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Copper-Catalyzed Redox-Triggered Remote C—H Functionalization: Highly Selective Formation of C—CF_3 and C—O Bonds

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A Cu-catalyzed remote sp^3 C—H/unactivated alkenes functionalization reaction for the concomitant construction of C—CF_3 and C—O bonds was described. An 1,5-H radical transfer involving an sp^3 C—H bond adjacent to a nitrogen atom and an α-CF_3-alkyl radical intermediate derived from unactivated alkenes was observed and demonstrated to proceed via the radical process.

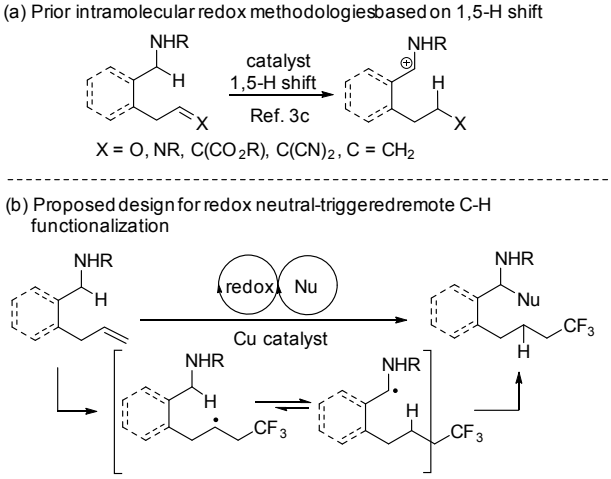
Keywords alkenes, radical trifluoromethylation, 1,5-H radical transfer, Togni's reagent

Introduction

The oxidative functionalization of sp^3 C—H bonds adjacent to a nitrogen atom without substrate prefunctionalization has been developed as a powerful and straightforward synthetic approach to nitrogen-containing compounds.[1,2] As a consequence of the oxidative character of these reactions, the use of an external oxidant is generally required.[2] Notably, redox-neutral process involving intramolecular hydride shift and further functionalization of α-position of certain nitrogen atoms has attracted considerable attention as it offers an appealing mechanistically complementary pathway in C—H activation chemistry.[3] Among the reported transformations, the hydride acceptors are mainly dominated by aldehydes, iminium ions, electron-deficient olefins, alkynes and allenes for the stabilization of the carbanions/heteroanions generated by the hydride shift (Scheme 1a).[3] However, the development of unactivated alkenes as hydride acceptors with concomitant alkene functionalization is still quite a challenging task due to the nature of diminished electrophilic character towards hydride compared to activated hydride acceptors, and its realization would improve the usefulness of the redox-neutral process in synthetic organic chemistry.

More recently, radical trifluoromethylation reactions of unactivated alkenes with trifluoromethylating reagents involving α-CF_3-alkyl radical intermediate have emerged as important synthetic tools for the synthesis of new potential pharmaceutical candidates.[4,5] In this context, we have also successfully developed direct difunctionalization of alkenes triggered by radical trifluoromethylation of unactivated alkenes, providing the most attractive strategy for the simultaneous formation of two vicinal chemical bonds, with concomitant formation of C—CF_3 bond and rings.[6] More recently, we have reported an effective approach to realize the remote asymmetric C—H bond functionalization of amide groups via intramolecular 1,5-HAT by inherently high-energy α-CF_3-alkyl radical *in situ*-generated from radical trifluoromethylation of alkenes, thereby enabling the assembly of functionalized chemical structures with remarkable precision and excellent functional-group tolerance via controlled activation of C—H bonds.[7] However, the cooperative catalyst composed of CuCN and chiral Brønsted acid is required to realize such reaction, in which Brønsted acid not only plays a vital role

Scheme 1 Transition-metal-catalyzed redox-neutral-triggered remote C—H functionalization



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in controlling the stereoselectivity, but also acts as an acid to successfully activate Togni's reagent together with copper catalyst.[7a] These results have recently prompted us to envision that a redox-neutral process involving intramolecular hydrogen radical shift and further remote C—H functionalization of α-position of certain nitrogen atoms using the inherent high reactivity of α-CF_3-alkyl radical intermediate derived from unactivated alkenes might be realized in the presence of simple transition metal catalysis (Scheme 1b). If this approach is successful, this would include the highly selective and concomitant formation of two new C—CF_3 and C—O bonds using radical processes via remote sp^3 C—H functionalization, and a convenient and economical route for facile access to trifluoromethyl-containing *N*,*O*-aminal motifs, which would be of particular interest as *N*,*O*-aminals are prevalent in natural products.[8] Herein, we describe a successful example of redox-neutral reaction through a C—CF_3 formation/1,5-H radical shift/remote functionalization of sp^3 C—H bond adjacent to amide tandem process in the presence of simple Cu salt.

Experimental

General information

All reactions were carried out under argon (Ar) atmosphere using Schlenk techniques with magnetic stirring. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. CuI was purchased from Aldrich, ethyl acetate (EA) was purchased anhydrous from commercial sources and transferred under an argon atmosphere. All alcohols are commercial available and were purified under standard methods or dried over molecular sieves (4 Å) before use. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates. Flash column chromatography was performed using Tsingdao silica gel (60, particle size 0.040—0.063 mm). Visualization on TLC was achieved by use of UV light (254 nm) or iodine. NMR spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR and 376 MHz for ^{19}F NMR in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. ^{19}F NMR spectra were recorded on a Bruker DPX 400 MHz spectrometer [$CFCl_3$ as an external reference (δ 0)]. HMRS were obtained on a Bruker Apex IV RTMS.

Typical procedures for Cu-catalyzed tandem reactions of *N*,*O*-aminals

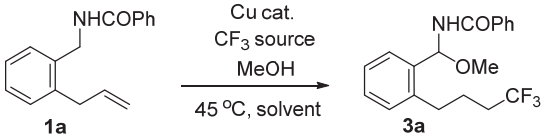
To a flame-dried Schlenk tube equipped with a magnetic stir bar were added **1** (0.2 mmol, 1.0 equiv.), Togni's reagent **2a** (88.5 mg, 0.28 mmol) and CuI (7.6 mg, 0.04 mmol). The tube was evacuated and backfilled with Ar three times, and then alcohol (32.5 μL, 0.8 mmol) and solvent (EtOAc, 1.0 mL) were added via syringe. The tube was stirred at 45 ℃. After reaction completed (monitored by TLC), the reaction solution was concentrated *in vacuo* and the crude residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 10/1 — 20/1) to give the corresponding *N*,*O*-aminal products.

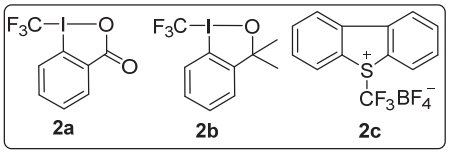
Results and Discussion

To validate the feasibility of the proposed redox-neutral processes, we selected *N*-(2-allylbenzyl)benzamide **1a** as the model substrate for the optimization of reaction conditions. As such, we initially examined the reaction of **1a** with 4 equiv. of MeOH as nucleophile in the presence of commercially available Togni's reagent (**2a**) (1.2 equiv.)[9] with CuCl as the catalyst. To our delight, we found that such system could activate this reaction in DCE at 45 ℃ to form the desired product **3a**, albeit with only 25% yield (Table 1, Entry 1). Encouraged by this result, we then screened a range of copper(I) and copper(II) catalysts, and found that CuI was most beneficial for the reaction to give the corresponding product in 72% yields via a selective 1,5-hydride shift/C—H functionalization tandem process (Entries 1—6). Next, the screening of solvents revealed EtOAc as being optimal to give **2a** in 93% yield (Entries 7—12), suggesting a significant solvent effect for this reaction. Examination of other CF_3 reagent from Togni's reagent **2a** to **2b** or Umemoto's reagent **2c** revealed that **2a** was the best for the reaction (Entries 13, 14). Next, the molar ratio of the reactants was screened, revealing the presence of an optimum ratio of **1a** to MeOH (**1a**∶MeOH=1∶4) in this system (Entry 12), whereas decreasing or increasing this ratio all led to inferior results (Entries 15—17). A control experiment revealed that no desired product was observed in the absence of copper catalyst (Entry 18), thus strongly supporting that copper catalyst is essential for this reaction.

With the optimal reaction conditions in hand, we set out to explore the scope of this protocol with respect to other *N*-(2-allylbenzyl)amide substrates. As shown in Table 2, the functional groups, such as methyl, methoxy, phenyl, chloro and NO_2 groups at the *para* position of the benzene ring at the α position of carbonyl group, were well-tolerated, giving the corresponding products **3b—3h** in good to excellent yields. Notably, the introduction of a methoxy group at the *para*-, *meta*-, or *ortho*-position in the benzene ring at the α position of carbonyl group did not affect the product yield either. In addition, this reaction shows excellent compatibility with naphtyl- and heteroaromatic-, and alkyl groups at the α position of carbonyl group. Furthermore, investigations into the effect of substitution on the phenyl ring of the substrates revealed that the reaction is also efficient for substrates with functional groups (R=Me) at different positions, furnishing products **3l—3m** with 53% and 61% yields, respectively. It is noteworthy that geminal-disubstituted alkene **1n** was also an excellent substrate, giving the product **3n** as a mixture of two dia-

Table 1 Screening results of reaction conditions[a]





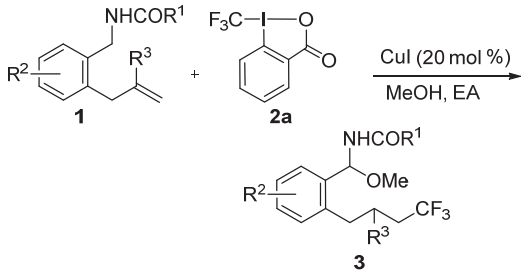
Entry	Catalyst	Solvent	Time/h	Yield[b]/%
1	CuCl	DCE	22	25
2	CuI	DCE	22	72
3	CuBr	DCE	22	29
4	CuOAc	DCE	22	53
5	CuTc	DCE	22	24
6	$Cu(OTf)_2$	DCE	22	10
7	CuI	MeOH	16	55
8	CuI	DCM	16	75
9	CuI	1,4-Dioxane	16	62
10	CuI	CH_3CN	16	53
11	CuI	THF	16	25
12	CuI	EtOAc	16	93
13[c]	CuI	EtOAc	16	57
14[d]	CuI	EtOAc	16	—[e]
15[f]	CuI	EtOAc	16	65
16[g]	CuI	EtOAc	16	72
17[h]	CuI	EtOAc	16	76
18	—[i]	EtOAc	16	—[e]

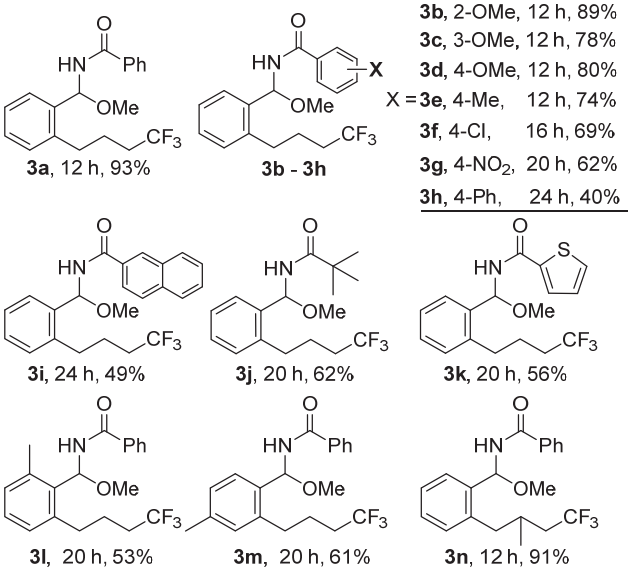
[a] Reaction conditions: **1a** (0.05 mmol), **2a** (1.2 equiv.), MeOH (4.0 equiv.), catalyst (20 mol%), solvent (0.5 mL), 45 ℃, Ar. [b] Determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. [c] Togni's reagent **2b** was used. [d] Umemoto's reagent **2c** was used. [e] Product was not detected. [f] 2.0 equiv. of MeOH was used. [g] 3.0 equiv. of MeOH was used. [h] 5.0 equiv. of MeOH was used. [i] no catalyst. CuTc＝copper(I)-thiophene-2-carboxylate.

stereomers (1∶1 *dr*) in 91% yield.

With these results, we next turned our attention to the redox-neutral reactions of **1a** with other alcohols using our efficient catalytic system. As a result, the use of primary alcohols like ethanol and 1-butanol provides excellent yields in all cases (Table 3, Entries 2, 3). Notably, the catalytic system can well tolerate other reactive groups, such as benzyl, and methoxy groups in the alcohol substrates (Entries 4 and 5), although those can be easily oxidized under oxidants in the presence of copper catalyst.[2] Secondary alcohols, such as isopropanol, cyclic alcohols are also applicable to give the products **3s** and **3t** in 88% and 76% yields, respectively (Entries 6 and 7). It is noteworthy that relatively sterically hindered alcohols, such as *t*-butyl alcohol and

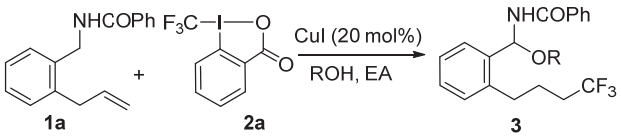
Table 2 Reaction scope for *N*-(2-allylbenzyl)amide[a,b]

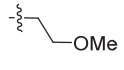




[a] Reaction conditions: **1** (0.2 mmol), **2a** (1.2 equiv.), MeOH (4.0 equiv.), CuI (20 mol %), EA (1.0 mL), 45 ℃, Ar. [b] Isolated yield.

Table 3 Reaction scope for alcohols[a,b]



Entry	R	Time/h	Yield[b]/%
1	Me	12	**3a**, 93
2	Et	12	**3o**, 94
3	*n*-Bu	12	**3p**, 80
4	Bn	12	**3q**, 70
5		12	**3r**, 93
6	*i*-Pr	16	**3s**, 88
7		18	**3t**, 76
8	*t*-Bu	18	**3u**, 66
9		12	**3v**, 68

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (1.2 equiv.), ROH (4.0 equiv.), CuI (20 mol %), EA (1.0 mL), 45 ℃, Ar. [b] Isolated yield.

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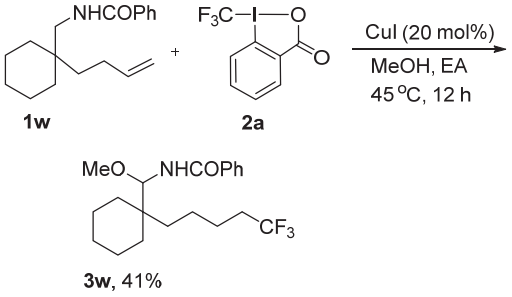
2-methylbutan-2-ol, were also found to be suitable partners to give the corresponding products **3u** and **3v** in good yields (Entries 8 and 9).

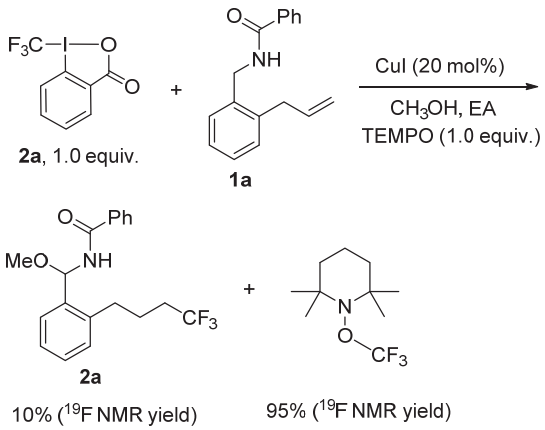
It is interesting to note that the redox-neutral protocol for the synthesis of CF_3-containing *N*,*O*-aminals could be extended to other aliphatic compound as viable substrate for this reaction. Thus, our preliminary result showed that, under the conditions identical to those of tandem reaction detailed above, the reaction of *N*-((1-(but-3-en-1-yl)cyclohexyl)methyl)benzamide (**1w**) gave trifluoromethylated product **3w** in 41% yield (eq. 1). This result indicates that the α-functionalization of the amine was not severely affected by switching the nature of the benzylic carbon to inactive methylene group.



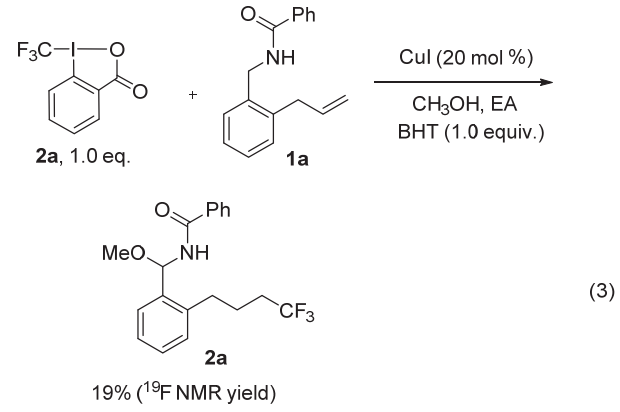
(1)

To provide more insights into the mechanism of the current reaction, a series of control experiments were conducted. First, the model reaction was performed in the presence of radical scavengers such as 2,6-di-*tert*-butyl-4-methylphenol (BHT) or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) under the standard conditions, and a significant drop in yield was observed (Eqs. 2 and 3). Notably, for the reaction in the presence of TEMPO, the TEMPO-CF_3 adduct was formed in 95% yield as estimated by ^{19}F NMR analysis. These results revealed that CF_3 radical is likely involved as the reactive species under the current reaction conditions.

On the basis of these experimental results and literature precedence,[5,7] the proposed reaction mechanism for the current system is depicted in Scheme 2. First, a CF_3 radical is generated from the reaction of **2a** with Cu(I), and then the radical addition to the alkene affords



(2)



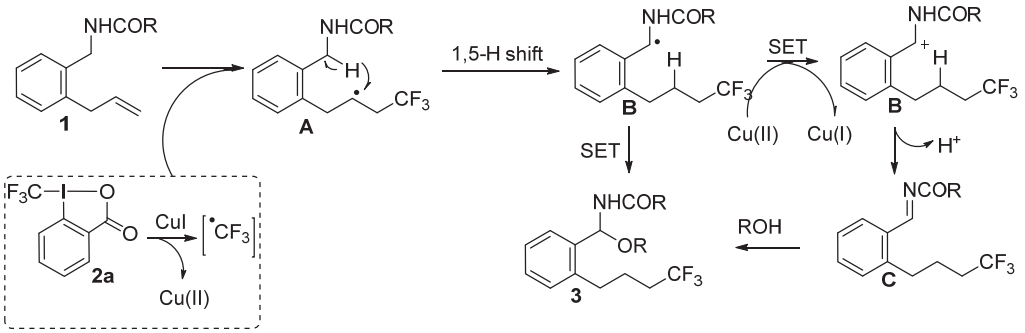
(3)

a nascent α-CF_3-alkyl radical intermediate **A**.[5] Once formed, this inherently high-energy radical **A** would abstract a proximal hydrogen atom[7a] adjacent to the nitrogen atom of amide to generate a lower energy alkyl radical **B**, followed by single-electron oxidation with Cu(II), to afford imine intermediate **C**. Finally, the attack of O nucleophiles to the imine intermediate furnishes final product **3**. Thus, O nucleophiles are substituted at the sp^3 carbon adjacent to the nitrogen atom, with concomitant generation of a C—CF_3 bond from unactivated alkenes.

Conclusions

In summary, we have presented here the successful

Scheme 2 Proposed mechanism for the current reaction system



example of a redox-neutral tandem process to realize highly selective and concomitant formation of two new C—CF_3 and C—O bonds *via* remote functionalization of sp^3 C—H bond adjacent to amide in the presence of simple Cu catalyst without any additive. This study led us to discover a 1,5-H radical transfer that involves an sp^3 C—H bond adjacent to a nitrogen atom and an α-CF_3-alkyl radical intermediate derived from unactivated alkenes. This protocol provides a highly efficient method for the synthesis of trifluoromethylated *N,O*-aminals with good to excellent yields and with excellent regio- and chemoselectivities as well as a very broad substrate scope. This operationally simple procedure provides a more straightforward alternative to the existing transition-metal-catalyzed trifluoromethylation methods.

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