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Synthesis of 2-Aryl- and 2-Vinylpyrrolidines via Copper-Catalyzed Coupling of Styrenes and Dienes with Potassium *β*-Aminoethyl Trifluoroborates

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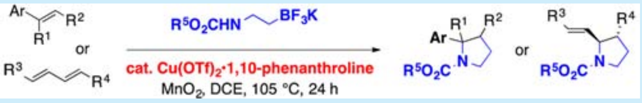
Ⓢ *Supporting Information*

ABSTRACT: 2-Arylpyrrolidines occur frequently in bioactive compounds, and thus, methods to access them from readily available reagents are valuable. We report a copper-catalyzed intermolecular carboamination of vinylarenes with potassium *N*-carbamoyl-*β*-aminoethyltrifluoroborates. The reaction occurs with terminal, 1,2-disubstituted, and 1,1-disubstituted vinylarenes bearing a number of functional groups. 1,3-Dienes are also good substrates, and their reactions give 2-vinylpyrrolidines. Radical clock mechanistic experiments are consistent with the presence of carbon radical intermediates and do not support participation of carbocations.

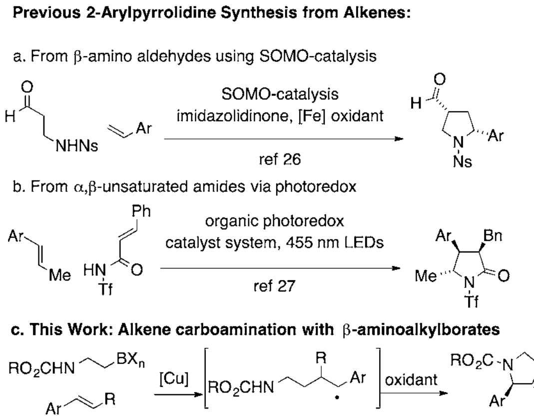


Functionalized pyrrolidines are important nitrogen heterocycles found in numerous bioactive compounds of both natural and synthetic origin. 2-Arylpyrrolidines, in particular, are ubiquitous.[1−3] The need to access these important moieties and related heterocycles has inspired the development of a number of methods.[4−26] Many of these methods, however, utilize strong bases[5] and water-sensitive organometallic reagents.[7,8] Additional intermolecular metal-catalyzed couplings[18−20] and intramolecular metal-catalyzed and Bronsted acid catalyzed cyclizations[21−25] have been developed, providing various routes to 2-arylpyrrolidines and related products. These latter methods, however, are mainly limited to sulfonamides.

More recently, readily available vinylarenes have been used to directly access 2-arylpyrrolidines and related saturated heterocycles via intermolecular coupling with bifunctional heteroatom-substituted reagents that can undergo polar/radical [3 + 2]-type bond-forming reaction sequences under mild reaction conditions.[26−31] The products of these reactions, by virtue of the required substrates, often contain additional functional groups (Schemes 1a,b) that may not be desired in all applications, and primarily *N*-sulfonyl pyrrolidine synthesis has been reported.

To address the existing limitations as well as to explore an orthogonal reactivity mode, we envisaged that a *β*-aminoethyl carbon radical could serve as a bifunctional three-atom unit to effect a net intermolecular carboamination in the presence of an oxidant (Scheme 1c). The resulting products of the coupling with vinylarenes are simple 2-arylpyrrolidines whose applications in medicinal chemistry endeavors can be readily envisioned. Herein is presented our development of this method and its extension to 1,3-dienes. The method is ideal for the synthesis of *N*-carbamoylpyrrolidines. Carbamates are generally considered to be more attractive than sulfonamides as the latter are higher molecular weight and often require more strenuous conditions to reveal the parent amine. The utility of carbamates in medicinal chemistry has been noted.[32]

Scheme 1. Polar/Radical Pyrrolidine Syntheses



We recently disclosed an oxidative alkyl Heck-type reaction between alkylboron reagents and vinylarenes.[33] In this transformation, alkyl radicals, generated in situ from [Cu(II)] oxidation of the alkylboron reagent, add to vinylarenes. Oxidation of the resulting benzyl radical then provides the observed higher substituted vinylarene products. We hypothesized that under the reaction conditions the benzylic radical, or carbocation derived thereof, could be intercepted with an amine, resulting in 2-arylpyrrolidine formation (Scheme 1c). The ready availability of *N*-carbamoyl-*β*-aminoethylboron reagents, due to the respective contributions of Overman and Molander,[34,35] presented an excellent opportunity to test this hypothesis.

Copper(II) 2-ethylhexanoate [Cu(eh)$_2$] is a readily available copper salt that has previously been shown to activate potassium alkyltrifluoroborates in coupling reactions with

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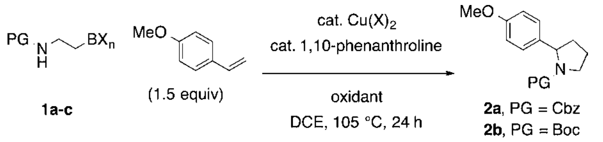
radical acceptors.[33,36] However, an attempt at the copper(II) 2-ethylhexanoate-catalyzed coupling of potassium *N*-Cbz-*β*-aminoethyltrifluoroborate **1a** with 4-methoxystyrene in the presence of MnO_2 (2.55 equiv) as stoichiometric oxidant did not result in pyrrolidine formation (Table 1, entry 1). Upon changing the catalyst to $[Cu(1,10\text{-phenanthroline})](OTf)_2$,[33] oxidative coupling readily occurred to give 82% yield of 2-arylpyrrolidine **2a** (Table 1, entry 2). The Boc analogue **1b** also provided the coupling product **2b**, but in lower yield (49%, entry 3). The boronic acid analogue **1c** underwent the coupling reaction but also less efficiently (Table 1, entry 4, 52% yield).[37] Lowering the copper loading from 20 mol % to 15 mol % led to a less efficient reaction with *N*-Cbz-*β*-aminoethyltrifluoroborate **1a** (Table 1, entry 5, 67% yield). Ag_2CO_3 (2 equiv) could also serve as a stoichiometric oxidant in place of MnO_2 (Table 1, entry 6).

Table 1. Effect of Alkylborane Structure, Catalyst Loading, and Oxidant on Reaction Efficiency[a]



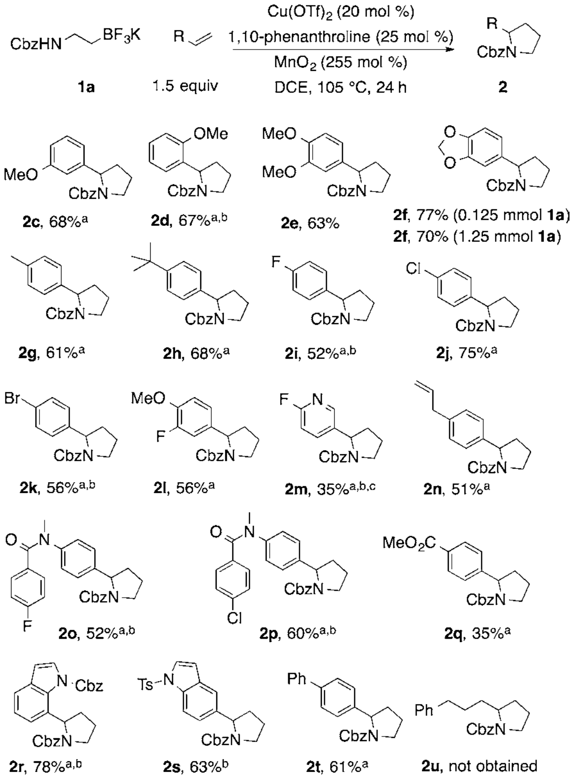
entry	PG	BX_n	oxidant	CuX_2 (mol %)	yield[c] (%)
1[b]	Cbz	BF_3K **1a**	MnO_2 (2.55 equiv)	$Cu(eh)_2$ (20 mol %)	NR
2	Cbz	BF_3K **1a**	MnO_2 (2.55 equiv)	$Cu(OTf)_2$ (20 mol %)	82
3	Boc	BF_3K **1b**	MnO_2 (2.55 equiv)	$Cu(OTf)_2$ (20 mol %)	46
4	Cbz	$B(OH)_2$ **1c**	MnO_2 (2.55 equiv)	$Cu(OTf)_2$ (20 mol %)	52
5[d]	Cbz	BF_3K **1b**	MnO_2 (2.55 equiv)	$Cu(OTf)_2$ (15 mol %)	67
6	Cbz	BF_3K **1b**	Ag_2CO_3 (2 equiv)	$Cu(OTf)_2$ (20 mol %)	63

[a] 25 mol % of 1,1-phenanthroline was used unless otherwise noted. [b] 1,10-Phenanthroline was not used. [c] Isolated yield. [d] 20 mol % of 1,10-phenanthroline was used. MnO_2 (85% by weight) was used in these reactions.

A number of styrenes underwent this reaction (Scheme 2). Styrenes with electron-donating substituents were most reactive. While most reactions were performed at the 0.125 mmol scale of **1a** (Scheme 2), a 1.25 mmol scale for the efficient (70% yield) production of **2f** was also performed. Ethers, alkyl substitutents, sulfonamides and amides were tolerated. Halide-substituted styrenes underwent the reaction, but longer reaction times were required. Substrates bearing two potentially reactive alkenes (terminal styrene, indole, terminal alkyl-substituted alkene) favored reaction at the terminal styrene. A styrene bearing a methyl ester also underwent the reaction but with lower efficiency. A 2-fluoropyridyl in place of a substituted phenyl was also tolerated, although the reaction was less efficient. 1-Phenyl-4-pentene, lacking conjugation, did not react.

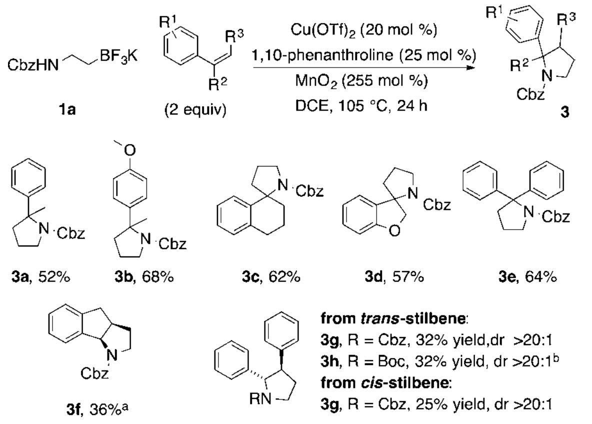
Disubstituted styrenes were next evaluated (Scheme 3). 1-Alkyl- and 1-arylstyrenes provided tertiary amines and spirocycles **3a**−**e**. Coupling with indene gave *cis*-fused bicyclic pyrrolidine **3f**. Both *trans* and *cis*-stilbene gave the same *trans*-pyrrolidine adduct **3g**. 1-Phenyl-1-cyclohexene, a trisubstituted alkene, was unreactive (not shown).

Scheme 2. Annulation with Terminal Styrenes



[a] Two equiv of styrene was used. [b] Reaction run for 48 h. [c] Reaction run at 95 °C.

Scheme 3. Annulation with Disubstituted Styrenes

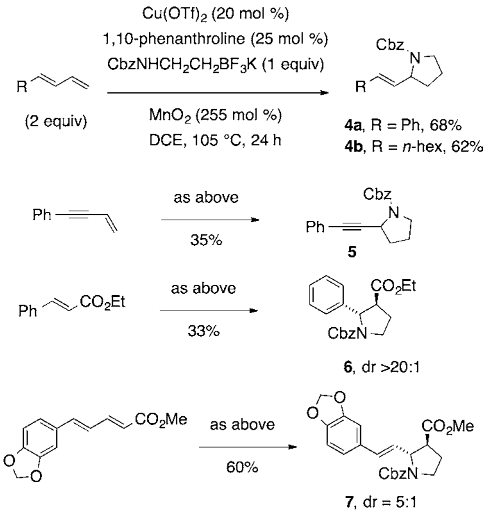


[a] Reaction run in anhydrous 1,4-dioxane at 120 °C. [b] Reaction run for 36 h.

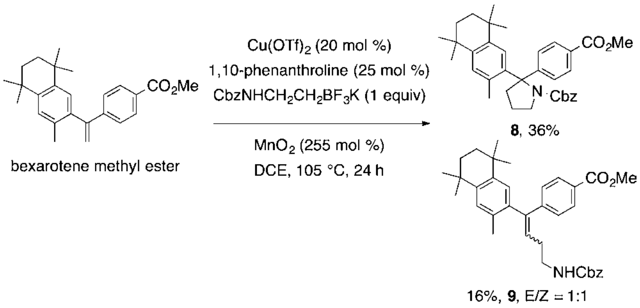
Dienes and an enyne also underwent the coupling reaction to give the corresponding 2-vinyl- and 2-propargylpyrrolidines **4** and **5** (Scheme 4). *trans*-Ethyl cinnamate and an *α*,*β*-unsaturated diene provided *β*-amino acid esters **6** and **7** with good diastereoselectivity for the 2,3-*trans* pyrrolidines (Scheme 4).

Bexarotene methyl ester, the methyl ester of a retinoid anticancer agent that has recently shown promise in the treatment and prevention of Alzheimer's disease,[38] provided pyrrolidine **8** from the coupling reaction along with two alkyl Heck-type diastereomers **9** (Scheme 5).

Scheme 4. Reactions of Dienes and a Dienoate

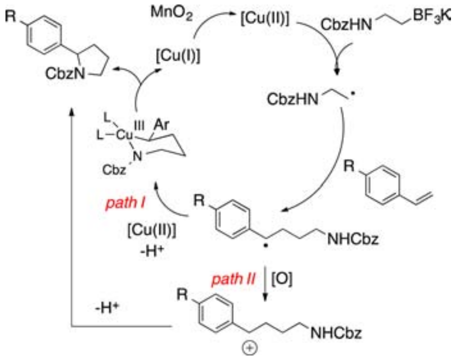


Scheme 5. Reaction of Bexarotene Methyl Ester



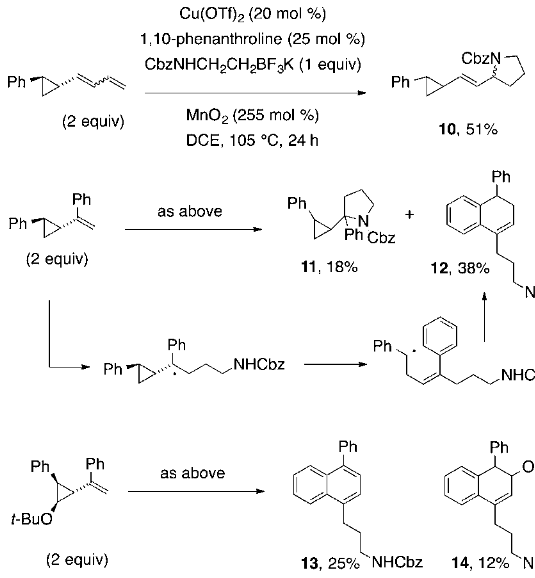
These intermolecular coupling reactions appear to occur through copper-catalyzed/MnO$_2$ mediated stepwise oxidative coupling sequence (Scheme 6). Copper(II)-catalyzed oxidation of the alkylborane to its corresponding alkyl radical initiates the process.[33,36,39] The alkyl radical then adds to the styrene to produce a stabilized benzylic radical intermediate. This intermediate can combine with [Cu(II)] to form an alkylcopper(III) intermediate capable of undergoing C−N bond formation via reductive elimination (path I).[40] Alternatively, the benzylic radical could be further oxidized by MnO$_2$ to provide a benzylic carbocation that is then trapped by the pendant amine (path II).[31] Oxidation of [Cu(I)] back to [Cu(II)] with MnO$_2$ then closes the catalytic cycle. At the onset of our mechanistic investigation, we could not differentiate between path I and path II because, on the basis of oxidation potentials, MnO$_2$ is capable of oxidizing both [Cu(I)] and a benzylic radical, although [Cu(I)] is the more easily oxidized species.[41]

Scheme 6. Proposed Reaction Mechanism



To investigate the mechanism further, a series of vinylcyclopropanes were submitted to the coupling reaction with *N*-Cbz-*β*-aminoethyltrifluoroborate **1a** (Scheme 7). Reaction with 2-(buta-1,3-dienyl)cyclopropylbenzene provided a mixture of pyrrolidine diastereomers **10**, and no cyclopropane ring-opened products were detected (Scheme 7). Reaction with 2-((phenylcyclopropyl)vinyl)benzene provided both pyrrolidine diastereomers **11** and dihydronaphthalene **12**.[33] The regiochemistry of **12** indicates that cyclopropane ring opening occurred at the phenyl-bearing carbon. This supports a radical cyclopropane ring-opening mechanism over a metal-mediated ring opening where the less substituted organometallic would have been preferred.[42] To differentiate between a carbocation and a radical cyclopropane opening, the 2-*tert*-butoxy-3-(1-phenylvinyl)cyclopropyl)benzene radical clock was applied (Scheme 7). Newcomb has demonstrated this kind of radical clock will open at the oxygen-bearing carbon in carbocationic mechanisms and at the phenyl-bearing carbon in radical mechanisms.[43] In the event, a mixture of 4-phenylnaphthylene **13** and dihydronaphthalene **14** were obtained in this reaction. Naphthalene **13** is likely formed by elimination of *t*-BuOH from **14**. The regioselectivity in these reactions support involvement of radical intermediates and do not provide evidence for carbocation intermediates. The lack of ring-opened product from reaction with the cyclopropyl diene probe could indicate that C−N bond formation is favored over ring-opening and/or radical addition to the arene when the carbon is less hindered. With increased steric hindrance at carbon, ring-opening and/or radical addition to the arene becomes competitive. While pyrrolidine formation without ring-opening is feasible, it is also possible the ring could open and subsequently close prior to pyrrolidine formation.[44]

Scheme 7. Radical Clock Mechanism Probes



In summary, we have developed new conditions for the synthesis of simple 2-arylpyrrolidines from vinylarenes and dienes. The scope of the alkene partner is broad. Radical clock experiments support a purely radical mechanism, likely involving C−N bond formation through a copper(III) intermediate. Our future efforts involve reaction refinement and scope expansion.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01259.

Experimental procedures and characterization of new compounds (PDF)
NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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