions are diastereoconvergent; regardless of starting configuration of the alkene, the *cis* γ-lactam product is obtained selectively. Given this broad scope, substitution at each position on the lactam core is easily controlled. Historically, such substituted γ-lactams require many synthetic operations to assemble; however, this protocol provides access to a customizable γ-lactam core in a single step from readily obtainable, inexpensive materials.[1a]

In addition to exploring the scope of this three-component carboamination reaction, we have also conducted preliminary mechanistic studies. A series of radical clock experiments were conducted to probe the fate of the radical addition intermediate. A cyclopropyl moiety adjacent to an olefin (**3**) was found to open under the reaction conditions, providing the corresponding carboamination product (**2al**) in 50% isolated yield (eq. 1). Interestingly, when *N,N*-diallylaniline (**4**) was subjected to the reaction conditions, 5-exo-trig cyclization was observed, affording the carbobromination product (**2ap**) in 69% isolated yield and 1.5:1 d.r. instead of the expected carboamination product (**2ap'**, eq. 2).[14] Our mechanistic proposal invokes the oxidation of radical addition intermediates to form an oxocarbenium species. We propose that the formation of this intermediate facilitates this key step in cases where this oxidation is more difficult, such as with aliphatic alkenes or electron poor vinylarenes.[15] In the case of both radical clock experiments, either ring-opening or radical cyclization occurs, making the oxocarbenium ion geometrically difficult to form. For **3**, the radical is benzylic and oxidation to the cation is facile, even without the intermediacy of the oxocarbenium ion; thus, carboamination can still occur. However, for **4**, unassisted oxidation of the radical intermediate would produce an unstable primary carbocation. Consequently, the rate of bromine atom transfer from Cu becomes competitive with the productive reaction pathway. It is important to note that products **2ad** and **2ap** eliminate the possibility of an atom-transfer radical addition mechanism followed by S$_N$2 amination.

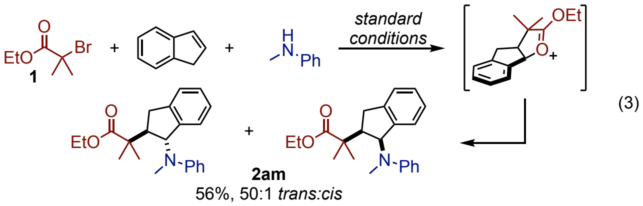


(1)



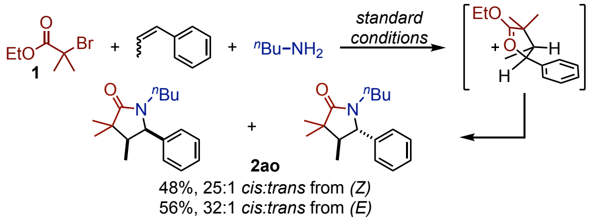
(2)

These radical trap experiments provide a clear demonstration of the importance of the carbonyl moiety to enable the carboamination of less reactive substrates. However, the results observed with **3** indicate that carboamination of vinylarene substrates could occur without proceeding through an oxocarbenium ion intermediate. Therefore, the viability of this intermediate was further established by a thorough consideration of the stereochemical outcomes from the internal alkene



(3)

substrates. In the case of **2am**, the system is conformationally locked, and opening of the purported oxoncarbenium would deliver only the *trans* product (eq. 3). For the carboamination of β-methylstyrene, the system may rotate freely, and the thermodynamically more stable *trans* oxocarbenium structure may form. Stereoinvertive opening of the oxocarbenium followed by lactamization delivers selectively the *cis* product **2ao** (eq. 4). Taken together, these mechanistic probes indicate that oxocarbenium ion intermediates form when geometrically permitted, though are not required for product formation if the radical addition intermediate is oxidizable by Cu(II), as is the case for the benzylic radical preceding the formation of **2al** (eq. 1).[8, 16]



(4)

In conclusion, we have developed a three-component carboamination reaction that couples readily available alkenes, functionalized alkyl halides, and amines. Yields are good to excellent, and the scope of the reaction in all three components is broad. Olefin classes that are traditionally challenging to functionalize through transition metal catalysis are exceptionally reactive in this system, which we attribute to the intermediacy of an oxocarbenium species. The molecules constructed through this method represent powerful examples of the potential of base metal catalysis to enable the rapid difunctionalization of olefins. Future work will focus on developing diastereoselective conditions for differentially substituted electrophiles, expanding nucleophile scope, and developing an asymmetric protocol.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectra. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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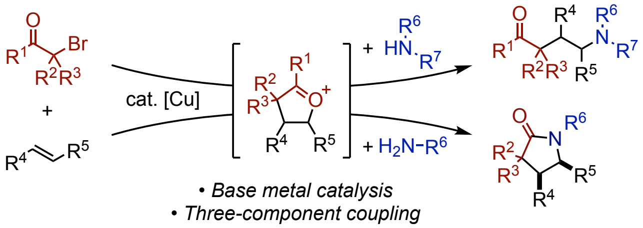
[16] For additional mechanistic information and a proposed catalytic cycle, see Supporting Information (SI).



- *Base metal catalysis*
- *Three-component coupling*
- *42 examples*