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Research Article

Oxidative Three-Component Carboamination of Vinylarenes with Alkylboronic Acids

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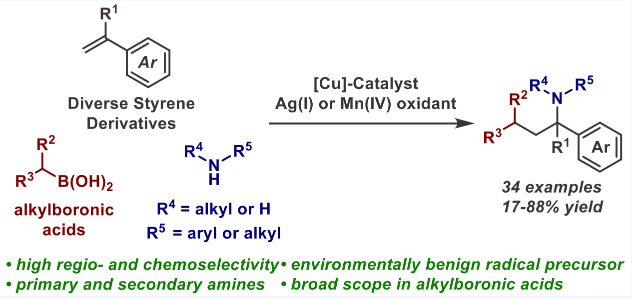
ABSTRACT: The three-component carboamination of alkenes is of significant interest due to the ease by which functionalized amines can be produced from readily available chemical building blocks. Previously, a variety of carbon-centered radical precursors have been studied as the carbon components for this reaction; however, the use of general alkyl sources has remained as an unsolved challenge. Herein we present our efforts to develop an oxidative carboamination protocol that utilizes alkylboronic acids as carbon-centered radical precursors. The presented work demonstrates 34 examples, ranging from 17 to 88% yields, with a broad scope in vinylarenes, amines, and alkylboronic acids. Preliminary mechanistic studies suggest that a single-electron oxidation of the alkylboronic acid generates a carbon-centered radical intermediate that adds across the olefin followed by C−N bond formation via Cu-mediated inner-sphere or carbocation-mediated pathways.



KEYWORDS: *copper catalysis, carboamination, oxidation, alkylboronic acids, Lewis acid−base interaction*

■ INTRODUCTION

Transition-metal-catalyzed alkene carboamination is an attractive strategy toward the synthesis of amine structures commonly represented in top-selling pharmaceuticals and drug candidates.[1] In contrast to its counterpart, the hydroamination reaction, alkene carboamination effects the addition of two functional groups across the π-system and can more rapidly deliver complex amine scaffolds.[2] Because carboamination is a multicomponent reaction, there are added regio- and chemoselectivity challenges that must be addressed (e.g., competitive two-component couplings). This is typically accomplished by conducting the reaction intramolecularly, wherein a substrate is designed in which two or more of the reacting components are tethered together, thereby constraining regio- and chemoselectivity.[3] Although effective, this tactic diminishes reaction modularity, requiring higher-order substrates to be preassembled prior to the coupling. To maximally harness the inherently high versatility of the carboamination reaction, there has been an interest in advancing fully intermolecular variants. Only recently have such reports been disclosed that successfully address this contemporary methodological challenge.[4]

With the recognition that β-hydride elimination and premature reductive elimination are major competing pathways in many metal-catalyzed alkene difunctionalization reactions, there has been significant recent interest in developing carboamination protocols that bypass these challenges by proceeding through single-electron mechanisms.[2c] Such strategies typically rely on the capacity of first-row transition metals or photocatalysts to generate a carbon-centered radical that adds rapidly and regioselectively to the olefin (Scheme 1). Many such examples require the use of privileged classes of alkyl radical precursors, such as α-halocarbonyls,[4f] alkyl nitriles,[4a,c] and perfluoroalkyl halides.[4i] Although synthetically useful, these reactions deliver products with constrained functional groups and substitution patterns. In contrast, carboamination reactions involving distally functionalized or completely unfunctionalized alkyl fragments would allow the desired functional groups to be flexibly installed at a given position on the elaborated alkyl chain. Such reactivity has only been explored recently; Li and Zhang reported methods utilizing NHPI esters[4h] and alkyl halides[4i] as radical precursors, applying visible light photocatalysis to access sufficiently negative reduction potentials. However, careful substrate selection is required to preclude uncatalyzed direct coupling between the alkylating agent and the nucleophile, with bulky amines and hindered tertiary alkyl sources providing the best yields.

Given these restrictions, we became interested in an oxidative carboamination strategy where the compatibility between the nucleophilic nitrogen and carbon coupling

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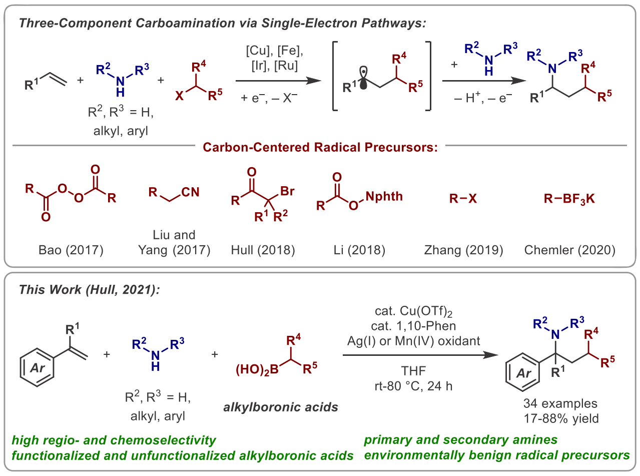
Scheme 1. Strategies toward Intermolecular Three-Component Carboamination and Efforts to Deliver General Alkyl Fragments

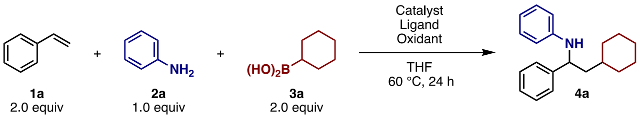


partners would prevent uncatalyzed coupling. Recognizing the ability to generate radicals under mild thermal conditions from alkylborons,[5,6] we undertook development of this reaction that utilizes widely available alkylboronic acids (>2800 commercially available) as radical precursors. Concurrent with our work, the Chemler group recently independently reported a similar strategy with alkyl-BF_3K salts.[4j]

RESULTS AND DISCUSSION

We initiated our investigation by studying the model carboamination of styrene (**1a**) with aniline (**2a**) and cyclohexylboronic acid (**3a**) to afford carboamination product **4a** (Table 1; see the Supporting Information for full optimization studies).

Table 1. Optimization Studies[a]



entry	catalyst	ligand	oxidant	yield (%)[b]
1	$Cu(OTf)_2$	1,10-Phen	Ag_2CO_3	79
2	$Cu(OTf)_2$	Bpy	Ag_2CO_3	60
3	$Cu(OTf)_2$	Tpy	Ag_2CO_3	NR
4	none	none	Ag_2CO_3	NR
5	$Cu(OAc)_2$	1,10-Phen	Ag_2CO_3	1
6	$Fe(OTf)_3$	1,10-Phen	Ag_2CO_3	10
7	$NiBr_2$·glyme	1,10-Phen	Ag_2CO_3	<1
8	$Cu(OTf)_2$	1,10-Phen	AgOAc	19
9	$Cu(OTf)_2$	1,10-Phen	Ag_2O	19
10	$Cu(OTf)_2$	1,10-Phen	MnO_2	54[c] (62[d])
11[e]	$Cu(OTf)_2$	1,10-Phen	Ag_2CO_3	8
12[f]	$Cu(OTf)_2$	1,10-Phen	Ag_2CO_3	26

[a] Reaction conditions unless specified otherwise (0.10 mmol **2a**): catalyst (10 mol %), ligand (10 mol %), oxidant (2.0 equiv), **1a** (2.0 equiv), **2a** (1.0 equiv), **3a** (2.0 equiv), solvent (0.20 M), 60 °C, N_2, 24 h. [b] *In situ* yields were determined by GC analysis of a crude reaction using 1-methylnaphthalene as an internal standard. [c] 3.0 equiv of MnO_2. [d] 3.0 equiv of MnO_2 and 4 Å MS (20 mg/0.2 mL) in THF (0.5 M). [e] MeCN instead of THF. [f] Set up under atmospheric air.

Among the various metal catalysts and ligands evaluated, $Cu(OTf)_2$-1,10-Phen proved most effective (entries 1−7). In the absence of a catalyst and ligand, complete suppression of carboamination reactivity was observed, thereby indicating the necessity of the Cu catalyst for this transformation (entry 4). To promote catalytic turnover, a range of oxidants were examined, including Ag and Mn salts and a range of organic oxidants (entries 8−10). These investigations revealed Ag_2CO_3 and MnO_2 to both be suitable oxidants. Further rigorous optimization studies of this new carboamination reaction enabled product **4a** to be obtained in a 79% *in situ* yield under the optimized reaction conditions: $Cu(OTf)_2$ (10 mol %), 1,10-Phen (10 mol %), and Ag_2CO_3(2.0 equiv) or MnO_2 (3.0 equiv) with 4 Å MS (20 mg/0.20 mL THF) in THF (0.20 or 0.50 M) at 60 °C for 24 h under N_2.

Next, the scope of vinylarene and amine reaction components was established by applying the alkylboronic acid **3a** as a representative alkyl fragment under the optimized reaction conditions. A broad reactivity profile in both components was observed (Scheme 2), with yields ranging from 17 to 88% depending on the electronic and steric properties. Generally, it was found that electron-rich or electron-neutral vinylarenes display good to excellent reactivity. However, in contrast to related carboamination reactions,[4a,j] a range of electron-deficient vinylarenes are also readily functionalized (**12**−**14** and **24**).

Relevant to drug development, a variety of heterocycles, such as 1,3-benzodioxoles (**18**−**20**), benzofurans (**22**), 4-methylthiazoles (**23**), and pyridines (**24**), are tolerated by this catalyst system, delivering the products in synthetically useful yields. Polyaromatic vinylarenes, such as biaryls and naphthalenes, are found to react smoothly under the optimized conditions, affording amines **16** and **17**. Further, 1,1-disubstituted olefins prove capable of providing access to a tertiary benzylic C−N bond (**25**), albeit in a reduced 32% yield. Unfortunately, the activated vinylboronic acid pinacol ester (vinylBpin, **26**) was unreactive under our reaction conditions. In a related reaction, Molander and co-workers succeeded in the dicarbofunctionalization of this substrate due to a radical stabilization effect from an empty p orbital in the boron center.[7] We hypothesize that the higher oxidation potential of the radical addition intermediate is likely out of the range of our catalyst. Similarly, unactivated α-olefins, such as 1-octene, are unreactive (**27**). Such results are well in accordance with our initial hypothesis due to the absence of radical or carbocation stabilization.

An assessment of the amine scope revealed that a wide range of aryl, cyclic (**19** and **20**), and aliphatic (**21**) substrates are all amenable reaction components, in some cases requiring tuning of the bulk oxidant. For instance, electron-neutral and -rich primary and secondary arylamines are more reactive with Ag_2CO_3, while carboamination with electron-poor nucleophiles requires the stronger MnO_2 oxidant. Benzocaine was functionalized using this new carboamination protocol, affording the derivatized product **6** in 39% yield, and an X-ray crystal structure was obtained that confirmed the structure (see the Supporting Information). Other electron-deficient nucleophiles were also found to be amenable toward functionalization (**9**, **16**, and **23**). Heterocyclic amines, such as carbazole (**19**) and 2-methylbenzimidazole (**20**), were also tolerated, given a judicious oxidant selection. With the use of strong oxidants, aliphatic amines were also viable amine partners when they were paired with 4-vinylanisole.

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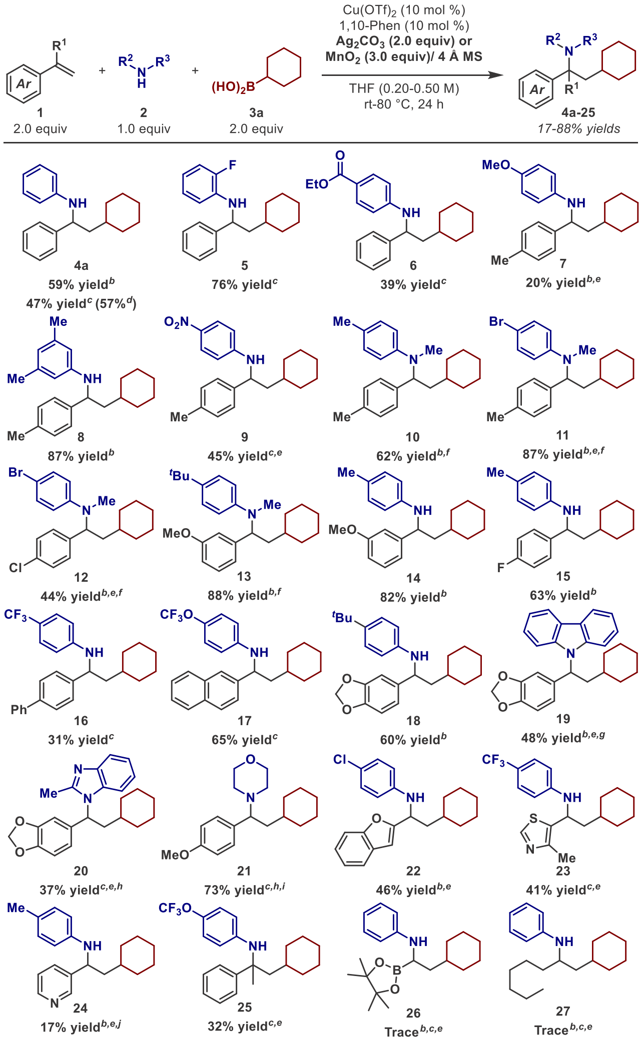
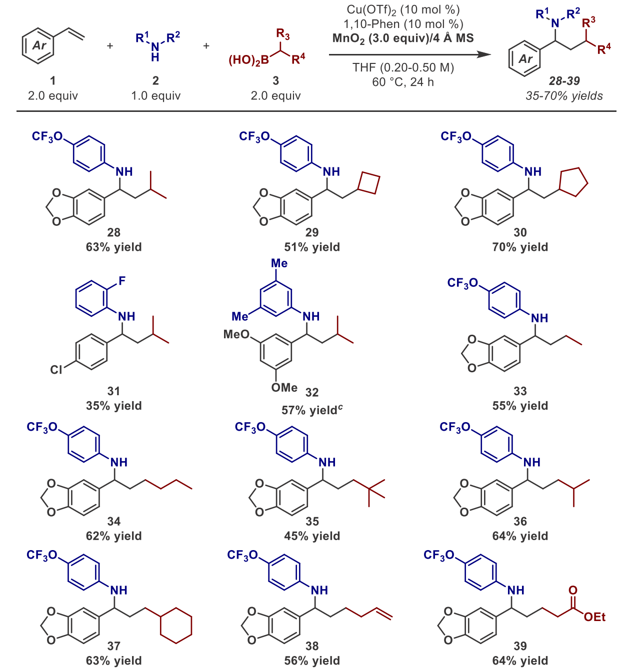
Scheme 2. Substrate Scope of Olefins and Amines[a]



[a] Isolated yields are in average of two runs (0.20 mmol scale). [b] Reaction conditions: Cu(OTf)$_2$ (10 mol %), 1,10-Phen (10 mol %), Ag$_2$CO$_3$ (2.0 equiv), **3a** (2.0 equiv), amines **2** (1.0 equiv), and alkenes **1** (2.0 equiv) in THF (0.20 M) at 60 °C for 24 h. [c] Reaction conditions: Cu(OTf)$_2$ (10 mol %), 1,10-Phen (10 mol %), MnO$_2$ (3.0 equiv), 4 Å MS (20 mg/0.20 mL), **3a** (2.0 equiv), amines **2** (1.0 equiv), and alkenes **1** (2.0 equiv) in THF (0.5 M) at 60 °C for 24 h. [d] 4.0 mmol scale. [e] With recrystallized boronic acid **3a**. [f] In THF (0.50 M) at rt. [g] 3.0 equiv of AgOAc instead of 2.0 equiv of Ag$_2$CO$_3$. [h] At 80 °C. [i] THF (0.33 M) at 80 °C. [j] 2.0 equiv of Ag$_2$O instead of 2.0 equiv of Ag$_2$CO$_3$ in THF (0.20 M) at 40 °C.

Scheme 3. Alkylboronic Acid Scope[a,b]



[a] Isolated yields are an average of two runs (0.20 mmol scale). [b] Reaction conditions: Cu(OTf)$_2$ (10 mol %), 1,10-Phen (10 mol %), MnO$_2$ (3.0 equiv), 4 Å MS (20 mg/0.20 mL), alkylboronic acids **3**, amines **2** (1.0 equiv), and alkenes **1** (2.0 equiv) in THF (0.50 M) at 60 °C for 24 h. [c] Ag$_2$CO$_3$ (2.0 equiv) instead of MnO$_2$ (3.0 equiv)/4 Å MS (20 mg/0.20 mL) in THF (0.20 M) at 60 °C for 24 h.

Finally, we were delighted that our carboamination reaction can be achieved on a gram scale to furnish the *N*-phenyl benzylamine product **4a** in 57% yield.

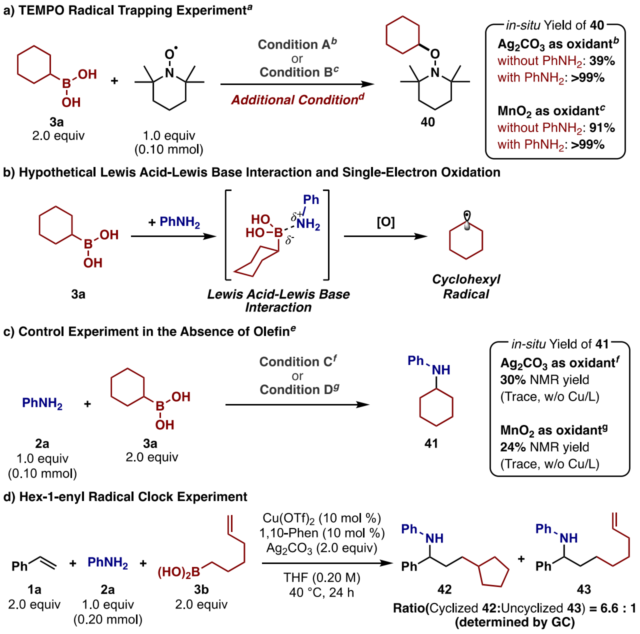
An important aspect of our carboamination reaction is its modular nature; we anticipated that a range of alkyl fragments could be incorporated that are not viable in previously disclosed carboamination protocols. Indeed, on an evaluation of the alkylboronic acid scope, a range of carbon components undergo the desired carboamination reaction smoothly with MnO$_2$ as the oxidant (Scheme 3).

Secondary cyclic and acyclic alkylboronic acids are suitable alkyl radical precursors (**28**−**32**). A range of primary alkyl chains, linear (**33** and **34**) or branched (**35**−**37**), can also be installed by this new reaction system, which is generally not possible in related carboamination reactions due to chemoselectivity challenges. Distally functionalized derivatives are also viable (**38** and **39**), thus demonstrating the ability to flexibly incorporate functional groups on the alkyl chain, again differentiating this protocol from prior work. Olefin-substituted product **38** was cleanly obtained with no reaction of the pendant olefin, thereby leaving this valuable functionality intact for further synthetic manipulation. In a similar vein, ester product **39** can be accessed with no amidation or lactamization, leaving the carbonyl building block untouched.

To gain a deeper understanding of the mechanism of this new carboamination reaction, a series of mechanistic investigations were performed. Experiments were designed to probe each of three proposed steps in the catalytic cycle, including (1) alkylboronic acid activation, (2) radical addition to the olefin, and (3) amination of the radical.

We initially expected that this oxidative carboamination reaction would involve the generation of the carbon-centered radical from the alkylboronic acid. To probe this step, a radical-trapping experiment was conducted with the standard oxidants, with TEMPO being applied as a spin-trapping agent (Scheme 4a). Formation of the TEMPO adduct **40** was observed, suggesting that a single-electron oxidation of boronic acid **3a** likely generates a cyclohexyl radical. Interestingly, MnO$_2$ proved to be an effective oxidant, providing **40** in 91% yield; Ag$_2$CO$_3$ only provided full conversion to **40** in the presence of the amine nucleophile. This observation suggests the potential for a Lewis acid−base interaction between the amine and alkylboronic acid, which presumably activates the C−B bond toward oxidation (Scheme 4b).[8] In support of this hypothesis, the high oxidation potential of secondary alkylboronic acids

Scheme 4. Preliminary Mechanistic Studies



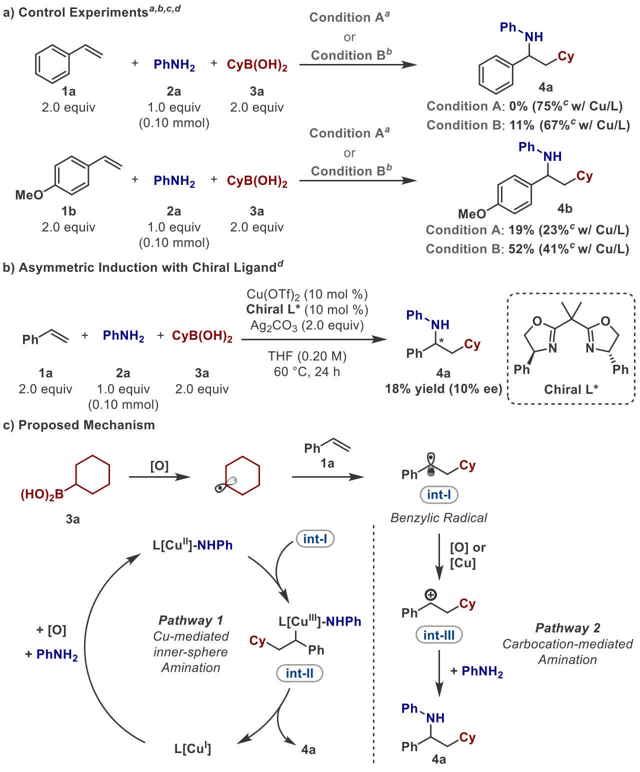
[a] *In situ* yields were determined by GC analysis of a crude reaction product using 1-methylnaphthalene as an internal standard. [b] Conditions A (0.10 mmol scale): Ag_2CO_3 (2.0 equiv) in THF (0.20 M) at 60 °C for 24 h. [c] Conditions B (0.10 mmol scale): MnO_2(3.0 equiv), 4 Å MS (20 mg) in THF (0.50 M) at 60 °C for 24 h. [d] With or without addition of 1.0 equiv $PhNH_2$. [e] NMR yields are an average of two runs and were determined using 1-methylnaphthalene as an internal standard. See the Supporting Information for details. [f] Conditions C (0.10 mmol scale): $Cu(OTf)_2$ (10 mol %), 1,10-Phen (10 mol %), Ag_2CO_3 (2.0 equiv) in THF (0.20 M) at 60 °C for 24 h. [g] Conditions D (0.10 mmol scale): $Cu(OTf)_2$ (10 mol %), 1,10-Phen (10 mol %), MnO_2(3.0 equiv), 4 Å MS (20 mg) in THF (0.50 M) at 60 °C for 24 h.

(+1.24 V vs Ag/AgCl[9a] or >2.5 V vs SCE[9b]) is well out of the range of Ag(I) reduction. Thus, Lewis acid−base interactions are critical for reactivity when Ag(I) is applied as the oxidant. The amine nucleophile therefore serves a dual role in this reaction as both a substrate and a Lewis basic activator. This could, in part, explain the diminished reactivity that is observed with more weakly Lewis basic electron-deficient amines and Ag_2CO_3.

During the reaction development, the direct coupling product **41** (i.e., Chan−Lam coupling) was only observed in trace quantities.[10] However, when the olefin was omitted from the standard reaction conditions, the direct coupling between **2a** and **3a** was promoted to a significant degree (Scheme 4c). This suggests that the initially formed cyclohexyl radical can undergo the direct Cu-mediated coupling with the amine if a radical addition step is absent or kinetically slow. We hypothesize that the excellent chemoselectivity of this reaction system is therefore due to a rapid radical addition step that outcompetes direct coupling. To gain insight into the relative rate of this step, a radical clock experiment with 1-hexenylboronic acid was performed. Under the reaction conditions with Ag(I) oxidant at 40 °C, both cyclized and uncyclized products (**42** and **43**) were observed in a ratio of 6.6:1 (Scheme 4d). This indicates that the radical addition to the olefin is competitive with 5-*exo*-trig cyclization of the 1-hexenyl radical and gives an estimate of the radical lifetime as 1 × 10^5 s^{-1}.[11]

Having gained evidence for the involvement of radical species in this new carboamination system, we sought to understand the mode of C−N bond formation. We were particularly interested in this mechanistic step, as a range of mechanisms for the oxidative functionalization of alkyl radicals are possible.[12−14] An initial evaluation of the alkene scope of this new method would suggest the involvement of carbocation formation, given the relatively steep decline in reactivity displayed by electron-deficient olefins in comparison to electron-rich counterparts. However, an inner-sphere amination pathway cannot be strictly refuted solely on the basis of this observation. To probe the potential for C−N bond formation via carbocation intermediates, a series of control experiments were conducted with selected vinylarenes **1a** and **1b** (Scheme 5a).

Scheme 5. Mechanistic Evidence for Amination and Proposed Mechanism



[a] Conditions A (0.10 mmol scale): Ag_2CO_3 (2.0 equiv) in THF (0.20 M) at 60 °C for 24 h. [b] Conditions B (0.10 mmol scale): MnO_2(3.0 equiv), 4 Å MS (20 mg) in THF (0.50 M) at 60 °C for 24 h. [c] With $Cu(OTf)_2$(10 mol %) and 1,10-Phen (10 mol %). [d] *In situ* yields were determined by GC analysis of a crude reaction using 1-methylnaphthalene as an internal standard.

In the model system with **1a**, carboamination reactivity is significantly suppressed in the absence of the Cu(II) catalyst, suggesting that it plays a key role in the C−N bond-forming step. In accordance with seminal studies from Kochi,[12] this step could involve an outer-sphere mechanism proceeding via carbocationic intermediates. To assess whether this reaction could indeed proceed through carbocationic intermediates, we studied the carboamination of an **1a** and *p*-methoxystyrene (**1b**) in the absence of the Cu(II) catalyst. With **1a**, no carboamination products were observed in the absence of Cu(II) with Ag(I) as the oxidant and trace products were observed with Mn(IV) (11% *in situ* yield). However, with *p*-methoxystyrene (**1b**), significant reactivity is observed without the Cu catalyst.[15] Although this initial experimentation suggests that outer-sphere amination can occur via carbocationic intermediates, the inner-sphere amination pathway could not be categorically refuted.

Given the significant difference in uncatalyzed reactivity displayed by **1a** and **1b**, we hypothesized that Cu-mediated inner-sphere C−N bond formation could occur along with the carbocation pathway. To probe this, we studied the stereochemical outcome of the reaction in the presence of a chiral bisoxazoline-ligated Cu catalyst. Indeed, a modest but significant degree of enantioinduction is observed with electron-neutral vinylarenes (Scheme 5b). However, no enantioinduction was observed with **1b** under the reaction conditions.[16] When they are taken together, these experiments demonstrate that both inner- and outer-sphere aminations are viable mechanisms for C−N bond formation, depending on the electronics of the styrene, as seen in Scheme 5c.

The reaction is initiated with *in situ* generation of an alkyl radical from boronic acid **3a** via single-electron oxidation. Then, the alkyl radical adds to **1a** to generate the resonance-stabilized benzylic radical intermediate **I**. On the basis of our mechanistic evidence, C−N bond formation can be mediated by Cu intermediate **II** or cationic intermediate **III**. Upon radical addition, the radical intermediate **I** can be captured by Cu^{II} to produce Cu^{III} intermediate **II**.[17] Subsequent reductive elimination would then afford product **4a** and a Cu^{I} species, which can be oxidized to Cu^{II} by the bulk oxidant. Alternatively, the radical intermediate **I** can be oxidized to carbocationic intermediate **III**, which can be further sequestered by amine to give product **4a**. As previously reported, both Cu-mediated (inner sphere)[4i] and carbocation-mediated (outer-sphere)[4a,b,f,h] amination pathways are viable to furnish carboamination product **4a** in our carboamination system.

In conclusion, we have developed a Cu-catalyzed oxidative three-component alkene carboamination reaction that utilizes widely available alkylboronic acids as a source of general alkyl fragments. We have demonstrated that our strategy provides direct, scalable access to diversely functionalized benzylic amines from a combination of vinylarenes, amines, and alkylboronic acids, with each component exhibiting broad scope. Mechanistic studies were performed to support the intermediacy of alkyl radicals derived from alkylboronic acids, and it was determined that amination could occur through both inner- and outer-sphere Cu-mediated mechanisms. Further investigations are currently in progress to examine the Lewis acid−base interaction between the amine and alkylboronic acid that is crucial for alkyl radical generation with some combinations of substrates as well as the development of an asymmetric variant of the reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c00105.

Experimental procedures, characterization, spectral data, and X-ray crystallographic data (PDF)

NMR spectra (ZIP)

X-ray crystal structure (CIF)

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Notes

The authors declare no competing financial interest.

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