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Copper-Catalyzed Trifluoromethylation of Alkenes with Redox-Neutral Remote Amidation of Aldehydes

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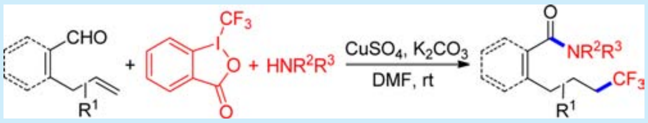
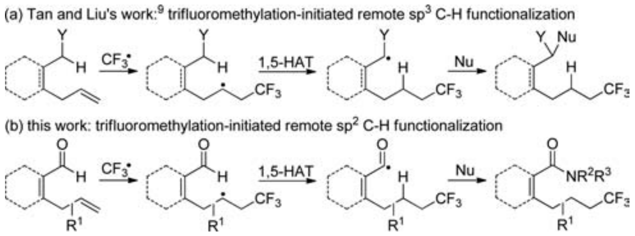
Ⓢ *Supporting Information*

ABSTRACT: A room-temperature and one-pot synthesis of ε-CF_3-substituted amides via the copper-catalyzed trifluoromethylation of alkenes with redox-neutral remote amidation of aldehydes is described. This reaction is featured by an unprecedented 1,5-H atom abstraction from aldehydic C−H bonds by α-CF_3-alkyl radicals resulting from the radical trifluoromethylation of alkenes, thus enabling a new possibility of the trifluoromethylation-initiated remote sp^2 C−H functionalization.



The trifluoromethyl group is of great interest in pharmaceuticals, agrochemicals, and materials because of its unique properties, including increased metabolic stability, hydrophobicity, bioavailability, and eletronegativity.[1] Consequently, a variety of methods have been developed for the synthesis of such compounds.[2] The alkene trifluoromethylation,[3,4] a notable reaction pioneered by Buchwald,[4a] Liu,[4b] and Wang,[4c] provides a straightforward and highly efficient route to construct C−CF_3 bonds. In this respect, the difunctionalization-type trifluoromethylation of C−C double bonds has attracted considerable attention[5−8] since the concurrent formation of C−CF_3 and C−Z (Z = C, O, N, S, or halide) bonds can be achieved efficiently in a single synthetic operation. Specifically, Tan and Liu[9] reported a series of alkene trifluoromethylation-initiated remote C−H functionalization reactions, giving streamlined access to CF_3-containing *N*,*O*-aminals, enamides, oxazoles, and carbonyl derivatives (Scheme 1a). These reactions feature the generation of α-CF_3-alkyl radical and a subsequent intramolecular 1,5-hydrogen atom transfer (1,5-HAT).[9,10] As compared to the prevalence of sp^3 C−H bonds as hydrogen donors, 1,5-hydrogen atom abstraction from sp^2 C−H bonds has not been realized so far, probably due to the higher dissociation energy of sp^2 C−H bonds and side reaction of the addition of carbon radicals to carbon−carbon or carbon−heteroatom multiple bonds.[11]

Scheme 1. Summary of This Work


(a) Tan and Liu's work:[9] trifluoromethylation-initiated remote sp^3 C-H functionalization
(b) this work: trifluoromethylation-initiated remote sp^2 C-H functionalization

On the other hand, amides are arguably among the most abundant motifs in natural products, agrochemicals, pharmaceuticals, and polymers. A traditional method for their preparation depends on the condensation between carboxylic acids and amines, which often suffers from high waste production, narrow substrate scope, and low atom economy.[12] Recently, the aldehyde → amide conversion has arisen as a very attractive alternative to the existing methods.[13] However, strong oxidants such as *tert*-butyl hydroperoxide and hydrogen peroxide[13a−f] are often required for performing the transformation, thus leading to unsatisfactory functional group tolerance. As such, the development of a redox-neutral direct transformation of aldehydes to amides remains to be underdeveloped and is in great demand. Following our ongoing interest in the Cu-catalyzed radical reactions,[11,14] we describe here a Cu-catalyzed, redox-neutral alkene trifluoromethylation-initiated remote aldehydic C−H functionalization using Togni's reagent (**I**),[15a] giving amides with the concomitant incorporation of CF_3 group at a specific site under mild reaction conditions (Scheme 1b).

Our study commenced with the coupling of 2-allyl benzaldehyde (**1a**), Togni's reagent (**I**), and pyrrolidine (**2a**) in the presence of 1.5 equiv of K_2CO_3 and 10 mol % of different copper complexes in *N*,*N*-dimethylformamide (DMF). To our delight, the reaction catalyzed by CuI gave **3aa** in 62% yield (Table 1, entry 1). Using $CuSO_4$ in place of CuI gave a clean reaction mixture, delivering **3aa** in 80% yield (entry 7). Employment of other solvents such as MeCN, tetrahydrofuran (THF), CH_2Cl_2, toluene, and dimethyl sulfoxide (DMSO) provided inferior results (entries 8−12). As for the trifluoromethylation reagent, Togni's reagent (**II**) and Umemoto's reagent (**III**)[15b] turned out to be far less efficient (entries 13 and 14). It is worth mentioning that essentially no reaction was observed in the absence of copper catalyst (entry 15). The addition of 1.5 equiv of K_2CO_3 had a positive effect on the reaction yield (entry 16). Therefore, the optimized reaction conditions comprised 10 mol % of $CuSO_4$, 1.5 equiv of Togni's

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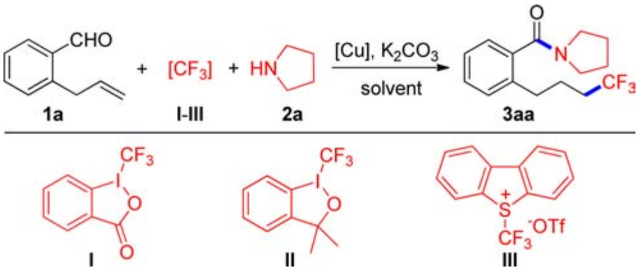
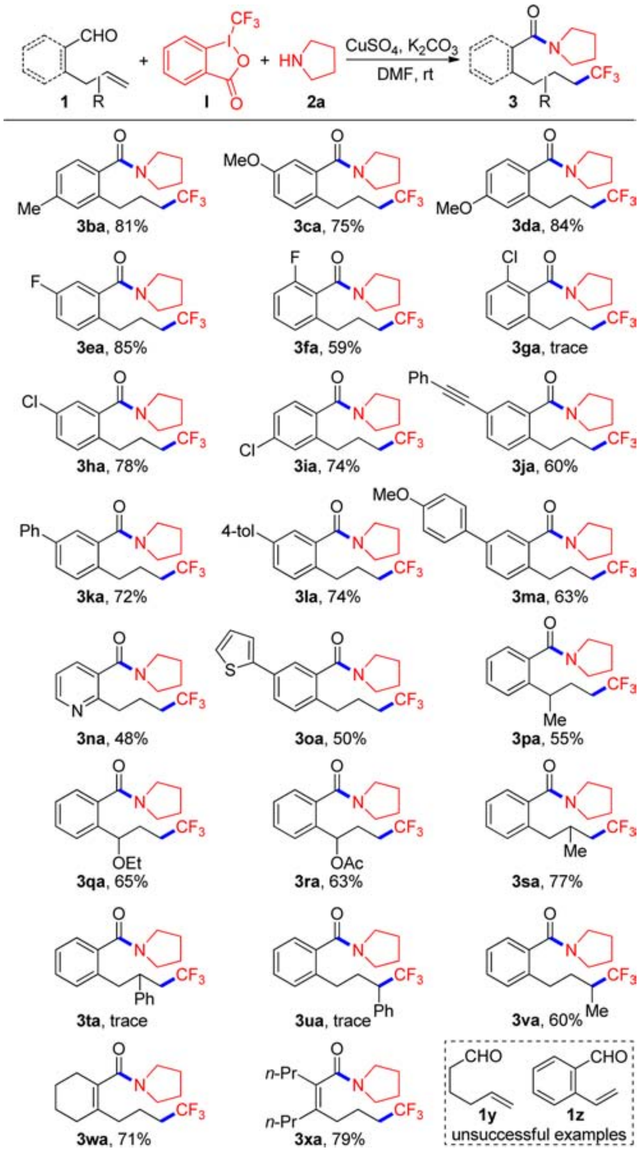
Table 1. Optimization of the Reaction Conditions[a]



entry	[Cu]	$[CF_3]$	solvent	yield[b] (%)
1	CuI	**I**	DMF	62
2	CuBr	**I**	DMF	40
3	CuCl	**I**	DMF	38
4	$CuBr_2$	**I**	DMF	45
5	$Cu(OTf)_2$	**I**	DMF	72
6	$Cu(MeCN)_4PF_6$	**I**	DMF	56
7	$CuSO_4$	**I**	DMF	80
8	$CuSO_4$	**I**	MeCN	72
9	$CuSO_4$	**I**	CH_2Cl_2	61
10	$CuSO_4$	**I**	toluene	10
11	$CuSO_4$	**I**	DMSO	67
12	$CuSO_4$	**I**	THF	15
13	$CuSO_4$	**II**	DMF	14
14	$CuSO_4$	**III**	DMF	18
15		**I**	DMF	0
16[c]	$CuSO_4$	**I**	DMF	56

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.375 mmol), [Cu] (10 mol %), $[CF_3]$ (0.375 mmol), K_2CO_3 (0.375 mmol), solvent (2 mL), under N_2, 25 °C, 10 h. [b]Isolated yield. [c]Without the addition of K_2CO_3.

Scheme 2. Scope of Aldehydes[a]



[a]Reaction conditions: **1** (0.25 mmol), **2a** (0.375 mmol), $CuSO_4$ (10 mol %), **I** (0.375 mol), K_2CO_3 (0.375 mmol), DMF (2 mL), under N_2, 25 °C, 10 h. Yields of the isolated products are given.

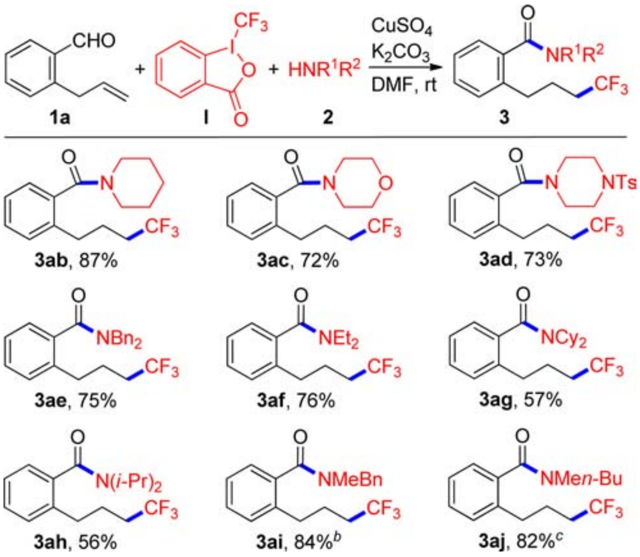
reagent (**I**), 1.5 equiv of **2a**, and 1.5 equiv of K_2CO_3 in DMF at room temperature for 10 h.

We then set out to explore the substrate scope of aldehydes with diverse substituents (Scheme 2). A wide range of functional groups, such as OMe, F, Cl, OEt, and OAc, were well tolerated under the reaction conditions, which may serve as useful reaction handles for further elaborations. Due to crowding near the reaction center, *ortho*-substituted aldehydes demonstrated decreased reaction efficiency (**3fa** and **3ga**). As illustrated by **3ja**, the alkyne-containing aldehyde **1j** proved suitable substrate for the transformation. Substrates bearing pyridyl and thienyl moieties were successfully transformed into the desired amides, albeit in moderate yields (**3na** and **3oa**). Moreover, we examined the effect of substituents on the allyl moiety. Substitution of the allylic position was also accommodated, giving the expected products **3pa**−**ra** in good yields. The reaction of 2-(2-methylallyl)benzaldehyde (**1s**) took place efficiently to afford **3sa** in 77% yield, while only a trace amount of **3ta** was observed when 2-(2-phenylallyl)benzaldehyde (**1t**) was employed as the starting material. The formation of a relatively stable benzyl radical that is less prone to 1,5-HAT (see the proposed mechanism) may account for the failure of this reaction. Aldehyde **1v**, with an internal alkene, underwent this reaction smoothly and produced **3va** in a good yield. Remarkably, *α,β*-unsaturated aldehydes **1w** and **1x** were also amenable to this transformation, affording **3wa** and **3xa** in 71% and 79% yield, respectively. In contrast, both hex-5-enal (**1y**) and 2-vinylbenzaldehyde (**1z**) failed to provide the desired products under the identical reaction conditions. The structure of resultant *ε*-CF_3-substituted amide **3ra** was determined by the X-ray diffraction analysis.[16]

Meanwhile, the scope with respect to amines was also investigated, and the results are summarized in Scheme 3. First, secondary amines were surveyed under the standard reaction conditions. We were pleased to find that both cyclic and acyclic amines reacted with **1a** efficiently to afford the desired *ε*-CF_3-containing amides in high yields (**3ab**−**af**). Reaction of sterically demanding substrates **2g** and **2h** took place as well, albeit in somewhat reduced yields (**3ag** and **3ah**). In contrast, primary amines including *n*-$BuNH_2$ (**2k**) and $PhNH_2$ (**2l**) did not work for this reaction (not shown) due to the formation of imine byproducts.

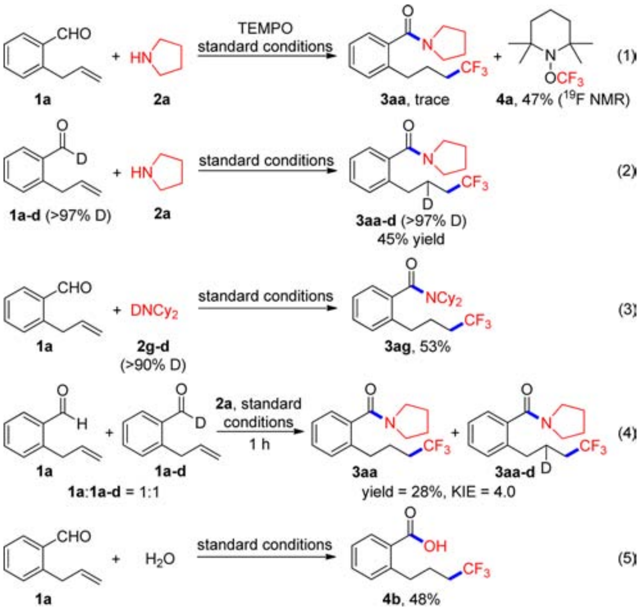
In order to obtain information on the reaction mechanism, the coupling of **1a** with **2a** was conducted in the presence of radical scavenger 2,2,6,6-tetramethylpiperidinooxy (TEMPO, 2 equiv). As a result, only a trace amount of **3aa** was observed, and instead, the TEMPO adduct **4a**[4c] was detected by ^{19}F

Scheme 3. Scope of Amines[a]



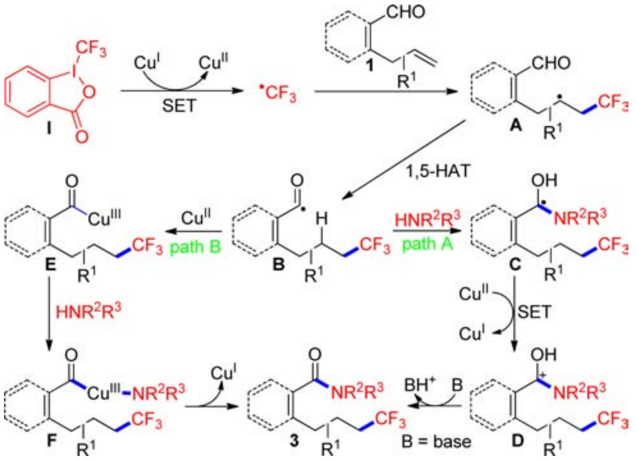
[a] Reaction conditions: **1a** (0.25 mmol), **2** (0.375 mmol), $CuSO_4$ (10 mol %), **I** (0.375 mmol), K_2CO_3 (0.375 mmol), DMF (2 mL), under N_2, 25 °C, 10 h. Yields of the isolated products are given. [b] Obtained as a 1.5:1 mixture of two rotamers. [c] Obtained as a 1:1 mixture of two rotamers.

NMR spectroscopy (eq 1). Running the reaction in the presence of electron-transfer scavenger 1,4-dinitrobenzene caused a dramatic drop of the yield (10%). Additionally, the coupling of **1a-d** with **2a** produced **3aa-d** with >97% deuterium incorporation, while that of **1a** and **2g-d** provided **3ag** in 53% yield (eqs 2 and 3), thus confirming the occurrence of a 1,5-HAT process. A mixture of substrates **1a** and **1a-d** in a 1:1 ratio was used to determine the intermolecular isotope effect, and consequently, a kinetic isotopic effect (KIE) value of 4.0 was observed (eq 4). This suggests that the aldehyde C−H bond breaking step may be the rate-determining step. In the presence of 2 equiv of H_2O, **4b** was obtained in 48% yield (eq 5), which means that the formation of an iminium intermediate is less likely for this Cu-catalyzed reaction.



In light of the above observations, a plausible mechanism depicted in Scheme 4 is proposed. In the first step, the Cu^I species, generated in situ from Cu^{II} via disproportionation,[17] undergoes the single-electron transfer (SET) with Togni's reagent (**I**) to afford the $^{\bullet}CF_3$ radical, which adds to the C−C double bond of **1** to deliver an α-CF_3-alkyl radical **A**. A 1,5-HAT then takes place, producing acyl radical **B**, which can be trapped by amines **2** to form a hemiaminal radical **C**.[18] Next, SET from radical **C** to Cu^{II} generates the cation intermediate **D**, accompanied by regenerating the Cu^I catalyst. Finally, the base-promoted deprotonation of **D** results in the formation of ε-CF_3-substituted amides **3** (Scheme 4, path A). An alternative pathway consisting of the generation of Cu^{III} species **E** via oxidation of Cu^{II} by the radical **B**,[19] transmetalation, and a subsequent reductive elimination cannot be excluded at the current stage (Scheme 4, path B).[20]

Scheme 4. Plausible Mechanism



In summary, we have developed a novel Cu-catalyzed trifluoromethylation of alkenes with redox-neutral remote amidation of aldehydes using Togni's reagent (**I**), giving a straightforward and a highly efficient access to ε-CF_3-substituted amides under very mild reaction conditions. A broad spectrum of functional groups, such as F, Cl, OMe, OEt, OAc, Ts, alkynyl, thienyl, and pyridyl groups, are well compatible with the current reaction. This finding represents a significant advance in the trifluoromethylation-initiated remote sp^2 C−H functionalization, which may be valuable for the one-pot synthesis of highly functionalized trifluoromethylated compounds. Further application and mechanistic investigation of this protocol are currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01113.

X-ray data for **3ra** (CIF)

Detailed experimental procedures and characterization data for all new compounds **3** and **4** (PDF)

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Notes

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(16) CCDC 1473753 (**3ra**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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