VIP Trifluoromethylation Very Important Paper

DOI: 10.1002/anie.201307245

Directing-Group-Assisted Copper-Catalyzed Olefinic Trifluoromethylation of Electron-Deficient Alkenes**

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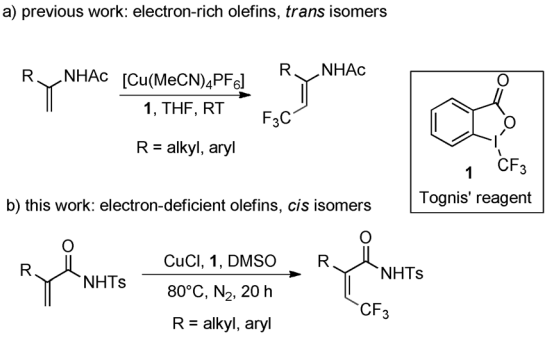
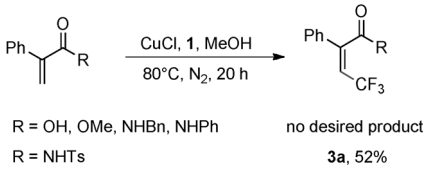
The synthesis of trifluoromethylated organic molecules is highly sought after because of the potential of these molecules in the pharmaceutical and agrochemical industry, materials science etc., owing to the unique effect the CF_3 modification has on organic molecules.[1] Accordingly, C–CF_3 bond-forming reactions have drawn much attention from the synthetic community. The development of effective and reliable methods for the easy introduction of a CF_3 group to a vast variety of synthetically useful molecules is highly desirable.[2] In this regard, transition-metal-catalyzed methods were appealing, because a variety of simple molecules, especially starting materials that are not prefunctionalized, can be transformed, which is advantageous from the viewpoint of green chemistry and sustainability.[3] In recent years, tremendous efforts have been made toward the formation of C–CF_3 bonds from hydrocarbon counterparts, and much progress has already been achieved. Specifically, Yu and co-workers have reported elegant solutions for the direct trifluoromethylation of aryl C–H bonds using a directing-group-assisted activation of *ortho* C–H bonds.[4] The final reductive elimination from the Pd^{IV} intermediate was proposed to accomplish the formation of aryl C–CF_3 bonds.[5] Recently, the groups of Buchwald, Wang, and Liu have independently explored the copper-catalyzed allylic trifluoromethylation of simple alkenes using electrophilic trifluoromethylation reagents, such as Togni's and Umemoto's reagents.[6] In addition, Qing and co-workers have demonstrated the copper-catalyzed oxidative trifluoromethylation of heteroarenes and terminal alkynes.[7] The groups of Sanford[8] and Brase[9] developed the silver-mediated trifluoromethylation of arenes through a radical process. While much progress has been made in the area of transition-metal-catalyzed aryl C–CF_3 and alkyl C–CF_3 bond formations, the trifluoromethylation of alkenes, especially of electron-deficient ones, has been relatively unsuccessful, thus proving to be a formidable challenge.[10] In continuation of our interest in olefin functionalization[11] and our recently disclosed olefinic trifluoromethylation of enamides (Scheme 1 a),[12] we herein report the C–H trifluoromethylation of electron-deficient alkenes by taking advantage of neighboring directing groups (Scheme 1 b).



Scheme 1. Copper-catalyzed olefinic trifluoromethylation. DMSO = dimethyl sulfoxide, Ts = 4-toluenesulfonyl.

The commonly accepted reactivity profile of electrophilic trifluoromethylation reagents, such as Togni's and Umemoto's reagents, is dichotomous, as they can react either as CF_3 radicals or cation donors. In the case of electron-deficient alkenes, the trifluoromethylation through electrophilic addition and hydrogen elimination is believed to be of little feasibility. However, we envisioned two other possibilities to realize this transformation: a sequence of directing-group-assisted C–H activation and reductive elimination, and another following a radical-addition pathway.

The ubiquity of acrylates in synthetic organic chemistry and the ease of their modification led us to select α-phenyl acrylate derivatives as templates for the direct incorporation of the CF_3 functionality. A systematic screening of the directing group was conducted with CuCl as catalyst, MeOH as solvent, and the Togni reagent (**1**) as electrophilic trifluoromethylation reagent (Scheme 2). While no desired product could be detected using acid, ester, benzyl amide, and phenyl amide as directing groups, the corresponding olefinic trifluoromethylation product was isolated in encouraging



Scheme 2. Directing group screening.

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[**] We gratefully acknowledge the USTC Research Fund, the Nanyang Technological University, and the Singapore Ministry of Education Academic Research Fund (ETRP 1002 111, MOE2010-T2-2-067, and MOE 2011-T2-1-013) for the funding of this research. We also thank Dr. Y. X. Li for support with X-ray analyses.

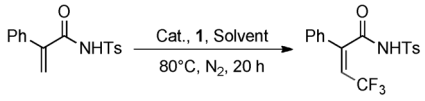
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201307245.

52% yield simply by employing a Ts-protected imide as the directing group, thus highlighting the importance of the acidity of the amide moiety in this olefinic C–CF_3 bond formation. In sharp contrast to the olefinic trifluoromethylation of enamides, this reaction occurs selectively in the *cis* position with respect to the Ts-protected imide group, thus indicating the possible involvement of this directing group in the formation of the C–CF_3 bond. The structure of **3a** was unambiguously confirmed by single-crystal X-ray diffraction analysis.[13]

The optimization of the reaction conditions was carried out with 2-phenyl-*N*-tosylacrylamide (**2a**) as the model substrate. Initially, various copper salts were tested with methanol as solvent in the hope to increase the efficiency of the reaction. Cu^I catalysts such as CuBr, CuI, and CuOAc catalyzed the reaction, but produced the desired product in relatively low yield compared with the use of CuCl (Table 1, entries 2–4). The cationic Cu^I analogue $[Cu(MeCN)_4PF_6]$ was not suitable as reaction catalyst, which is in sharp contrast to the olefinic trifluoromethylation of enamides (Table 1, entry 5). Pleasingly, the yield of the reaction could be improved to 65% when Cu_2O was employed as catalyst (Table 1, entry 6). In contrast, the use of $Cu(OAc)_2$ as catalyst did not improve the yield (Table 1, entry 7). We noted that in reactions with methanol as the solvent, $TsNH_2$ could be detected in the crude mixture. In order to obviate unproductive reaction pathways and to further improve the yield, we therefore examined a series of solvents. Disappointingly, when solvents such as *t*BuOH, HFIP, MeCN, THF, toluene, and DCE were used instead of MeOH, trace amounts or even no desired product was obtained, thus highlighting the importance of the solvent for the success of this olefinic trifluoromethylation (Table 1, entries 8–13). Much to our surprise, the reaction efficiency dramatically improved when polar aprotic solvents were employed. Among all the solvents examined, DMSO proved to be the best choice, affording product **3a** in 83% yield (Table 1, entry 14). Interestingly, the yield of the reaction marginally improved to 85% with the use of CuCl as the catalyst (Table 1, entry 16). We reasoned that the excellent results with DMSO as solvent may, to a large extent, be due to the fact that it acts as an effective ligand, stabilizing the reaction intermediate in the catalytic cycle. Expectedly, no desired product was obtained in the absence of a copper catalyst (Table 1, entry 17).

With the optimized reaction conditions in hand, the scope of the reaction was investigated (Scheme 3). In general, the reaction tolerated a wide variety of substrates with both electron-donating and electron-withdrawing substituents to produce the desired trifluoromethylation products in moder-

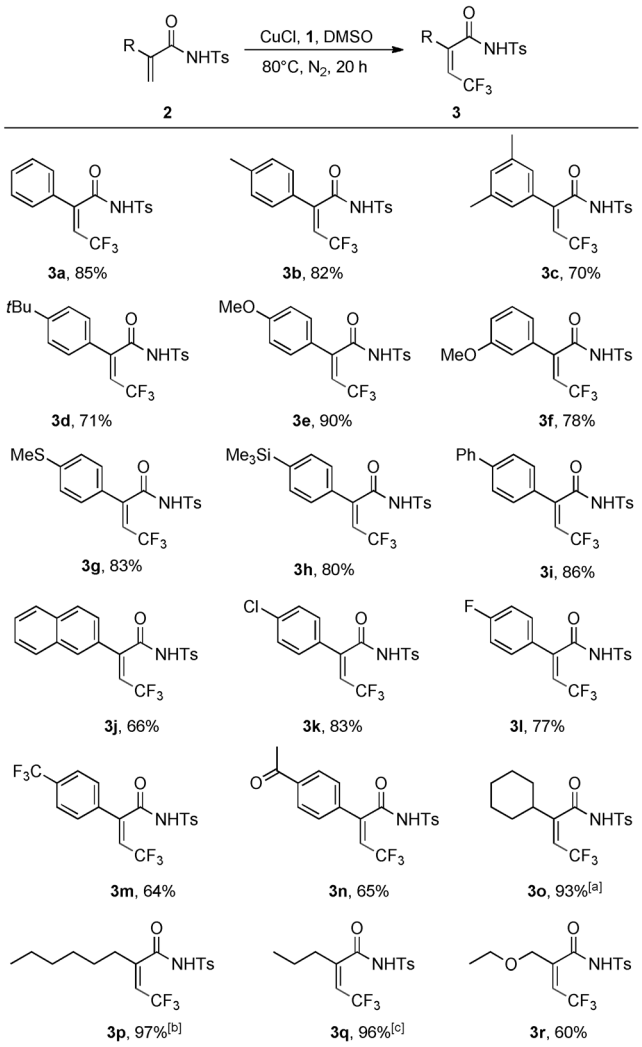
Table 1: Optimization of reaction conditions.[a]



2a **3a**

Entry	Catalyst	Solvent	Yield [%][b]
1	CuCl	MeOH	52
2	CuBr	MeOH	40
3	CuI	MeOH	48
4	CuOAc	MeOH	46
5	$[Cu(MeCN)_4PF_6]$	MeOH	12
6	Cu_2O	MeOH	65
7	$Cu(OAc)_2$	MeOH	38
8	Cu_2O	*t*BuOH	trace
9	Cu_2O	HFIP	trace
10	Cu_2O	MeCN	–
11	Cu_2O	THF	–
12	Cu_2O	toluene	trace
13	Cu_2O	DCE	–
14	Cu_2O	DMSO	83
15	Cu_2O	DMF	78
16	CuCl	DMSO	85
17	–	DMSO	–

[a] Reaction conditions: **2a** (0.1 mmol), **1** (0.12 mmol), catalyst (0.01 mmol), solvent (0.5 mL), 80°C, 20 h. [b] Yields of isolated products are given. DCE = dichloroethane, DMF = *N*,*N*-dimethylformamide, HFIP = hexafluoroisopropanol.

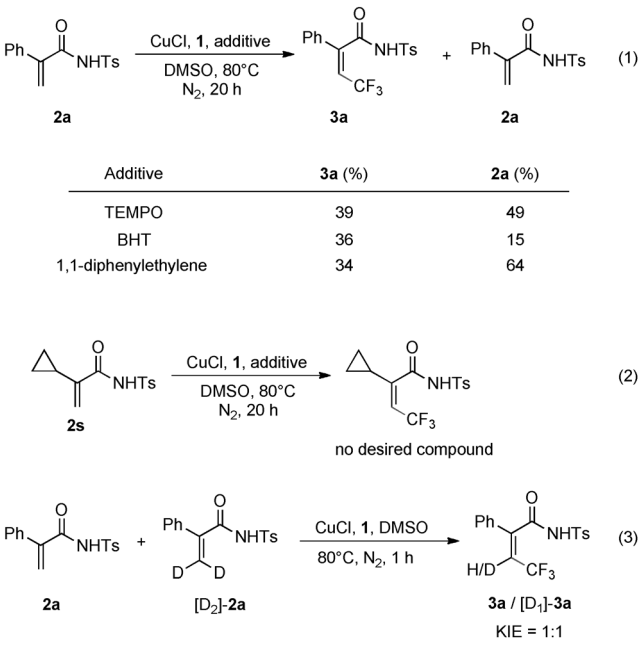


Scheme 3. Reaction scope of acrylate derivatives. Reaction conditions: **2** (0.1 mmol), **1** (0.12 mmol), CuCl (0.01 mmol), DMSO (0.5 mL), 80°C, 20 h. Yields of isolated products are given. [a] O:A = 8.3:1. [b] O:A = 5.6:1. [c] O:A = 5.3:1. O:A = olefinic versus allylic trifluoromethylation.

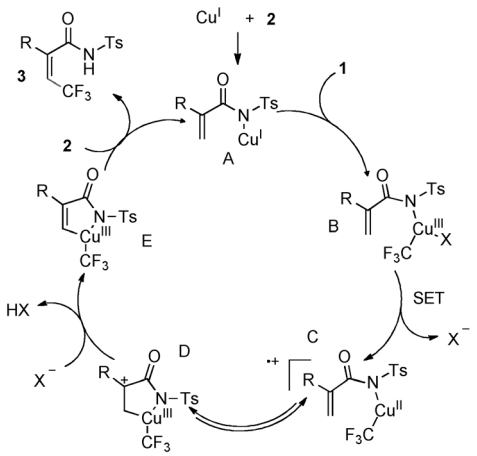
ate to excellent yields. α-Aryl acrylate derivatives with electron-donating groups were good substrates and afforded the desired products (**3b**–**3h**) in high yields, especially in the case of *p*-OMe-substituted substrate **2e**, which was transformed to the corresponding product **3e** in 90% yield. It is noteworthy that sulfur-containing compounds (e.g. **2g**) are compatible with this reaction and do not have a deleterious effect originating from catalyst deactivation. The reaction of biphenyl substrate **2i** was also highly effective, delivering product **3i** in 86% yield. When **2j**, derived from 2-naphthyl acrylate, was employed as substrate, the product was isolated in 66% yield. Halogen substituents are also tolerated in this olefinic trifluoromethylation, thus enabling further elaboration of the products (**3k**, **3l**) into more complex molecules. In addition, substrates that contain electron-withdrawing substituents were also amenable to the reaction conditions, but afforded the corresponding products (**3m**, **3n**) in moderate yields. Much to our surprise, this reaction also allows the use of α-alkyl acrylate derivatives as viable substrates. It is generally accepted that alkenes that possess a hydrogen atom in α position are more inclined to undergo allylic trifluoromethylation to form a $C(sp^3)$–CF_3 bond,[6] whereas they are more apt to participate in the olefinic trifluoromethylation in the present reaction. In all α-alkyl acrylate derivatives examined, the olefinic trifluoromethylation was the dominant reaction, accompanied by the minor formation of an allylic C–CF_3 bond. For example, in the case of **2o** the ratio of olefinic versus allylic trifluoromethylation products was as high as 8.3:1. It is worth mentioning that when Baylis–Hillman adduct **2r** was employed, the reaction proceeded selectively and afforded the olefinic trifluoromethylation product **3r** in 60% yield. We believe that the reversal of the reaction pattern is a result of the effect of the directing group and the discrimination of proton elimination because of the introduced CF_3 functionality.

In order to gain more insights into the reaction mechanism, several control experiments were conducted (Scheme 4). Under the optimized reaction conditions but with the addition of a radical scavenger, such as TEMPO, BHT, and 1,1-diphenylethylene, the yield of the reaction between **2a** and **1** decreased significantly, with none reaching full conversion.[14] When the substrate **2q** was subjected to the optimized reaction conditions as a radical clock, the reaction turned out to be rather messy, with no trace of the desired olefinic trifluoromethylation product being detected. Furthermore, in the hope to find out whether the C–CF_3 bond formation in this reaction follows a C–H activation pathway, an intermolecular KIE experiment was carried out using **2a** and [D_2]-**2a**, affording a KIE value of 1:1. This result clearly showed that the cleavage of the olefinic C–H bond is not involved in the rate-determining step. Collectively, these experiments indicate the involvement of radical species in this catalytic process.

Based on all experimental results, a reaction mechanism was tentatively proposed (Scheme 5). The reaction starts with a ligand exchange between the Cu^I catalyst and substrate **2** to give intermediate **A**, which further undergoes oxidation by **1** to produce Cu^{III} intermediate **B**. At this stage, intramolecular single-electron transfer (SET) affords intermediate



Scheme 4. Control experiments.



Scheme 5. Proposed reaction mechanism.

C, which is characterized by its cationic radical nature. The association of the pendant cationic alkene radical with the metal center in an intramolecular fashion produces the Cu^{III} intermediate **D**, which bears a positive charge in *α* position to the carbonyl group. Once **D** is formed, the ensuing hydrogen elimination delivers the Cu^{III} intermediate **E**, which undergoes reductive elimination and further ligand exchange with another molecule of **2** to afford the desired *cis* olefinic trifluoromethylation product **3** and regenerate intermediate **A** for the next catalytic cycle.

In conclusion, we have reported the copper-catalyzed olefinic trifluoromethylation of electron-deficient alkenes. The directing group was found to have a tremendous effect on the success of this C–CF_3 bond formation. This reaction tolerates α-aryl- as well as α-alkyl-substituted acrylate derivatives and a broad range of synthetically useful func-

tionalities. Furthermore, the reaction mechanism was briefly investigated through a set of control experiments, which proved the involvement of radical species in this catalytic cycle.

Experimental Section

An oven-dried Schlenk tube (5 mL) was charged with **1** (0.12 mmol), **2** (0.1 mmol), and CuCl (0.01 mmol) in this sequence. The Schlenk tube was evacuated and backfilled with nitrogen for three times, followed by the addition of anhydrous DMSO (0.5 mL) through a syringe, and then closed tightly. After stirring at 80 °C for 20 h, water (20 mL) was added and the resulting mixture was extracted with dichloromethane (2 × 20 mL). Removal of the solvent in vacuo and purification of the residue by column chromatography on silica gel afforded the desired product **3**.

Received: August 18, 2013
Published online: October 2, 2013

Keywords: alkenes · C–H activation · copper · cross-coupling · trifluoromethylation

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[13] CCDC 941581 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] Yields were determined through ^{1}H NMR analysis using mesitylene as internal standard.

