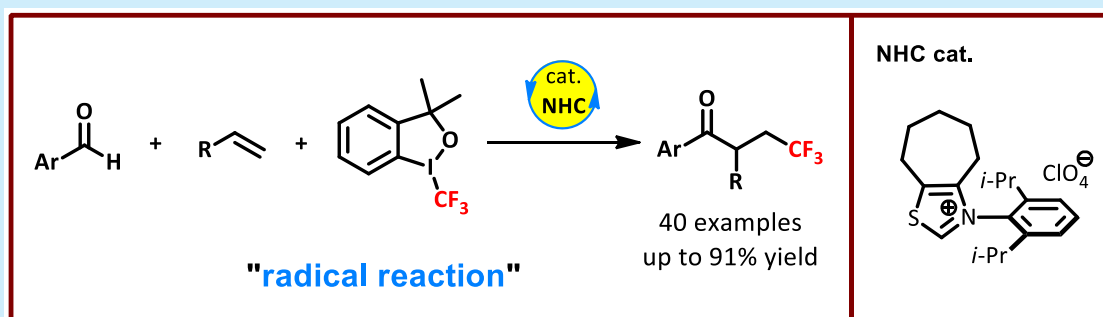


NHC-Catalyzed Radical Trifluoromethylation Enabled by Togni Reagent

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S 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 its unique physicochemical 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 $\text{C}(\text{sp}^2)\text{--CF}_3$ 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 $\text{C}(\text{sp}^2)\text{--CF}_3$ 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 organocatalysts⁶ 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 $\text{C}(\text{sp}^3)\text{--CF}_3$ bond via the NHC-bound homoenolate intermediates.¹² It is worth mentioning that the Togni reagent is used as an electrophile in

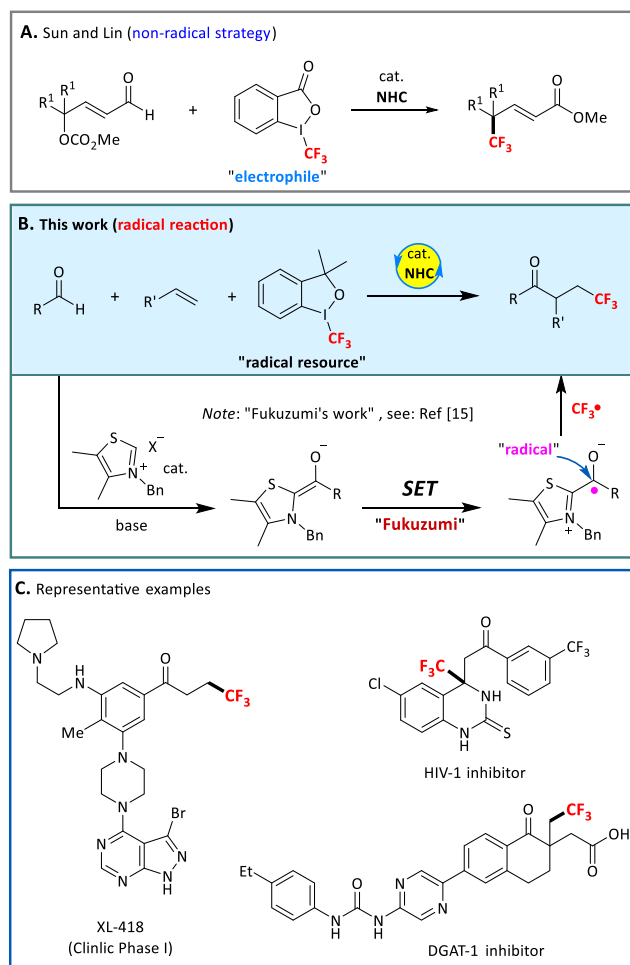
this case. Very recently, the Ohmiya group reported two elegant examples of NHC-catalyzed decarboxylative coupling of aldehydes.¹³ In these reactions,¹⁴ the deprotonated Breslow intermediate can serve as a single electron reductant to reduce the redox-active esters, and the resulting alkyl radical could 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 organocatalysis¹⁶ 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(sp³)-CF₃ Bond Formation and Representative CF₃-Containing Structures



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 Cs₂CO₃ as the base and DCM/H₂O 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**).

Table 1. Optimization of the Reaction Conditions^a

NHC cat.

CF₃ reagent:

A: Ar = Mes
B: Ar = C₆F₅
C: Ar = 2,4,6-Cl₃C₆H₂

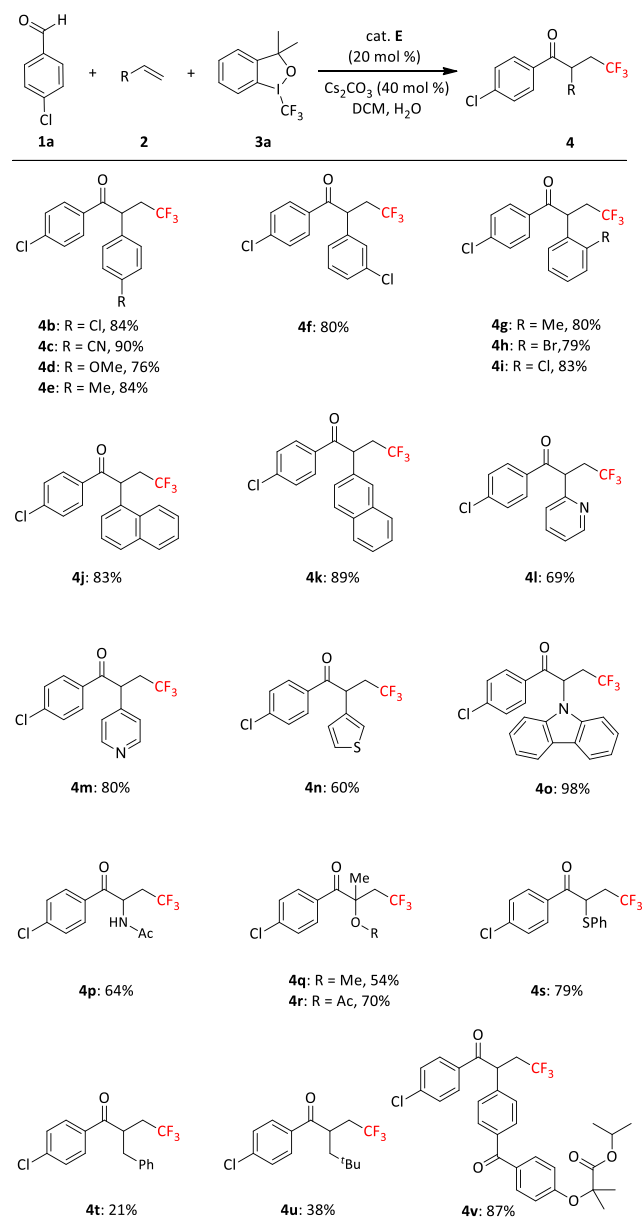
entry **cat.** **CF₃** **base** **solvent** **yield (%)^b**

1	A	3a	Cs ₂ CO ₃	DCM	32
2	B	3a	Cs ₂ CO ₃	DCM	21
3	C	3a	Cs ₂ CO ₃	DCM	24
4	D	3a	Cs ₂ CO ₃	DCM	67
5	E	3a	Cs ₂ CO ₃	DCM	71
6	E	3b	Cs ₂ CO ₃	DCM	<5
7	E	3c	Cs ₂ CO ₃	DCM	<5
8	E	3a	TEA	DCM	trace
9	E	3a	DBU	DCM	trace
10	E	3a	Cs ₂ CO ₃	THF	trace
11	E	3a	Cs ₂ CO ₃	toluene	trace
12	E	3a	Cs ₂ CO ₃	MeCN	41
13	E	3a	Cs ₂ CO ₃	DCM + H ₂ O (10 uL)	69
14	E	3a	Cs ₂ CO ₃	DCM + H ₂ O (20 uL)	84
15	E	3a	Cs ₂ CO ₃	DCM + H ₂ O (100 uL)	58

^aReaction conditions: **1a** (0.12 mmol), **2a** (0.1 mmol), **3a–c** (0.15 mmol), NHC cat. (20 mol %), Cs₂CO₃ (40 mol %), solvent (1.0 mL), Ar, room temperature, 4 h. ^bIsolated yield after column purification.

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 CF₃, F, NO₂, 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 alkoxy 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 CF₃-containing adducts (**5k–v**) in acceptable yield under the current standard conditions. However, non-aromatic aldehydes showed disappointing results. (See the Supporting Information.)

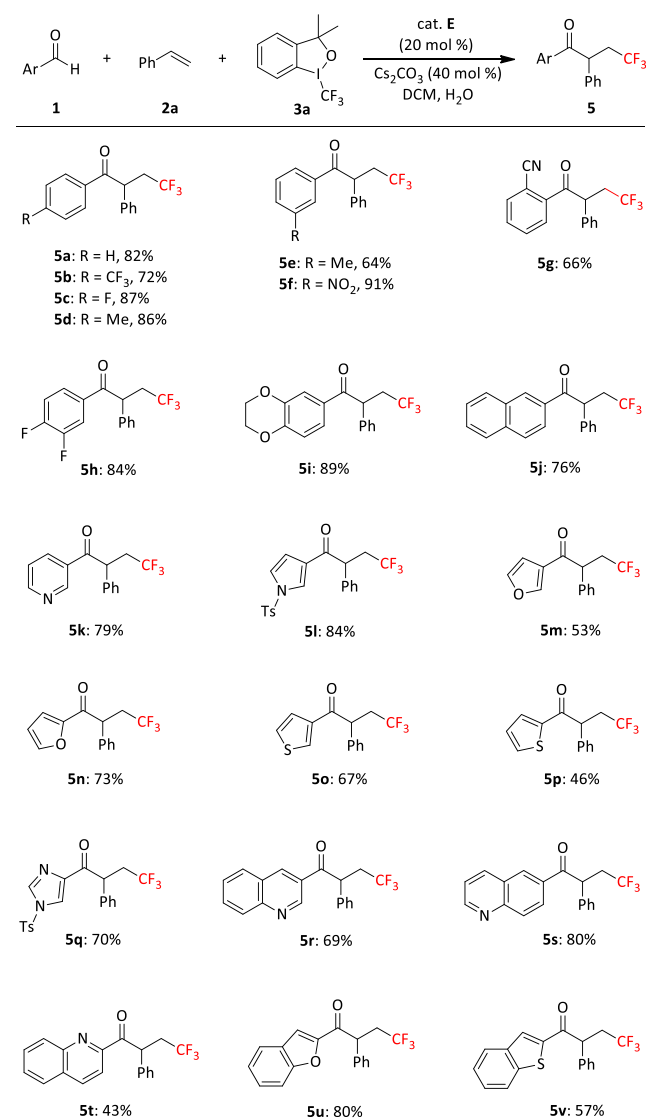
Postulated mechanisms are illustrated in Scheme 4. In the presence of a base, the NHC precatalyst was deprotonated to a free carbene catalyst, which then combined with an aryl aldehyde to generate the Breslow intermediate I. Meanwhile, the single-electron reduction of the Togni reagent via the electron-rich Breslow intermediate I occurred and resulted in a CF₃ radical and NHC-bound persistent radical II. The addition of the CF₃ radical to the olefin generated a CF₃-containing alkyl radical. Subsequently, a radical–radical cross-coupling between the CF₃-containing alkyl radical and the NHC-bound persistent radical II forms the NHC-bound intermediate III (pathway A),

Scheme 2. Scope of Olefins^a

^aReaction conditions: **1a** (0.24 mmol), **2** (0.2 mmol), **3a** (0.4 mmol), cat. **E** (20 mol %), Cs₂CO₃ (40 mol %), DCM (2.0 mL), H₂O (40 μ L), Ar, room temperature, 4–12 h.

which undergoes acylation to release a free carbene catalyst for the next catalytic cycle. In addition, the generated CF₃-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

Scheme 3. Scope of Aldehydes^a

^aReaction conditions: **1** (0.24 mmol), **2a** (0.2 mmol), **3a** (0.4 mmol), cat. **E** (20 mol %), Cs₂CO₃ (40 mol %), DCM (2.0 mL), H₂O (40 μ L), Ar, room temperature, 4–12 h.

on new NHC-bound 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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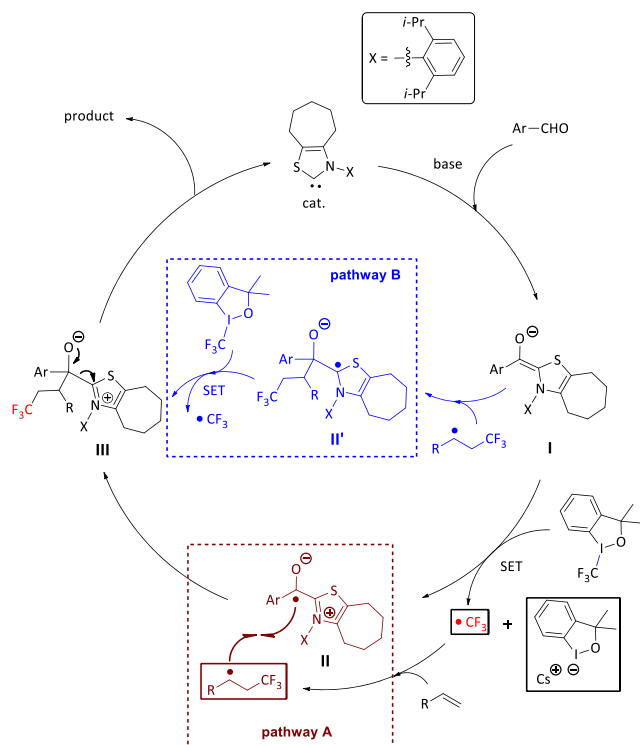
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Notes

The authors declare no competing financial interest.

Scheme 4. Postulated Mechanism



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