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Copper-Catalyzed Three-Component Azidotrifluoromethylation/Difunctionalization of Alkenes

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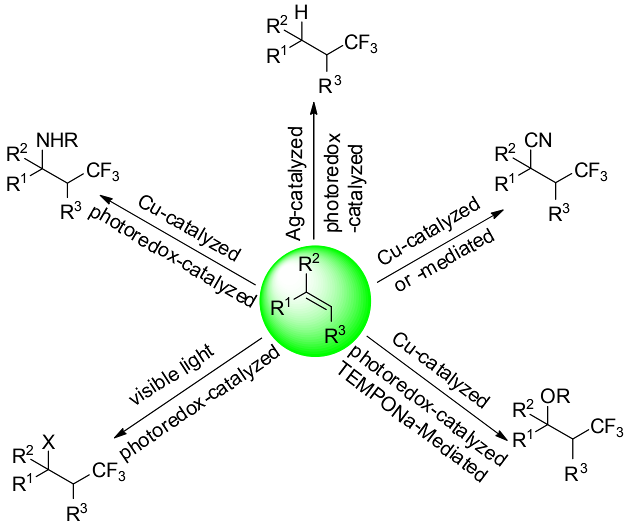
A novel three-component strategy for the azidotrifluoromethylation of alkenes has been presented here. The reaction proceeded smoothly under gentle temperature and gave the bifunctional olefins in high yields. Furthermore, 1,3-dipolar reactions between azide-containing products and phenylacetylene revealed great potential in molecular modification by using this method.

Keywords azidotrifluoromethylation, alkenes, azide-containing

Introduction

Transition-metal-catalyzed alkene difunctionalization has been proved to be a powerful strategy for constructing carbon-carbon/carbon-heteroatom bonds in a single step and has been widely used for the preparation of functionalized organic compounds.[1] Compounds containing a trifluoromethyl group, especially heterocycles played an important role as pharmaceuticals, agrochemicals and functional materials due to their significantly increased lipophilicity, metabolic stability, membrane permeability and bioavailability.[2,3] Thus, much attention has been given to the introduction of trifluoromethyl group into organic molecules to improve their properties.[4,5] Indeed, a series of transition-metal-catalyzed difunctionalization of alkenes reactions have been reported, in particular reactions involving trifluoromethyl group, such as halotrifluoromethylation,[6] carbotrifluoromethylation,[7] oxytrifluoromethylation,[8] hydrotrifluoromethylation,[9] and aminotrifluoromethylation.[10] However, many traditional approaches to the generation of these CF_3-containing compounds based on the difunctionalization strategy were still limited to intramolecular process[11] or required photoredox catalytic system.[12] Seeking transition-metal-catalyzed multicomponent reactions is a highly attractive and sustainable approach for introducing the trifluoromethyl functionality in synthetic chemistry. To meet this demand, Loh and Qing groups,[13] independently, reported intermolecular Cu-catalyzed oxytrifluoromethylation of alkenes by using Togni's reagent and sodium trifluoromethane sulfinate. In 2013, Szabó and Liang group[14] reported the three-component cyanotrifluoromethylation of alkenes to construct two vicinal chemical bonds under copper catalysis (Scheme 1).

Scheme 1 Intermolecular difunctionalization of alkenes



Nitrogen-containing compounds, which were found in many bioactive chemicals and drug molecules, have been also studied extensively, and numerous synthetic methods have been developed to construct carbon-nitrogen bonds.[15] As one of the most important nitrogen sources, organic azides were widely applied in synthetic chemistry.[16] For instance, they could be reduced to amines under various reducing agents. The click chemistry, in particular the copper-catalyzed azide-alkyne [3+2] cycloaddition (CuAAC) reaction has attracted interests of many chemists. On account of our research in alkene functionalization, we envisioned that the addition

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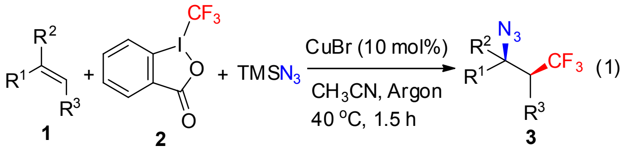
of azide group and trifluoromethyl group across a double bond could be achieved in one step. Herein, we reported a novel three-component azidotrifluoromethylation of alkenes with Togni's reagent (**2**)[17] and trimethylsilyl azide ($TMSN_3$) by copper catalysis under mild conditions (Eq. 1). This methodology allows a wide range of substrate scope to access azidotrifluoromethylation products. It should be indicated that, when we finished our work, Liu and co-workers[18] reported the trifluoromethylazidation of alkenes.



(1)

Experimental

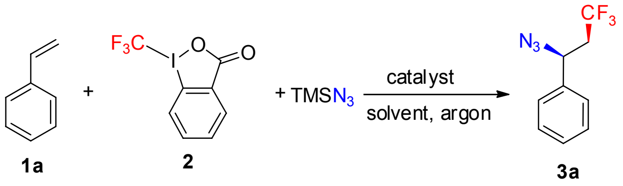
An oven-dried tube was charged with Togni's reagent **2a** (75.8 mg, 0.24 mmol) and CuBr (2.86 mg, 0.02 mmol). The tube was evacuated and backfilled with argon (repeated three times). Then, $TMSN_3$ (0.5 mmol) and alkenes (0.2 mmol) dissolved in CH_3CN (2 mL) were added into the tube. The reaction mixture was stirred at 40 ℃ for 1.5 h and extracted with DCM. The combined corganic layers were washed with saturated brine, dried over Na_2SO_4, concentrated in vacuum (Note: the control of temperature and pressure is very important) and purified by flash column chromatography (silica gel) to afford the product.

Azide **3** (0.1 mmol) and phenylacetylene (0.25 mmol) was suspended in a mixture of *t*-BuOH (0.5 mL) and water (0.5 mL) in a Schlenk tube with a magnetic bar. Then $CuSO_4$ (0.01 mmol) and sodium ascorbate (0.01 mmol) were added to the mixture. The resulting material was stirred for 4 h at 70 ℃ before it was diluted with EtOAc. Water (10 mL) was added and the mixture was extracted with EtOAc. The organic layer was combined and washed with brine (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was purified by column chromatography to give **4**.

Results and Discussion

To probe the feasibility of our envisioned strategy, we started the investigation by exploring the reaction of styrene **1a** with Togni's reagent and $TMSN_3$ in the presence of 10 mol% $Cu(OTf)_2$ at 40 ℃ under argon conditions. Unfortunately, only trace amount of the desired product **3a** was obtained in DMF (Table 1, Entry 1). However, screening of the solvent showed that CH_3CN was effective and the product **3a** was obtained in 25% yield (Table 1, Entry 3). Inspired by this finding, further screening of different copper catalysts exhibited that CuBr was the best and increased the yield to 86% (Table 1, Entry 10). The reaction time could be decreased to 1.5 h with no influence on the reaction outcome (Table 1, Entry 13). We also tested NaN_3 as the azide source and the reaction proceeded smoothly as well, leading to the desired azidotrifluoromethylation product in 74% yield. The reaction did not occur without copper catalyst (Table 1, Entry 15). Therefore, heating the reactants at 40 ℃ for 1.5 h and using 10 mol% CuBr as the catalyst under argon atmosphere were chosen as the optimized reaction conditions.[19]

Table 1 Screening of reaction conditions[a]



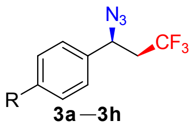
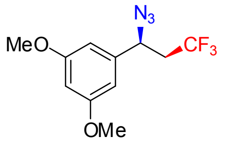
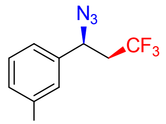
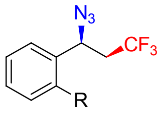
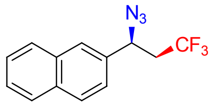
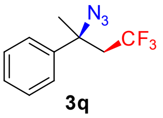
Entry	Catalyst	Solvent	*T*/h	Yield[b]/%
1	$Cu(OTf)_2$	DMF	3.0	Trace
2	$Cu(OTf)_2$	DMSO	3.0	Trace
3	$Cu(OTf)_2$	CH_3CN	3.0	25
4	$Cu(OTf)_2$	DCE	3.0	Trace
5	$Cu(OTf)_2$	1,4-Dioxane	3.0	Trace
6	$Cu(OAc)_2$	CH_3CN	3.0	75
7	CuF_2	CH_3CN	3.0	76
8	$Cu(MeCN)_4PF_6$	CH_3CN	3.0	71
9	CuCl	CH_3CN	3.0	84
10	CuBr	CH_3CN	3.0	86
11	CuI	CH_3CN	3.0	78
12	CuBr	CH_3CN	2.0	85
13	**CuBr**	**CH_3CN**	**1.5**	**86**
14[c]	CuBr	CH_3CN	1.5	74
15[d]	—	CH_3CN	1.5	NR

[a] Reaction conditions: **1a** (0.2 mmol), Togni's reagent (0.24 mmol), $TMSN_3$ (0.5 mmol), copper catalyst, solvent (2.0 mL), 40 ℃, under argon. [b] Isolated yield. [c] NaN_3 was used. [d] Without copper catalyst.

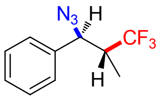
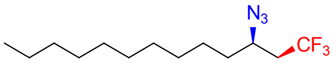
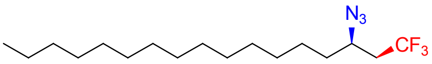
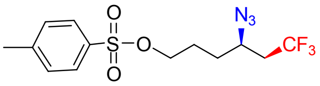
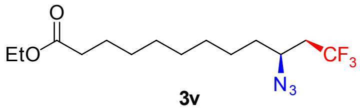
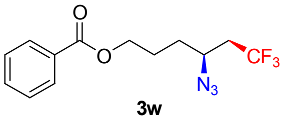
Under the optimal reaction conditions, the scope of alkenes was investigated. As demonstrated in Table 2, a series of alkenes bearing both electron-donating and electron-withdrawing groups at the aromatic rings were converted into the corresponding difunctionalization products in good to excellent yields. Naphthalenes bearing vinyl groups at 2-position furnished the desired product **3p** in 87%. Notably, *α*-methylstyrene was still very effective in our catalytic system, which gave the difunctionalization product in high yield. The hindered 1,2-disubstituted alkene **1r** reacted smoothly, gaving a mixture of diastereoisomers (*d.r.*=3.3∶1) in 67%. The success of azidotrifluoromethylation of alkenes encouraged us to further investigate the scope of this reaction. We found that the linear olefins were also well tolerated, with the corresponding product obtained in good yields.

For simple alkenes **1s** and **1t**, the desired products **3s** and **3t** were afforded in 76% and 77% yields, respectively. Terminal olefins bearing ester (**1v**) and benzoate (**1w**) groups reacted equally well to give **3v** and **3w** in high yields. To verify the synthetic usefulness of this process, we derivatized some of our azidotrifluoromethylation products in click reaction (Table 3). The cycloaddition occurred when the azidotrifluoromethylation compounds reacted with phenylacetylene in the presence of $CuSO_4$ (10 mol%) and sodium ascorbate (10 mol%) at 70 ℃ for 4 h, the yields of CF_3-containing 1,2,3-triazoles were excellent. In addition, the azidotrifluoromethylation product **3a** was efficiently reduced to the corresponding amine **5** in the presence of PPh_3 or $NaBH_4$ as the reductant (Scheme 1). All of these illustrated the potential applications in discoveries of lead compounds, synthesis of biologically active compounds, and other useful CF_3-containing heterocycles.

Table 2 Substrate scope of the azidotrifluoromethylation of alkenes[a]

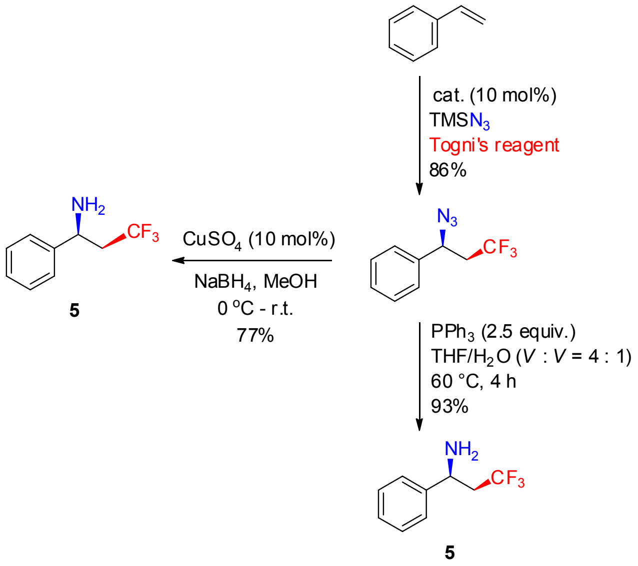
Compound 3		Yield/%
 3a—3h	**3a** R=H	86
	3b R=Me	88
	3c R=OMe	89
	3d R=*t*-Bu	91
	3e R=OCOMe	85
	3f R=Ph	83
	3g R=F	82
	3h R=Cl	79
 3i		81
 3j—3m	**3j** R=Me	88
	3k R=OMe	90
	3l R=Cl	79
	3m R=Br	73
 3n, 3o	**3n** R=Me	84
	3o R=Cl	74
 3p		87
 3q		80

Continued

Compound 3		Yield/%
 3r (*d.r.* = 3.3 : 1)[b]		67
 3s		76
 3t		77
 3u		61
 3v		86
 3w		81

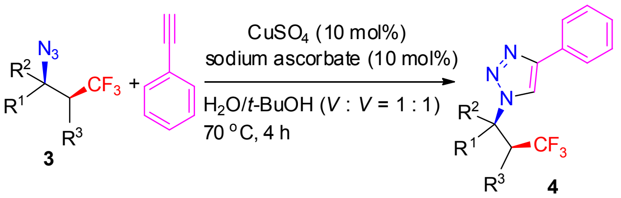
[a] Reaction conditions: **1** (0.2 mmol), Togni's reagent (0.24 mmol), $TMSN_3$ (0.5 mmol), CuBr (0.02 mmol), CH_3CN (2 mL), 40 ℃, 1.5 h, under argon, isolated yield. [b] The ratio of diastereomers was determined by crude ^{19}F NMR. Structure of the major diastereomer is shown.

Scheme 1 Reduction of the azidotrifluoromethylation products

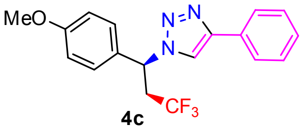
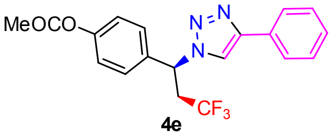
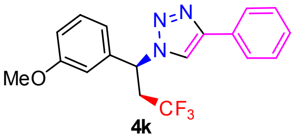
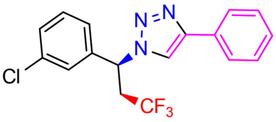
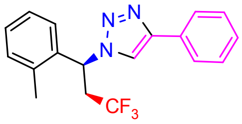
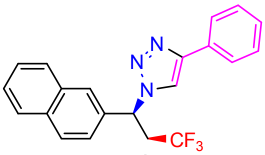
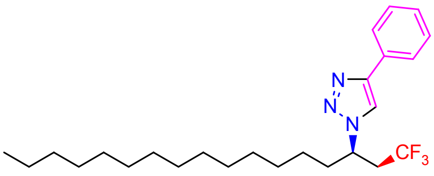
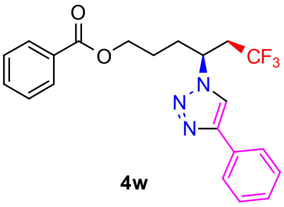


To elucidate the mechanism of the above reactions, a stoichiometric amount of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was used in the reaction. A signifi-

Table 3 Cycloaddition of phenylacetylene to azidotrifluoromethylation products[a]

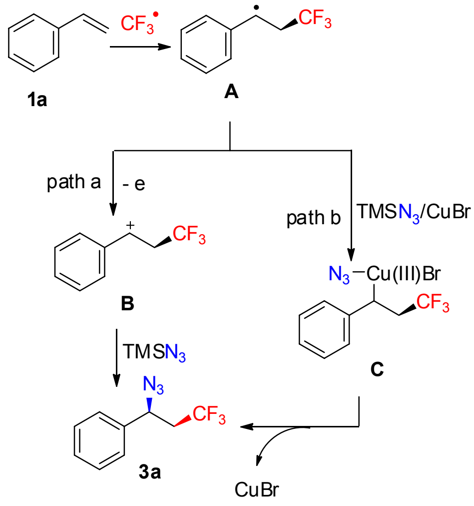


3 + → **4**

Compound **4**	Yield/%
 **4c**	92
 **4e**	85
 **4k**	85
 **4l**	93
 **4n**	86
 **4p**	88
 **4t**	86
 **4w**	81

cant drop in yield (39%) was obtained and the TEMPO-CF_3 adduct was detected in 49% using GC-MS, indicating that the present reaction included a radical pathway. On the basis of the above result and previous studies,[20] the mechanism for the azidotrifluoromethylation process is illustrated in Scheme 2. Togni's reagent **2** was activated by copper catalysis, leading to the CF_3-containing radical species. Then, a single-eletron oxidation **B** of a radical intermediate was formed from the radical intermediate **A**, which was further trapped by $TMSN_3$ to led to the difunctionalization product **3a** (Path a). The radical intermediate **A** reacted with the copper species and $TMSN_3$ to afford the copper(III) azide complex **C**. Subsequent elimination of the copper(III) azide complex **C** would afford the desired azidotrifluoromethylation product **3a** (Path b).

Scheme 2 Proposed reaction mechanism



Conclusions

In conclusion, we have developed copper-catalyzed three-component azidotrifluoromethylation of alkenes. The mild reaction conditions allow a wide range of substrate scope to achieve the difunctionalization. Accompanied with the subsequent transformation, such as CuAAC reaction and reduction of azide, it would be an excellent strategy in olefin modification. Further investigations on the scope and synthetic applications of this reaction are currently underway in our group.

Acknowledgement

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