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Graphical Abstract

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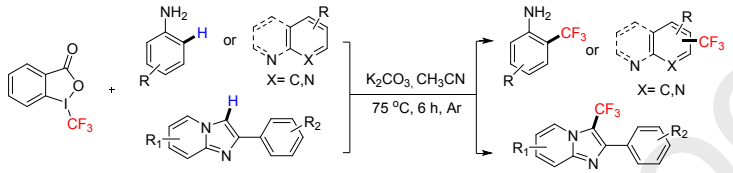

- Transition Metal-free
- Simple operations and mild conditions
- Direct C-H trifluoromethylation
- Wide substrate scope and scale-up synthesis

37 examples
Up to 96% yield

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Transition Metal-free Direct C-H Trifluoromethyltion of (Hetero)arenes with Togni's Reagent

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ABSTRACT

A new transition-metal-free direct C−H trifluoromethylation reaction of (hetero)arenes with Togni's reagent was developed. This transformation proceeded smoothly under mild conditions and exhibited good tolerance of many synthetically relevant functional groups. It provided an alternative approach for the synthesis of trifluoromethylated (hetero)arenes.

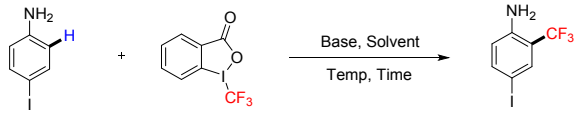
Introduction

The trifluoromethyl group prevails in pharmaceuticals and agrochemicals as well as functional organic materials,[1] mainly because of its unique metabolic stability, lipophilicity and strong electron-withdrawing nature.[2] Therefore, the development of an efficient and selective trifluoromethylation process is currently an important research topic in organic synthesis.[3] In general, the trifluoromethylation agents are as follows: Langlois reagent (CF_3SO_2Na),[4] Ruppert−Prakash reagent (CF_3SiMe_3),[5] Umemoto's reagent [6] and Togni's reagent.[7] Among them, Togni's reagent is proved to be a particularly powerful electrophilic trifluoromethylation agent for a variety of chemical functions,[8] owing to its stability, versatility, and commercial accessibility. Although Togni's reagent can react directly with nucleophiles,[9] an auxiliary medium is required to generate the CF_3 radical, such as Bronsted acid,[10] a transition metal complex acting as Lewis acid,[11] or transition metal acting as reducing agent.[12] Moreover, although visible-light-promoted direct C-H trifluoromethylation of (hetero)arenes with Togni's reagent avoids the addition of oxidant, the uses of specific light sources and photocatalysts still limit its practical application.[13] Thus, the development of transition metal or precious photocatalyst-free efficient C−H trifluoromethylative process using Togni's reagent as trifluoromethylating reagent under mild conditions is still challenging.[7m]

The trifluoromethylated free anilines and N-heteroaromatic compounds are very important structural motifs in many bioactive substrates.[14, 15] With the development of transition-metal-catalyzed C-H activation, by using Pd, Fe, Cu or Ni as catalysts, the highly efficient method for the construction of regioselective C-H trifluoromethylation of anilines were achieved.[15,16] But these reactions require transition-metal catalysts, which can potentially contaminate products, especially in the pharmaceutical industry and advanced functional materials. Although transition metal-free C−H trifluoromethylation of free anilines with Umemoto type sulfonium salts have been reported,[17] there are still some drawbacks: relatively expensive reagents, and multiple steps of sample preparation. Coupling reactions of aryl halides, aromatic amines or aryl zinc reagents with trifluoromethylating reagents for the construction of 8-trifluoromethylquinoline have also been developed.[18] Despite these progress, using pre-prepared substrates and generating stoichiometric amounts of metal salts reduce the efficiency of these methods.[18b,18c,18e] With our ongoing efforts on clean C−H functionalization and fluorine chemistry,[19] herein, we report a transition metal-free direct C−H trifluoromethylation of (hetero)arenes with Togni's reagent under mild and simple reaction conditions.

Results and Discussion

Table 1. Optimization of the Reaction Conditions.[a]



1a **2** **3a**

Entry	Base	Solvent	Temperature (ºC)	Time (h)	Yield (%)[b]
1	Cs_2CO_3	CH_3CN	75	12	80
2	NaH_2PO_4	CH_3CN	75	12	28
3	CsF	CH_3CN	75	12	80

4					mL)
5	K_2CO_3	CH_3CN	75	12	88
6	KO^{t}Bu	CH_3CN	75	12	32
7	---------	CH_3CN	75	12	46
8	K_2CO_3	CH_3CN	75	3	83
9	K_2CO_3	CH_3CN	75	6	91
10	K_2CO_3	CH_3CN	75	9	87
11	K_2CO_3	CH_3CN	75	12	88
12	K_2CO_3	DMSO	75	6	62
13	K_2CO_3	DMF	75	6	51
14	K_2CO_3	HFIP	75	6	nr[c]
15	K_2CO_3	Dioxane	75	6	45
16	K_2CO_3	THF	75	6	17
17[d]	K_2CO_3	CH_3CN	75	6	95
18	K_2CO_3	CH_3CN	55	6	58
19	K_2CO_3	CH_3CN	rt	6	30
20	K_2CO_3	CH_3CN	85	6	85
21[e]	K_2CO_3	CH_3CN	75	6	10

[a] Reaction conditions: **1a** (0.75 mmol, 3.0 equiv), **2** (0.25 mmol, 1.0 equiv), K_2CO_3 (0.375 mmol, 1.5 equiv), CH_3CN (2.0 mL), 75 °C, under Ar, 12 h.

[b]The product **3a** are determined by GC analysis using dipentyl phthalate as an internal standard.

[c] nr = no reaction.

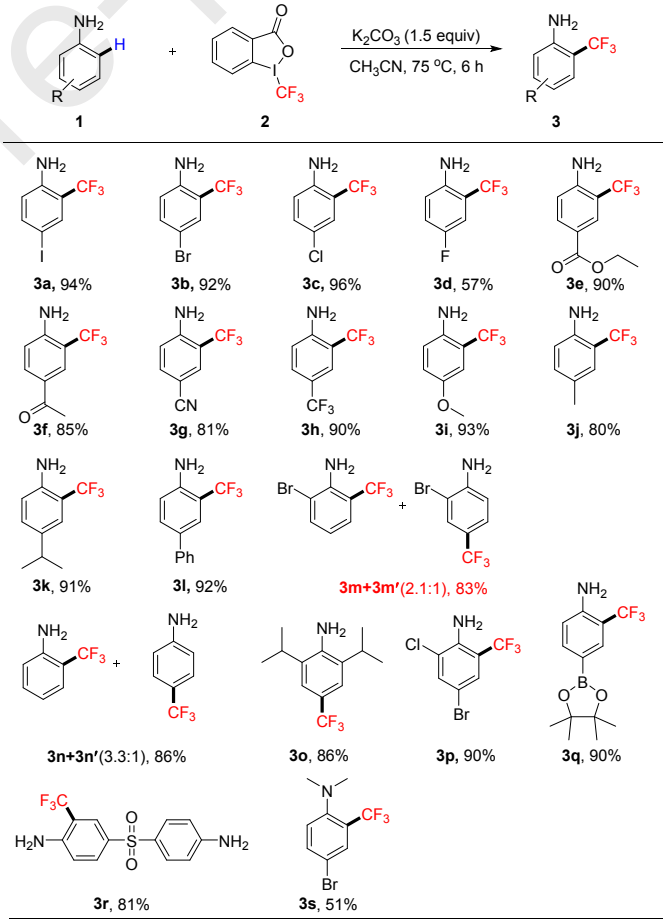
[d]The reaction was conducted in CH_3CN (1.5 mL).

[e]The reaction was conducted in air.

At the outset of our investigation, 4-iodoaniline (**1a**) and Togni's reagent (**2**) were chosen as model substrates to optimize the reaction. Surprisingly, when **1a** (0.75 mmol, 3.0 equiv) and **2** (0.25 mmol, 1.0 equiv) were stirred with Cs_2CO_3 (0.375 mmol, 1.5 equiv) in CH_3CN (2.0 mL) at 75°C under argon for 12 h, the desired product **3a** was obtained with 80% yield (Table 1, entry 1). Then, other bases such as NaH_2PO_4, CsF, K_3PO_4, K_2CO_3, and KO^{t}Bu were tested. When K_2CO_3 was used in the reaction, the yield of the desired product increased to 88% (Table 1, entries 2–6). In the absence of base, the yield of the target product decreased to 46% (Table 1, entry 7), indicating that base was essential for this reaction. After that, a survey of reaction time illustrated that 6 h was the best choice (Table 1, entries 8-11). Other solvents such as dimethyl sulfoxide (DMSO), dimethyl formamide (DMF), hexafluoroisopropanol (HFIP), dioxane and tetrahydyofuran (THF) were found to be less effective for the reaction (Table 1, entries 12–16). When 1.5 mL CH_3CN was used, the desired product was obtained in 95% yield (Table1, entry 17). Decreasing the reaction temperature from 75 °C to 55 °C, the yield of **3a** was decreased to 58% (Table 1, entry 18). When the reaction was carried out at ambient temperature, the conversion was very low and a dramatically decreased yield was observed (30%) (Table 1, entry 19). Increasing the reaction temperature to 85 °C, the yield of **3a** was also decreased (Table 1, entry 20). The ratio of substrates **1a** and Togni's reagent **2** was also studied, and the results indicated that the substrates ratio has a great influence on the yield of the reaction (see Supporting Information for details). In addition, when the reaction was conducted in air, the desired product was only obtained in 10% yield (Table1, entry 21). Finally, the optimized reaction conditions for direct C−H trifluoromethylation of (hetero)arenes were determined as follows: 4-iodoaniline (**1a**, 3.0 equiv, 0.75 mmol) and Togni's reagent (**2**, 1.0 equiv, 0.25 mmol) in the at 75 °C under argon for 6 h.

With the optimized reaction conditions in hand, the reactions between free anilines (**1**) and Togni's reagent (**2**) were carried out to explore the scope of trifluoromethylation method, and the results were summarized in Scheme 1. Satisfyingly, anilines bearing halogens groups (iodo, bromo, chloro, fluo) at the *para* positions were well-tolerated, and the desired products were obtained in moderate to good yields (**3a-3d**). The procedure seemed to be not sensitive to electron density of the anilines. Anilines possessing electron-withdrawing groups (such as, ester, carbonyl, cyano and trifluoromethyl) and electron-donating groups (such as, methoxyl, methyl and isopropyl) were successfully converted into the desired products with yield range from 80% to 93% (**3e-3k**). 4-Biphenylamine gave the product **3l** in 90% yield. When 2-bromobenzenamine or aniline was used, mixtures of *ortho*- and *para*-trifluoromethyl substituted products **3m**/**3m′** or **3n**/**3n′** were acquired, which is similar to the results previous reported by Ma and co-workers.[13c] Di-substituted anilines could be converted to its trifluoromethylated products in high yields (**3o-3p**). Moreover, trifluoromethylation of boronate and sulphone-containing anilines proceeded smoothly to provide the target products **3q** and **3r** in 90% and 81% yields, respectively. In case of 4-bromo-N,N-dimethylaniline, the trifluoromethyl group can be readily incorporated into arene, furnishing the product **3s** in 51% yield.

Table 2. Substrate Scope of Amine [a, b]

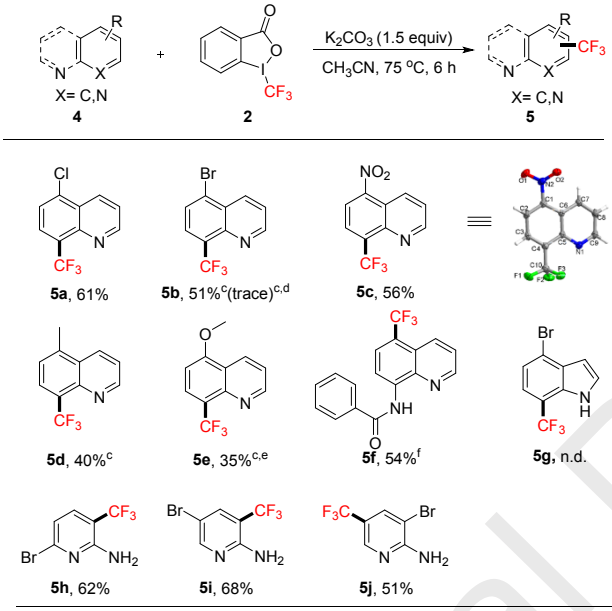


[a]Reaction conditions: **1** (0.75 mmol, 3.0 equiv), **2** (0.25 mmol, 1.0 equiv), of substrates **1a** and **2** K_2CO_3 (0.375 mmol, 1.5 equiv), CH_3CN (1.5 mL), 75 °C, 6 h, Ar.

[b]Isolated yields.

subsequently studied a series of heteroarenes (Table 3). Quinolines bearing chloro and bromo atom at C5 position were compatible in this transformation to afford the desired C8 trifluoromethyl-substituted products in moderate yields (**5a**-**5b**). Quinolines possessing electron-withdrawing group gave the desired products in higher yields than the substrates with electron-donating groups (**5c** *vs* **5d, 5e**). The structure of the compound **5c** was further confirmed by the single-crystal X-ray diffraction (see the Supporting Information). When the substrate contained a substituent group at C8 position, the C5 trifluoromethyl-substituted product was acquired (**5f**). Unfortunately, 1H-indole (**4g**) was unreacted under the optimal reaction conditions. It could be noted that the bromide-substituted pyridin-2-amines underwent this C–H trifluoromethylation smoothly, providing the target product (**5h-5j**) in modest yields.

Table 3. Substrate Scope of Heteroarenes [a,b]



[a]Reaction conditions: **4** (0.75 mmol, 3.0 equiv), **2** (0.25 mmol, 1.0 equiv), K_2CO_3 (0.375 mmol, 1.5 equiv), CH_3CN (1.5 mL), 75 °C, 6 h, Ar.

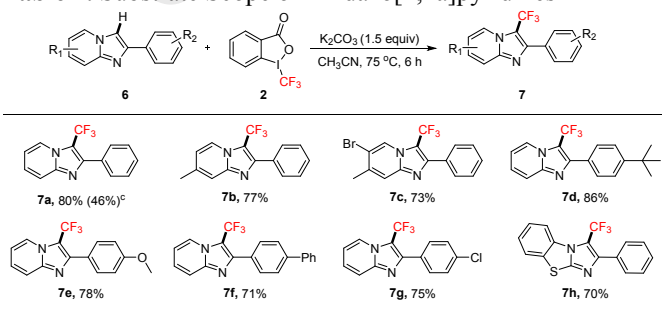
[b]Isolated yields.

[c]A substrate ratio of **4**/**2** =1:2 was used.

[d]The reaction was conducted in air.

Under the optimized reaction conditions, various imidazo[1,2a]pyridines (**6a-6g**) and Togni's reagent (**2**) was reacted to give the desired products in 70-86% yields (**7a-7g**) (Table 4). When 2-phenylbenzo[d]imidazo[2,1-b]thiazole was checked, the corresponding product **7h** was obtained in 70% yield.

Table 4. Substrate Scope of Imidazo[1,2a]pyridines [a,b]



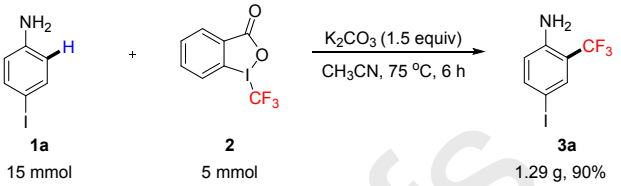
[a]Reaction conditions: **6** (0.50 mmol, 2.0 equiv), **2** (0.25 mmol, 1.0 equiv),

[b]Isolated yields.

[c]The reaction was conducted in air.

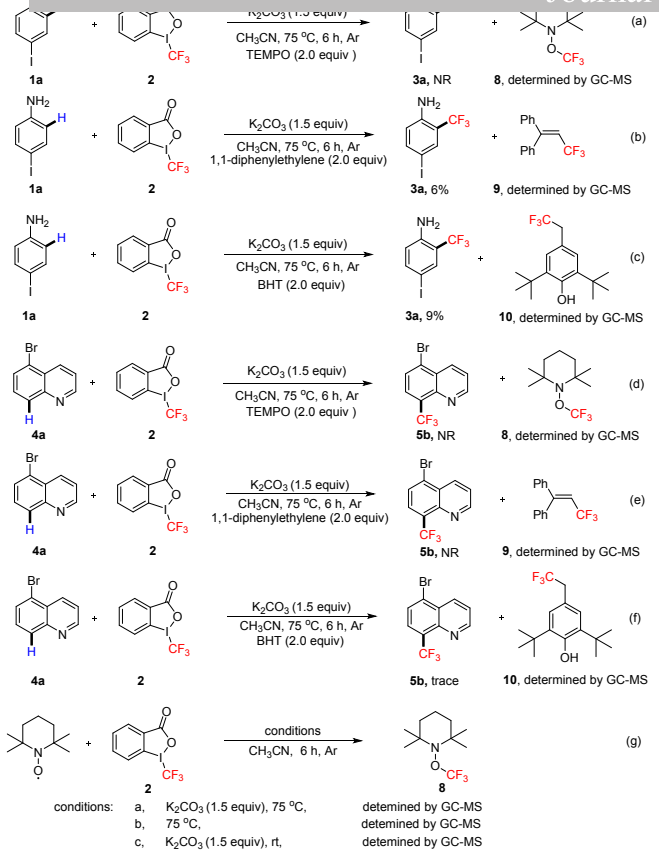
To further demonstrate the application of the method in organic synthesis, 4-iodo-2-(trifluoromethyl)aniline **3a** was synthesized in a gram scale under the standard reaction conditions to afford the desired product in 90% yield (Scheme 1).

Scheme 1. Scale-up Reaction



In order to gain insight into the reaction mechanism, a series of control experiments were subsequently carried out (Scheme 2). Initially, the ICP-AES data indicated that not trace metal contaminants were involved in the reaction (see Supporting Information for details). When the reaction was conducted in dark, the yield of the desired product was not affected. Thus, the influence of light exposure on the generation of CF_3 radical by decomposition of Togni's reagent was ruled out (see Supporting Information for details). When the radical trapping reagent TEMPO (2.0 equiv, 0.5 mmol, 2,2,6,6-tetramethyl-1-piperidinyloxyl) was added to the reaction of **1a** and **2**, no desired product was detected and the TEMPO-CF_3 adduct **8** was detected by GC-MS (Scheme 2a). When 1, 1-diphenylethylene (2.0 equiv, 0.5 mmol) as a radical scavenger was added to the reaction mixture, the yield of **3a** dramatically decreased to 6% and the 1,1-diphenylethylene–CF_3 adduct **9** could be detected by GC-MS (Scheme 2b). In addition, when 2.0 equiv. of 2,6-di-tert-butyl-4-methyl phenol (BHT) was added into the reaction system, the reaction was inhibited and only 9% of the product was detected. Meanwhile, the BHT-CF_3 adduct **10** was detected

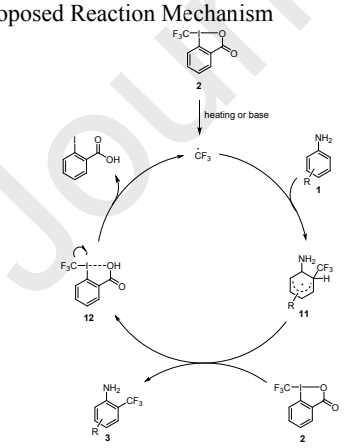
Scheme 2. Control Experiments



by GC-MS (Scheme 2c). The similar results were also observed in the case of 5-bromoquinoline (Scheme 2d, 2e and 2f). Then TEMPO (2.0 equiv, 0.5 mmol) instead of **1a** was added to the reaction system, and the adduct **8** was detected by GC-MS (Scheme 2g, condition a). When the reaction was kept in the absence of K_2CO_3 or at room temperature, the adduct **8** could be detected by GC-MS (Scheme 2g, condition b, c). These phenomena indicated that the CF_3 radical was produced under the optimal reaction conditions, and the base or heating were necessary factors for the generation of CF_3 radical.

Based on the above experiment results and previous literature reports, [8, 20, 21] a plausible reaction mechanism for the trifluoromethylation of anilines is proposed in Scheme 3. First,

Scheme 3. Proposed Reaction Mechanism



Togni's reagent **2** was activated to generate the CF_3 radical under the effects of base or heating. Then CF_3 radical was added to the electron-rich position of anilines to form the intermediate **11**. Subsequently, the intermediate **11** was deprotonated by reagent **2** to form the product **3** and intermediate **12**.[8, 20] Finally, the reactive intermediate **12** was rapidly consumed by transferring a CF_3 radical to the substrate, closing the cycle.

In summary, we have successfully developed a new transition metal-free direct C−H trifluoromethylation reaction of (hetero)arenes with Togni's reagent. The reaction protocol is operationally simple and can be conducted under mild conditions. A variety of synthetically important functional groups are well-tolerated. In addition, a mechanism study shows that a radical-type reaction is involved in this reaction system, and temperature and base as significant factors promoted the formation of the CF_3 radical.

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Supporting Information

All Compounds NMR spectra were provided as Supplementary material.

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Highlights

• An efficient protocol to synthesize trifluoromethylated (hetero)arenes

• The reaction proceeds under transition metal-free conditions

• Wide substrate scope and good functional compatibility

•The reaction protocol is operationally simple

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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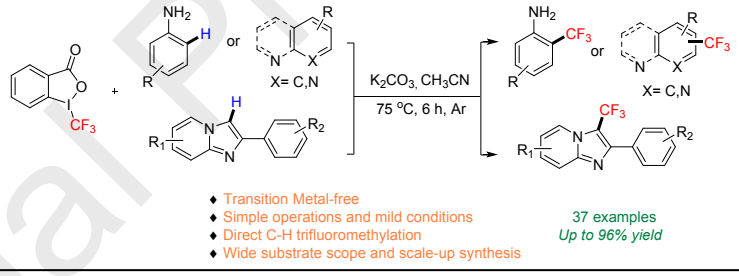

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