Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: C. Xia, K. Wang, G. Wang and D. Y. Duan, *Org. Biomol. Chem.*, 2018, DOI: 10.1039/C8OB00511G.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C8OB00511G

Journal Name

COMMUNICATION

Iron-catalyzed *ortho* trifluoromethylation of anilines *via* picolinamide assisted photoinduced C-H functionalization †

0Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Chengcai Xia,* Kai Wang, Guodong Wang and Guiyun Duan

A convenient, oxidant free protocol was developed for *ortho* trifluoromethylation of aniline *via* picolinamide assisted Fe-promoted C-H functionalization under ultraviolet irradiation. Acetone in this transformation essentially acted as both solvent to dissolve reactants and low-cost radical initiators to generate CF_3 radical from Langlois' reagent efficiently. A broad substrate scope was tolerated and picolinamide bearing strong electron withdrawing groups also could be transformed into corresponding products with acceptable yields. Furthermore, the value of this method has been highlighted *via* the efficient synthesis of nonsteroidal anti-inflammatory drug floctafenine.

Introduction

In recent years, because of the unique properties, the trifluoromethyl group has been introduced into important structural units to improve the physicochemical property of a great deal of organic compounds, such as drug candidates and biomolecules (Figure 1).[1] Especially trifluoromethylated arenes have played an significant part in numerously vital organic compounds.[2] Therefore, the development of practical, safe as well as environmentally friendly methods for their preparation is a hot topic in today's organic synthesis.

The traditional approaches for the synthesis of trifluoromethylated arenes are based on the utilization of dangerous reagents, such as chlorine and hydrogen fluoride.[3] Subsequently, an increasing number of trifluoromethylation methods were demonstrated grounded on the use of aryl halides,[4] aryl boronic acids[5] and arylamines[6] as substrates, providing safe approaches to synthesize trifluoromethylated arenes. By contrast, the more effective route to CF_3-substituted arenes would be direct trifluoromethylation of C-H bonds of arenes.[7] For instance, Greaney and coworkers reported C-H trifluoromethylation by utilizing electron-rich arenes as substrate.[7c] Yu group developed *ortho* trifluoromethylation of benzamides through a directed C-H cupuration approach.[7d] And Zhang *et al*. demonstrated transition-metal-free direct trifluoromethylation of quinoline amides through radical cross-coupling.[7k] Despite these utilities represent very inspiring progress, excess oxidant, noble metal catalyst as well as harsh reaction temperature were usually indispensable. There is no doubt that the synthesis of concentrated peroxides is energy-intensive and dangerous. In this respect, the advance of an oxidant free trifluoromethylation methodology to access trifluoromethylated compounds under environmentally friendly and safe conditions has become a very important and challenging task for modern organic synthesis.

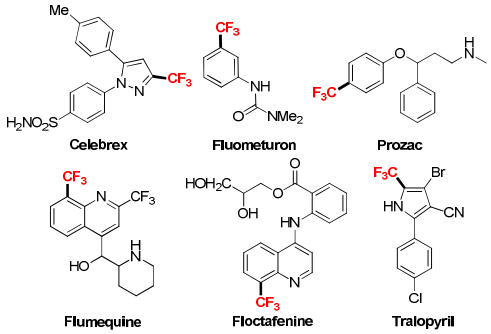
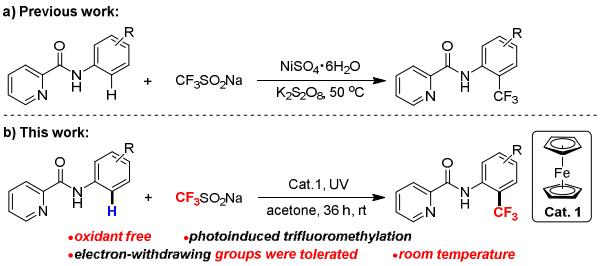


Figure 1 Representative compounds of (trifluoromethyl)arenes.



Scheme 1 *Ortho* C-H trifluoromethylation of anilines assisted by PA

So far, photoinduced reaction has attracted more and more attention in organic synthesis, on account of these transformations meet the green concept of energy saving and environmental protection.[8] For example, Li *et al.* described a photoinduced method for the direct trifluoromethylation of arenes by using Langlois' reagent (CF_3SO_2Na,) as CF_3 source in acetone under ultraviolet irradiation.[8a] This result brings a new view for the radical couplings under oxidant free condition. Intrigued by this simple and efficient strategy, we envisioned that this method could be utilized to affect the direct *ortho* trifluoromethylation of anilines.

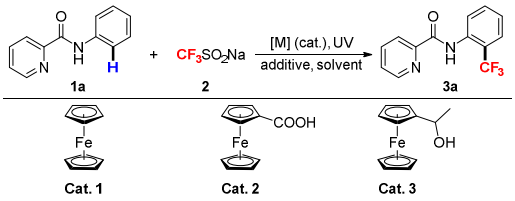
Very recently, Zhang and coworkers reported an example for *ortho* trifluoromethylation of anilines by using nickel as catalyst

Pharmacy College, Taishan Medical University, Taian 271016 (China).
E-mail: xiachc@163.com

†Electronic Supplementary Information (ESI) available: Detailed experimental procedures and analytical data. For ESI or other electronic format see DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C8OB00511G

Table 1 Initial studies for the trifluoromethylation [a]



Entry	Catalyst	Additive	Solvent	Yield [%][b]
1	$Cu(OTf)_2$	-	Acetone	21
2	$Ni(OTf)_2$	-	Acetone	trace
3	$Co(OAc)_2$	-	Acetone	trace
4	$FeCl_3$	-	Acetone	66
5	$FeCl_2$		Acetone	34
6	Cat. 1	-	Acetone	72(71)[c]
7	Cat. 2	-	Acetone	41
8	Cat. 3	-	Acetone	30
9	-	-	Acetone	trace
10	Cat. 1	-	DCE	23
11	Cat. 1	-	MeCN	32
12	Cat. 1	-	MeOH	trace
13	Cat. 1	-	DMSO	trace
14	Cat. 1	-	H_2O	trace
15	Cat. 1	Na_2CO_3	Acetone	57
16	Cat. 1	KH_2PO_4	Acetone	43
17	Cat. 1	Ac_2O	Acetone	70
18	Cat. 1	PivOH	Acetone	64
19[d]	Cat. 1	-	Acetone	58
20[e]	Cat. 1	-	Acetone	69
21[f]	Cat. 1	-	Acetone	65
22[g]	Cat. 1	-	Acetone	trace
23[h]	Cat. 1	-	Acetone	0

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), catalyst (15 mol %), additive (0.4 mmol), solvent (2 mL), irradiation supplied by a photoreactor (λ = 254 nm, intensity of 4.0 mW cm^{-2}), rt, 36 h. [b] Isolated yields. [c] 48 h. [d] Cat. 1 (10 mol %). [e] Cat. 1 (20 mol %). [f] Under O_2. [g] Under N_2. [h] The reaction was performed in the dark.

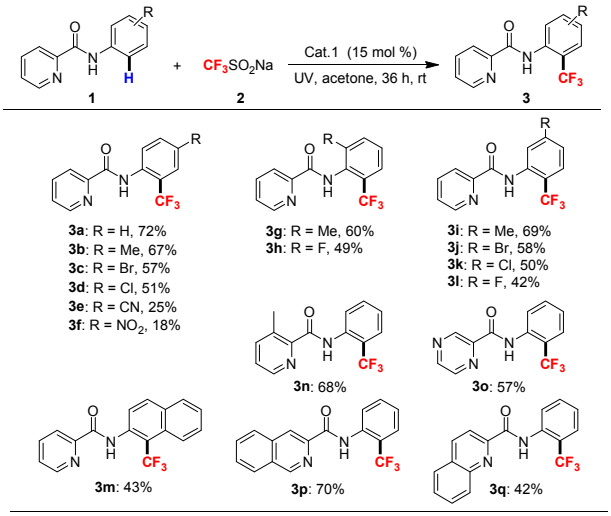
(Scheme 1a).[10b] In this transformation, however, stoichiometric potassium peroxodisulfate ($K_2S_2O_8$) was employed as oxidant, making this method did not meet the requirement of green synthesis. Furthermore, the substrates with electron-withdrawing groups were inapplicable in their catalytic system.

Recently, iron-catalyzed C-H functionalization reactions have found applications to introduce various functional groups to many substrates. And preeminent advances have been demonstrated by many groups.[9] However, iron-catalyzed trifluoromethylation is seldom reported.[9p,q] From the standpoint of energy saving and being environmentally friendly, we demonstrated an iron-catalyzed protocol for *ortho* trifluoromethylation of anilines *via* picolinamide assisted[10] photoinduced C-H functionalization in the absence of any oxidants (Scheme 1b).

Results and discussion

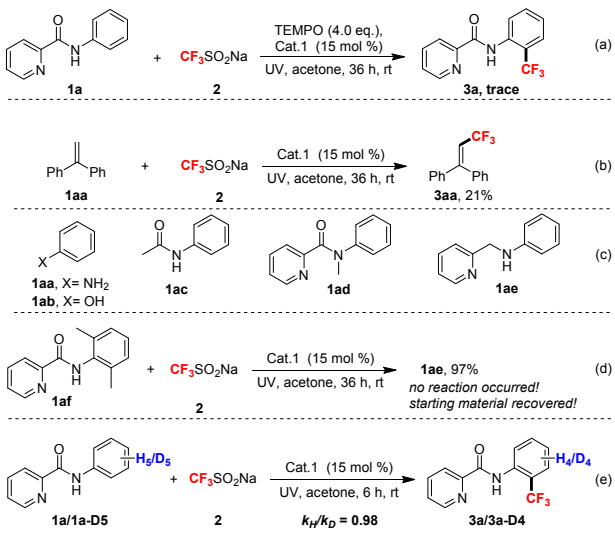
We started our research with the trifluoromethylation of the amide **1a**, which was prepared from the amidation of 2-picolinic acid and aniline. Treating **1a** with 15 mol % $Cu(OTf)_2$, 2 equivalents of Langlois' reagent (**2**), 2 mL acetone under ultraviolet irradiation

Table 2 Scope investigation for the trifluoromethylation [a]



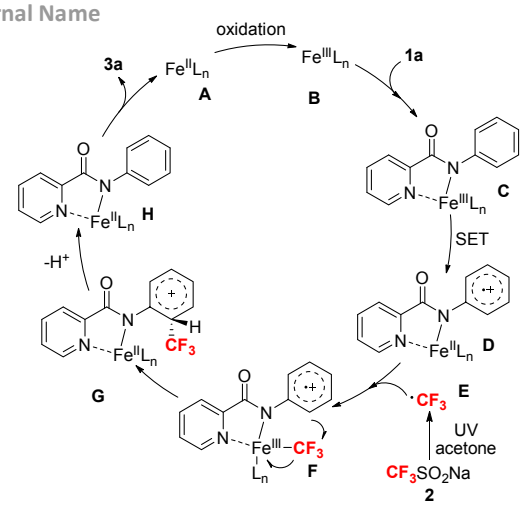
[a] Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), Cat.1 (15 mol %), acetone (2 mL), irradiation supplied by a photoreactor (λ = 254 nm, intensity of 4.0 mW cm^{-2}), rt, 36 h, isolated yields.

(λ= 254 nm) at room temperature gave the desired trifluoromethylated product **3a** in a promising 21% yield (Table 1, entry 1). Examination of other metal catalysts, such as $Ni(OTf)_2$, $Co(OAc)_2$ and some iron salts was also performed, the yield of **3a** was improved to 72% when ferrocene was employed as a catalyst (Table 1, entry 6). It was also worth noting that in the absence of any metal catalyst no reactivity was observed (Table 1, entry 9). Besides acetone, several solvents were investigated, 1,2-dichloroethane (DCE) and acetonitrile (MeCN) were not effective to improve the yield of **3a** (Table 1, entry 10 and 11). Other solvents such as methanol (MeOH), dimethylsulfoxide (DMSO) as well as water (H_2O) did not provide target product **3a** (Table 1, entry 12 - 14). Further investigations in additives, catalyst loading and atmosphere did not increase the yield (Table 1, entries 15–22). The transformation was retarded when the reaction was carried out in the dark (Table 1, entry 23).



Scheme 2 Mechanistic considerations

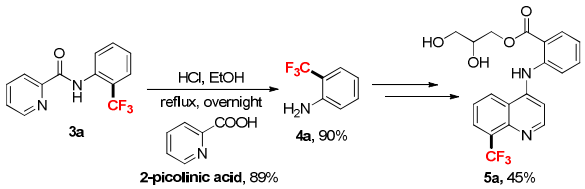
View Article Online
DOI: 10.1039/C8OB00511G



Scheme 3 Proposed mechanism

With the optimized reaction condition in hand, we next sought to study the substrate scope of this trifluoromethylation (Table 2). Numerous picolinamide derivatives could be efficiently transformed into desired products in moderate to good yields. Functional groups such as methyl, bromo and chloro groups at *para*-position of anilines were well tolerated (**3b**-**d**). It was worth mentioning that picolinamide with strong electron withdrawing groups also could be converted into corresponding products (**3e**, **3f**). Substrates with methyl and fluoro groups at *ortho*-position underwent the transformation smoothly in 60% and 49% yields respectively (**3g**, **3h**). For the *meta*-substituted anilines, the reactions tend to occur on the less hindered site due to the steric bias (**3i**-**l**). Pleasingly, naphthyl derived picolinamide also could take place in this reaction as well, affording the target product **3m** in 43% yield. The amides, which were synthesized from the amidation of the analogues of 2-picolinic acid and aniline could also turn into corresponding products in acceptable yields (**3n**-**q**).

Based on the previous work,[8a] we knew that the electronic excitation of acetone involves the transition of a lone pair electron from oxygen atom to the carbonyl carbon under ultraviolet irradiation (λ = 254 nm), the resulting electron-deficient oxygen atom of the carbonyl n, π* state may abstract one electron from CF_3SO_2Na to generate a CF_3 radical. In order to obtain more understanding of the mechanism, several control experiments were performed. Firstly, the transformation was completely inhibited when 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was used as a free radical inhibitor (Scheme 1a). Meanwhile, the trifluoromethyl radical was captured by 1,1-diphenylethylene (**1aa**), and the corresponding adduct **3aa** was isolated in 21% yield (Scheme 1b). It was showed that a radical pathway might be involved in this trifluoromethylation. Subsequently, aniline **1aa**, phenol **1ab**, substrates **1ac**, **1ad** and **1ae** were tested under standard conditions respectively, but no target product was detected. These results revealed that the N atom of pyridine and amide group were indispensable (Scheme 1c). When the C2- and C6-positions hydrogen of **1a** was substituted by methyl (**1af**), no product was acquired and the starting material **1af** was recovered (Scheme 1d). This phenomenon showed that this strategy has a high regioselectivity. Further exploration about kinetic isotope effects (KIE) was carried out, giving a low ratio (k = 0.98), revealing that the C-H cleavage process was not the rate determining step (Scheme 2e).[11]



Scheme 4 Removal of PA group and synthesis of floctafenine

According to experimental results, we made sure that the crucial role of both heterocyclic nitrogen and amide, most likely as bidentate binding site for a metal atom.[10d] But the role of carbonyl of amide could not be confirmed. Therefore, two possible mechanisms were proposed. First of all, based on the previous work,[10b] a possible mechanism which involve the coordination of $Fe^{III}CF_3L_n$ and oxygen atom of carbonyl was presented in the supporting information. In the second place, carbonyl of amide just enhanced the acidity of NH to make it good for deprotonation in some case. Therefore, a different mechanism was suggested (Scheme 3). Firstly, $Fe^{II}L_n$ **A** converted into $Fe^{III}L_n$ **B** through the oxidation of air. Then, $Fe^{III}L_n$ combined with substrate **1a** to generate aryl-$Fe^{III}L_n$ complex **C**. Subsequently, aryl-$Fe^{II}L_n$ complex **D** was formed through the process of single electron transfer (SET). Meanwhile, aryl-$Fe^{II}L_n$ complex **D** transformed into aryl-$Fe^{III}CF_3L_n$ complex **F** in the presence of trifluoromethyl radical, which was generated from Langlois' reagent **2** under ultraviolet irradiation. Next, aryl-$Fe^{III}CF_3L_n$ complex **F** underwent intramolecular trifluoromethylation *via* pentacyclic transition state to give cationic intermediate **G**. After the formation of aryl-$Fe^{II}L_n$ complex **H** via deprotonation, target product **3a** was obtained through a metal dissociation process.

Finally, we proved the synthetic utility of our method by the removal of the PA group in a facile way, affording the 2-(trifluoromethyl) aniline **4a** in 90% yield, which was further transformed, yielding the nonsteroidal anti-inflammatory drug floctafenine (**5a**) in 45% yield (Scheme 3).[12]

Conclusions

In summary, we have developed a simple and practical protocol for photoinduced *ortho* trifluoromethylation of anilines under oxidant free condition. This clean photochemical protocol demonstrated a broad substrate scope and variously desired products were efficiently obtained in moderate to good yields. Furthermore, the nonsteroidal anti-inflammatory drug floctafenine was efficiently synthesized through this strategy. Preliminary researches verified that a radical mechanism is involved.

Conflicts of interest

There are no conflicts to declare

Acknowledgements

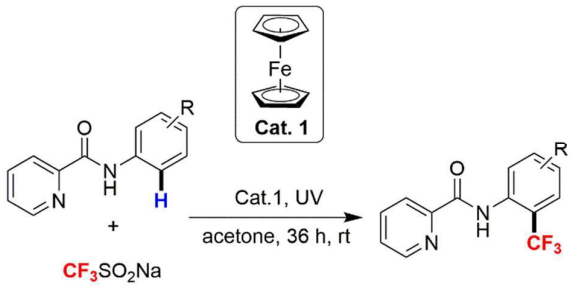
This work was supported by the Projects of Medical and Health Technology Development Program in Shandong Province (No. 2015WS0102), the Shandong Provincial Natural Science Foundation (ZR2017LB006) and Science Foundation of Educational Commission of Shandong Province of China (J17KA248).

View Article Online
DOI: 10.1039/C8OB00511G

Notes and references

1. (a) P. Kirsch, *Modern Fluororganic Chemistry*, Wiley-VCH, Weinheim, 2004; (b) M. Schlosser, *Angew. Chem. Int. Ed*. 2006, **45**, 5432; (c) K. L. Kirk, *Org. Process Res. Dev*. 2008, **12**, 305; (d) K. William, W. K. Hagmann, *J. Med. Chem*. 2008, **51**, 4359; (e) S. Preshlock, M. Tredwell, V. Gouverneur, *Chem. Rev.* 2016, **116**, 719.
2. (a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (b) K. Meller, C. Faeh, F. Diederich, *Science* 2007, **317**, 1881; (c) T. Hiyama, Organofluorine Compounds: Chemistry and Applications, Springer, Berlin, 2000; (d) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* 2014, **114**, 2432; (e) A. Studer, *Angew. Chem. Int. Ed.* 2012, **51**, 8950.
3. A. Marhold, E. Klauke, *J. Fluorine Chem*., 1980, **16**, 516.
4. (a) M. G. Mormino, P. S. Fier, J. F. Hartwig, *Org. Lett.*, 2014, **16**, 1744; (b) K. Aikawa, Y. Nakamura, Y. Yokota, W. Toya, K. Mikami, *Chem. Eur. J.* 2015, **21**, 96; (c) A. Hafner, S. Bräse, *Adv. Synth. Catal.* 2011, **353**, 3044; (d) Y. Huang, M. J. Ajitha, K.-W. Huang, Z. Zhang, Z. Weng, *Dalton Trans.*, 2016, **45**, 8468; (e) X. Lin, C. Hou, H. Li, Z. Weng, *Chem. Eur. J.* 2016, **22**, 2075; (f) E. J. Cho, T. D. Senecal, T. Kinzel, Y. Zhang, D. A. Watson, S. L. Buchwald, *Science* 2010, **328**, 1679; (g) R. J. Lundgren, M. Stradiotto, *Angew. Chem. Int. Ed.* 2010, **49**, 9322; (h) J. M. Larsson, S. R. Pathipati, K. J. Szabj, *J. Org. Chem.* 2013, **78**, 7330; (i) X. Li, J. Zhao, L. Zhang, M. Hu, L. Wang, J. Hu, *Org. Lett.* 2015, **17**, 298; (j) Y. Gu, X.-B. Leng, Q. Shen, *Nat. Commun.* 2014, **5**, 5405.
5. (a) Y. Ye, M. S. Sanford, *J. Am. Chem. Soc.*, 2012, **134**, 9034; (b) L. Chu, F. -L. Qing, *Org. Lett.* 2010, **12**, 5060; (c) Y. Li, L. Wu, H. Neumann, M. Beller, *Chem. Commun.* 2013, **49**, 2628.
6. (a) G. Danoun, B. Bayarmagnai, M. F. Grenberg, L. J. Gooßen, *Angew. Chem. Int. Ed.* 2013, **52**, 7972; (b) J.-J. Dai, C. Fang, B. Xiao, J. Yi, J. Xu, Z.-J. Liu, X. Lu, L. Liu, Y. Fu, *J. Am. Chem. Soc.* 2013, **135**, 8436; (c) X. Wang, Y. Xu, F. Mo, G. Ji, D. Qiu, J. Feng, Y. Ye, S. Zhang, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* 2013, **135**, 10330.
7. (a) L.-S. Zhang, K. Chen, G. Chen, B.-J. Li, S. Luo, Q.-Y. Guo, J.-B. Wei, Z.-J. Shi, *Org. Lett.* 2013, **15**, 10; (b) S. Cai, C. Chen, Z. Sun, C. Xi, *Chem. Commun.,* 2013, **49**, 4552; (c) S. Seo, J. B. Taylorb, M. F. Greaney, *Chem. Commun.*, 2013, **49**, 6385; (d) M. Shang, S.-Z. Sun, H.-L. Wang, B. N. Laforteza, H.-X. Dai, J.-Q. Yu, *Angew. Chem. Int. Ed*. 2014, **53**, 10439; (e) E. Merino, C. Nevado, *Chem. Soc. Rev.,* 2014, **43**, 6598; (f) C. Alonso, E. M. Marigorta, G. Rubiales, F. Palacios, *Chem. Rev.* 2015, **115**, 1847; (g) F. Sladojevich, E. McNeill, J. Börgel, S.-L. Zheng, T. Ritter, *Angew. Chem. Int. Ed*. 2015, **54**, 3712; (h) R. Rey-Rodriguez, P. Retailleau, P. Bonnet, I. Gillaizeau, *Chem. Eur. J.* 2015, **21**, 3572; (i) L. Chu, F.-L. Qing, *J. Am. Chem. Soc*. 2012, **134**, 1298; (j) C. Fan, J. Song, G. Qiu, G. Liu, J. Wu, *Org. Chem. Front.*, 2014, **1**, 924; (k) J. Xu, L. Qiao, B. Ying, X. Zhu, C. Shen, P. Zhang, *Org. Chem. Front*., 2017, **4**, 1116; (l) C. Shen, J. Xu, B. Ying, P. Zhang, *ChemCatChem*, 2016, **8**, 3560; (m) F. Yang, P. Klumphu, Y.-M. Liang, B. H. Lipshutz, *Chem. Commun.,* 2014, **50**, 936;
8. (a) L. Li, X. Mu, W. Liu, Y. Wang, Z. Mi, C.-J. Li, *J. Am. Chem. Soc.,* 2016, **138**, 5809; (b) Y. An, Y. Kuang, J. Wu, *Org. Chem. Front.*, 2016, **3**, 994; (c) Y. An, Y. Li, J. Wu, *Org. Chem. Front.*, 2016, **3**, 570.
9. (a) Y. Ma, D. Zhang, Z. Yan, M. Wang, C. Bian, X. Gao, E. E. Bunel, A. Lei, *Org. Lett*. 2015, **17**, 2174; (b) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev*. 2011, **111**, 1417; (c) K. Gopalaiah, *Chem. Rev*. 2013, **113**, 3248; (d) I. Bauer, H.-J. Knölker, *Chem. Rev*. 2015, **115**, 3170; (e) B. M. Monks, E. R. Fruchey, S. P. Cook, *Angew. Chem. Int. Ed.* 2014, **53**, 11065; (f) R. B. Bedford, *Acc. Chem. Res*. 2015, **48**, 1485; (g) K. R. Babu, N. Zhu, H. Bao, *Org. Lett*. 2017, **19**, 46; (h) H. Wang, L. Wang, J. Shang, X. Li, H. Wang, J. Gui, A. Lei, *Chem. Commun*., 2012, **48**, 76; (i) L. C. M. Castro, H. Li, J.-B. Sortais, C. Darcel, *Green Chem.*, 2015, **17**, 2283; (j) A. Correa, B. Fiser, E. Gómez-Bengoa, *Chem. Commun.*, 2015, **51**, 13365; (k) W. Liu, H. Cao, A. Lei, *Angew. Chem. Int. Ed*. 2010, **49**, 2004; (l) T. Yang, L. Lu, Q. Shen, *Chem. Commun.* 2015, **51**, 5479; (m) R. Shang, L. Ilies, E. Nakamura, *Chem. Rev.* 2017, **117**, 9086; (n) T. J. Osberger, D. C. Rogness, J. T. Kohrt, A. F. Stepan, M. C. White, *Nature*, DOI:10.1038/nature18941; (o) G. Cera, T. Haven, L. Ackermann, *Angew. Chem. Int. Ed.,* 2016, **55**, 1484; (p) Z.-R. Li, X.-X. Bao, J. Sun, J. Shen, D.-Q. Wu, Y.-K. Liu, Q.-H. Deng, F. Liu, *Org. Chem. Front.*, 2016, 3, 934; (q) R. Rey-Rodriguez, P. Retailleau, P. Bonnet, I. Gillaizeau, *Chem. Eur. J.*, 2015, **21**, 3572; (r) B. Vinayak, P. NavyaSree, M. Chandrasekharam, *Org. Biomol. Chem.*, 2017, **15**, 9200.
10. (a) Q. Li, S.-Y. Zhang, G. He, Z. Ai, W. A. Nack, G. Chen, *Org. Lett.*, 2014, **16**, 1764; (b) J. Xu, L. Qiao, J. Shen, K. Chai, C. Shen, P. Zhang, *Org. Lett.*, 2017, **19**, 5661; (c) J.-M. Li, Y.-H. Wang, Y. Yu, R.-B. Wu, J. Weng, G. Lu, *ACS Catal.*, 2017, **7**, 2661; (d) S. Liang, M. Bolte, G. Manolikakes, *Chem. Eur. J.*, 2017, **23**, 96; (e) P. Bai, S. Sun, Z. Li, H. Qiao, X. Su, F. Yang, Y. Wu, Y. Wu, *J. Org. Chem*., DOI: 10.1021/acs.joc.7b01917; (f) G. Rouguet, N. Chatani, *Angew. Chem., Int. Ed.* 2013, **52**, 11726; (g) M. Iwasaki, W. Kaneshika, Y. Tsuchiya, K. Nakajima, Y. Nishihara, *J. Org. Chem.*, 2014, **79**, 11330; (h) V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.*, 2005, **127**, 13154; (i) E. T. Nadres, O. Daugulis, *J. Am. Chem. Soc.* 2012, **133**, 7.
11. (a) M. Gjmez-Gallego, M. A. Sierra, *Chem. Rev.*, 2011, **111**, 4857; (b) E. M. Simmons, J. F. Hartwig, *Angew. Chem. Int. Ed.*, 2012, **51**, 3066.
12. G. Mouzin, H. Cousse, J. M. Autin, *Synthesis*, 1980, 55.

View Article Online
DOI: 10.1039/C8OB00511G



An oxidant free protocol was developed for *ortho* trifluoromethylation of aniline *via* picolinamide assisted Fe-promoted C-H functionalization under ultraviolet irradiation.