Trifluoromethylation

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Photoredox-Catalyst-Enabled *para*-Selective Trifluoromethylation of *tert*-Butyl Arylcarbamates

Yaqiqi Jiang[+], Bao Li[+], Nana Ma, Sai Shu, Yujie Chen, Shan Yang, Zhibin Huang, Daqing Shi, and Yingsheng Zhao**

Abstract: *The direct incorporation of a trifluoromethyl group on an aromatic ring using a radical pathway has been extensively investigated. However, the direct highly para-selective C–H trifluoromethylation of a class of arenes has not been achieved. In this study, we report a light-promoted 4,5-dichlorofluorescein (DCFS)-enabled para-selective C–H trifluoromethylation of arylcarbamates using Langlois reagent. The preliminary mechanistic study revealed that the activated organic photocatalyst coordinated with the arylcarbamate led to para-selective C–H trifluoromethylation. Ten-gram scale reaction performs well highlighting the synthetic importance of this new protocol.*

The site-selective functionalization of a specific C–H bond poses significant challenges in synthetic chemistry. To this point, various approaches to realize selective C–H functionalizations have been extensively explored. For example, the directing group strategy provided an effective way to achieve the *ortho*[1] or *meta*[2]-selective C–H functionalizations. The application of noncovalent interactions served as another pathway to perform *meta* or *para*-selective C–H functionalizations, which have been cleverly developed by the groups of Nako,[3] Chattopadhyay,[4] Kuninobu,[5] Kanai,[6] Phipps,[7] and Yu[8] groups. A recent report on a cyclometalated ruthenium complex indicated uniquely promoted remote, selective C–H functionalizations, in which it acted as a strong bulk-electronic-transient-metal functional group.[9] Although these methods greatly improved routes to selectively install a functional group on arenes, there is still no efficient method to realize *para*-selective C–H trifluoromethylation reactions. The CF_3 moiety is an important functional group in drug candidates, as it imparts stability during oxidative metabolism, and improves the solubility, lipophilicity, and antioxidizability of bioactive compounds.[10] Hence, the development of practical strategies for the preparation of trifluoromethylated compounds has always been an important topic in synthetic chemistry. The MacMillan[11] group initially demonstrated that a CF_3 radical (generated using CF_3SO_2Cl as the CF_3 radical precursor) reacted directly with aromatic compounds to yield trifluoromethylated products (Figure 1).

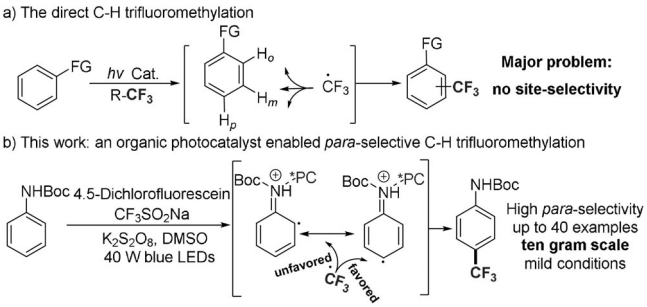

Figure 1. C–H trifluoromethylation. a) Direct C–H trifluoromethylation. b) This work: Organic photocatalyst-enabled *para*-selective C–H trifluoromethylation.

Later, other reagents, such as Tf_2O,[12] $ArI(OCOCF_3)$,[13] CF_3-containing sulfones,[14,15] CF_3X,[16] $(CF_3CO)_2O$,[17] and Togni reagents[18] were all used to introduce a CF_3 group successfully onto an aromatic ring via a free-radical mechanism. But the lack of site selectivity of these methods has always posed a problem and considerably affected the use of these routes in synthetic chemistry. Herein, we report an organic photocatalyst 4,5-dichlorofluorescein (DCFS)-enabled *para*-selective trifluoromethylation of anilides through a novel radical/radical cross-coupling pathway. Various arylcarbamates were suitable for this reaction and led to the formation of *para*-trifluoromethylated products in moderate to good yields. Importantly, several bioactive compounds, such as chlorzoxazone,[19] a vorinostat precursor, chlorpropham and a teriflunomide precursor were also well suited. The ten-gram scale reaction further highlights the importance of this new synthetic method. A study of the reaction mechanism revealed the activated organic photocatalyst coordinated with the arylcarbamate to alter the spatial environment of the *ortho* and *meta* positions on the phenyl ring and was the key to achieve *para*-selectivity.

[*] Y. Jiang,[+] S. Shu, Y. Chen, S. Yang, Z. Huang, Prof. Dr. D. Shi, Prof. Dr. Y. Zhao
Key Laboratory of Organic Synthesis of Jiangsu Province
College of Chemistry, Chemical Engineering and Materials Science
Soochow University, Suzhou 215123 (P. R. China)
and
School of Chemistry and Chemical Engineering
Henan Normal University, Xinxiang 453000 (P. R. China)
E-mail: dqshi@suda.edu.cn
yszhao@suda.edu.cn
B. Li,[+] N. Ma
Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, School of Chemistry and Chemical Engineering, Henan Normal University
Xinxiang 453000 (P. R. China)
[+] These authors contributed equally to this work.
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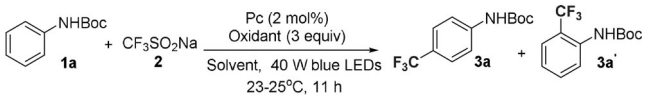
Aniline is an important compound and a key skeletal component in various drugs and natural products.[20] Among the reported direct C–H trifluoromethylation reactions, *ortho*-selective C–H trifluoromethylation of anilides has been well developed.[21] However, direct *para*-selective C–H trifluoromethylation has always posed a challenge.[22] Recently, the site-selective introduction of a CF_3 group onto arenes was accomplished via the radical route reported by Ritter et al.[23] However, only one example of a trifluoroacetyl-protected aniline was used as the substrate; the two-step procedure and complex reaction conditions slightly limited reaction feasibility. Recently, our group discovered the steric hindrance of a ligand significantly affected site-selectivity when the free radical reacted with aromatic rings;[24] therefore, a matched catalyst would coordinate with the protected aniline, change the spatial environments of the *ortho* and *meta* positions, and might lead to a *para*-selective trifluoromethylation.

With these conditions in mind, Langlois reagent (CF_3SO_2Na) was selected as the source of CF_3 radicals owing to its low toxicity and cost, and the commonly used *tert*-butoxycarbonyl- protected aniline was shortlisted as the standard substrate. First, *tert*-butyl carbanilate (**1a**) was directly treated with CF_3SO_2Na (**2**) and potassium persulfate (3 equiv) in the presence of the photoredox catalyst (2 mol%) in acetonitrile at room temperature for 11 h (Table 1). The photoredox catalysts *fac*-Ir(ppy)$_3$ and Ru(Phen)$_3$Cl$_2$ provided the trifluoromethylated product in low yields; meanwhile, the *ortho* and *para* selectivity was rather poor. Several organic photoredox catalysts, such as Eosin B, TPT (2,4,6-triphenylpyrylium tetrafluoroborate), and Fluorescein were further investigated. Interestingly, better selectivity and yield was obtained when fluorescein was used as the catalyst. Several fluorescein derivatives were further screened and we found that 4,5-dichlorofluorescein (DCFS) could be used to generate the *para*-trifluoromethylated product **3a** in 57% yield with high site-selectivity. Next, we screened solvents including DMSO, acetone, DCM, and DMF, and found that DMSO could lead to a considerable improvement in yield and selectivity (80%, *para/ortho* > 20/1). The other oxidants such as $(NH_4)_2S_2O_8$, TBHP, and $Na_2S_2O_8$ were further tested; however, none can give better yields than that of $K_2S_2O_8$ (see the Supporting Information). Control experiments showed that potassium persulfate and photoredox catalysts were both indispensable for this transformation.

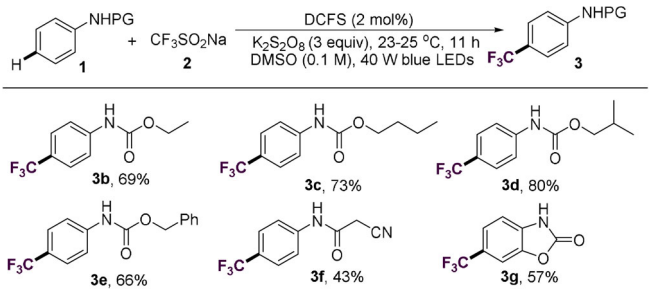
Table 1: Optimization of reaction conditions.[a]



Entry	Photocatalyst	Oxidant	Solvent	(3a + 3a′) Yield [%]	3a/3a′ (p/o)
1	*fac*-Ir(ppy)$_3$	$K_2S_2O_8$	CH_3CN	21	2:1
2	Ru(Phen)$_3$Cl$_2$	$K_2S_2O_8$	CH_3CN	11	3:2
3	Eosin B	$K_2S_2O_8$	CH_3CN	21	5:1
4	TPT	$K_2S_2O_8$	CH_3CN	35	6:1
5	Fluorescein	$K_2S_2O_8$	CH_3CN	37	9:1
6	DCFS	$K_2S_2O_8$	CH_3CN	57	13:1
7	DCFS	$K_2S_2O_8$	DMSO	80	> 20:1
8	DCFS	–	DMSO	trace	
9	–	$K_2S_2O_8$	DMSO	trace	

[a] Reaction conditions: **1a** (0.2 mmol), **2** (2 equiv), DCFS (2 mol%), $K_2S_2O_8$ (3 equiv), DMSO (2 mL) at room temperature (23–25 °C) using irradiation with 40 W blue LEDs for 11 h. Yields were based on GC with tridecane as the internal standard.

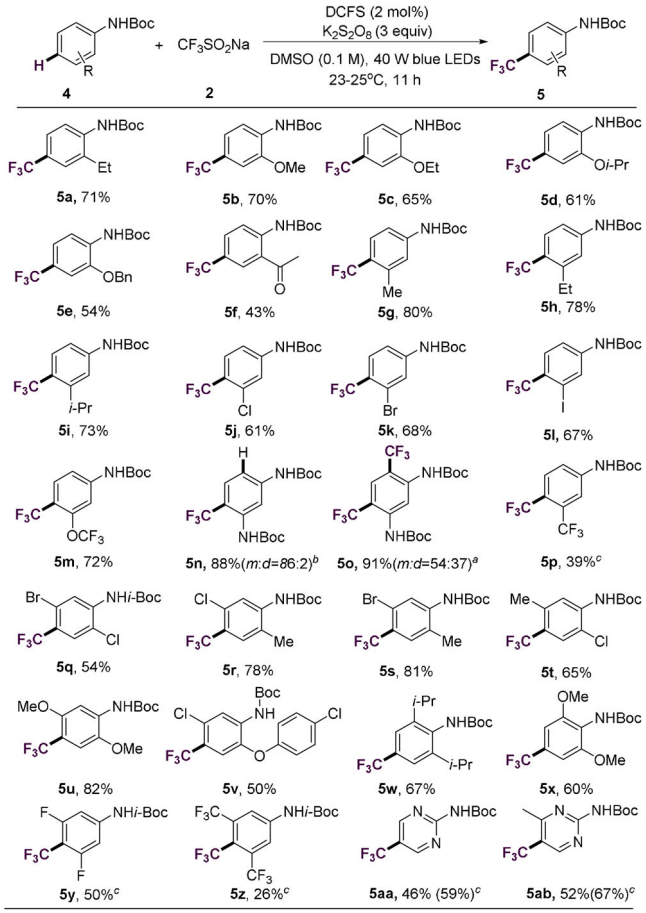
With the optimized reaction protocol, we next screened protecting groups for photoredox catalyst-enabled light-induced *para*-selective C–H trifluoromethylation (Scheme 1). We found ethyl-, *n*-butyl-, and *i*-butyl-*N*-phenyl-



Scheme 1. Comparison of different protecting groups.[a] [a] Reaction conditions: **1** (0.2 mmol), **2** (2 equiv), DCFS (2 mol%), $K_2S_2O_8$ (3 equiv), DMSO (2 mL) at room temperature (23–25 °C) using irradiation with 40 W blue LEDs for 11 h, isolated yield.

carbamates to be good substrates, which led to the corresponding product in good yields (**3b**–**3e**). The use of Cbz-protected aniline resulted in a single *para*-trifluoromethylated product **3e** in 66% yield. Unfortunately, *N*-phenylbenzamide and trifluoro-*N*-phenylmethanesulfonamide were completely unreactive, along with starting material recovery. The substrate **1f**, which is a key precursor of teriflunomide, could be transformed into product **3f** with an acceptable yield. Further study revealed that 2-benzoxazolinone was also an effective substrate, affording a highly *para*-selective trifluoromethylated product **3g** in 57% yield.

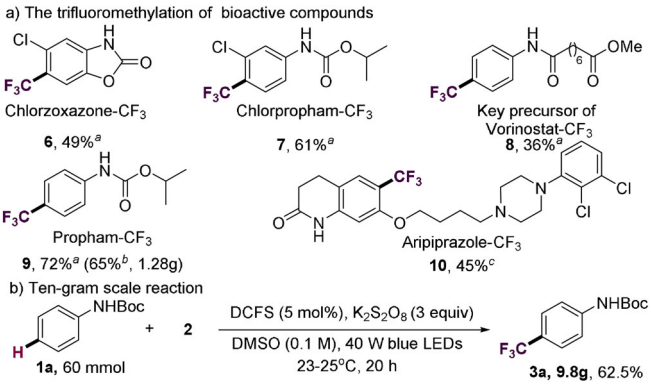
Encouraged by these promising results, we next examined if Boc-protected aniline derivatives could be tolerated in the *para*-selective trifluoromethylation. Gratifyingly, both *ortho* and *meta*-substituted aniline derivatives were well tolerated and afforded the corresponding products in moderate to good yields (Scheme 2). The functional groups, including OMe, OEt, OBn, Me, Et, Ac, Cl, Br, and OCF_3, were well tolerated and led to the corresponding products in moderate to good yields (**5a**–**5k, 5m**). It is noteworthy that the sensitive iodo group on the *meta*-position was also a good substrate, which led to the trifluoromethylated product **5l** in 67% yields. Unfortunately, the use of N-Boc-3-(trifluoromethyl)aniline only afforded the trifluoromethylated product in 39% yield (**5p**), along with recovery of the starting material. This is likely due to the strong electron-withdrawing effect of the trifluoromethyl group, which affected the reactivity of the aromatic ring. Interestingly, when *tert*-butoxyacyl-protected *m*-phenylenediamine **1n** was used, a mixture of mono and di-trifluoromethylated products were obtained in a total yield of 91% (m/d = 1.45). When the quantity of CF_3SO_2Na was



Scheme 2. Substrate scope of the aniline derivatives.[a] [a] Reaction conditions: **1a** or **4** (0.2 mmol), **2** (2 equiv), DCFS (2 mol%), $K_2S_2O_8$ (3 equiv), DMSO (2 mL) at room temperature (23–25 °C) using irradiation with 40 W blue LEDs for 11 h, isolated yield. [b] 1.5 equiv CF_3SO_2Na was used. [c] **4** (0.2 mmol), **2** (2 equiv), DCFS (5 mol%), $(NH4)_2S_2O_8$ (3.5 equiv), DMSO (2 mL) at room temperature (23–25 °C) using irradiation with 40 W blue LEDs for 15 h, isolated yield.

reduced (1.5 equiv), the trifluoromethylated product **5n** was obtained in 88% yield with trace amounts of the double-trifluoromethylated product. Next, a more challenging synthetic route was undertaken and *N*-Boc-protected disubstituted anilines were subjected to standard conditions. Each of these substrates afforded *para*-trifluoromethylated products in good yields (**5q**–**5z**). Impressively, the 2,6-disubstituted anilines were compatible, leading to the trifluoromethylated product in good yields (**5w**, **5x**). It is worth noting that although various approaches have been reported to achieve C–H trifluoromethylation, none of these studies mention *para*-trifluoromethylation data of the substituted aniline derivatives.

Owing to the importance of incorporation of the CF_3 group into arenes, it would be highly attractive to introduce a trifluoromethyl group on bioactive compounds. We found that this photoredox catalyst could promote *para*-selective C–H trifluoromethylation, and could, therefore, be used to functionalize several well-known drugs and chemicals including Propham, Chlorpropham, Chlorzoxazone, the key precursor of Vorinostat and Aripiprazole (Scheme 3, **6–8, 10**).

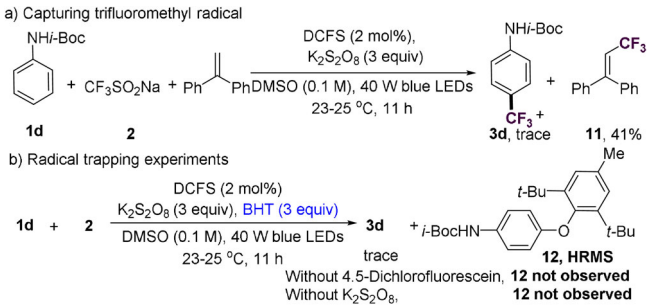


Scheme 3. Synthetic application. [a] Reaction conditions: substrate (0.2 mmol), **2** (2 equiv), DCFS (2 mol%), $K_2S_2O_8$ (3 equiv), DMSO (2 mL) at room temperature (23–25 °C) using irradiation with 40 W blue LEDs for 11 h, isolated yield. [b] Propham (8 mmol), **2** (2 equiv), DCFS (2 mol%), $K_2S_2O_8$ (3 equiv), DMSO (40 mL) at room temperature (23–25 °C) using irradiation with 40 W blue LEDs for 11 h, isolated yield. [c] Aripiprazole (0.2 mmol), **2** (2 equiv), DCFS (5 mol%), $(NH4)_2S_2O_8$ (3.5 equiv), DMSO (2 mL) at room temperature (23–25 °C) using irradiation with 40 W blue LEDs for 15 h, isolated yield.

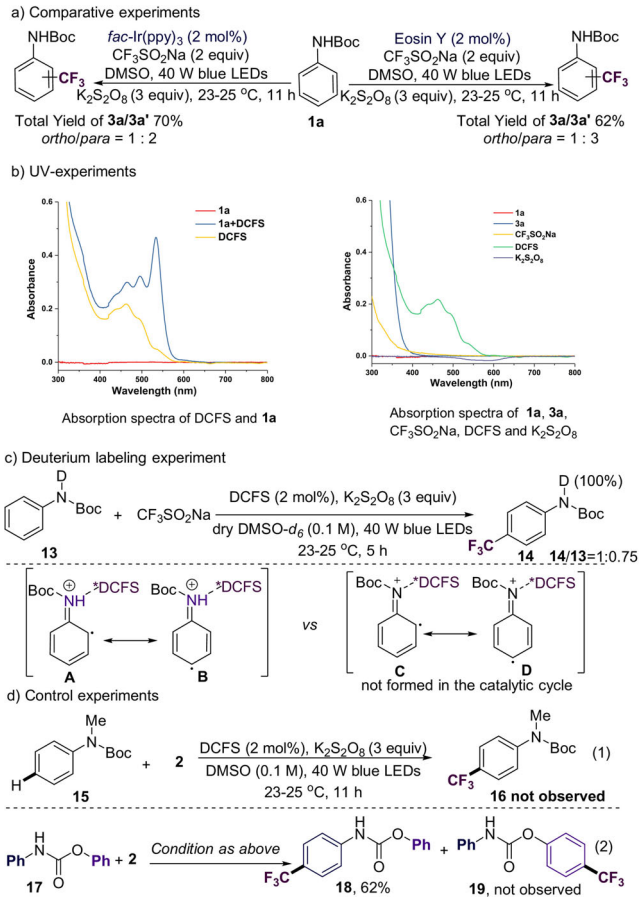
We further demonstrated that the reaction could be scaled up to gram level for Propham, leading to trifluoromethylated propham in 65% yield (1.28 g) (Scheme 3, **9**). Impressively, the ten-gram reaction is possible for this transformation, highlighting the importance of this new protocol (Scheme 3, b).

Several control experiments were performed to understand the reaction route for this transformation. First, radical-trapping experiments were performed, and the radical scavenger TEMPO or BHT could both arrest this transformation.[21] When 1,1-diphenylethylene was used as the radical scavenger, compound **11** was formed in 41% yields (Scheme 4a). We found that product **12** could be detected by using HRMS[25] with the BHT as the radical scavenger (Scheme 4b). These results suggested that a free-radical pathway was the mechanism of this reaction wherein an arene radical was formed through the single electron transfer (SET) process.

When *fac*-Ir(ppy)$_3$ and Ecosin Y were used instead of the photoredox catalyst DCFS, a mixture of *ortho* and *para*-trifluoromethylated products was obtained (Scheme 5a). Based on the findings from our previous study, we speculated that DCFS will interact with *N*-Boc-anilines. Based on this



Scheme 4. Free radical trapping experiments.

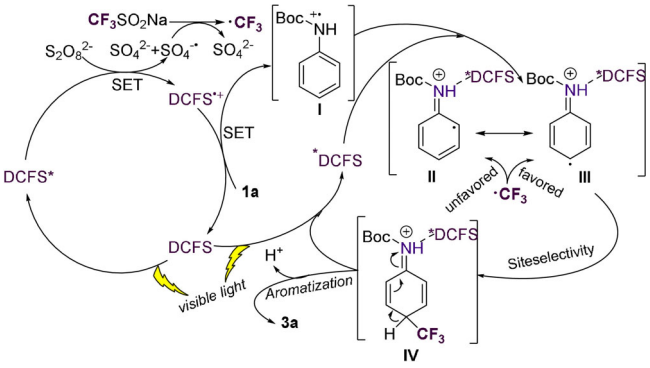


Scheme 5. Preliminary mechanistic studies.

hypothesis, experiments involving UV treatment were carried out. We found that a new peak was generated when *N*-Boc-anilines combined with DCFS (Scheme 5b). Fluorescence quenching experiments[26] of fluorescence show the quenching effect with **1a**. The Stern–Volmer plot indicates that the excited state of DCFS was quenched by **1a** and the quenching effect increased with the increase of the concentration of **1a** (see the Supporting Information for more details). These results indicate that there is a weak interaction between DCFS and the substrate during the catalytic cycle. However, ^{1}H-NMR data do not reveal a clear interaction of the substrate and catalyst (see the Supporting Information). It may suggest the weak interaction between *N*-Boc-aniline and the catalyst should be under the light. The substrate **13** can also provide the tyrifluoromethylated product **14**, and the deuterium hydrogen completely retained. It may support our hypothesis that intermediate A and B were formed during the catalytic cycle, while intermediate C and D cannot be formed (Scheme 5c). While *tert*-butyl methyl(phenyl)carbamate was used, the starting material was completely recovered (Scheme 5d, 1). Interestingly, the phenyl phenylcarbamate, which has two electron-rich phenyl rings, afforded compound **18** in 62% yield, whereas compound **19** was not formed (Scheme 5d, 2). These results indicated the importance of the N–H bond and further offer further evidence that the photoredox catalyst DCFS had a weak interaction with the substrate in the presence of light.

In regard to these results, we may speculate that the steric effect of the photoredox catalyst DCFS would alter the spatial environment of the *ortho* and *meta* positions on the phenyl ring, which would cause the highly *para*-selective C–H trifluoromethylation. Although the mode of the reaction is not clear, an interaction of activated DCFS with *N*-Boc-anilines via intermolecular hydrogen bonds is likely (see the Supporting Information).

Based on our results and previously published studies, a plausible reaction mechanism was proposed (Scheme 6). A trifluoromethyl radical was produced using an established process with 4,5-DCFS as an organic photocatalyst and $K_2S_2O_8$ as the oxidant. The $DCFS^{\cdot+}$ provided the key intermediate I through the SET process, which further



Scheme 6. Plausible mechanism.

tautomerized to yield intermediates **II** and **III** with the activated DCFS. The steric effect of DCFS would increase the steric hindrance of the *ortho* and *meta* positions on the phenyl ring, thereby leading to the highly *para*-selective trifluoromethylation. However, it cannot be completely ruled out that the free trifluoromethyl radical reacted with the DCFS-activated phenyl ring.

To summarize, we developed a photoirradiation reaction and achieved DCFS-enabled *para*-selective C–H trifluoromethylation of arylcarbamates using Langlois reagent. Several arylcarbamates were found to be well-suited for this reaction and led to the formation of *para*-trifluoromethylated products in moderate to good yields. Importantly, several bioactive compounds, such as chlorzoxazone, vorinostat precursor, chlorpropham, and teriflunomide precursor, were also found to be suitable. The preliminary mechanistic study revealed that the activated organic photocatalyst coordinated with the arylcarbamate to alter the spatial environments of the *ortho* and *meta* positions on the phenyl ring and led to *para*-selectivity.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: photoirradiation · site selectivity · ten gram scale · trifluoromethylation

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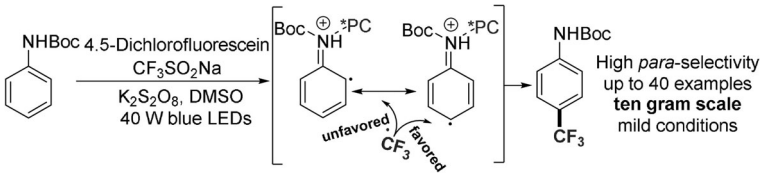
Communications

Trifluoromethylation

Y. Jiang, B. Li, N. Ma, S. Shu, Y. Chen, S. Yang, Z. Huang, D. Shi,* Y. Zhao* ——— ■■■■–■■■■

Photoredox-Catalyst-Enabled *para*-Selective Trifluoromethylation of *tert*-Butyl Arylcarbamates



We report a light-promoted 4,5-dichlorofluorescein (DCFS)-enabled *para*-selective C–H trifluoromethylation of arylcarbamates using the Langlois reagent. Arylcarbamates, including the bioactive compound chlorzoxazone, vorinostat precursor, chlorpropham, and teriflunomide precursors, were suitable for this reaction, leading to the formation of the corresponding products in moderate to good yields.