ORGANIC
LETTERS

2013
Vol. 15, No. 10
2502–2505

Sultam Synthesis via Cu-Catalyzed Intermolecular Carboamination of Alkenes with *N*-Fluorobenzenesulfonimide

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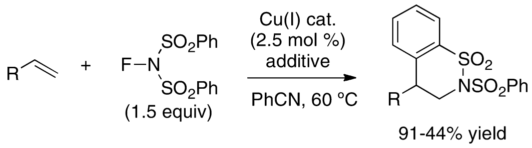
Received April 9, 2013

ABSTRACT



Cu-catalyzed intermolecular carboamination of alkenes is described. The reaction of terminal alkenes and an internal alkene with *N*-fluorobenzenesulfonimide was promoted by 2.5 mol % of a Cu(I)-salt at 60 °C, and six-membered ring sultams were obtained in 91–44% yields.

The sultam subunit is an important structural motif found in many biologically active compounds, such as a carbonic anhydrase inhibitor brinzolamide, which is used clinically to lower intraocular pressure, an anticonvulsant agent sultiame, a potent HIV integrase inhibitor, and a calpain I selective inhibitor (Figure 1).[1] Various divergent but multistep synthetic methods for sultams have been reported, including transition-metal catalyzed processes.[2] The current strong demand for environmentally benign synthetic processes makes the development of a new step-economical[3] method for sultam synthesis highly desirable. The catalytic aminative difunctionalization of alkenes[4,5] is an attractive straightforward approach for producing sultams. Dauban, Dodd and co-workers reported a Cu(I)-catalyzed intramolecular aziridination of sulfonamides in the presence of a hypervalent iodine reagent, followed by nucleophilic ring opening of aziridines (eq 1).[6] Chemler and co-workers reported an efficient and stereoselective Cu(II)-catalyzed carboamination of alkenes for the concise synthesis of sultams (eq 2). These methods, however, focused

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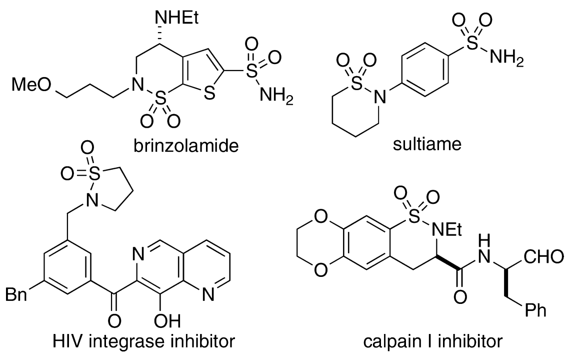
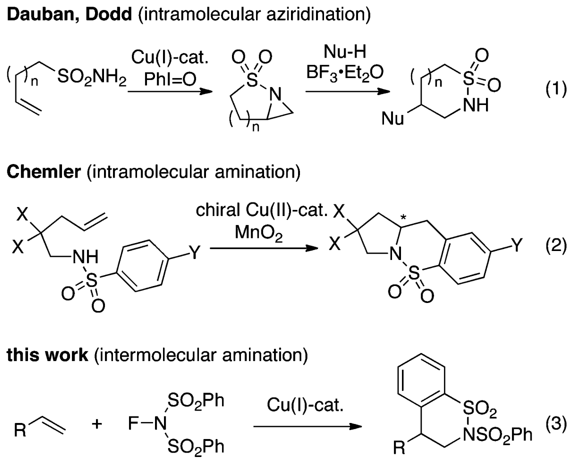


Figure 1. Structures of biologically active sultams.

on the *intramolecular* amination of alkenes bearing a tethered nitrogen nucleophile (eqs 1 and 2).[6,7] Thus, the development of a new catalytic system enabling *intermolecular* carboamination of alkenes for sultam synthesis is in high demand.

In contrast to recent advances in the intramolecular carboamination of alkenes,[4,6−12] the available methods for catalytic carboamination of alkenes involving an intermolecular amination step are quite limited.[13−15] To realize the intermolecular carboamination of unactivated alkenes, we selected *N*-fluorobenzenesulfonimide (NFSI), which acts as both a nitrogen source and an oxidant. A Cu(I)-salt (2.5 mol %)[16] efficiently catalyzed the intermolecular amino-arylation of unactivated alkenes with NFSI, giving six-membered ring sultams in one step (eq 3).



The optimization studies using NFSI and alkene **1a** are summarized in Table 1. CuOTf•1/2tol (2.5 mol %) promoted the desired carboamination in CH$_3$CN at 60 °C, albeit in moderate yield (48%, entry 1). Solvent screening revealed that a nitrile group in the solvent was essential to obtain product **2a**, and other solvents, such as CHCl$_3$, THF, and benzene, only afforded complex mixtures of byproducts. The best yield of **2a**, 59%, was achieved using benzonitrile as the solvent (entry 5). Cu(I)-salts affected the reactivity to some extent, and Cu(CH$_3$CN)$_4$BF$_4$ gave product **2a** in slightly better yield than other Cu-salts (entry 10, 67%). Although strongly coordinating bipyridyl and phenathroline-type ligands **3a**−**3b** (Figure 2) adversely affected the reactivity (entries 11−12), other coordinating additives **3c**−**3f** bearing carbonyl groups were applicable in the present reaction. The amounts of byproducts decreased when using **3f** as an additive (entry 16, 68%), and the best yield was obtained with 1.6 mol % of **3f** (entry 17, 70% isolated yield).[17] Further trials to improve the yield by adding an inorganic base were not successful, and the conditions in entry 17 were selected as optimum.

The substrate scope of alkenes in the present intermolecular carboamination reaction under the optimized reaction conditions is summarized in Scheme 1. Not only simple aliphatic terminal alkenes (**1a**−**1c**) but also various terminal alkenes **1d**−**1l** with functional groups were applicable. Although the yield varied depending on the functional groups, products **2d**−**2l** bearing an imide, halogen, nitro group, free-hydroxy group, benzyl ether, or ester

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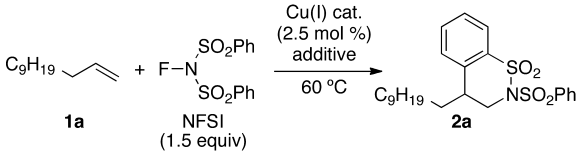
(17) Although the reason is not clear, the optimum reactivity was observed when the amount of additive **3f** was in the range of 1.25−2.0 mol %. Greater than 2.5 mol % of **3f** had slightly adverse effects on the reactivity.

Table 1. Optimization Studies



entry	Cu cat. (mol %)	time (h)	solvent	additive (mol %)	yield[a] (%)
1	CuOTf•1/2tol	10	CH_3CN	none	48
2	CuOTf•1/2tol	10	$CHCl_3$	none	0
3	CuOTf•1/2tol	10	THF	none	0
4	CuOTf•1/2tol	10	benzene	none	0
5	CuOTf•1/2tol	1	PhCN	none	59
6	CuOAc	1	PhCN	none	60
7	CuTC	1	PhCN	none	55
8	CuCl	1	PhCN	none	60
9	$Cu(CH_3CN)_4ClO_4$	1	PhCN	none	61
10	$Cu(CH_3CN)_4BF_4$	1	PhCN	none	67
11	$Cu(CH_3CN)_4BF_4$	1	PhCN	**3a** (2.5)	0
12	$Cu(CH_3CN)_4BF_4$	1	PhCN	**3b** (2.5)	0
13	$Cu(CH_3CN)_4BF_4$	1	PhCN	**3c** (2.5)	56
14	$Cu(CH_3CN)_4BF_4$	1	PhCN	**3d** (2.5)	67
15	$Cu(CH_3CN)_4BF_4$	1	PhCN	**3e** (2.5)	63
16	$Cu(CH_3CN)_4BF_4$	1	PhCN	**3f** (2.5)	68
17	$Cu(CH_3CN)_4BF_4$	1	PhCN	**3f** (1.6)	74 (70)[b]

[a] Determined by ^{1}H NMR analysis of crude mixture using 1,1,2,2-tetrabromoethane as an internal standard. [b] Number in parentheses is the isolated yield of **2a** after purification by silica gel column chromatography.

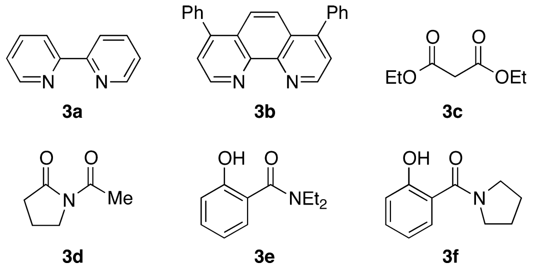
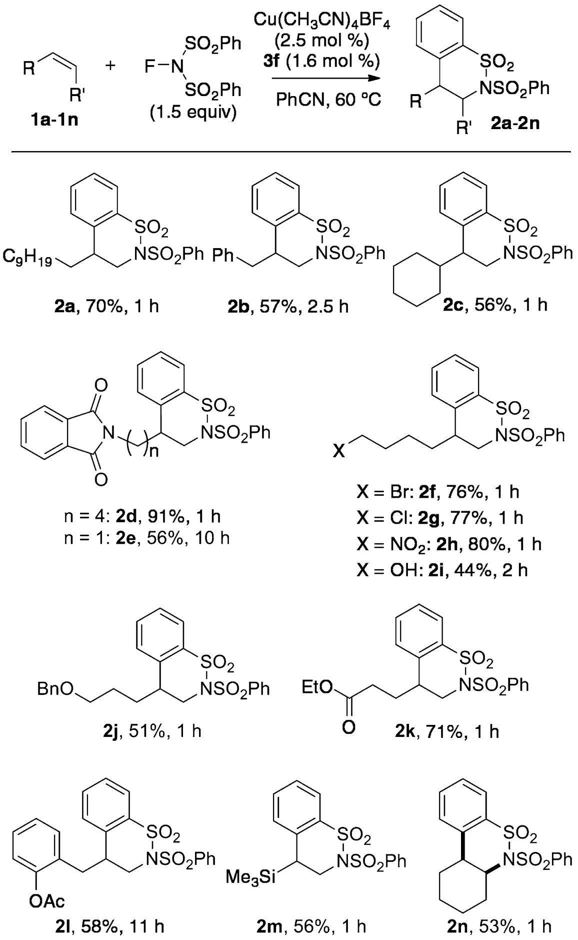


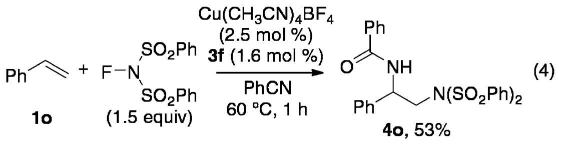
Figure 2. Structures of additives **3a**–**3f**.

were obtained in 44–91% yield. Vinylsilane also gave product **2m** in 56% yield. Not only terminal alkenes but also internal alkene **1n** were applicable in the present system, giving *cis*-adduct **2n** in 53% yield.[18] On the other hand, the desired sultam was not obtained from styrene **1o**, because benzonitrile reacted as a nitrogen source to give the diamination adduct **4o** instead of an amino-arylation adduct (eq 4).[19]

Scheme 1. Cu-Catalyzed Intermolecular Carboamination of Alkenes **1a**–**1n** with NFSI[a]



[a] Reaction was run using alkene **1** (0.20 mmol), NFSI (0.30 mmol), $Cu(CH_3CN)_4BF_4$ (2.5 mol %), **3f** (1.6 mol %) in PhCN (0.4 M) at 60 °C. Isolated yield of products **2** after purification by silica gel column chromatography are shown.



The postulated catalytic cycle of the intermolecular carboamination reaction based on earlier reports of related Cu-catalyzed reactions[7,15] is shown in Figure 3. Oxidation of Cu(I) with NFSI affords Cu(III) species **A**,[20] which would exist in equilibrium with Cu(II)-stabilized nitrogen-centered radical species **B**.[15a,21] Amino-cupration from Cu(III) species **A** followed by homolysis of the Cu–C

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(18) Acyclic *E*- or *Z*-disubstituted internal alkenes and geminal disubstituted alkenes were not applicable in the present system, showing much less satisfactory reactivity.

(19) Cu(I)-catalyzed diamination of styrenes with NFSI and nitriles as the second nitrogen source to give **4** was recently reported by Zhang and co-workers; see ref 15a.

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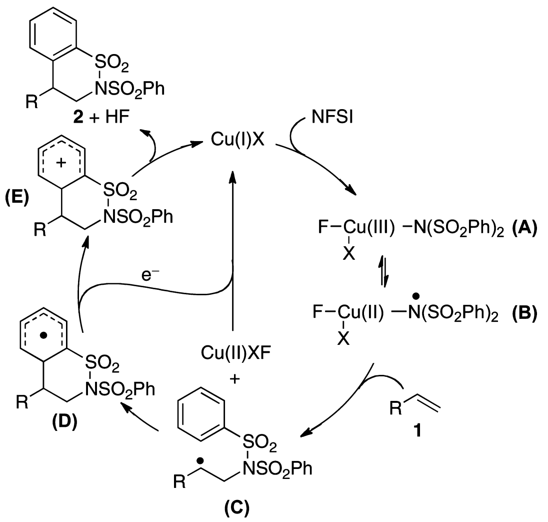

Figure 3. Postulated catalytic cycle of Cu(I)-catalyzed intermolecular carboamination of alkenes.

bond or the reaction of a nitrogen-centered radical **B** with alkene provided the carbon radical intermediate **C**. Intramolecular addition of the carbon radical to the neighboring aromatic ring, followed by oxidation of **D** with Cu(II) and rearomatization, afforded sultam **2** and regenerated the Cu(I) catalyst. Studies to clarify the reaction mechanism will be reported in due course.[22]

In summary, we succeeded in developing an intermolecular aminoarylation of aliphatic alkenes that provides straightforward access to sultams. The reaction of terminal and internal alkenes with NFSI was efficiently promoted by 2.5 mol % of a Cu(I)-salt at 60 °C, giving sultams in 91–44% yield. Further studies to expand the scope of the alkenes and nitrogen reactants are ongoing in our group.

Acknowledgment. This work was supported in part by the ACT-C program from JST and a Grant-in-Aid for Scientific Research on Innovative Areas "Molecular Activation Directed toward Straightforward Synthesis" from MEXT. T.Y. thanks JSPS for fellowships.

Supporting Information Available. Experimental procedures, and spectral data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[22] Preliminary trials on "radical clock" experiments did not afford clear results, giving complex mixtures of byproducts.
