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Selective C-H Trifluoromethylation of Benzimidazoles Through Photoredox Catalysis

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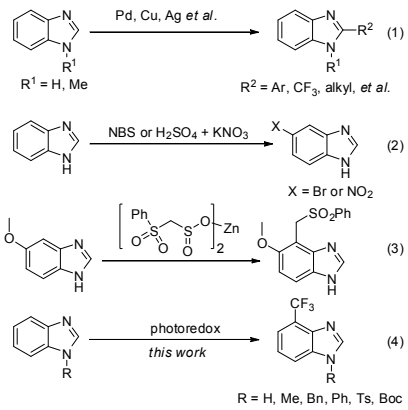
This protocol presented a new strategy for visible-light induced C-H trifluoromethyltion at C4 of benzimidazoles using Togini's reagent in the presense of *fac*-Ir(ppy)$_3$. It's Highlighted by its operational simplicity, mild reaction conditions, low catalyst loading and wide substrate scope in which electron-withdrawing, electron-donating groups and different protecting groups were tolerated.

Trifluoromethylated arenes and heteroarenes are widely present in pharmaceuticals, agrochemicals and drug candidates as the trifluoromethyl group can improve the chemical activity, stability and biological properties of the target molecules.[1] Therefore, the synthesis of trifluoromethyl compounds containing (hetero)arenes have attracted considerable attentions from the chemists and become as a hot topic in organic chemistry.[2] However, traditional methods for introducing trifluoromethyl group into organic molecule by SF_4, SbF_4, SbF_4, BrF_3, or HF, limited its applications because of harsh conditions, bad tolerance of other functional groups and utility of toxic reagents.[3] More recently, several major progress were made in transition-metal catalyzed direct trifluoromethylation of (hetero)arenes wherein stoichiometric amounts of metal salts, organometallic complexes, preactivated substrates, directing groups and/or high temperatures were employed.[4-6] Beyond the above advances, visible light induced photoredox reaction has emerged as a novel and powerful strategy for direct trifluoromethylation of (hetero)arenes.[7] For example, pivotal progress has been recently reported from the Macmillan's group on the direct trifluoromethylation of unactivated (hetero)arenes using comercial available photocatalyst and household light source.[8] However, room still exists for the development of mild and effective strategies for the synthesis of trifluoromethyl (hetero)arenes with various substituent groups for feasible synthetic transfromations.



Scheme 1. Direct C-H functionlization of benzimidazoles

The benzimidazole motifs are well-known skeleton in nature alkaloids and pharmaceuticals[9] and thus considerable effort has been made to develop efficient methods for the preparation and modification of benzimidazole derivatives.[10] Among which the most efficient way for the structural modification is the direct C-H functionalization of benzimidazoles. However, in this regard most methods were focused on C2-functionalization by dimerization,[11] alkylation,[12] thiolation,[13] difluoroethylation,[14] acyl/aroylation,[15] arylation[16] and halogenation[17] (Scheme 1, eq. 1). Only few reports were documented on C5-bromination,[18] C5-nitration,[19] as well as C4-(phenylsulfonyl)methylation[20] (Scheme 1. eq. 2-3). To our best knowledge, only three examples of direct trifluoromethylation of benzimidazole were reported on C2-trifluoromethylation of benzimidazole which were from Qing, Togni and Cohen groups.[21] In the methodologies of Qing and Togni, C2 trifluoromethylation products of benzimidazoles were obtained in high to moderate yields. And in Cohen's protocol, without blocking certain positions in benzimidazoles, bad regioselective trifluoromethylation products were observed. Herein, we present the first example of

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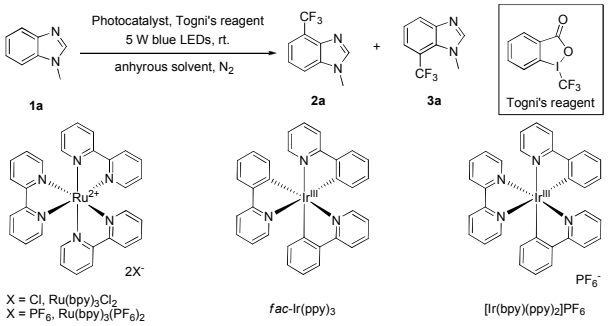
photocatalytic selective C4-trifluoromethylation of benzimidazole using *fac*-Ir(ppy)$_3$ as photocatalyst and Togni's reagent as CF_3 source.

Table 1. Optimization of C4-trifluoromethylation of N-methyl-benzimidazole[a]

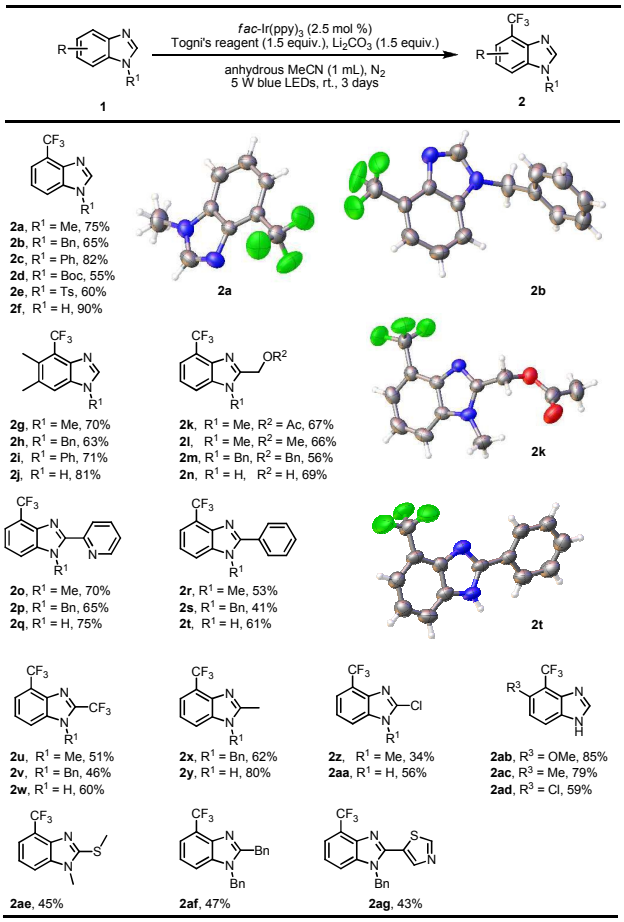


entry	photocatalyst (mol %)	Togni's reagent (equiv.)	base (equiv.)	solvent (anhydrous, mL)	time (d)	yield (%)[b] **2a** (**3a**)
1	$Ru(bpy)_3Cl_2$ (5)	1	none	MeCN	3	13 (10)
2	$Ru(bpy)_3Cl_2$ (5)	1	K_2CO_3 (1)	MeCN	3	25 (18)
3	$Ru(bpy)_3(PF_6)_2$ (5)	1	K_2CO_3 (1)	MeCN	3	10 (7)
4	*fac*-Ir(ppy)$_3$ (5)	1	K_2CO_3 (1)	MeCN	3	30 (trace)
5	[Ir(bpy)(ppy)$_2$]PF_6 (5)	1	K_2CO_3 (1)	MeCN	3	18 (trace)
6	*fac*-Ir(ppy)$_3$ (5)	1	K_2CO_3 (1)	DMF	3	21 (trace)
7	*fac*-Ir(ppy)$_3$ (5)	1	Cs_2CO_3 (1)	MeCN	3	30 (trace)
8	*fac*-Ir(ppy)$_3$ (5)	1	Li_2CO_3 (1)	MeCN	3	60 (trace)
9	*fac*-Ir(ppy)$_3$ (5)	1.5	Li_2CO_3 (1.5)	MeCN	3	75 (trace)
10	*fac*-Ir(ppy)$_3$ (5)	2	Li_2CO_3 (2)	MeCN	3	70 (trace)
11	*fac*-Ir(ppy)$_3$ (2.5)	1.5	Li_2CO_3 (1.5)	MeCN	3	75 (trace)
12	none	1.5	Li_2CO_3 (1.5)	MeCN	3	ND.
13[c]	*fac*-Ir(ppy)$_3$ (5)	1.5	Li_2CO_3 (1.5)	MeCN	3	ND.

[a]Reaction condition: **1a** (0.1 mmol), photocatalyst, Togni's reagent, base, solvent (anhydrous, 1.0 mL), nitrogen atmosphere, 5 W blue LEDs light, rt. [b]Isolated yield. [c]In darkness.

Initially, N-methyl-benzimidazole (**1a**) was used as model substrate for the condition optimization. When **1a** was reacted with 1.0 equiv. of Togni's reagent in 1.0 mL anhydrous CH_3CN using 5 mol % of $Ru(bpy)_3Cl_2$ as catalyst under nitrogen atmosphere, 13% of 1-methyl-4-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (**2a**) as well as 10% of 1-methyl-7-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (**3a**) was obtained (Table 1, entry 1) after irradiation with 5 W LEDs for 3 days. The yields of **2a** and **3a** were increased to 25% and 18% respectively by addition of 1.0 equiv. of K_2CO_3 to the reaction mixture (Table 1, entry 2). Subsequently, different catalysts such as $Ru(bpy)_3(PF_6)_2$, *fac*-Ir(ppy)$_3$, [Ir(bpy)(ppy)$_2$](PF_6) were screened and *fac*-Ir(ppy)$_3$ proved to show best efficient and regioselectivity (Table 1, entries 3-5). When the solvent, CH_3CN was switched to DMF, lower yield was obtained (Table 1, entry 6). Common bases, such as Cs_2CO_3, K_2CO_3 and Li_2CO_3 were also examined and Li_2CO_3 was shown to be beneficial for the reaction and the yield of **2a** was improved to 60% (Table 1, entries 4, 7, 8). The amount of base and Togni's reagent were also investigated, 1.5 equiv. of Li_2CO_3 and Togni's reagent under reaction condition increased the yield of **2a** up to 75% (Table 1, entries 8-10). It was glad to find that same yield of **2a** was obtained when the loading of catalyst was decreased to 2.5 mol % (Table1, entry 11). Further investigation indicated that both the light and photocatalyst were essential for the reaction (Table 1, entries 12-13).

Table 2. Scope study of selective C4-trifluoromethylation of benzimidazole[a]



[a]Reaction condition: 1 (0.1 mmol), 2.5 mol % *fac*-Ir(ppy)$_3$ (0.0025 mmol), 1.5 equiv. Togni's reagent (0.15 mmol), 1.5 equiv. Li_2CO_3 (0.15 mmol), anhydrous MeCN (1.0 mL), nitrogen atmosphere, 5 W blue LEDs light, rt., 3 days, isolated yield.

With the optimized conditions in hand, we then continued to elucidate the scope of this reaction, and the results were summarized in Table 2. As depicted in Table 2, for all tested substrates with different substituents, medium to good yields of final products were obtained. Different protecting groups on the nitrogen atom, such as Me (methyl), Bn (benzyl), Ph (phenyl), Ts (tosyl) and Boc (*t*-butyloxy carbonyl), were suitable for this reaction to afford the corresponding products in good yields (Table 2, **2a**-**2e**) in which the electron-donating protecting groups gave higher yields than the electron-withdrawing ones. As a bonus, the structures of **2a** and **2b** were confirmed by X-ray crystallographic analysis (SI, Table S1 and S2). Notably, benzimidazole without substituent and protecting groups delivered the desired product in excellent 90% yield (Table 2, **2f**). The presence of methyl groups at C5 and C6 positions of benzimidazole did not retard the reaction, and the desired products were formed in good yields (Table 2, **2g**-**2j**). Furthermore, substrates bearing ether, thioether, ester and free hydroxyl groups were successfully converted into the products in moderated yields (Table 2, **2k**-**2n**, **2ae**). The

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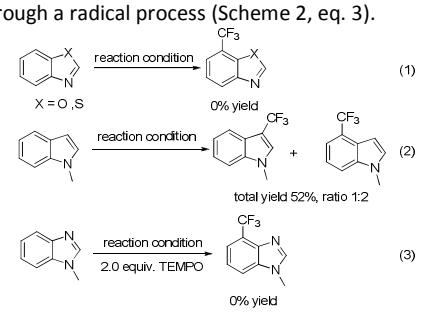
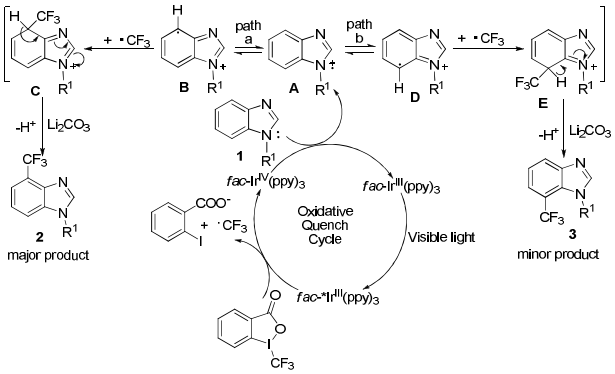
structure of **2k** was also identified by X-ray diffraction analysis (SI, Table S3). Remarkably, the imidazole ring bearing substituent groups, such as aryl, heteroaryl, CF_3, alkyl and halogen groups were also tolerant to form the corresponding products in good yields (Table 2, **2o**-**2z**, **2aa**, **2ag**) in which the structure of **2t** was further illustrated by X-ray crystallographic analysis (SI, Table S4). It worth noting that N-H benzimidazoles bearing electron withdrawing or donating groups at C5 position of the phenyl ring were also tolerant with the reaction conditions to form the desired products along with a trace amount of C7 trifluoromethylation products which might be owing to the similarity electron density at C4 and C7 with the effect of steric hindrance (Table 2, **2ab**-**2ad**).

To have a more insight into the reaction pathway, we also performed the following reactions as shown in Scheme 2. Firstly, if benzoxazole or benzothiazole was used as substrate, no expected product was obtained (Scheme 2, eq. 1). When N-methyl-indole replaced **1a** in this reaction, C3 and C4 trifluoromethylation of N-methyl-indole mixed isomers were isolated as main products with a ratio of 1:2 (Scheme 2, eq. 2).[22] In addition, if 2.0 equiv. TEMPO were added into the reaction system, no desired products were observed by TLC and GC-MS, which suggested the reaction might undergo through a radical process (Scheme 2, eq. 3).



Scheme 2. Scope study and control experiments



Scheme 3. Plausible mechanism

Herein, based on the above results and previous literatures[23], a plausible radical mechanism for this reaction was proposed in Scheme 3. Initially, with the irradiation of visible light, photoredox catalyst [*fac*-Ir$^{\square}$(ppy)$_3$] was excited to [*fac*-Ir$^{\square}$(ppy)$_3$]* which was oxidized by Togni's reagent to generate [*fac*-Ir$^{\square}$(ppy)$_3$] and CF_3 radical.[24] The formed [*fac*-Ir$^{\square}$(ppy)$_3$] was then reduced by substrate **1** to regenerate [*fac*-Ir$^{\square}$(ppy)$_3$] and furnish a radical cation intermediate **A** which could either undergo pathway a or b *via* electron resonation to form intermediate **B** or **D**, respectively. The CF_3 radical addition to intermediate **B** or **D** led to intermediate **C** or **E** which underwent a deprotonation in the presense of base to deliver the major product **2** or minor product **3**, respectively. In summary, we developed a visible light induced C4 selective C-H trifluoromethylation of benzimidazoles using Togni's reagent as CF_3 source and *fac*-Ir(ppy)$_3$ as photoredox catalyst under mild conditions. The protocol was highlighted by its low catalyst loading, simple operations, and wide substrate scope. Furthermore, this methodology has potential to be extended to other (hetero)arenes trifluoromethylation reactions.

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