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Visible-light-induced direct C(sp3)–H difluromethylation of tetrahydroisoquinolines with the *in situ* generated difluoroenolates†

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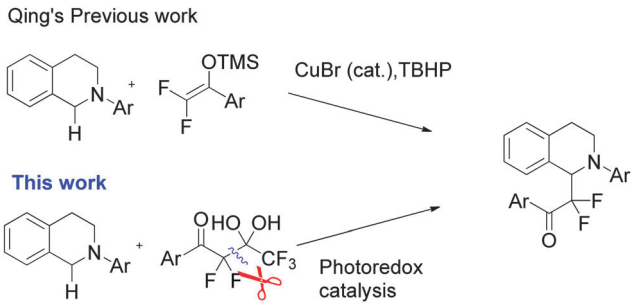
An effective approach to C1-difluoromethylated tetrahydroisoquinoline derivatives has been developed through C–H functionalization of tertiary amines by visible-light photoredox catalysis. This method uses stable, easily obtained α,α-difluorinated gem-diol as the CF_2 source. The corresponding products were obtained in moderate to high yields at ambient temperature.

Fluorinated organic compounds have attracted considerable attention from the pharmaceutical, chemical, and agrochemical industries due to their beneficial effects on the physiochemical properties and pharmacological profiles of drugs.[1] Over the past decades, great efforts have been dedicated to developing efficient methods to introduce trifluoromethyl and monofluoromethyl groups into molecules.[2] However, the development of available and practical difluoromethylation methods remains largely elusive and represents a challenge.[3] Recently, it was found that generation of nucleophilic α,α-difluoroenolates using α,α-difluorinated gem-diols is an efficient strategy to install the CF_2 group into useful scaffolds.[4] For the past few years, visible light photoredox catalysis has emerged as a powerful method to functionalize a large number of organic compounds.[5] With our continual interest in photoredox catalysis,[6] we focus our attention on direct C–H difluoromethylation of tertiary amines by means of visible-light photoredox catalysis, since the tertiary amines could produce the highly active iminium ions by irradiation with visible-light.[7] In 2009, Qing and co-workers reported copper-catalyzed oxidative difluoromethylation of tertiary amines by using TBHP as an oxidant.[8] Thus, our protocol to use gem-diols for visible light photoredox difluoronation of tertiary amines could be a new and efficient protocol to introduce difluoromethylene into nitrogen-containing compounds (Scheme 1).



Scheme 1 Difluoromethylation of tertiary amines.

We began our study by coupling *N*-aryl substituted tetrahydroisoquinoline **1a** with α,α-difluorinated gem-diol **2a** in the presence of a catalytic amount of commercially available $Ru(bpy)_3Cl_2$. Unfortunately only a trace amount of desired product was detected accompanied by the difluorinated compound due to the mismatch between reaction rates of the C–C bond cleavage and the formation of imine (see details in ESI†). We envisioned that adding the α,α-difluorinated gem-diol to the reaction system after full conversion of the iminiums[7q,r] should be helpful to prevent the undesired side reaction.

Next, we investigated the reaction using $Ru(bpy)_3Cl_2$ as a catalyst and CCl_4 as an oxidant, and 58% yield was obtained (Table 1, entry 1). Encouraged by this result, the reaction conditions were screened in detail. Firstly, different oxidants were tested and it was found that the oxidant played an important role in the reaction because the yields decreased sharply when either $CBrCl_3$ or CBr_4 was used (Table 1, entries 2 and 3). It was found that CH_3CN was the best solvent after screening various organic solvents (Table 1, entries 4–7). Notably, the yield could be improved to 77% by increasing the NEt_3 loading to 4 equiv. (entry 9). In addition, other bases could not efficiently improve the yields (Table 1, entries 10–13).

With the established optimal reaction conditions in hand, we next engaged in expanding substrate scope. First, various tetrahydroisoquinolines were tested and the desired products could be obtained in good to excellent yields (60–95%, Table 2, entries 1–15). It was found that *N*-aryl substituted tetrahydroisoquinolines

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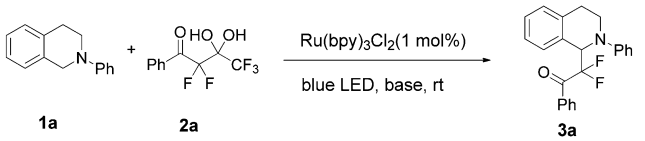
Table 1 Optimization of reaction conditions[a]



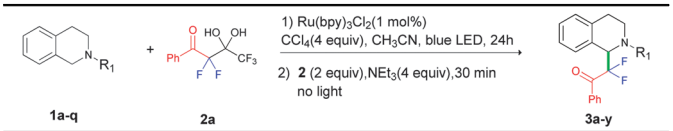
1a 2a 3a

Entry	Oxidant	Solvent	Base	Yield[b] (%)
1	CCl_4	CH_3CN	NEt_3 (2 equiv.)	58
2	$CBrCl_3$	CH_3CN	NEt_3 (2 equiv.)	22
3	CBr_4	CH_3CN	NEt_3 (2 equiv.)	28
4	CCl_4	CH_2Cl_2	NEt_3 (2 equiv.)	54
5	CCl_4	THF	NEt_3 (2 equiv.)	NR
6	CCl_4	DMF	NEt_3 (2 equiv.)	36
7	CCl_4	DMSO	NEt_3 (2 equiv.)	25
8	CCl_4	CH_3CN	NEt_3 (3 equiv.)	69
9	**CCl_4**	**CH_3CN**	**NEt_3 (4 equiv.)**	77
10	CCl_4	CH_3CN	DABCO (4 equiv.)	56
11	CCl_4	CH_3CN	K_2CO_3 (4 equiv.)	55
12	CCl_4	CH_3CN	K_3PO_4 (4 equiv.)	44
13	CCl_4	CH_3CN	$Mg(OtBu)_2$ (4 equiv.)	25

[a] The reactions were carried out with **1a** (0.2 mmol), an oxidant (0.8 mmol,), and $Ru(bpy)_3Cl_2$ (1 mol%) in CH_3CN (2 mL) at room temperature and 5 W blue LED for 24 hours. Then light was turned off, **2a** (0.4 mmol) and base (0.8 mmol) were added, and the reaction was carried for another 30 minutes at room temperature. [b] Isolated yield.

bearing electron-donating groups could furnish higher yields than those bearing electron-withdrawing groups. For example, *N*-3,4-dimethylphenyl substituted tetrahydroisoquinoline afforded the desired product **3h** in 95% yield, but the substrate bearing a strong electron-withdrawing CF_3 on the phenyl ring could only produce the product **3i** in 36% yield, even when the oxidation reaction time was increased to 60 hours. The position of substituents on the *N*-aryl groups also significantly influenced

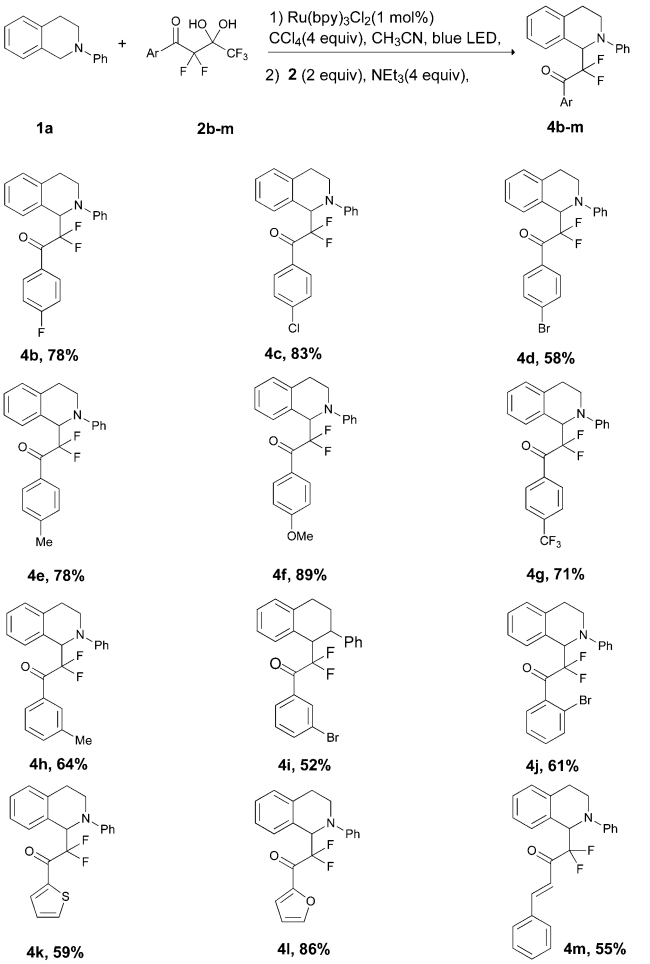
Table 2 The reaction scope[a]



1a-q 2a 3a-y

Entry	R_1	1	3	Yield[b] (%)
1	C_6H_5	**1a**	**3a**	77
2	4-F-C_6H_4	**1b**	**3b**	72
3	4-Cl-C_6H_4	**1c**	**3c**	63
4	4-Br-C_6H4	**1d**	**3d**	55
5	4-OMe-C_6H_4	**1e**	**3e**	77
6	4-Me-C_6H_4	**1f**	**3f**	63
7	4-*t*-Bu-C_6H_4	**1g**	**3g**	89
8	3,4-Me-C_6H_3	**1h**	**3h**	95
9[c]	4-CF_3-C_6H_4	**1i**	**3i**	36
10	3-F-C_6H_4	**1j**	**3j**	60
11	3-Br-C_6H_4	**1k**	**3k**	52
12	2-F-C_6H_4	**1l**	**3l**	62
13	2-OMe-C_6H_4	**1m**	**3m**	87
14[d]	C_6H_5	**1n**	**3n**	76
15	Bn	**1o**	**3o**	61
16	*N*,*N*-Dimethylaniline			NR

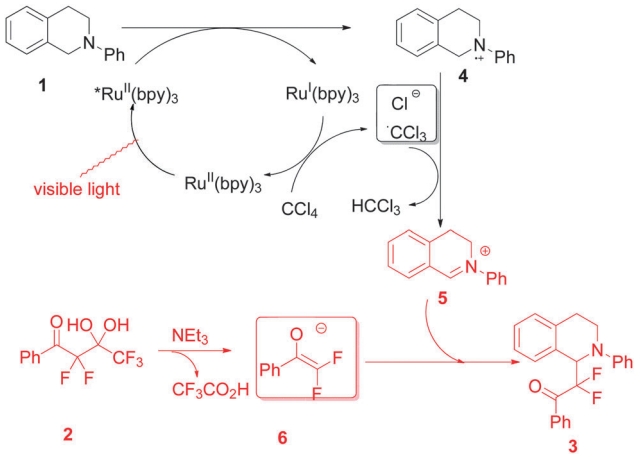
[a] The reactions were carried out with **1** (0.2 mmol), CCl_4 (0.8 mmol,), and $Ru(bpy)_3Cl_2$ (1 mol%) in CH_3CN (2 mL) at room temperature and 5 W blue LED for 24 hours. Then light was turned off, **2a** (0.4 mmol) and NEt_3 (0.8 mmol) were added, and the reaction was carried out for another 30 minutes at room temperature. [b] Isolated yield. [c] Reaction time for the oxidation step lengthened to 60 hours. [d] 6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline was used. NR = no reaction.



Scheme 2 The reactions were carried out with **1a** (0.2 mmol), CCl_4 (0.8 mmol) and $Ru(bpy)_3Cl_2$ (1 mol%) in CH_3CN (2 mL) at room temperature and 5 W blue LED for 24 hours. Then **2** (0.4 mmol) and NEt_3 (0.8 mmol) were added, and the reaction was carried out for another 30 minutes at room temperature. Isolated yields.

the reaction results. *para*-Substituted analogues generally provided higher yields compared to *meta*-substituted (**3b** *vs.* **3j**, **3d** *vs.* **3k**) and *ortho*-substituted (**3b** *vs.* **3j**) substrates. *N*-Benzyl substituted substrate **1o** was also found to be effective for the reaction, and 61% yield was obtained. When *N*,*N*-dimethylaniline was tested, no desired product was detected (Table 2, entry 16). Next, we examined the reaction scope with various substituted gem-diol derivatives (Scheme 2). The experimental results suggested that α,α-difluorinated gem-diols with a variety of substituted groups could give the desired products in moderate to good yields. Electronic properties of substituted groups had little influence on reaction yields (**4b–4m**). In consideration of the prevalence of heteroarenes in drug molecules, heteroaromatic substrates (**4k**, **4l**) were tested, and good yields were obtained. It is worth mentioning that the delocalized conjugated substrate (**4m**) was also a viable participant which further expanded the substrate scope.

The possible mechanism is shown in Scheme 3. At first, irradiation of $Ru(bpy)_3$(II) by visible light generates the excited-state *$Ru(bpy)_3$(II) which could be reductively quenched by *N*-phenyl-tetrahydroisoquinoline accompanied by the formation



Scheme 3 Possible mechanism.

of radical cation **4** and Ru(bpy)$_3$(I).[7q] The resulting Ru(bpy)$_3$(I) reduces CCl_4 to the chlorine anion and the trichloromethyl radical. The trichloromethyl radical abstracts the H-atom from radical cation **4** generating iminium **5**. Under basic conditions, α,α-difluorinated gem-diol **2** undergoes trifluoroacetate-release through C–C bond fragmentation which could *in situ* generate difluoroenolate **6**. This active intermediate could be rapidly trapped by iminium **5** to generate product **3**.

In summary, we have developed an effective method to synthesize C1-difluoromethylated *N*-aryltetrahydroisoquinolines by means of visible-light photoredox catalysis using α,α-difluorinated gem-diol as a difluoromethylene reagent under mild conditions. This protocol was fairly feasible and easy-to-handle, and inexpensive reagent CCl_4 was used here as the sacrificial oxidant.

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Notes and references

1 Recent reviews: (*a*) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; (*b*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320.

2 For selected reviews, see: (*a*) T. Furuya, A. S. Kamlet and T. Ritter, *Nature*, 2011, **473**, 470; (*b*) O. A. Tomashenko and V. V. Grushin, *Chem. Rev.*, 2011, **111**, 4475; (*c*) T. Besset, C. Schneider and D. Cahard, *Angew. Chem., Int. Ed.*, 2012, **51**, 5048; (*d*) C. Hollingworth and V. Gouverneur, *Chem. Commun.*, 2012, **48**, 2929.

3 For recent examples, see: (*a*) X. Shen, W. Miao, C. Ni and J. Hu, *Angew. Chem., Int. Ed.*, 2014, **53**, 775; (*b*) X. Shen, Z. Min, C. Ni, W. Zhang and J. Hu, *Chem. Sci.*, 2014, **5**, 117; (*c*) Q. Min, Z. Yin, Z. Feng, W. Guo and X. Zhang, *J. Am. Chem. Soc.*, 2014, **136**, 1230; (*d*) Z. Feng, Q. Min, Y. Xiao, B. Zhang and X. Zhang, *Angew. Chem., Int. Ed.*, 2014, **53**, 1669; (*e*) X. Wang, G. Liu, X. Xu, N. Shibata, E. Tokunaga and N. Shibata, *Angew. Chem., Int. Ed.*, 2014, **53**, 1827; (*f*) P. S. Fier and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2013, **52**, 2092; (*g*) L. Li, F. Wang, C. Ni and J. Hu, *Angew. Chem., Int. Ed.*, 2013, **52**, 12390; (*h*) G. K. Surya Prakash, C. Ni, F. Wang, Z. Zhang, R. Haiges and G. A. Olah, *Angew. Chem., Int. Ed.*, 2013, **52**, 10835.

4 (*a*) P. Zhang and C. Wolf, *Angew. Chem., Int. Ed.*, 2013, **52**, 7869; (*b*) P. Zhang and C. Wolf, *J. Org. Chem.*, 2012, **77**, 8840; (*c*) C. Han, E. H. Kim and D. A. Colby, *J. Am. Chem. Soc.*, 2011, **133**, 5802; (*d*) J. P. John and D. A. Colby, *J. Org. Chem.*, 2011, **76**, 9163.

5 Representative reviews: (*a*) M. N. Hopkinson, B. Sahoo, J. Li and F. Glorius, *Chem. – Eur. J.*, 2014, **20**, 3874; (*b*) J. Xie, H. Jin, P. Xu and C. Zhu, *Tetrahedron Lett.*, 2014, **55**, 36; (*c*) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322; (*d*) J. Xuan and W. Xiao, *Angew. Chem., Int. Ed.*, 2012, **51**, 6828; (*e*) J. M. R. Narayanam and C. R. J. Stephenson, *Chem. Soc. Rev.*, 2011, **40**, 102.

6 (*a*) J. Xie, X. Yuan, A. Abdukader, C. Zhu and J. Ma, *Org. Lett.*, 2014, **16**, 1768; (*b*) P. Xu, A. Abdukader, K. Hu, Y. Cheng and C. Zhu, *Chem. Commun.*, 2014, **50**, 2308; (*c*) P. Xu, J. Xie, Q. Xue, C. Pan, Y. Cheng and C. Zhu, *Chem. – Eur. J.*, 2013, **19**, 14039; (*d*) Q. Xue, J. Xie, H. Jin, Y. Cheng and C. Zhu, *Org. Biomol. Chem.*, 2013, **11**, 1606; (*e*) J. Xie, P. Xu, H. Li, Q. Xue, H. Jin, Y. Cheng and C. Zhu, *Chem. Commun.*, 2013, **49**, 5672; (*f*) J. Xie, Q. Xue, H. Jin, H. Li, Y. Cheng and C. Zhu, *Chem. Sci.*, 2013, **4**, 1281.

7 Selected examples: (*a*) A. G. Condie, J. C. Gonzalez-Gomez and C. R. J. Stephenson, *J. Am. Chem. Soc.*, 2010, **132**, 1464; (*b*) J. Xuan, Y. Cheng, J. An, L. Lu, X. Zhang and W. Xiao, *Chem. Commun.*, 2011, **47**, 8337; (*c*) Y. Zou, L. Lu, L. Fu, N. Chang, J. Rong, J. Chen and W. Xiao, *Angew. Chem., Int. Ed.*, 2011, **50**, 7171; (*d*) M. Rueping, C. Vila, R. M. Koenigs, K. Poscharny and D. C. Fabry, *Chem. Commun.*, 2011, **47**, 2360; (*e*) M. Rueping, S. Zhu and R. M. Koenigs, *Chem. Commun.*, 2011, **47**, 8679; (*f*) D. P. Hari and B. Konig, *Org. Lett.*, 2011, **13**, 3852; (*g*) M. Rueping, S. Zhu and R. M. Koenigs, *Chem. Commun.*, 2011, **47**, 12709; (*h*) M. Rueping, D. Leonori and T. Poisson, *Chem. Commun.*, 2011, **47**, 9615; (*i*) S. Maity, M. Zhu, R. Shinabery and N. Zheng, *Angew. Chem., Int. Ed.*, 2012, **5**, 222; (*j*) D. B. Freeman, L. Furst, G. A. Condie and C. R. J. Stephenson, *Org. Lett.*, 2012, **14**, 94; (*k*) M. Rueping, R. M. Koenigs, K. Poscharny, D. C. Fabry, D. Leonori and C. Vila, *Chem. – Eur. J.*, 2012, **18**, 5170; (*l*) M. Rueping, J. Zoller, D. C. Fabry, K. Poscharny, R. M. Koenigs, T. E. Weirich and J. Mayer, *Chem. – Eur. J.*, 2012, **18**, 3478; (*m*) S. Cai, X. Zhao, X. Wang, Q. Liu, Z. Li and D. Z. Wang, *Angew. Chem., Int. Ed.*, 2012, **51**, 8050; (*n*) J. W. Tucker, Y. Zhang, T. F. Jamison and C. R. J. Stephenson, *Angew. Chem., Int. Ed.*, 2012, **51**, 4144; (*o*) S. Zhu and M. Rueping, *Chem. Commun.*, 2012, **48**, 11960; (*p*) D. A. DiRocco and T. Rovis, *J. Am. Chem. Soc.*, 2012, **134**, 8094; (*q*) D. B. Freeman, L. Furst, A. G. Condie and C. R. J. Stephenson, *Org. Lett.*, 2012, **14**, 94; (*r*) G. Bergonzini, C. S. Schindler, C. Wallentin, E. N. Jacobsen and C. R. J. Stephenson, *Chem. Sci.*, 2014, **5**, 112.

8 L. Chu, X. Zhang and F.-L. Qing, *Org. Lett.*, 2009, **11**, 2197.