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NHC-Catalyzed Radical Trifluoromethylation Enabled by Togni Reagent

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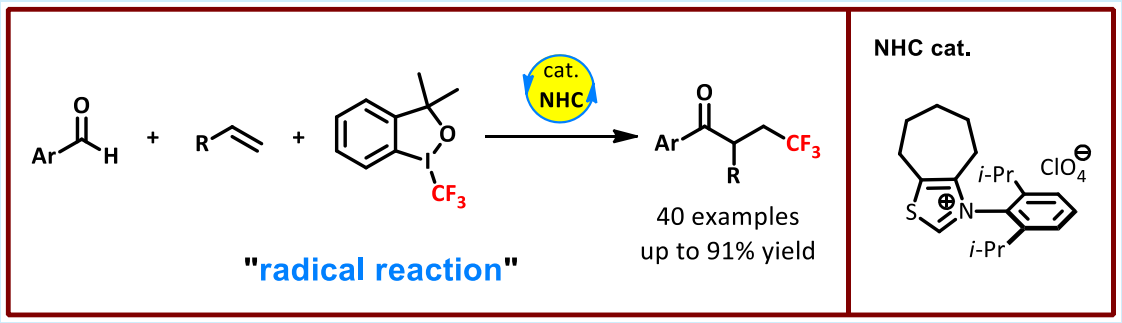
Supporting Information



ABSTRACT: An unprecedented carbene-catalyzed radical trifluoromethylation of olefins with aldehydes in the presence of Togni reagent was developed, thus providing the β-trifluoromethyl-α-substituted ketones with a broad scope and moderate to high chemical yields. Notably, this process includes a single-electron-transfer process and utilizes the persistent N-heterocyclic-carbene-bound radical as a key intermediate to trigger the cascade radical cross-coupling.

Over the past few decades, fluorine (F) has received much attention owing to it is unique physiochemical and biological properties.[1] In particular, the trifluoromethyl (CF_3) group has been recognized as an important structural motif that can enhance the metabolic stability, binding selectivity, and lipophilicity of pharmaceuticals.[2] Consequently, the development of efficient methods for the installation of the "CF_3" group into target molecules has become a hot research field.[3] In this context, the direct cross-coupling reaction is one of the most efficient methods to construct CF_3−aryl molecules via a $C(sp^2)$−CF_3 bond formation.[4] These protocols can avoid the use of expensive fluorinated building blocks but partially tolerate the scope generality. In some molecules, the CF_3 substitution is anchored on the skeleton of drug candidates (Scheme 1C).[5] In these cases, the trifluoromethylation of alkenes has proven to be a robust strategy via the direct $C(sp^2)$−CF_3 bond formation. Despite these achievements in advancement, the development of new and amenable protocols for the rapid and diverse assembly of CF_3-containing structures is still in a high demand.

On the contrary, N-heterocyclic carbenes (NHCs) as versatile organocatalysts[6] have enabled a variety of carbonyl molecules to be transformed into significant intermediates, such as NHC-bound acyl anion equivalents,[7] acyl azoliums,[8] enolates,[9] homoenolates,[10] and vinylogous enolates,[11] which then react with another counterpart, thus leading to a diverse set of important structures. In 2018, Lin and Sun reported a nonradical catalytic trifluoromethylation to achieve the $C(sp^3)$−CF_3 bond via the NHC-bound homoenolate intermediates.[12] It is worth mentioning that the Togni reagent is used as an electrophile in this case. Very recently, the Ohmiya group reported two elegant examples of NHC-catalyzed decarboxylative coupling of aldehydes.[13] In these reactions,[14] the deprotonated Breslow intermediate can serve as a single electron reductant to reduce the redox-active esters, and the resulting alkyl radical could react with the NHC-bound radical to deliver the cross-coupling products. In fact, Fukuzumi and coworkers already disclosed the single-electron-transfer (SET) process between the Breslow intermediate and its persistent radical in 1997 (Scheme 1B).[15] In a continuation of our efforts in NHC organocatalysis[16] and inspiration from the previously mentioned literature, we report herein a novel NHC-catalyzed radical trifluoromethylation process enabled by Togni reagents (Scheme 1B). We envisioned that the rapid generated CF_3 radical via a SET process could promote the cascade radical conjugate addition to alkenes, followed by radical−radical cross-coupling to furnish β-trifluoromethyl-α-substituted ketones.

We commenced our studies by investigating the reaction of 4-Cl-benzaldehyde **1a**, olefin **2a**, and Togni reagent **3a** as the model substrates, Cs_2CO_3 as the base, and dichloromethane (DCM) as the solvent, and the results are briefly summarized in Table 1. When the triazolium precatalysts **A**−**C** were exploited, the expected adduct was obtained in low yield (entries 1−3). However, replacing catalysts **A**−**C** with the cycloheptane-fused thiazolium precatalyst **D** gave the desired product **3a** in 64% yield (entry 4). Furthermore, when the cycloheptane-fused

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Scheme 1. Catalytic Strategies for C(sp^3)–CF_3 Bond Formation and Representative CF_3-Containing Structures

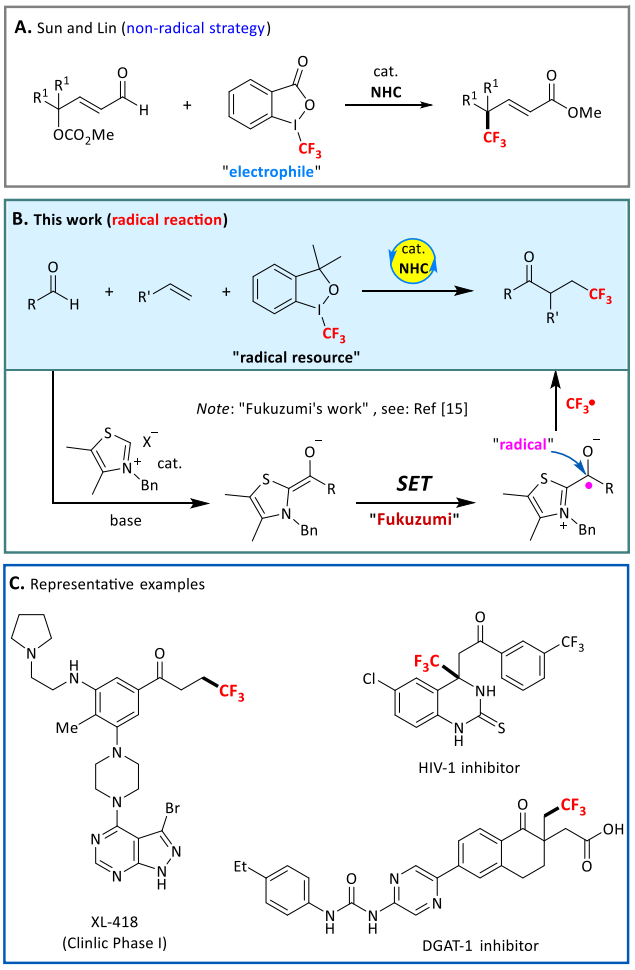
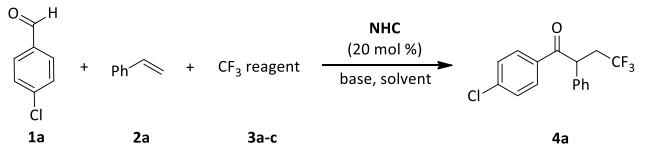
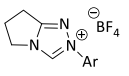
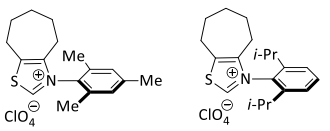


Table 1. Optimization of the Reaction Conditions[a]

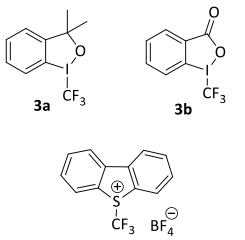


NHC cat.





CF_3 reagent:



entry	cat.	CF_3	base	solvent	yield (%)[b]
1	**A**	**3a**	Cs_2CO_3	DCM	32
2	**B**	**3a**	Cs_2CO_3	DCM	21
3	**C**	**3a**	Cs_2CO_3	DCM	24
4	**D**	**3a**	Cs_2CO_3	DCM	67
5	**E**	**3a**	Cs_2CO_3	DCM	71
6	**E**	**3b**	Cs_2CO_3	DCM	<5
7	**E**	**3c**	Cs_2CO_3	DCM	<5
8	**E**	**3a**	TEA	DCM	trace
9	**E**	**3a**	DBU	DCM	trace
10	**E**	**3a**	Cs_2CO_3	THF	trace
11	**E**	**3a**	Cs_2CO_3	toluene	trace
12	**E**	**3a**	Cs_2CO_3	MeCN	41
13	**E**	**3a**	Cs_2CO_3	DCM + H_2O (10 uL)	69
14	**E**	**3a**	**Cs_2CO_3**	**DCM + H_2O (20 uL)**	**84**
15	**E**	**3a**	Cs_2CO_3	DCM + H_2O (100 uL)	58

[a]Reaction conditions: **1a** (0.12 mmol), **2a** (0.1 mmol), **3a–c** (0.15 mmol), NHC cat. (20 mol %), Cs_2CO_3 (40 mol %), solvent (1.0 mL), Ar, room temperature, 4 h. [b]Isolated yield after column purification.

thiazolium derivative precatalyst **E** was tested, the reaction yield of **3a** was slightly increased to 71% (entry 5). After evaluating bases and solvents, we found that a combination of Cs_2CO_3 as the base and DCM/H_2O as the solvent system was the best choice (entries 8–15). An improvement in yield was found when a suitable amount of water was used as the additive, but the reason is unclear so far (entry 14). In addition, Togni **I** reagent **3b** and Umemoto reagent **3c** were also examined. However, frustrated conversions were observed (entries 6 and 7).

With the optimal catalytic system in hand, we moved our attention to explore the generality of this three-component trifluoromethylation reaction. As illustrated in Scheme 2, by reacting with 4-Cl-benzaldehyde **1a** in the presence of Togni reagent **3a**, an array of aryl olefins were first examined. In the reactions to generate the trifluoromethylated product **4**, yields were found to be less affected by the electronic properties of the substituents on the aryl group in substrate **2** (**4b–k**). When the heteroaryl olefins were reacted with aldehyde **1a** under optimal conditions, their corresponding adducts (**4l–o**) were obtained as well. Reactions of functionalized olefins with aldehyde **1a** also gave the desired adducts in good yield (**4p–s**). In addition, benzyl or alkyl olefin can participate in this reaction but is tolerated in a low yield (**4t** and **4u**). Notably, the pharmaceutical derivative proved to be compatible with this system as well as other substrates (**4v**).

Next, we turned our attention to investigate the scope of aldehydes **1** (Scheme 3). Different substituents and substitution patterns on the benzene skeleton were comprehensively examined. Electron-withdrawing substituents such as CF_3, F, NO_2, and CN (**5b**, **5c**, **5f**, **5g**, and **5h**) units on the phenyl ring of the aldehyde substrates were well tolerated. Electron-releasing groups such as methyl (**5b** and **5e**) and alkyloxyl unit (**5i**) could also be installed on the benzene scaffold of the aldehyde substrates. It is worth noting that this protocol could be extended to a variety of heteroaryl aldehydes, affording their corresponding CF_3-containing adducts (**5k–v**) in acceptable yield under the current standard conditions. However, non-aromatic aldehydes showed disappointing results. (See the Supporting Information.)

Postulated mechanisms are illustrated in Scheme 4. In the presence of a base, the NHC precatalyst was deprotonated to a free carbene catalyst, which then combined with an aryl aldehyde to generate the Breslow intermediate **I**. Meanwhile, the single-electron reduction of the Togni reagent via the electron-rich Breslow intermediate **I** occurred and resulted in a CF_3 radical and NHC-bound persistent radical **II**. The addition of the CF_3 radical to the olefin generated a CF_3-containing alkyl radical. Subsequently, a radical–radical cross-coupling between the CF_3-containing alkyl radical and the NHC-bound persistent radical **II** forms the NHC-bound intermediate **III** (pathway A),

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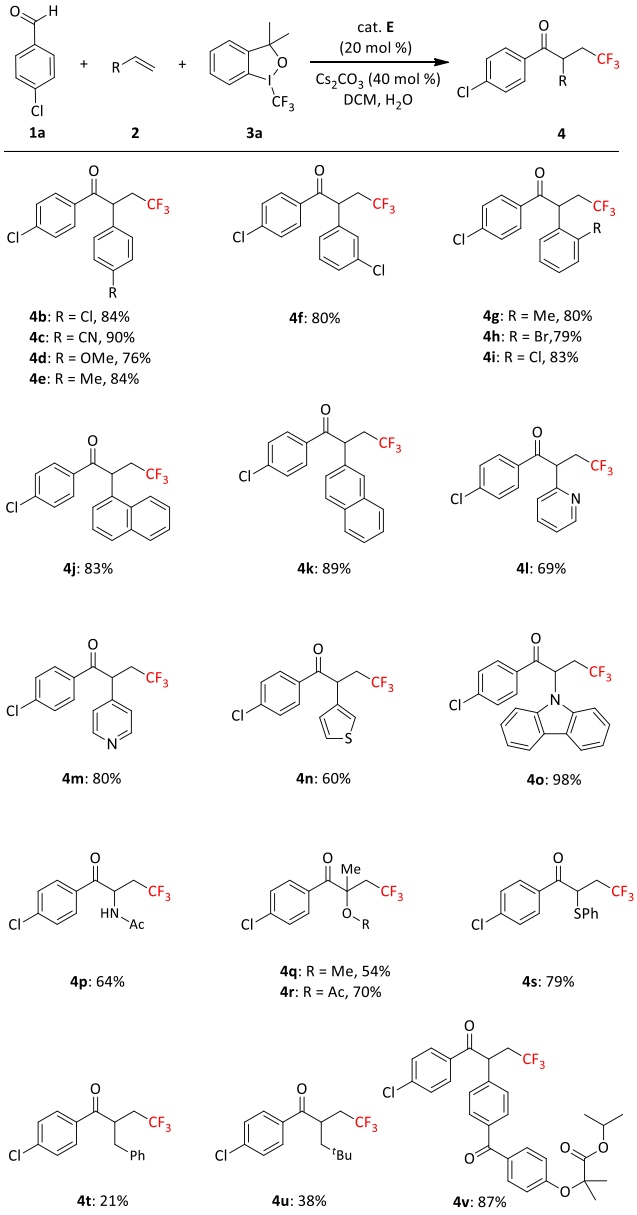
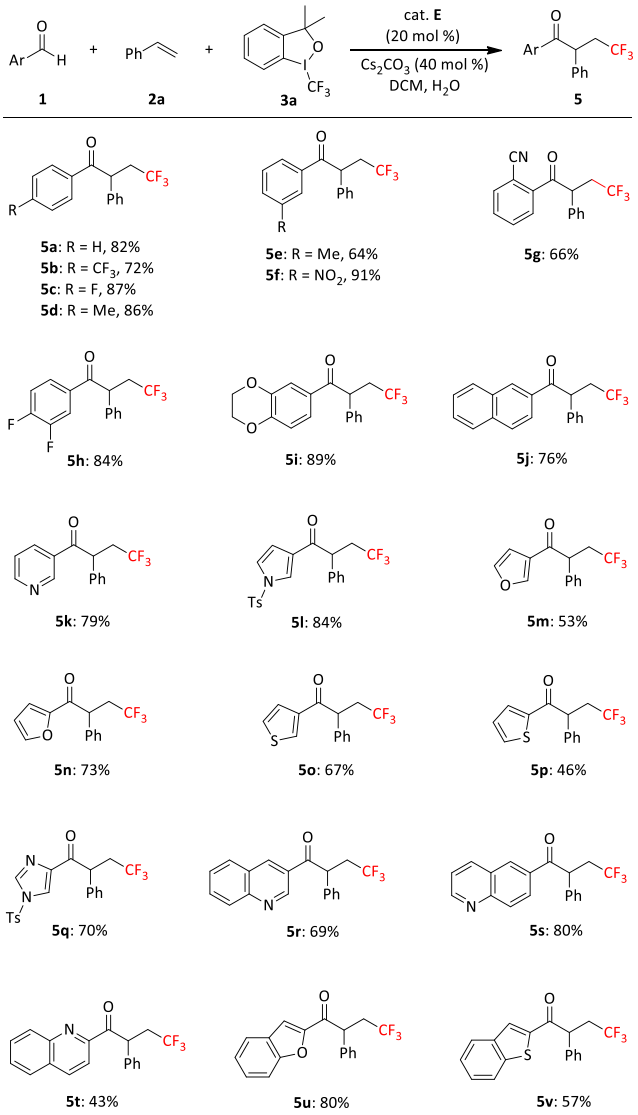
Scheme 2. Scope of Olefins[a]



[a]Reaction conditions: **1a** (0.24 mmol), **2** (0.2 mmol), **3a** (0.4 mmol), cat. **E** (20 mol %), Cs_2CO_3 (40 mol %), DCM (2.0 mL), H_2O (40 uL), Ar, room temperature, 4−12 h.

Scheme 3. Scope of Aldehydes[a]



[a]Reaction conditions: **1** (0.24 mmol), **2a** (0.2 mmol), **3a** (0.4 mmol), cat. **E** (20 mol %), Cs_2CO_3 (40 mol %), DCM (2.0 mL), H_2O (40 uL), Ar, room temperature, 4−12 h.

which undergoes acylation to release a free carbene catalyst for the next catalytic cycle. In addition, the generated CF_3-containing alkyl radical also can react with the electron-rich Breslow intermediate **I** to furnish another plausible NHC-bound radical intermediate **II′**. Then, the NHC-bound radical intermediate **II′** turns to intermediate **III** via a SET process (pathway B).

In conclusion, an NHC-catalyzed radical trifluoromethylation enabled by a three-component reaction of aldehydes, olefins, and Togni reagents has been developed. This process includes a single-electron-transfer process and utilizes the persistent NHC-bound radical as a key intermediate to trigger the cascade radical cross-coupling. This new protocol allows the rapid assembly of β-trifluoromethyl-α-substituted ketones from readily available starting materials under mild conditions. Further investigations on new NHC-bounded radicals and their applications in asymmetric synthesis are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04203.

Experimental procedures, product characterization, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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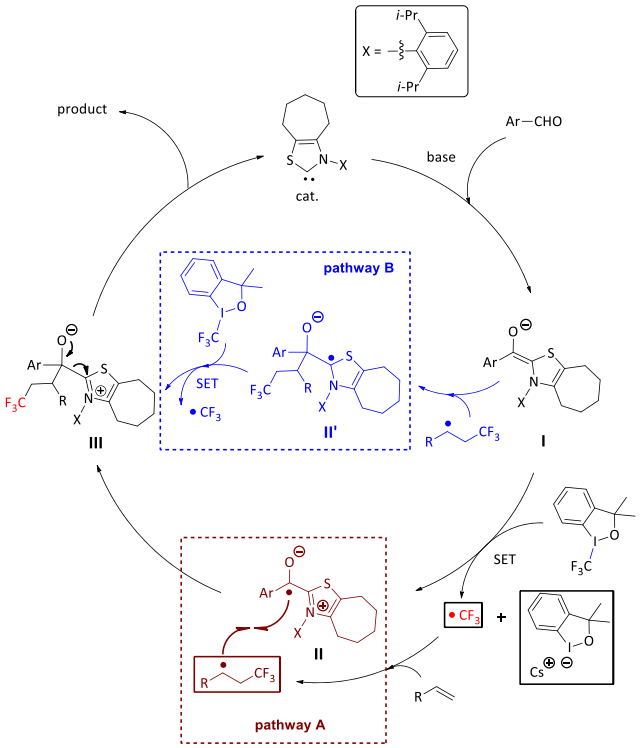
Scheme 4. Postulated Mechanism



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