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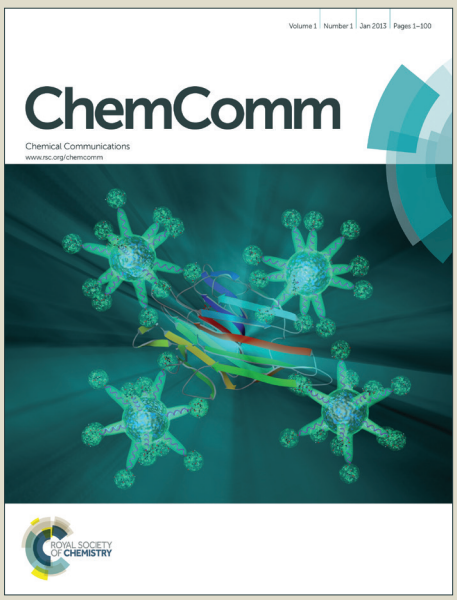

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Visible-light-induced direct C(sp3) -H difluromethylation of tetrahydroisoquinolines with the in-situ generated difluoroenolates

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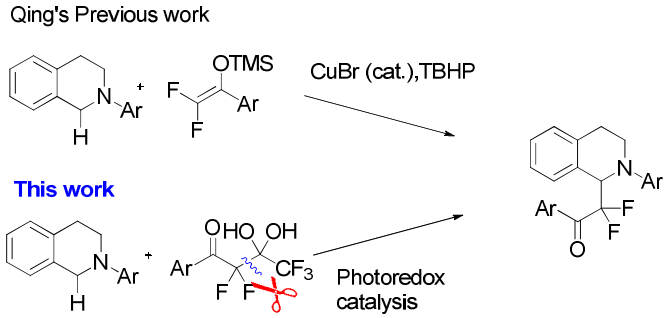
Weipeng Li,[a] Xuebin Zhu,[a] Haibin Mao,[a] Zhongkai Tang,[a] Yixiang Cheng,[a] and Chengjian Zhu*[ab]

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 were dedicated to developing efficient methods to introduce trifluoromethyl and monofluoromethy groups into molecules.[2] However, the development of available and practical difuoromethylation methods remains largely elusive and represents a challenge.[3] Recently, it was found that generation of nucleophilic α, α-difluoroenolates with α, α-difluorinated gem-diols is an efficient strategy to install 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 upon direct C-H difluoromethylation of tertiary amines by menas 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 a copper-catalyzed oxidative difluoromethylation of tertiary amines by using TBHP as 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).

We began our study by coupling of *N*-aryl substituted tetrahydroisoquinoline **1a** with α, α-difluorinated gem-diol **2a** in the presence of catalytic amount of commercial available $Ru(bpy)_3Cl_2$. Unfortunately only 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, 7r] should be helpful to prevent the undesired side reaction.



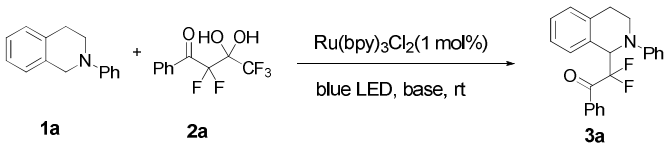
Scheme 1 Difluoromethylation of tertiary amines

Next, we investigated the reaction using $Ru(bpy)_3Cl_2$ as catalysis and CCl_4 as 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 oxidant played an important role in the reaction because the yields decreased sharply when $CBrCl_3$ 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 bearing electron-donating groups could furnish higher yields than that bearing electron -withdrawing groups. For example, *N*-3, 4- dimethylphenyl substituted tetrahydroisoquinoline afforded the desired product **3h** in 95% yield, but 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 the reaction results. Para-substituted analogues generally provided higher yields compared to meta-substituted (**3b** vs **3j**, **3d** vs **3k**) and orth-substituted (**3b** vs **3j**) substrates. *N*-benzyl substituted substrate **1o** was also effective for the reation, and 61% yield was obtained. When *N,N*-dimethylaniline was tested, and 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. Electron 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 delocalized conjugated substrate (**4m**) was also viable participant which further expanded the substrates scope.

Table 1 Optimization of reaction conditions [a]

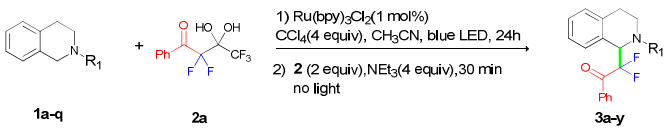


1a **2a** **3a**

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), oxidant (0.8 mmol,) $Ru(bpy)_3Cl_2$ (1 mol%) in CH_3CN(2 ml) at room temperature and 5W blue LED for 24 hours. Then turn light off, add **2a** (0.4 mmol), base (0.8 mmol), reaction for another 30 minutes at room temperature. [b] Isolated yield

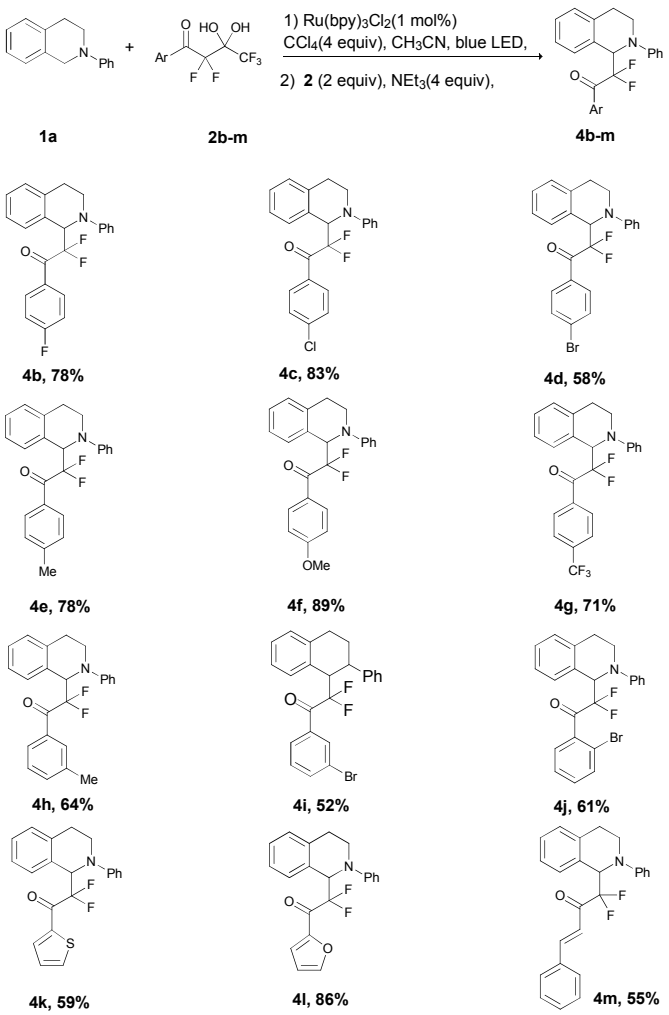
Table 2 The reaction scope [a]



1a-q **2a** **3a-y**

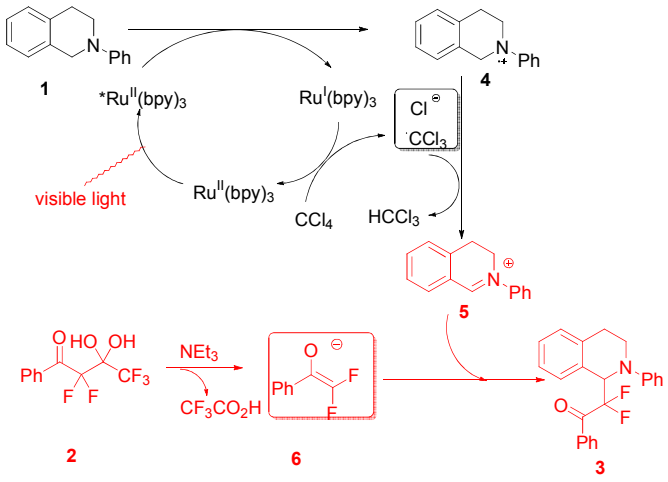
Entry	R_1	1	3	Yield[b](%)
1	C_6H_5	**1a**	**3a**	77
2	4-F-C_6H_4	**1b**	**3b**	72
3	4-Cl-C_6H_4	**1c**	**3c**	63
4	4-Br-C6H4	**1d**	**3d**	55
5	4-OMe-C_6H_4	**1e**	**3e**	77
6	4-Me-C_6H_4	**1f**	**3f**	63
7	4-t-Bu-C_6H_4	**1g**	**3g**	89
8	3,4,-Me-C_6H_3	**1h**	**3h**	95
9 [c]	4-CF_3-C_6H_4	**1i**	**3i**	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,) $Ru(bpy)_3Cl_2$ (1 mol%) in CH_3CN (2 mL) at room temperature and 5W blue LED for 24 hours. Then turn light off, add **2a** (0.4 mmol), NEt_3 (0.8 mmol), reaction 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) $Ru(bpy)_3Cl_2$ (1 mol%) in CH_3CN (2 mL) at room temperature and 5W blue LED for 24 hours. Then add **2** (0.4 mmol), NEt_3 (0.8 mmol), reaction for another 30 minutes at room temperature. Isolated yields.

The possible mechanism is showed in Scheme **3**. At first, irradiation of $Ru(bpy)_3(II)$ by visible light generates the excited-state $*Ru(bpy)_3(II)$ which could been reductive quenched by N-phenyl-tetrahydroisoquinoline accompanied by the formation of radical cation **4** and $Ru(bpy)_3(I)$.[7q] The resulting $Ru(bpy)_3(I)$ reduces CCl_4 to the chlorine anion and trichloromethyl radical. The trichloromethyl radical abstracts H-atom from radical cation **4** generating iminium **5**. Under base condition, α, α-difluorinated gem-diol **2** undergoes trifluoroacetate-release through C-C bond fragmentation which could in situ generates difluoroenolate **6**. This active intermediate could be rapidly trapped by iminium **5** to generate product **3**.



Scheme 3 Possible mechanism

Conclusions

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 difluoromethylene reagent under mild conditions. This protocol was fairly feasible and easy-to-handle, and inexpensive reagent CCl_4 was used here as the sacrificed oxidant.

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Notes and references

[a]*State Key Laboratory of Coordination Chemistry, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, P. R. China. E-mail: cjzhu@nju.edu.cn*
[b]*Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, 200032, China*

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1. Recent reviews: (a) K. Mu□ller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; (b) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320.
2 For selected reviews: (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, V. Gouverneur, *Chem. Commun.* 2012, **48**, 2929.
3 For rencent examples: (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; (d) X. Wang, G. Liu, X. Xu, N. Shibata, E. Tokunaga and N. Shibata, *Angew. Chem. Int. Ed.,* 2014, **53**, 1827; (e) P. S. Fier and J. F. Hartwig, *Angew. Chem. Int. Ed.*, 2013, **52**, 2092; (f) L. Li, F. Wang, C. Ni and J. Hu, *Angew. Chem. Int. Ed.*, 2013, **52**, 12390; (g) 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, 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.