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Monofluoromethylation of Tetrahydroisoquinolines by Visible-light Induced Direct C(sp^3)–H Bond Activation

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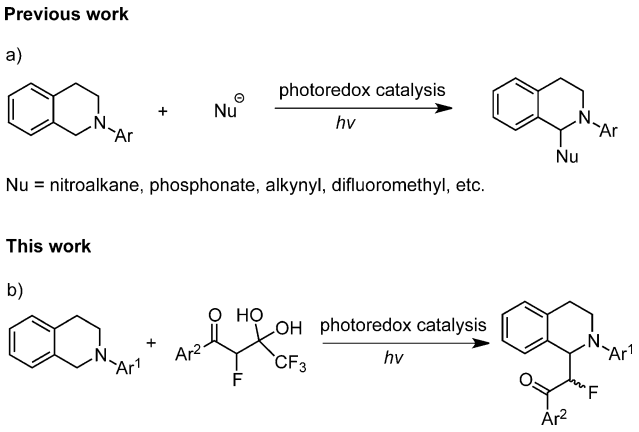
Abstract: A visible-light photoredox-catalyzed reaction of tetrahydroisoquinolines with β-fluorinated *gem*-diols results in the formation of C1-monofluoromethylated tetrahydroisoquinolines via C(sp^3)–H bond activation. This protocol provides a new method to introduce a CF group with stable, easily-prepared monofluorinated *gem*-diol as CF source. A mechanistic investigation is presented based on control experiments.

Keywords: C(sp^3)–H activation; monofluoromethylation; photoredox catalytic; tetrahydroisoquinolines.; visible light

The direct functionalization of C(sp^3)–H bonds provides a potent strategy to access numerous complex molecules,[1] as C(sp^3)–H bonds are universal in organic compounds. Despite the great achievements in this area, the development of a mild and effective method to activate C(sp^3)–H bond with clean and renewable energy is of high interest. Visible light is an abundant and non-polluting energy source in nature. For the past few years, visible-light induced photoredox catalysis has aroused more and more attention,[2] and some fundamental chemical transformations have been brought out *via* visible light irradiation.[3] In this context, direct activation of C(sp^3)–H bonds promoted by visible-light has been well developed (Scheme 1-a).[4,5]

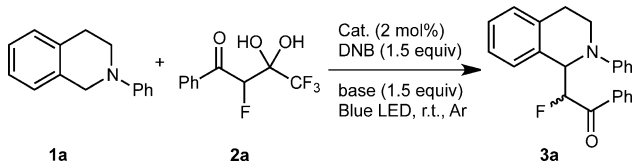
Fluoroalkyl containing organic compounds are of great importance due to their special biological properties, such as binding affinity, and bioavailability.[6] Over the past decades, many methods have been demonstrated to introduce fluoroalkyl groups into useful molecules,[7] but the development of practical fluoroalkylation methods under mild conditions remains in high demand. Visible-light photoredox catalysis has been applied to fluoromethylations.[8] Recently, our group achieved visible-light-induced difluoromethylation of tetrahydroisoquinolines with β,β-difluorinated *gem*-diols as CF_2 sources.[9] It was found that generation of nucleophilic α-fluoroenolates with β-fluorinated *gem*-diols is an efficient strategy to install CF group into useful scaffolds.[10] Given our interest in visible-light promoted C–H bond activation[11] and in consideration of the importance of fluoro-containing organic compounds, herein we report monofluoromethylation of tetrahydroisoquinolines with easily-prepared trifluoromethyl β-fluorinated *gem*-diols as CF sources.

We started our investigation by subjecting *N*-phenyl substituted tetrahydroisoquinoline **1a** and α-trifluoromethyl β-fluorinated *gem*-diol **2a** in the presence of catalytic amount of commercial available Ru(bpy)$_3$Cl$_2$. With air as the oxidant, tetrahydroisoquino-



Scheme 1. Photoredox catalytic functionalization of tetrahydroisoquinolines.

Table 1. Optimization of reaction conditions[a]



Entry	Cat.	Solvent	Base	Yield [%][b]	dr[c]
1	**5a**	DCM	DABCO	55	1.2:1
2	**5b**	DCM	DABCO	65	1.2:1
3	**5c**	DCM	DABCO	40	1.2:1
4	**5d**	DCM	DABCO	26	ND
5	**5b**	DCE	DABCO	29	1.2:1
6	**5b**	CH_3CN	DABCO	56	1.2:1
7	**5b**	THF	DABCO	trace	ND
8	**5b**	DMF	DABCO	18	1.2:1
9	**5b**	DMSO	DABCO	15	ND
10	**5b**	DCM	NEt_3	73	1.3:1
11	**5b**	DCM	DIPEA	57	1.2:1
12	**5b**	DCM	2,6-lutidine	41	1.2:1
13	**5b**	DCM	Na_2CO_3	52	1:1.2
14	**5b**	DCM	K_2CO_3	58	1.2:1
15	**5b**	DCM	K_3PO_4	20	1.4:1
16[d]	**5b**	DCM	NEt_3	68	1.3:1
17[e]	**5b**	DCM	NEt_3	trace	–
18[f]	**5b**	DCM	NEt_3	trace	–
19[g]	**5b**	DCM	NEt_3	NR	–

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), DNB (0.3 mmol), cat. (2 mol%), base (0.3 mmol), solvent (1 mL), irradiated with a 5W blue LED for 48 h under Ar at r.t.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] 1 mol% catalyst irradiated with a 5W blue LED for 60 h.
[e] No catalyst.
[f] No light.
[g] No DNB. DNB = 1,3-dinitrobenzene. ND = not determined. NR = no reaction.

line **1a** was rapidly consumed, but only a 29% yield of the desired product was obtained (see Table S1 in the SI). The side reaction to the oxidized amide was the main reason responsible for the low yield. In order to improve the yield, we tested different oxidants (see Table S1 the in SI). Finally, we chose *meta*-dinitrobenzene (DNB) as an ideal oxidant and obtained the expected product in 55% yield (Table 1, Entry 1). Encouraged by this result, we then surveyed different photocatalysts, additives and solvents (Table 1, Entries 2–15). First, a range of iridium and ruthenium photocatalysts (Figure 1) were tested (Table 1, Entries 1–4), $[Ru(phen)_3]Cl_2$ (**5b**) was chosen as a catalyst for further study because it exhibited best reaction yield. A careful survey of solvents was then performed, which revealed CH_2Cl_2 as optimal (Table 1, Entries 3, 6–9). To further improve the yield, various bases were investigated (Table 1, Entries 10–15), which indicated that NEt_3 showed the best result (Table 1, Entry 10). However, all of the bases tested provided poor diastereoselectivity. Final optimization showed that the reaction could also provide comparable result with prolonged reaction time when the catalyst loading was reduced to 1 mol% (Table 1, Entry 16). Control experiments indicated that only a small amount of desired product was generated without light and catalyst (Table 1, entries 17, 18), and no product was detected without DNB as oxidant (Table 1, Entry 19). The reaction showed the best reactivity with 2 mol% $[Ru(phen)_3]Cl_2$, 1.5 equivalents of DNB and 1.5 equivalents of triethylamine under irradiation by 5W blue LED (Table 1, Entry 10).

With the optimal reaction conditions established, we then explored the substrates scope of the visible-light induced photoredox reaction. First, various *N*-aryltetrahydroisoquinolines were tested, and the corresponding results were showed in Table 2. The position of substituents on the *N*-aryl groups also significantly influenced the reaction results. Generally, *para*-substituted substrates (Table 2, Entries 2–6) proved products in very good yields, whereas *meta*-substituted and *ortho*-substituted substrates (Table 2, Entries 10–13) resulted in moderate to good yields. The investigation of substituents effect showed that substrates bearing electron-donating groups furnished higher yields than substrates with electron-withdrawing groups. When a strong electron-withdrawing CF_3 group was installed on the *N*-substituted aromatic ring, the reaction proceeded sluggishly and only 26% yield was obtained, but with good diastereoselectivity (Table 2, Entry 8). When the substituted tetrahydroi-

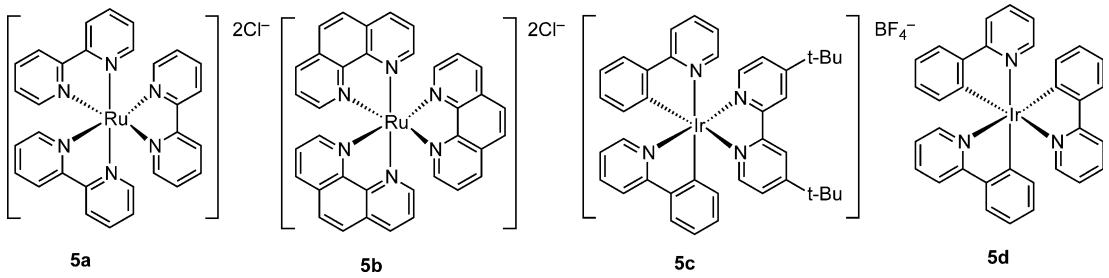
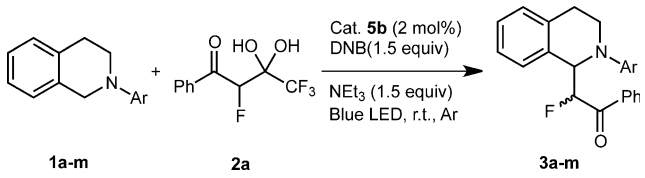


Figure 1. Iridium and ruthenium photocatalysts.

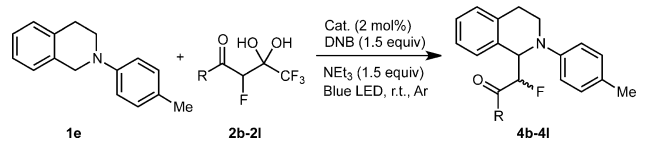
Table 2. The reaction scope of tertiary amines[a]

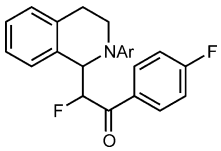
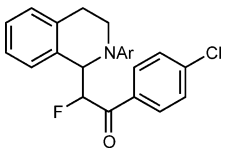
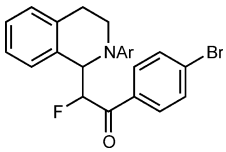
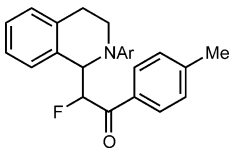
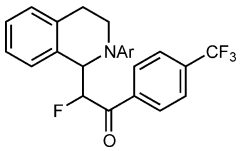
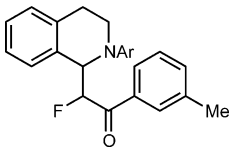
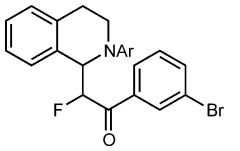
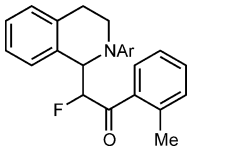
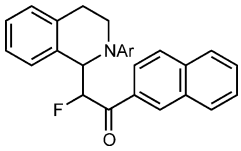
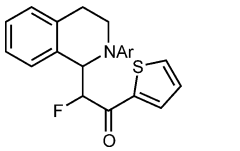
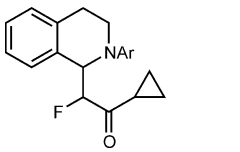


Entry	Ar	1	3	Yield [%][b]	dr[c]
1	Ph	**1a**	**3a**	73	1.3:1
2	4-F-C_6H_4	**1b**	**3b**	71	3:1
3	4-Cl-C_6H_4	**1c**	**3c**	64	2.5:1
4	4-Br-C_6H_4	**1d**	**3d**	60	2:1
5	4-Me-C_6H_4	**1e**	**3e**	85	1.2:1
6	4-*t*Bu-C_6H_4	**1f**	**3f**	88	1.3:1
7	3,4-Me-C_6H_4	**1g**	**3g**	78	1.1:1
8[d]	4-CF_3-C_6H_4	**1h**	**3h**	26	>10:1
9[e]	Ph	**1i**	**3i**	80	1.1:1
10	3-F-C_6H_4	**1j**	**3j**	61	2:1
11	3-Br-C_6H_4	**1k**	**3k**	59	3:1
12	3-Me-C_6H_4	**1l**	**3l**	65	1.3:1
13	2-F-C_6H_4	**1m**	**3m**	57	1.5:1

[a] Reaction conditions: see details in Experimental Section.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] Reaction time: 72 h.
[e] 6,7-Dimethoxy substituted tetrahydroisoquinoline was used.

Table 3. The reaction scope of β-fluorinated *gem*-diols[a]

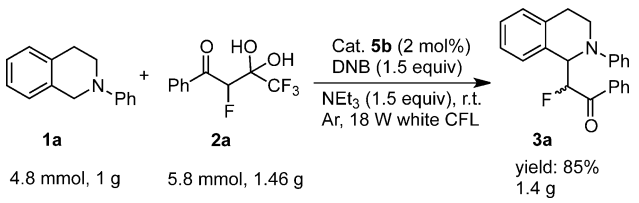


Entry	4	Product[b]	Yield [%][c]	dr[d]
1	**4b**		63	1.3:1
2	**4c**		69	1.2:1
3	**4d**		75	1.2:1
4	**4e**		68	1.2:1
5	**4f**		72	1.5:1
6	**4g**		71	1.1:1
7	**4h**		79	1.3:1
8	**4i**		66	1.2:1
9	**4j**		73	1.3:1
10	**4k**		76	2:1
11	**4l**		42	>10:1

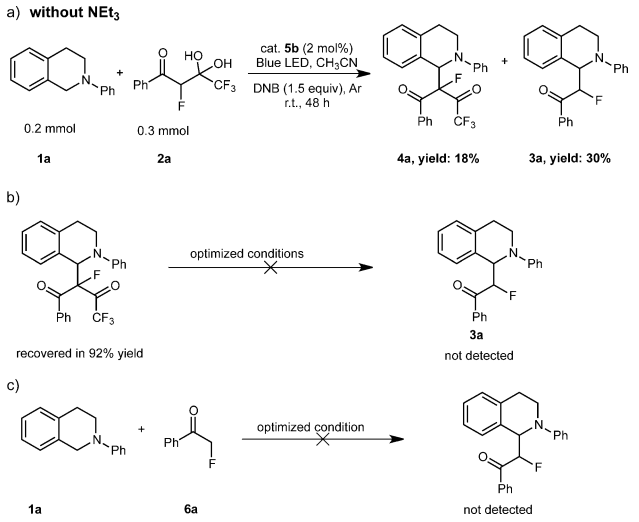
[a] Reaction conditions: see details in Experimental Section.
[b] Ar = 4-Me-C_6H_4.
[c] Isolated yield.
[d] Determined by ^{1}H NMR.

soquinoline derivative **1i** was employed, the desired product **3i** could be isolated in 80% yields (Table 2, Entry 9).

We next sought to investigate the scope of β-fluorinated *gem*-diols in this reaction. As shown in Table 3, a variety of structurally diverse compounds undergo efficient reaction with *N*-aryltetrahydroisoquinoline **1e**. Substrates with various electron-donating or electron-withdrawing groups on the aromatic rings were compatible in the reaction (Table 3, Entries 1–9). Heteroarenes such as thiophene also showed good result (Table 3, Entry 10). Note that an aliphatic substituted substrate could provide the corresponding product in 42% yield (Table 3, Entry 11).



Scheme 2. Scale-up experiment.

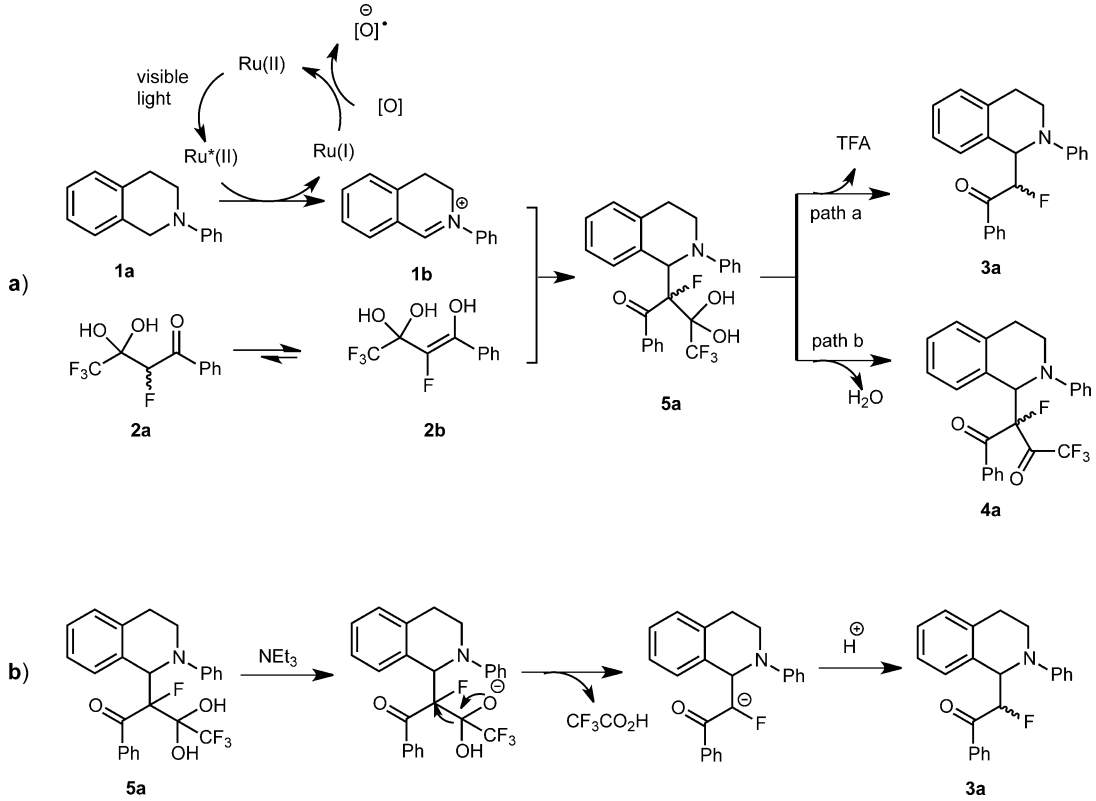


Scheme 3. Investigation of possible mechanism.

Furthermore, an additional scale-up experiment was performed to show the potential of this method in practical application (Scheme 2). By treatment of **1a** (4.8 mmol, 1 g) with **2a** (5.8 mmol, 1.46 g) in the presence of 2 mol% **5b**, the desired product was obtained in 85% yield (1.4 g), showing that this protocol could be suitable for large-scale synthesis.

Then we engaged in exploring the possible mechanism of this reaction. First, we conducted the reaction without the presence of NEt_3. To our surprise, besides the decarboxylated product **3a**, we also detected compound **4a** in 18% yield (Scheme 3-a). To determine the relationship between **3a** and **4a**, we isolated pure **4a** and subjected it to the optimized conditions, and no decarboxylated product **3a** was generated (Scheme 3-b). This indicated that **3a** was not derived through C–C bond cleavage of **4a**. As shown in Scheme 3-c, exposure of **6a**[12] and *N*-phenyl tetrahydroisoquinoline **1a** to the optimized conditions provided no desired product, suggesting that Mannich addition took place before the release of trifluoroacetate.

Based on the studies described above, we propose a plausible mechanism (Scheme 4). At first, iminium **1b** is formed by SET/dehydrogenation procedures under photocatalysis conditions.[3b,f] Coupling of this highly active intermediate with **2b** (enolization formation of **2a**) provides intermediate **5a**, which could fur-



Scheme 4. Possible mechanism.

ther participates in next transformation in two possible pathways: a) loss of trifluoroacetate from intermediate **5a** to give desired product **3a** and b) dehydration of **5a** to give **4a** (Scheme 4-a). Under alkaline condition, intermediate **5a** prefers to undergo C–C bond cleavage, resulting in **3a** as the major product (Scheme 4-b).

In summary, we have developed a mild monofluoromethylation of tetrahydroisoquinolines via visible light-induced photoredox catalysis with stable and easily-obtained β-fluorinated *gem*-diols as the CF source. This transformation allowed us to introduce the CF group to the corresponding tetrahydroisoquinolines in good yields. Preliminary investigations provide a general understanding of the reaction mechanism.

Experimental Section

General Procedure

To a 10 mL Schlenk flask equipped with a magnetic stir bar was added tetrahydroisoquinoline (0.2 mmol), β-fluorinated *gem*-diol (0.24 mmol), DNB (0.3 mmol), and $[Ru(phen)_3]Cl_2$ (**5b**, 0.004 mmol, 2 mol%). The tube was degassed by alternating vacuum evacuation (5 min) and argon backfill three times. CH_2Cl_2 (1 mL) was added followed by NEt_3 (0.3 mmol). The mixture was then irradiated with a 5W blue LED 200 cm strip at room temperature for 48 h. After the starting material was consumed as indicated by TLC, the mixture was subjected to flash chromatography (petroleum ether 60–90/EtOAc, 15:1) on silica gel to give the desired product.

Procedure of Scale-up Experiment

To a 50 mL Schlenk flask equipped with a magnetic stir bar was added tetrahydroisoquinoline **1a** (4.8 mmol, 1.0 g), β-fluorinated *gem*-diol **2a** (5.8 mmol, 1.46 g), DNB (7.2 mmol, 1.2 g), $[Ru(phen)_3]Cl_2$ (**5b**, 0.096 mmol, 68 mg, 2 mol%). The tube was degassed by alternating vacuum evacuation (5 min) and argon backfill three times. CH_2Cl_2 (24 mL) was added followed by NEt_3 (7.2 mmol, 0.73 g). The mixture was then irradiated by two 18W white fluorescent light at room temperature for 3 days. Then the mixture was washed with brine, dried, and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel to give monofluoromethylated tetrahydroisoquinoline **3a** as a yellow oil; yield: 1.4 g (85%).

Acknowledgements

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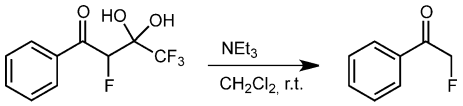
[12] Substrate **2a** slowly decomposes into **6a** under basic conditions at room temperature.



2a **6a**

Monofluoromethylation of Tetrahydroisoquinolines by Visible-light Induced Direct C(sp^3)–H Bond Activation

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