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Synthesis of Benzylureas and Related Amine Derivatives via Copper-Catalyzed Three-Component Carboamination of Styrenes

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Abstract

A direct assembly of secondary benzylureas and related amine derivatives via copper-catalyzed carboamination of styrenes with potassium alkyltrifluoroborates and ureas, anilines, or an amide is reported. Terminal and 1,2-disubstituted alkenes, as well as dienes, participate in this three-component coupling reaction. The reaction mechanism likely involves the addition of an alkyl radical to the styrene, followed by metal-mediated oxidative coupling of the resulting benzylic radical with the amine derivative. Factors that impact substrate reactivity and regioselectivity are discussed.

Graphical Abstract

Benzylureas are found in compounds with significant bioactivity including those that show potential for the treatment of pain and inflammation (see Figure 1).^{1–3} Benzylureas are typically made from benzylamines. Historically, benzylamines have been synthesized by additions of nucleophiles to carbonyl derivatives such as imines (or their derivatives),^{4–8} including reductive amination,⁹ or by substitution reactions between amines and benzylic alcohol derivatives^{10,11} or benzylic halides,¹² often using multistep sequences.

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Author Contributions

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Supporting Information

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Experimental procedures, characterization data and NMR spectra for all new compounds (PDF)

Accession Codes

CCDC 1994321 and 1994816 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Alkenes are also readily available feedstock substrates. In recent years, alkene hydroamination has become a competitive approach for the synthesis of benzylamines.¹³ A developing complementary alkene substitution approach to benzylamines is carboamination. This approach enables, in theory, a broad scope of side chains brought in by the reactive carbon component. Many intermolecular alkene carboaminations involving the addition of alkyl^{14,15} or aryl¹⁶ radicals and amines to styrenes have been reported (see Scheme 1).¹⁷ For these carboaminations, alkyl radicals have been generated from hypervalent iodine reagents (R-[I]),¹⁸ perfluoroalkyl iodides,¹⁴ α -halo carbonyls,^{19,20} nitriles,^{21–23} and peroxides (R-[O]).²⁴ The complementary regioisomer (β -arylamines) can be obtained if the coupling is initiated by the addition of a nitrogen radical to the alkene.^{21,25,26} An alternative three-component alkene carboamination has also been accomplished using a directing group strategy involving polar addition to nonconjugated carbonyl-functionalized alkenes.^{27,28}

We^{29–31} and others^{32–35} have disclosed that potassium alkyltrifluoroborates are an excellent source of alkyl radicals.³⁶ Alkyl radicals generated from alkyltrifluoroborates can be primary, secondary, or tertiary and do not need to contain specific functionality such as carbonyls, nitriles, or multiple halides. In particular, the formation of benzylic radicals from potassium benzyltrifluoroborates occurs readily^{29,31} and may offer advantages over other radical generating approaches where examples involving benzylic radical intermediates in such couplings are lacking. In addition, alkyltrifluoroborates offer a higher degree of stability, compared to alternative general alkyl radical precursors (for example, peroxides).³² At the onset, the participation of alkyltrifluoroborates in a three-component alkene carboamination was unclear, given the possibility of competing formation of either Chan-Lam amine alkylation products^{37,38} or alkyl Heck-type products.²⁹

Using *p*-methoxystyrene and *N,N'*-dibenzylurea (**2a**) as test substrate combination for the three-component copper-catalyzed coupling with benzyltrifluoroborate, we screened reaction variables such as copper salt, ligand, oxidant and solvent (Table 1). 1,10-Phenanthroline (**L1**) and bis(oxazoline) (**L2**) were applied as oxidant-insensitive ligands to stabilize and solubilize the [Cu] salt catalyst. A [Cu] loading of 10 mol % was generally applied as higher loading (not shown), which resulted in the formation of a greater amount of 1,2-dibenzylethane (a benzyl radical dimer). These reactions were run with excess styrene (3 equiv) and the potassium benzyltrifluoroborate and urea **2a** were added in two portions to minimize the formation of 1,2-diphenylethane and the Chan-Lam product, *N,N,N'*-tribenzylurea.

The reaction is thought to initiate with oxidation of the alkyltrifluoroborate to its corresponding radical with [Cu(II)].²⁹ Stoichiometric oxidant is required to restore the [Cu(I)] catalyst to the active [Cu(II)] oxidation state. Optimal conditions employ Cu(OTf)₂ (10 mol %), **L1** (12.5 mol %), MnO₂ (2.6 equiv), and 4 Å molecular sieves in 1,2-dichloroethane (DCE) at 105 °C in a sealed tube for 48 h (81% yield of **3a**; see Table 1, entry 1). The reaction also worked well (79% yield of **3a**) under higher oxidant loading (4.3 equiv of MnO₂) (Table 1, entry 2), and this higher loading gave higher isolated yield in some cases (vide infra). The reaction could be run on 1 mmol scale, giving **3a** in 71% yield (Table 1, entry 3). Alternative oxidants Ag₂CO₃ and K₂S₂O₈ (Table 1, entries 4 and 5) did not work as well as MnO₂. 1,10-Phenanthroline **L1** proved a moderately better ligand than the

bis(oxazoline) **L2** (Table 1, entry 6). When the reaction is run without ligand, trace product **3a** is obtained (Table 1, entry 7). The yield of **3a** is also diminished without inclusion of flame-activated 4 Å molecular sieves (Table 1, entry 8). Surprisingly, the addition of K₂CO₃ as a base impedes this reaction (Table 1, entry 9; 21% isolated **3a**). Reducing the reaction time to 24 h also diminishes the amount of isolated **3a** (Table 1, entry 10). Further lowering the amount of [Cu] catalyst, either by removing it or changing copper ligands, resulted in diminished amounts of isolated **3a** (Table 1, entries 11–15). Other solvents were briefly examined (Table 1, entries 16–19), but none were superior to DCE.

The scope of the amine coupling partner, using conditions from Table 1, entry 1, was examined as illustrated in Scheme 2. While *N,N'*-dibenzylurea gave the highest isolated yield (81%), other ureas also underwent the three-component coupling. Monobenzyl urea coupled at the primary amine selectively, generating benzylic urea **3b** in 34% isolated yield. *N,N,N'*-Trisbenzylurea did not undergo the coupling, but underwent Chan-Lam coupling instead, forming *N,N,N',N'*-tetrabenzylurea. *N,N'*-Dimethylurea provided **3d** in modest yield; higher isolated yield of **3d** was obtained with higher oxidant loading. Benzamide underwent the three-component coupling to give **3e** in low yield, because of the significant formation of *N*-benzyl benzamide, the Chan-Lam coupling product. Most mixed *N*-aryl-*N'*-benzylureas coupled exclusively at the arylated nitrogen. Electron-donating and mildly electron-withdrawing aryl substituents were compatible with the conditions and favored coupling at the aryl amine, giving adducts **3f–3i** in moderate yields. 1,2-Diphenylethane was the predominant side product in these reactions. Interestingly, the *N*-(4-CF₃-phenyl)-*N'*-benzyl urea underwent coupling predominantly at the benzyl-substituted amine to give **3j**, indicating a strong electronic effect on the regioselectivity. Anilines also underwent the reaction, giving *N*-arylbenzyl-amines **3k–3o** with varying degrees of efficiency. Interestingly, the electron-deficient 4-CF₃-aniline underwent coupling with the highest isolated yield (**3n**, 69%). Side products from the lower yielding couplings with anilines (e.g., to give **3k** and **3o**) were Chan-Lam coupling adducts (*N*-benzylanilines).

Amine derivatives that did not work in this coupling (trace product observed) include *N,N'*-bis(phenyl)urea, tosamide, benzylcarbamate, and morpholine. In the reactions of the tosamides and benzylcarbamate, *N*-benzylation (Chan-Lam coupling) predominated. The alkyl-Heck type coupling²⁹ predominated in the reaction with morpholine. Note that *N*-alkylamines can be accessed from the product ureas by hydrolysis with refluxing 1-butanol (shown for **3a** and **3g** in the Supporting Information).^{39,40}

Commercially available benzylic, primary, and secondary alkyltrifluoroborates were compatible in the three-component coupling (Scheme 3). Potassium 4-fluorobenzyltrifluoroborate underwent an efficient coupling with 4-methoxystyrene and *N,N'*-dibenzylurea, forming **3ab** in 66% isolated yield. The homobenzylic alkyltrifluoroborate underwent successful coupling to give **3ac**, albeit in modest yield. β -Cyano and β -ester-functionalized ethyltrifluoroborates provided coupling adducts **3ad** and **3ae** in moderate yields. Potassium isopropyl trifluoroborates, cyclopentyl trifluoroborates, and tetrahydro-pyranyl trifluoroborates also formed the respective benzylic ureas **3af**, **3ag**, and **3ah**, in moderate yields.

A styrene scope was examined (Scheme 4). Styrenes bearing aryl substituents that could donate electron density to the benzylic carbon (e.g., *ortho*- and *para*-methoxy) gave the highest isolated yields (e.g., giving **3a**, **3s**, and **3z**). 3-Methoxystyrene preferred to polymerize under the reaction conditions (**3t** was not obtained). 3,4-Bis(alkoxy)styrenes formed benzylic ureas **3u** and **3v** with higher efficiency under higher oxidant loading. Styrene and 4-alkylstyrenes underwent the reaction, forming ureas **3p–3r** with moderate isolated yields. 1,2-Disubstituted internal alkenes underwent the three-component coupling to give modest yields of **3**, favoring one major diastereomer. In the case of indene derivatives **3y** and **3z**, the *trans*-diastereomer was formed exclusively (assigned by X-ray structure of **3z**). 1-Isopropenyl-4-methoxybenzene, a 1,1-disubstituted alkene, did not form the respective benzylamine **3** but instead gave primarily the corresponding alkyl-Heck-type product.⁴¹

Cinnamic esters and 1-phenyl-butadiene were explored as the alkene components (eqs 1–3). Methyl cinnamate **4** underwent alkylation at the α -position and amination at the β -position, which is consistent with benzylamine formation. However, the coupling product formed was pyrimidine dione **5**, the result of in situ cyclization of the remaining urea nitrogen onto the pendant ester. Only the *trans*-diastereomer was isolated, and the crude ¹H NMR was consistent with high diastereoselectivity (ca. 10:1) for this reaction. The observed regioselectivity and diastereoselectivity is analogous to that observed in [Fe]-catalyzed three-component carboamination reactions, which are thought to involve alkyl radical addition to enones.²⁴ Dienoate **6** gave the 1,4-addition adducts **7**. *Trans*-1-phenyl-1,3-butadiene provided a 2:1 mixture of 1,4- and 1,2-addition products **9a** and **9b**, respectively.

A proposed catalytic cycle is presented in Scheme 5. The [Cu(II)] catalyst (and/or MnO₂) initiates the reaction by

(1)

(2)

(3)

oxidation of the BnBF₃K to benzyl radical **I**. Radical **I** adds to styrene **1a** to give benzylic radical **II**.²⁹ Radical **II** can be oxidized by MnO₂ or [Cu(II)] to carbocation **IIIa**, which can undergo addition by the amine. The carbocation mechanism is the likely mechanism for the control reaction when [Cu(II)] is omitted (Table 1, entry 12; 13% yield of **3a**). The superior reactivity of styrenes with *para*- and *ortho*-methoxy substituents can be rationalized by both stabilization of a benzylic radical or benzylic carbocation. In an alternative mechanism, radical **II** can add to [Cu(II)] (e.g., complex **IV**) to form a [Cu(III)] intermediate, **IIIb**, which can undergo reductive elimination to give **3**. Support for this mechanism includes the sensitivity to steric hindrance at the benzylic carbon as tertiary benzylureas are not formed (a 1,1-disubstituted alkene did not produce **3**). Both the carbocation mechanisms^{19,23,24} and carbon radical mechanisms¹⁴ have previously been proposed for related metal-catalyzed three-component alkene carboaminations involving radical intermediates, and it is probable that both pathways are viable.^{30,31}

It is interesting to note the trends in urea reactivity illustrated in Scheme 1. The preference for Chan-Lam coupling over three-component coupling of *N,N,N'*-trisbenzylurea (**3c** was not formed) indicates that ureas with two NH groups are required where they may engage in bidentate coordination with the [Cu] or perhaps coordination to a second [Cu] species. In one scenario, the second nitrogen could serve as a fifth ligand, defined as **L**, in complexes **IIIb**, **IV**, and **V** (Scheme 5). The arylamine of the unsymmetrical ureas undergoes coupling preferentially (Scheme 1). The isolated yield trend for these mixed *N*-aryl-*N'*-benzylureas correlates with amidyl radical stability and redox potentials, where the 4-methoxyaniline derivative has the lowest oxidation potential and is most reactive, while the less reactive 4-chloroaniline *N*-benzyl urea, and the “unreactive at aniline” 4-CF₃-aniline *N*-benzyl urea, should have much higher oxidation potentials.⁴² If an amidyl radical were formed by oxidation of the urea (e.g., with [Cu(II)] or MnO₂), the amidyl radical would be able to convert a [Cu(II)] intermediate to a [Cu(III)] intermediate (an alternative path to intermediate **IIIb**). This reactivity would also be consistent with reaction between an amidyl-[Cu(II)] species reaction with an alkyl-[Cu(II)] species (intermediate **IIIc**).⁴⁰ The selective coupling at the arylated nitrogen of most mixed ureas is less consistent with the carbocation mechanism, since the arylamine should be less nucleophilic than the benzylamine.

This three-component alkene carboamination enables the expedient synthesis of diverse benzylamine derivatives. Electronic preferences for the amine and styrene component were especially notable. Further examination of the scope of each component, and efforts toward an enantioselective method are under investigation in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Bioactive benzylic ureas.

Scheme 1. Three-Component Alkene Carboamination ($X = H, [O], \text{Halogen}, [I], [B]$ (This Work))

^bConditions from Table 1, entry 2 were used.

Scheme 3.

Alkyltrifluoroborate Scope^a^aConditions from Table 1, entry 1 were used.

Scheme 4. Styrene Scope^a^aConditions from Table 1, entry 1 were used.^bConditions from Table 1, entry 2 were used.

Scheme 5.
Proposed Mechanism

Table 1.

Factors That Impact Carboamination Efficiency^a

entry	change from standard conditions	yield (%)
1	none	81
2	4.3 equiv MnO ₂	79
3	1 mmol of 2a and BnBF ₃ K	71
4	Ag ₂ CO ₃ (2 equiv) instead of MnO ₂	52
5	K ₂ S ₂ O ₈ (2.1 equiv) instead of MnO ₂	13
6	L2 instead of L1	66
7	no external ligand	trace
8	no 4 Å molecular sieves	62
9	K ₂ CO ₃ (1 equiv) additive	21
10	24 h instead of 48 h	49
11	5 mol % Cu(OTf) ₂ , 6.25 mol % L1	63
12	no [Cu] or L	13
13	Cu(2-ethylhexanoate) ₂ instead of Cu(OTf) ₂	34
14	Cu(F ₆ acac) ₂ instead of Cu(OTf) ₂	39
15	CuCl instead of Cu(OTf) ₂	37
16	PhCH ₃ instead of DCE	14
17	PhCF ₃ instead of DCE	8
18	CH ₃ CN instead of DCE	34
19	MeO <i>t</i> -Bu instead of DCE, at 75 °C	15

^aAll reactions were run with 0.125 mmol of BnNHC(O)NHBn (**2a**), 0.125 mmol of BnBF₃K, and 0.375 mmol of 4-methoxystyrene (**1a**), unless otherwise noted. **2a** and BnBF₃K were added in two portions. Yields are the amount of **3a** isolated following purification by flash chromatography on silica gel.