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Catalytic C−H α-Trifluoromethylation of α,β-Unsaturated Carbonyl Compounds

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Supporting Information

ABSTRACT: A copper(I)-catalyzed, regioselective C−H α-trifluoromethylation of α,β-unsaturated carbonyl compounds using Togni's reagent was developed. Diverse substrates, including enones as well as α,β-unsaturated esters, thioesters, and amides, stereospecifically afforded the corresponding (*E*)-α-trifluoromethylated products in moderate to high yields. Further, this method was applied to the C−H trifluoromethylation of drugs.

The trifluoromethyl (CF_3) group is an essential structural motif in diverse pharmaceuticals, agrochemicals, and organic materials.[1] Therefore, extensive efforts are directed toward developing methods for introducing the CF_3 group to organic molecules.[2] To date, methodologies based on functional group transformations to trifluoromethyl have been a major focus of study.[3] C−H bond functionalization would be the most efficient method for incorporating the CF_3 group into complex molecules. In this context, remarkable progress on the direct C−H trifluoromethylation has been witnessed in the past few years.[4] Diverse C−H bonds, such as (hetero)aryl,[5] alkenyl,[6] alkynyl,[7] allylic,[8] activated alkyl,[9] and azomethine,[10] have been trifluoromethylated. Despite the diversity, there are still many disadvantages in most of these reactions, e.g., a low level of regioselectivity, limitation to electron-rich π-systems, or dependence on an auxiliary directing group for regiocontrol. Therefore, the development of a general, regioselective C−H trifluoromethylation, particularly related to the electron-deficient π-systems, remains highly desirable.

α,β-Unsaturated carbonyls that contain an electron-deficient carbon−carbon double bond are not only versatile synthetic intermediates but also a structural motif in biologically active molecules.[11] Consequently, the regioselective trifluoromethylation of the alkenyl C−H bonds would be of great interest; however, such reactions have been rarely reported.[5b,12−14] Loh and co-workers developed a stereoselective β-trifluoromethylation of acrylamides using Togni's reagent (**1**),[12] even though both a tosyl-protected imide, as the directing group, and an occupied α-position of acrylamides were essential for the reaction (Figure 1a).[13] The Wang and Szabó groups reported the C−H trifluoromethylation of quinones; however, other types of electron-deficient double bonds could not be functionalized (Figure 1b).[14] Recently, the MacMillan group reported the α-trifluoromethylation of methyluracil and flavone by photoredox catalysis, one of the few examples known to date for the C−H α-trifluoromethylation of α,β-unsaturated carbonyls (Figure 1c).[5b,15] In continuation of our efforts on copper-catalyzed transformations of inert chemical bonds,[16] we herein report a regioselective C−H α-trifluoromethylation of α,β-unsaturated carbonyls using Togni's reagent, affording (*E*)-specific products (Figure 1d).

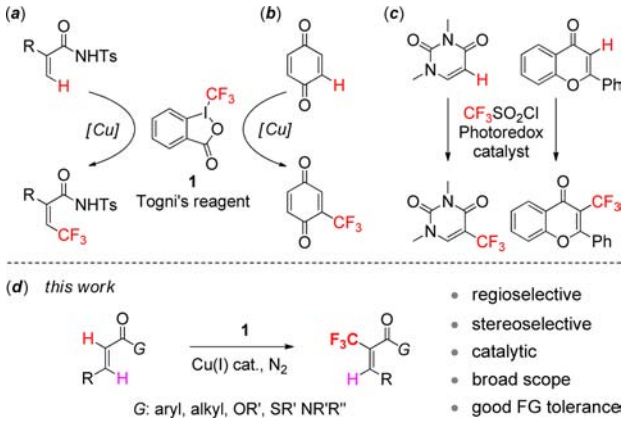

Figure 1. Direct trifluoromethylation of alkenyl C−H bonds of electron-deficient olefins.

The reaction conditions were optimized by the reaction of chalcone (**2a**) and Togni's reagent (**1**) as the model reaction. Selected results are shown in Table 1. Solvent has significant influence on the reaction. For example, acetonitrile (CH_3CN) and toluene turned out to be ineffective (entries 1 and 2), whereas the use of 1,4-dioxane afforded a trace amount of desired product **3a** (entry 3). The (*E*)-configuration of the product was confirmed by the NOE experiments. Delightfully, a good yield (78%) of **3a** was obtained when dimethylformamide (DMF) was used as the solvent (entry 4). In the control experiment, the necessity of the copper catalyst was demonstrated (entry 5). Other copper salts such as Cu_2O

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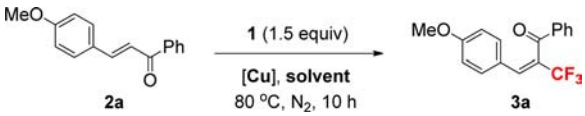
Table 1. Optimization of Reaction Conditions[a]



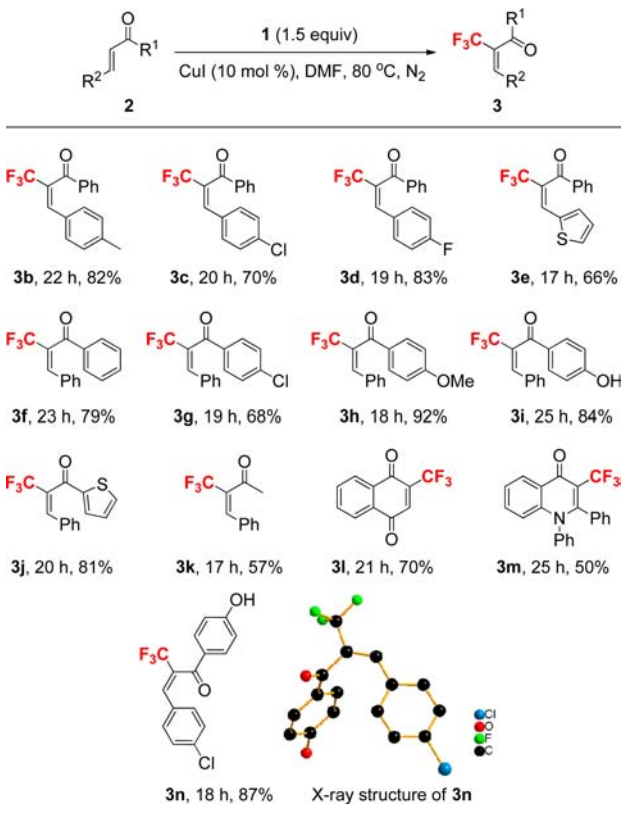
entry	[Cu]	solvent	yield (%)[b]
1	CuI	CH_3CN	0
2	CuI	toluene	0
3	CuI	1,4-dioxane	trace
4	CuI	DMF	78
5	–	DMF	0
6	Cu_2O	DMF	48
7	$Cu(OAc)_2$	DMF	30
8[c]	CuI	DMF	15

[a]Reactions were performed on 1.0 mmol scale, at 0.5 M. [b]Yields refer to isolated products. [c]Under open-air conditions.

and $Cu(OAc)_2$ with different valence states were screened in DMF at 80 °C under a nitrogen atmosphere; poor to moderate yields (30–48%) were obtained. A poor yield (15%) of **3b** was obtained under open-air conditions, proving the necessity for oxygen-free conditions (entry 8). Consequently, the optimal conditions listed in entry 4 were selected for further investigations.

Diverse enones were investigated with the optimized catalyst and reaction conditions (Scheme 1). In general, the enone substrates bearing either electron-withdrawing or -donating groups reacted smoothly with Togni's reagent to afford the corresponding trifluoromethylated products in moderate to excellent yields. Remarkably, oxidation-sensitive groups, such as phenolic hydroxyl and thienyl groups, were all well tolerated

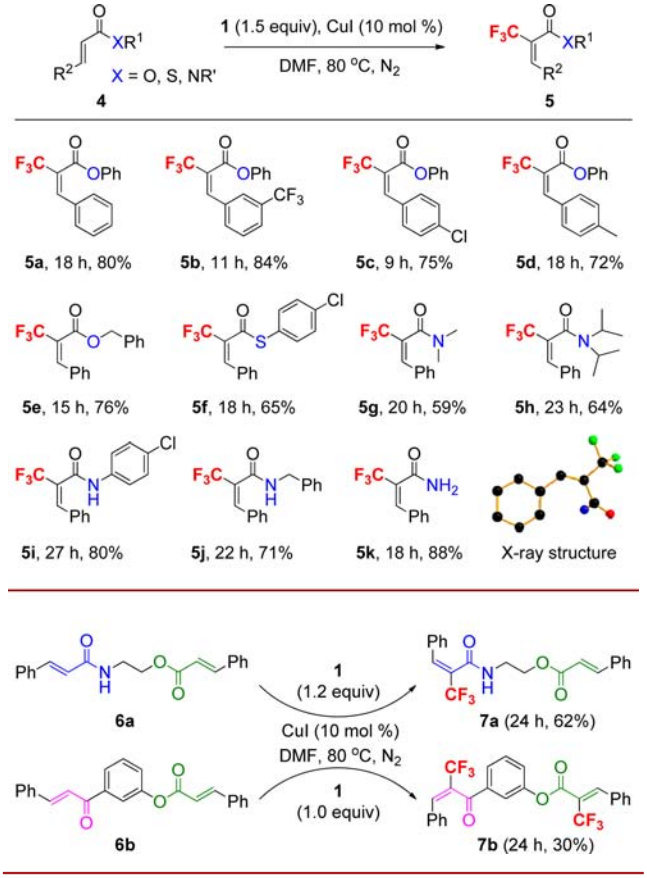
Scheme 1. C–H α-Trifluoromethylation of Enones



under the reaction conditions (**3e**, **3i**, **3j**, and **3n**). The stereoconfiguration of the α-trifluoromethylated enones was established as *E* by the single-crystal diffraction (XRD) of compound **3n**. Interestingly, naphthalene-1,4-dione, previously used by Wang and Szabó under open-air conditions, was also a suitable substrate under the current oxygen-free conditions, affording the corresponding trifluoromethylated product (**3l**) in 70% yield. Furthermore, the quinolone derivative was subjected to the C–H trifluoromethylation and afforded the corresponding α-trifluoromethylated quinolone **3m** in 50% yield, albeit with a significant amount of substrate left.

Encouraged by the results obtained with the enones, we employed this C–H α-trifluoromethylation protocol to other α,β-unsaturated carbonyl systems, such as α,β-unsaturated esters, thioesters, and amides. The results are shown in Scheme 2. All the reactions smoothly produced the corresponding α-

Scheme 2. C–H α-Trifluoromethylation of α,β-Unsaturated Esters, Thioesters, and Amides



trifluoromethylated products (**5a–5k**) in moderate to high yields. The stereochemistry of products was also unambiguously confirmed by the XRD of compound **5k**. Notably, the nitrogen-activated benzyl group (**5j**) and electron-rich arenes (**5a–5d**, **5f**, and **5i**) that were reactive in electrophilic trifluoromethylation reactions[5,9] remained intact under our trifluoromethylation conditions. In addition, the type of amides did not affect the reaction outcome because the primary, secondary, and tertiary amides were all compatible under the reaction conditions (**5g–5k**). Taken together, the results listed in Schemes 1 and 2 demonstrated the broad scope and excellent regio- and stereoselectivity of this copper(I)-catalyzed C–H α-trifluoromethylation of α,β-unsaturated carbonyl

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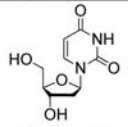
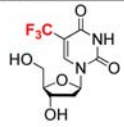
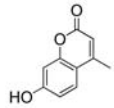
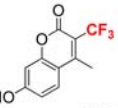
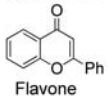
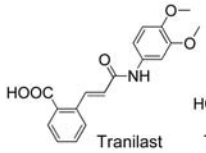
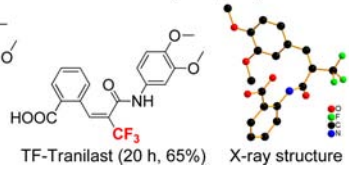
compounds. The presence of a trifluoromethyl moiety in the product promises the subsequent conversion to more functionalized trifluoromethylated compounds.[11]

The reactivities of different α,β-unsaturated carbonyls in the copper(I)-catalyzed C−H α-trifluoromethylation were compared by utilizing substrates **6a** and **6b**. We found that cinnamamide had the highest reactivity because single α-trifluoromethylation product **7a** was obtained from substrate **6a**. Enone and cinnamate showed similar reactivity, as bistrifluoromethylated product **7b** was obtained as the major product from substrate **6b** when using a reduced amount (1.0 equiv) of Togni's reagent.

In order to explore the synthetic potential of our method in thelate-stage synthetic modifications, biologically active molecules were subjected to the copper(I)-catalyzed trifluoromethylation protocol to prepare their CF_3 analogs (Table 2).

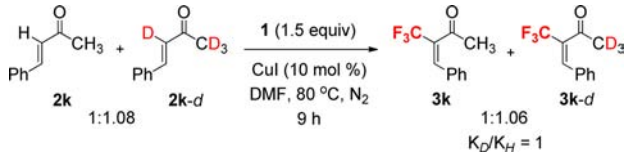
Table 2. Direct C−H Trifluoromethylation of Drugs to Their Analogs

entry	substrate	product[a]
1	 2'-Deoxyuridine	 Trifluridine (23 h, 76%)
2	 Hymecromone	 TF-Hymecromone (23 h, 83%)
3	 Flavone	 TF-Flavone (25 h, 78%)
4	 Tranilast	 TF-Tranilast (20 h, 65%) X-ray structure

[a]Isolated yields.

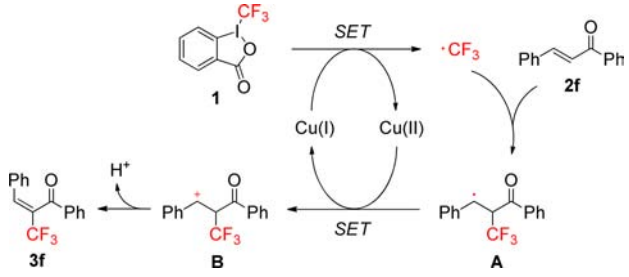
For instance, a DNA deoxynucleotide (2′-deoxyuridine), an antispasmodic drug (Hymecromone), a vitamin (flavone), and an antiallergic drug (Tranilast) were each selectively trifluoromethylated at a single position in good yields (65−83%). The structure of product TF-Tranilast was also confirmed by XRD. TF-Tranilast and TF-Hymecromone were for the first time prepared. In all these cases, highly regioselective reactions were observed, presumably corresponding to the positions being relevant to metabolic susceptibility. The simultaneous identification and capping of such positions with a CF_3 group may be useful in medicinal research.

Control experiments were carried out to offer insights into the reaction mechanism. The deuterium labeling studies showed no primary kinetic isotope effect (KIE) ($K_H/K_D \approx 1$) in an intermolecular competition experiment using deuterated substrate **2k**-*d*.[17] In addition, a radical scavenger such as TEMPO or oxygen significantly prohibited the reaction, because only a trace amount of product **3a** could be detected by TLC in the reaction of **2a** with Togni's reagent. These results clearly indicated that the reaction proceeded via a radical trifluoromethylation process.



Based on the mechanistic studies and literature precedents,[6,10,14] a plausible reaction mechanism was proposed (with **2f** as the example). As shown in Scheme 3, electrophilic Togni's

Scheme 3. A Plausible Reaction Mechanism



reagent is first reduced by CuI to afford a CF_3 radical by a single-electron-transfer (SET) process, with the release of Cu^{2+} species. The CF_3 radical then regioselectively attacks the α-position of **2f** that has a slightly higher electron density, thus generating radical intermediate **A**. Following another SET process, carbocation intermediate **B** is produced, with regeneration of the active Cu(I) catalyst. Finally, product **3f** with the stable (*E*)-configuration is obtained after the deprotonation.

In conclusion, we developed the first general, regioselective C−H α-trifluoromethylation of α,β-unsaturated carbonyl compounds using Togni's reagent. This reaction allows diverse substrates to afford the corresponding (*E*)-specific α-trifluoromethylated products in moderate to high yields. The value of this transformation has been highlighted by the trifluoromethylation of biologically active molecules. The findings described herein represent a significant advance in C−H trifluoromethylation and also would inspire further research on new radical α-C−H functionalization reactions of α,β-unsaturated carbonyl compounds.[18]

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectra copies. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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