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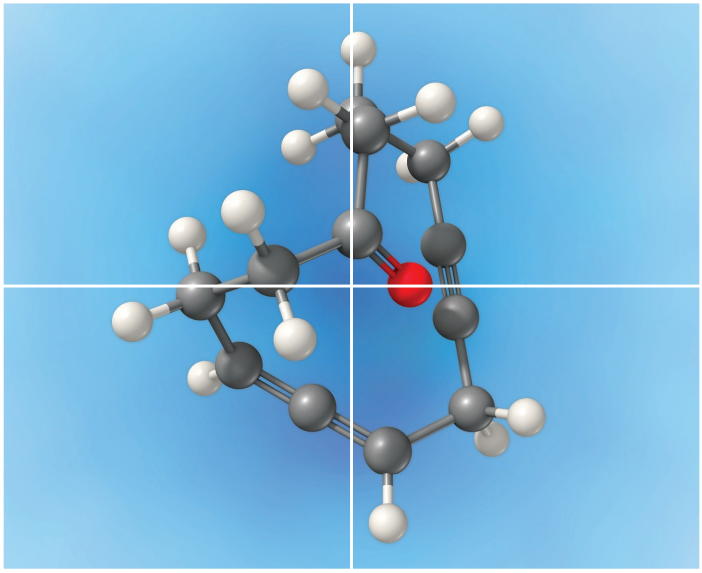

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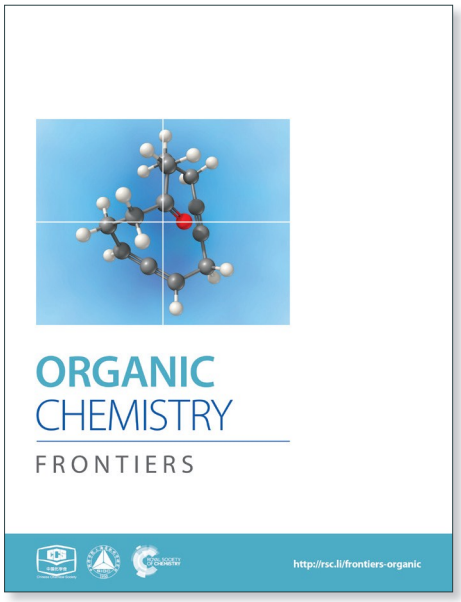

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COMMUNICATION

Copper-catalyzed aminotrifluoromethylation of alkenes: a facile synthesis of CF_3-containing lactams

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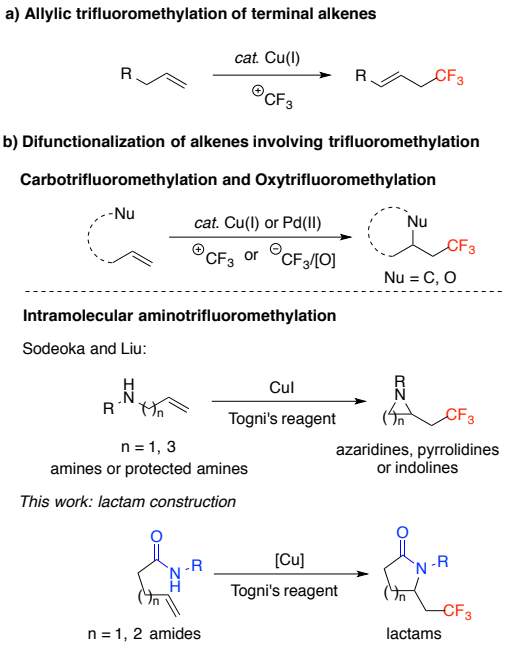
Kun Shen and Qiu Wang*

A copper-catalyzed aminotrifluoromethylation of alkenes using amides as nucleophiles has been developed. It provides a rapid and efficient access to a variety of CF_3-containing lactams. The reaction proceeds under mild conditions with a good scope and functional group tolerance, offering a valuable method to prepare CF_3-containing lactams that are of great potential in pharmaceuticals and agrochemicals.

The pharmacological profile of organic molecules can be significantly improved through the introduction of fluorine.[1] In particular, the trifluoromethyl group has attracted substantial attention in the fields of pharmacology and agrochemistry due to its favorable influence on lipophilicity, hydrophobicity, and metabolic stability.[2] A variety of synthetic methods has been developed towards the installation of the trifluoromethyl group into organic molecules.[2-4] Over the past several years, transition-metal-mediated alkene trifluoromethylation has emerged as a powerful approach.[3] For example, copper-catalyzed allylic trifluoromethylation of terminal alkenes has been reported by several groups (Scheme 1, a).[5] In addition, multiple alkene difunctionalization reactions incorporating trifluoromethylation have been successfully established,[6,7] including carbotrifluoromethylation,[8] oxytrifluoromethylation,[9] and aminotrifluoromethylation[10] of simple alkenes (Scheme 1, b). The Buchwald group reported an elegant work on the copper-catalyzed intramolecular oxytrifluoromethylation of alkenes with Togni's reagent, employing carboxylic acids, phenols or alcohols as nucleophiles to form oxygen-containing heterocycles.[9d-9e] Recently, aminotrifluoromethylation of terminal alkenes with Togni's reagent was reported by the Sodeoka[10c] and Liu[10d-e] groups using amines or protected amines as nucleophiles to construct trifluoromethylated aziridines, pyrrolidines and indolines. Though a wide range of



Scheme 1. Alkene trifluoromethylation

trifluoromethylated scaffolds are accessible through current methods, there are no examples of the aminotrifluoromethylation of unsaturated amides towards the synthesis of CF_3-containing lactams. In contrast to the successful oxytrifluoromethylation of unsaturated carboxylic acids, it remains challenging to employ amides as nucleophiles in trifluoromethylation-incorporated olefin difunctionalization.[9d] With the ubiquitous presence of lactams in synthetic building blocks, bioactive compounds, natural products and pharmaceuticals,[11] it would be of great value to synthesize CF_3-containing lactams. Herein, we report the first example of the introduction of the trifluoromethyl group into lactams via aminotrifluoromethalytion of simple alkenes.

Department of Chemistry, Duke University
124 Science Drive, Durham, NC 27708, USA
Email: qiu.wang@duke.edu

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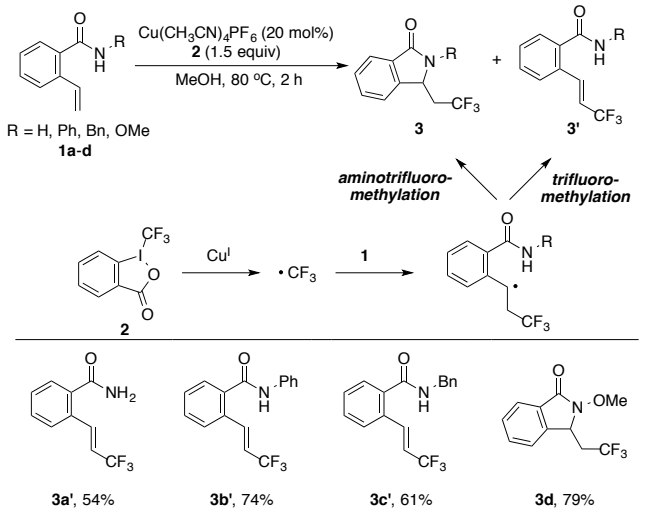
Table 1. Trifluoromethylation reactions of 2-vinylbenzamides[a]

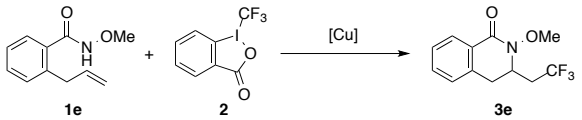


[a] Reaction conditions: **1** (0.2 mmol, 1 equiv), **2** (0.3 mmol, 1.5 equiv), $Cu(CH_3CN)_4PF_6$ (0.04 mmol, 20 mol%), MeOH (1 mL), 80 °C, 2 h.

Recently, our goup has reported a copper-catalyzed alkene diamination reaction in which the protecting group on the amide played a critical role in the formation of the lactam products.[12] We postulated that the protecting group on the amide would once again be critical in the proposed aminotrifluoromethylation reaction. Thus, we examined the copper-catalyzed reactions of 2-vinylbenzamides **1** containing different protecting groups using Togni's reagent **2** (Table 1). Interestingly, two types of trifluoromethylation products were observed depending on the protecting groups. In the case of **1a–1c** with H, Ph, or Bn groups, trifluoromethylated alkenes **3a'–3c'** were formed.[13] However, in the reaction of **1d** with an OMe group, aminotrifluoromethylated lactam **3d** was successfully formed. These results suggested that the alkoxyl group on the nitrogen played an important role on the trifluoromethylation reaction and facilitating the radical cyclization via nitrogen trapping.

With our preliminary success, we next used unactivated 2-allyl-*N*-methyoxybenzamide **1e** as the model substrate to optimize the aminotrifluoromethylation conditions (Table 2). In contrast with the successful formation of isoindolinone product **3d**, the aminotrifluoromethylated product 3,4-dihydroisoquinolinone **3e** was formed in only 17% yield under the initial conditions with $Cu(CH_3CN)_4PF_6$ as the catalyst in MeOH at 80 °C (Table 2, entry 1). Among the set of copper catalysts examined, $Cu(acac)_2$ was found to be the best, providing **3e** in 45% yield (Table 2, entries 1–8). Methanol proved to be the optimal solvent for the formation of the desired product **3e** (Table 2, entries 8–15). Lowering reaction temperatures resulted in a significant decrease in efficiency (Table 2, entries 16–18). Finally, increasing the amount of Togni's reagent (2 equivalents) led to a much improved yield of **3e** (72%), which was chosen as the standard conditions for alkene aminotrifluoromethylation.

Table 2. Condition optimization for alkene aminotrifluoromethylation[a]



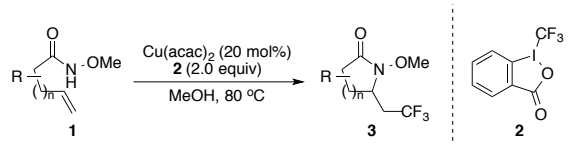
entry	catalyst	solvent	temp (°C)	yield[b]
1	$Cu(CH_3CN)_4PF_6$	MeOH	80	17%
2	CuOTf	MeOH	80	14%
3	CuOAc	MeOH	80	33%
4	CuTc	MeOH	80	32%
5	CuCN	MeOH	80	17%
6	CuCl	MeOH	80	28%
7	$Cu(OAc)_2$	MeOH	80	30%
8	$Cu(acac)_2$	MeOH	80	49%
9	$Cu(acac)_2$	DMF	80	7%
10	$Cu(acac)_2$	toluene	80	5%
11	$Cu(acac)_2$	DCE	80	11%
12	$Cu(acac)_2$	1,4-dioxane	80	3%
13	$Cu(acac)_2$	THF	80	3%
14	$Cu(acac)_2$	MTBE	80	25%
15	$Cu(acac)_2$	CH_3CN	80	8%
16	$Cu(acac)_2$	MeOH	60	45%
17	$Cu(acac)_2$	MeOH	40	18%
18	$Cu(acac)_2$	MeOH	rt	3%
19[c]	**$Cu(acac)_2$**	**MeOH**	**80**	**72%**

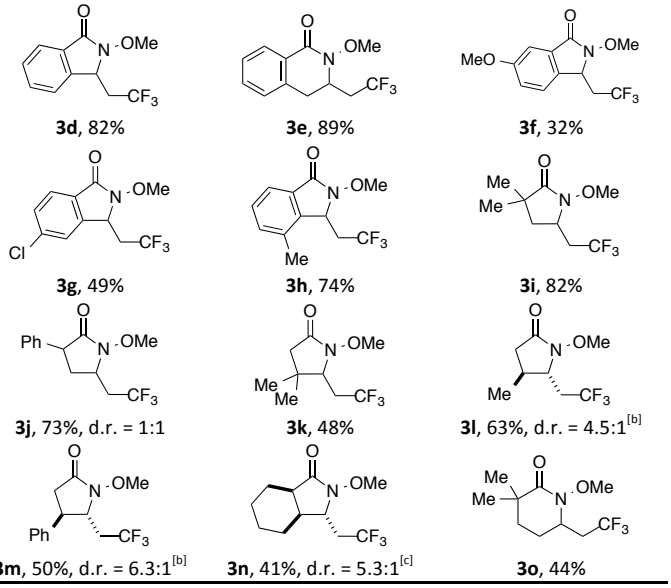
[a] Reaction conditions: **1** (0.2 mmol, 1 equiv), **2** (0.30 mmol, 1.5 equiv), $Cu(acac)_2$ (0.04 mmol, 20 mol%), MeOH (2 mL), 80 °C, 12 h, unless otherwise noted. [b] Yields determined by ^{19}F NMR with CF_3Ph as an internal standard. [c] **2** (0.4 mmol, 2 equiv), 12 h.

With these optimized conditions, we examined the scope of this alkene aminotrifluoromethylation (Table 3). Both 5- and 6-membered lactam products (isoindolione **3d** and 3,4-dihydroisoquinolione **3e**) were readily formed in 82% and 89% yields, respectively. The reaction displayed compatibility with a wide range of substitutions on the aryl group, including those that were electron-donating (**3f**), electron-withdrawing (**3g**), or located at a sterically obstructing *ortho* position (**3h**). In addition to *N*-methoxybenzamides **1d–1h**, *N*-methoxyamides **1i–1n** bearing different substituents on the alkenyl chain underwent smooth 5-exo cyclization to afford γ-lactam **3i–3n**. In the amide substrates that contained a stereocenter, moderate to good diastereoselectivity was observed in the formation of lactams **3l–3n**. Finally, the formation of 6-membered lactam **3o** was also effective.

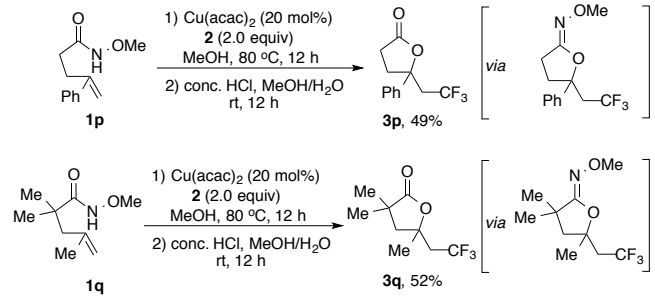
When 1,1-disubstituted terminal alkenes **1p** and **1q** were examined under standard conditions, interestingly, the desired aminotrifluoromethylation products were not observed; rather the oxytrifluoromethylation products **3p** and **3q** were formed upon the subsequent acid-catalyzed hydrolysis. These results suggest that *O*-trapping is favored over the *N*-trapping upon the increased steric hindrance (Scheme 2).[14]

Table 3. Aminotrifluoromethylation of Unactivated Alkenes[a]

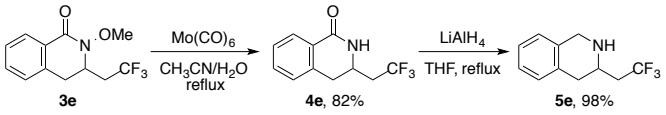




[a] Reaction conditions: **1** (0.3 mmol, 1 equiv), **2** (0.6 mmol, 2 equiv), $Cu(acac)_2$ (0.06 mmol, 20 mol%), MeOH (3 mL), 80 °C, 2–5 h. Isolation yields. [b] d.r = diastereomeric ratio, determined by ^{19}F NMR of the crude reaction mixture. Isolation yield includes both isomers. [c] d.r. determined by GC-MS of the crude reaction mixture, only one diastereomer isolated.



Scheme 2. Oxytrifluoromethylation of 1,1-disubstituted alkenes



Scheme 3. Deprotection of *N*-methoxyamide **3e**

While the mechanistic details of this copper-catalyzed aminotrifluoromethylation reaction remain unclear at present, the current results suggest it would be analagous to the copper-catalyzed oxytrifluoromethylation.[9d-9e] Furthermore, the addition of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), a known radical scavenger, was found to largely inhibit the aminotrifluoromethylation reaction.[15]

To demonstrate synthetic utility of the products derived from this reaction, 3,4-dihydroisoquinolinone **3e** was treated with $Mo(CO)_6$, readily providing free lactam **4e** in 82% yield (Scheme 3). Furthermore, reduction using $LiAlH_4$ afforded the CF_3-containing tetrahydroisoquinoline **5e**, providing an effective access to trifluoromethylated piperidine derivatives.

Conclusions

In summary, an efficient copper-catalyzed aminotrifluoromethylation of alkenes has been achieved using amides as nucleophiles under mild conditions. These reactions provide CF_3-containing lactams in good yields. It offers a useful method to access a variety of CF_3-containing lactams, which are valuable building blocks in organic synthesis and drug development. Further investigations of the reaction mechanism are currently underway.

Acknowledgements

We acknowledge financial support of Duke University and the National Science Foundation (CHE-1455220) to this work.

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14 The observed *O*-trapping pathway may also arise from the different electronic nature of the 1,1-disubstituted alkenes.

15 The formation of **3e** was decreased significantly (12% ^{1}H NMR yield) with the addition of TEMPO under the optimized reaction conditions, indicating the involvement of radical intermediates.