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Heterogeneous Catalyst CS@Copper(II)-Catalyzed Remote Trifluoromethylation of Aminoquinolines with CF_3SO_2Na *via* Radical Cross-Coulping

Chao Shen,[a] Jun Xu,[b] Beibei Ying,[b] Pengfei Zhang,*[b]

Abstract: First remote C–H trifluoromethylation of *N*-(quinolin-8-yl)benzamide derives were accomplished with a user-friendly chitosan-based heterogeneous copper catalyst in mild condition. The positional selective C-H activation protocol afforded the corresponding coupling products in good to excellent yields with excellent reusability using low-cost and stable Langlois reagent (CF_3SO_2Na) as "CF_3" sources. Furthermore, control experiments suggest a single-electron-transfer process plays a vital role in the heterogeneous C-CF_3 cross-coupling.

Introduction

The incorporation of trifluoromethyl group into organic molecules may significantly modify their physical, chemical, and biological properties. Consequently, more and more efforts have been made in order to develop useful methodologies for successfully introducing CF_3 into agrochemicals, pharmaceuticals and organic materials (Figure 1).[1] Until now, a variety of Pd-,[2] Ag-,[3] Ru-[4] and Cu-catalyzed[5] and metal-free[6] cross-coupling methods have been developed for the trifluoromethylation of arylboronic acids,[7] aryl halides,[8] carboxylic acid,[9] aromatic amine[10] as

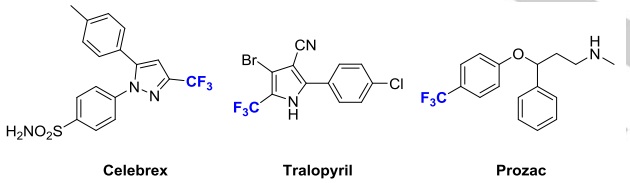


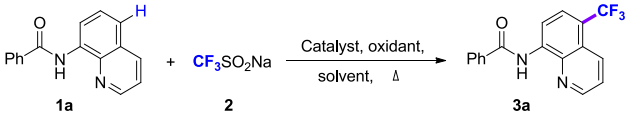
Figure 1 The representative drugs containing trifluoromethyl

well as C-H compounds.[11] Despite their utilities, most are homogeneous reactions, the metal catalysts can not been recycled. What is more, expensive trifluoromethylating reagents, such as Togni's reagent,[12] Umemoto's reagent[13] and Shibata's reagent[14] were employed. In the considerations of atom economy and environmentally friendly, a much more mild and available method must be established for the synthesis of trifluoromethyl compounds. Despite these undisputable advances, C-H trifluoromethylations were thus far solely accomplished with homogeneous catalysts. For example, Huang and Kanai reported a similar C-CF_3 couplings by using quinoline as substrates, respectively. However, long reaction times were required to finish the reaction and the underlying mechanism for the remains unclear.[15] Furthermore, these transformatioms rendered recycling and reuse of the metal catalysts challenging and led to considerable amounts of undesired metal impurities in the target products.

Quinolines, due to they have revealed excellent biologically activities, have received increasing attentions.[16] Therefore, high demands for the modification of quinolines are indispensable. And it's note that the status of quinoline functionalization at the C5 position is rising step by step.[17]

Currently, supported catalysts have received tremendous attentions because of they can been used recurrently. Various catalyst supports were prepared,[18] such as zeolites, silica, magnetic materials and polymers. Based on our

Table 1 Optimize the condition of trifluoromethylation[a]



1a 2 3a

Entry	Catalyst	Oxidant	Solvent	Yield[%][b]
1	CS@Cu(OAc)$_2$	TBHP	DMF	31
2	CS@Cu(OAc)$_2$	BPO	DMF	21
3	CS@Cu(OAc)$_2$	DTBP	DMF	trace
4	CS@Cu(OAc)$_2$	DCP	DMF	trace
5	CS@Cu(OAc)$_2$	*m*-CPBA	DMF	trace
6	CS@Cu(OAc)$_2$	Oxone	DMF	trace
7	CS@Cu(OAc)$_2$	$K_2S_2O_8$	DMF	45
8	CS@Cu(OAc)$_2$	$K_2S_2O_8$	toluene	15
9	CS@Cu(OAc)$_2$	$K_2S_2O_8$	Acetone	18
10	CS@Cu(OAc)$_2$	$K_2S_2O_8$	DCE	26
11	CS@Cu(OAc)$_2$	$K_2S_2O_8$	H_2O	0
12	**CS@Cu(OAc)$_2$**	**$K_2S_2O_8$**	MeCN	**89(43)[c]**
13	CS@CuI	$K_2S_2O_8$	MeCN	47
14	CS@$CuSO_4$	$K_2S_2O_8$	MeCN	32
15	-	$K_2S_2O_8$	MeCN	0
16[d]	CS@Cu(OAc)$_2$	$K_2S_2O_8$	MeCN	89
17[e]	CS@Cu(OAc)$_2$	$K_2S_2O_8$	MeCN	88

[a] Reaction conditions: **1a** (0.2 mmol), catalyst (loading 15 mol%), CF_3SO_2Na (1.5 equiv.), oxidant (1.5 equiv.), solvent (2.0 mL), stirred at 40 ℃, under air, 45 min. [b] Isolated yields. [c] Stirred at RT. [d] Under N_2. [e] Under O_2.

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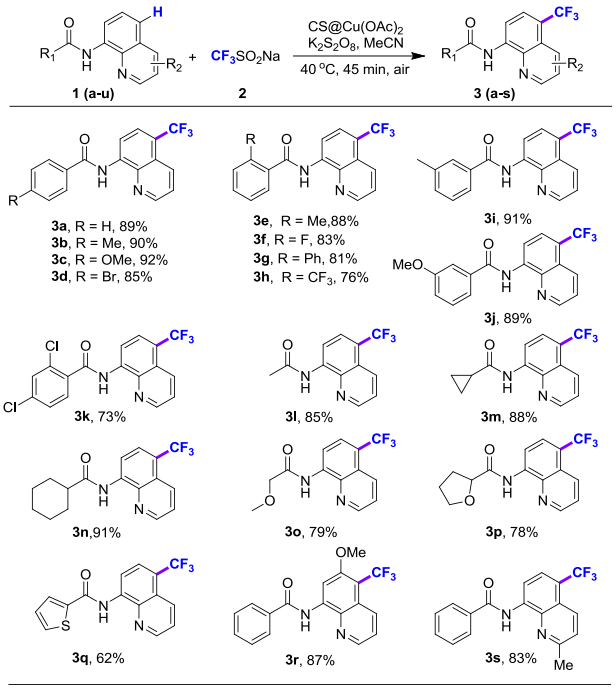
Table 2 Substrate scope of the trifluoromethylation[a]



[a] Reaction conditions: **1** (0.2 mmol), CS@Cu(OAc)$_2$ (36.4 mg, loading 15 mol%), **2** (1.5 equiv.), $K_2S_2O_8$ (1.5 equiv.), MeCN (2.0 mL), stirred at 40 ℃, under air, 45 min, isolated yields.

previous works on chitosan (CS),[19] the supported catalyst CS@Cu(OAc)$_2$ has been prepared and used for the C-CF_3 cross-coupling reaction.

Results and Discussion

Our initial efforts focused on the C-H trifluoromethylation of *N*-(quinolin-8-yl)benzamide **1a** by Langlois reagent (CF_3SO_2Na) **2** in the presence of CS@Cu(OAc)$_2$ and *t*-butylhydroperoxide (TBHP) in dimethylformamide at 40 °C (**Table 1, entry 1**). Amazingly, we indeed obtained the corresponding trifluoromethylated product **3a** in 31% yield (**Table 1, entry 1**). Notably, in this reaction, no product resulting from the trifluoromethylation of the benzamide ring was observed. On account of the exhilaratingly preliminary study, firstly, oxidants such as benzoyl peroxide (BPO), *di-t*-butyl peroxide (DTBP), dicumyl peroxide(DCP), *m*-chloroperoxybenzoic acid (*m*-CPBA), oxone and $K_2S_2O_8$

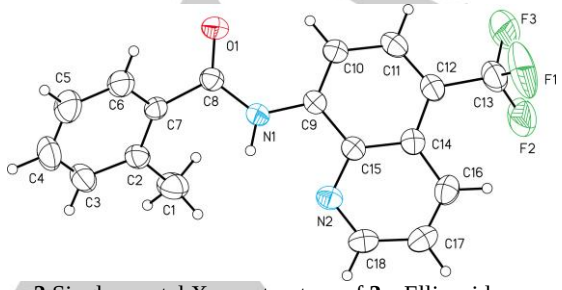
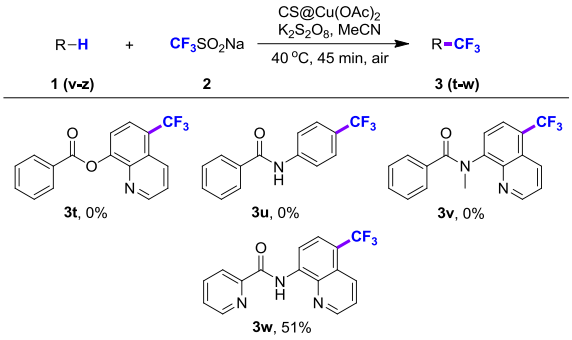


Figure 2 Single-crystal X-ray structure of **3e**. Ellipsoids are represented at 30% probability.

Table 3 Analogue substrate scope of the trifluoromethylation[a]

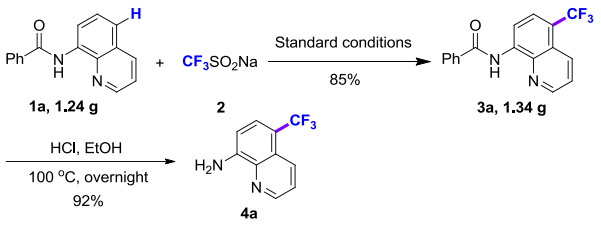


[a] Reaction conditions: **1** (0.2 mmol), CS@Cu(OAc)$_2$ (36.4 mg loading 15 mol%), **2** (1.5 equiv.), $K_2S_2O_8$ (1.5 equiv.), MeCN (2.0 mL), stirred at 40 ℃, under air, 45 min, isolated yields.

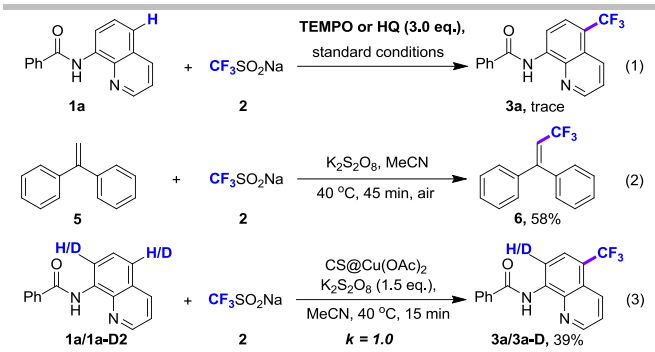
were tested (**Table 1, entries 2-7**), to our delight, higher yield (45%) was detected when $K_2S_2O_8$ was used as oxidant. Subsequently, several solvents were inspected (**Table 1, entries 8-11**), when toluene, acetone, 1,2-dichloroethane (DCE) and H_2O were used as solvents, the yields of **3a** were 15%, 18%, 26% and 0%, respectively, and the highest yield (89%) was monitored when the reaction was allowed to run in MeCN (**Table 1, entry 12**). Nextly, other CS@copper catalysts such as CS@CuI and CS@$CuSO_4$ were investigated, however, the yields of target product were lower (**Table 1, entries 13 and 14**). What is more, no product was gained in the absence of catalyst (**Table 1, entry 15**). Finally, the investigation of reaction atmosphere did not alter the reaction yield (**Table 1, entries 16 and 17**).

Having established the optimized conditions, we further studied the effect on the transformation of structural variations in 8-aminoquinoline amide (**Table 2**). A variety of 8-aminoquinoline amides were tested in remote trifluoromethylation, the desired products were obtained in moderate to good yields (**Table 2**). And the structure of product **3e** was quite proved by single-crystal X-ray diffraction (**Figure 2**). In general, the substrates with electron-donating groups (**3a-c, 3e, 3i, 3j, 3r, 3s**) relative to electron-withdrawing groups (**3d, 3f-h, 3k**) gave slightly higher yields. Pleasingly, Alkyl derivatives were also gained the products in synthetically useful yields (**3l-p**). Due to the effect of chelation, heterocyclic amides were obtained in slightly lower yields (**3q**).

The influence of heteroatom in the substrate molecules on the efficiency of the trifluoromethylation (**Table 3**) was researched. The hypothetical products **3t-v** were not generated under the standard conditions. It was worth noting that product **3w** which has three nitrogen-atoms was got in 51% yield. These phenomenons implied that bidentate



Scheme 1 Application of trifluoromethylation



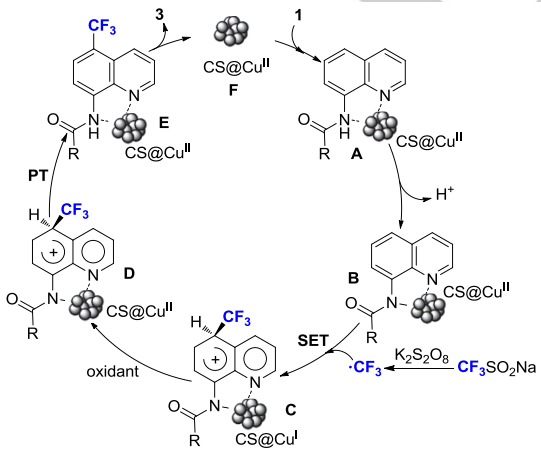
Scheme 2 Control experiments

nitrogen structure was very significant for the process and a free NH was necessary.

So as to embody the application value of remote trifluoromethylation, we carried out a gram scale reaction (**Scheme 1**), Firstly, the cross-coupling product **3a** could been easily obtained in 85% yield under standard condition. Subsequently, the product **3a** could been further transformed into **4a** in 92% yield by hydrolysis reaction. These process showed that the trifluoromethylation reaction is a useful procedure which provided a simple and efficient protocol for the synthesis of 5-trifluoromethyl quinoline derivatives.

In order to further understand the reaction mechanism, a series of control experiments including radical inhibition, radical capture as well as kinetic isotope effect study were carried out (**Scheme 2**). The trifluoromethylation was absolutely suppressed in the presence of TEMPO or HQ (**eq 1**), suggesting that a radical pathway might be involved in the reaction. Therefore, the experiment of capturing trifluoromethyl radical was carried out in the absence of $CS@Cu(OAc)_2$ (**eq 2**). As expected, the radical coupling product **6** was isolated in 58% yield. Meanwhile, further experiment about intramolecular kinetic isotope effects (KIE) gave a low result (k = 1.0) (**eq 3**), declaring that the C-H bond breakage was not the rate-limiting step.[20]

Based on our previous reports[16b] and the analysis of the previously mentioned results, we trust that the trifluoromethylation we reported was controlled by a single-electron transfer (**Scheme 3**). First, the substrate **1a** was combined with $CS@Cu(OAc)_2$ to produce complex **A**,



Scheme 3 Plausible mechanism

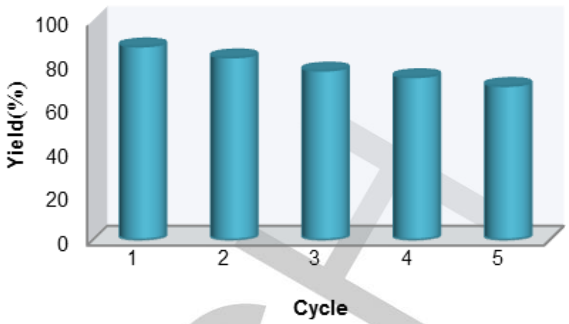


Figure 3 Catalyst recycling for the reaction

followed by the departure of AcOH, intermediate **B** is generated. Then, the intermediate **B** is attacked by trifluoromethyl radical which is generated through oxidation of Langlois reagent (CF_3SO_2Na) and $K_2S_2O_8$. Thereafter, Compound **C** turns into **D** by oxidation. Eventually, after the production of complex **E** through a proton transfer process (**PT**), target product **3a** is acquired via a metal dissociation process.

From the points of economy and environment, the recycling of the catalyst is a major consideration with a transition-metal catalyzed reaction for sustainability. Hence, the recyclability of $CS@Cu(OAc)_2$ catalyst was studied in the C-CF_3 cross-coupling reaction and the results were shown in **Figure 3**. In the recycling experiment, the separated $CS@Cu(OAc)_2$ was recharged with a fresh substrate for the next run under the same reaction conditions. It was noteworthy that the activity of the catalyst remained stable after five times of recycle. To determine whether the observed catalysis is derived from the $CS@Cu(OAc)_2$ catalyst or leached copper species,[19b] an additional hot filtration experiment has been carried out and the catalyst was removed from the reaction mixture by hot filtration after 20 min (at this time, approximately 50% conversion). After removal of the catalyst, the reaction was carried out in the same reaction condition and found that no more product conversion was further observed even during the extended time. The TEM analysis showed that the average diameter of the copper nanoparticles had increased from 5–8 nm to 10–30 nm after the 5th run (see Figure S1, ESI†). The copper loading levels of catalysts was measured to be 15% (weight percentage) before the reaction and 14.3% after the five reactions by ICP-AES analysis. These results confirm the fact that chitosan provides enough binding sites on the surface to minimize deterioration and supports the heterogeneous nature of the reaction.

Conclusions

In summary, we have developed the first C-H trifluoromethylation of quinolines using low-cost Langlois reagent (CF_3SO_2Na) as "CF_3" sources by a heterogeneous catalyst. This transformation showed low-loss, high efficiency and well-tolerated functionalization. What is more, the $CS@Cu(OAc)_2$ catalyst can be reused five times without significant loss of catalytic performance. The chitosan-based catalyst further set the stage for the efficient reuse of the

heterogeneous copper catalyst in positional selective C-H activations. Some control experiments confirmed that a single electron transfer (**SET**) mechanism was involved in the reaction.

Experimental Section

General Information

All the chemicals were obtained commercially and used without any prior purification. All products were isolated by short chromatography on a silica gel (200-300 mesh) column using petroleum ether (60-90°C) and ethyl acetate. ^{1}H, ^{13}C and ^{19}F NMR spectras were recorded on a Bruker Advance 500 spectrometer at ambient temperature with $CDCl_3$ as solvent and tetramethylsilane (TMS) as the internal standard. Melting points were determined on an X-5 Data microscopic melting point apparatus. The small-angle X-ray diffraction(SAXRD) data was taken on a German Bruker D4 X-ray diffractometer. Analytical thin layer chromatography (TLC) was performed on Merk precoated TLC (silica gel 60 F254) plates. Compounds for HRMS were analyzed by positive mode electrospray ionization (ESI) using Agilent 6530 QTOF mass spectrometer.

General procedure for synthesis of compound 3.

A mixture of **1** (0.2 mmol), Langlois reagent (CF_3SO_2Na) (1.5 eq.), CS@Cu(OAc)$_2$ (36.4 mg, loading 15 mol%) and $K_2S_2O_8$ (1.5 eq.) in MeCN (2.0 mL) in a 25 mL schlenk tube was stirred at 40 ºC for 45 min. After cooling to room temperature, the mixture filtered through a pad of Celite. The solvent was removed under reduced pressure. The gathered residue was then purified by silica gel column chromatography (200–300 mesh silica gel, PE/EA = 20:1).

General procedure for gram-scale synthesis of compound 3a

A mixture of *N*-(quinolin-8-yl)benzamide **1a** (1.3 g, 5.0 mmol), Langlois reagent (CF_3SO_2Na) (1.2 g, 1.5 eq.), CS@Cu(OAc)$_2$ (910 mg, loading 15 mol%) and $K_2S_2O_8$ (2.0 g, 1.5 eq.) in MeCN (40 mL) in a 100 mL reaction flask was stirred at 40 ºC for 45 min. After cooling to room temperature, the mixture filtered through a pad of Celite. The solvent was removed under reduced pressure. The gathered residue was then purified by silica gel column chromatography (200–300 mesh silica gel, PE/EA = 20:1).

General procedure for synthesis of compound 4a

To a 25mL schlenk tube equipped with a magnetic stir bar was added a mixture of **3a** (316.0 mg, 1.0 mmol), concentrated hydrochloric acid (2.5 mL), and EtOH (5.0 mL). Upon completion of the reaction at 100 ºC for 12 h, the mixture was cooled to room temperature and neutralized with NaOH aqoeous solution. Then extracted with EtOAc (10 mL). The collected organic layer was washed with brine (10 mL), dried with $MgSO_4$, and filtered through a pad of Celite gradually. The solvent was removed under reduced pressure. The gathered residue was then purified by silica gel column chromatography (200–300 mesh silica gel, PE/EA = 10:1).

General procedure for synthesis of the chitosan@Cu(OAc)$_2$ catalyst

The approach for the synthesis of the chitosan@Cu(OAc)$_2$ catalyst was according to the known literatrues[19]

The catalyst recycling experiment

In order to probe whether the CS@Cu(OAc)$_2$ is recyclable, the trifluoromethylation was repeated five times with the same catalyst sample, which was recovered after each reaction. The initial amount of catalyst was 36.4 mg (loading 15 mol%). Reactions were carried out for 45 min. When the reaction was completed, the catalyst was filtered off, washed with ethyl acetate and water twice, and then dried for 3 h at 60 °C. It was then stored under ambient conditions overnight and used again.

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Keywords: Heterocatalysis • Trifluoromethylation • Chitosan • Quinoline • Radical cross-coupling

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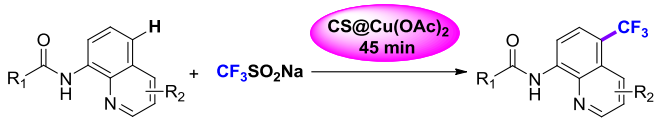

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Heterogeneous Catalyst CS@Copper(II)-Catalyzed Remote Trifluoromethylation of Aminoquinolines with CF_3SO_2Na via Radical Cross-Coulping