Organic LETTERS

Letter

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Visible-Light-Promoted Radical C−H Trifluoromethylation of Free Anilines

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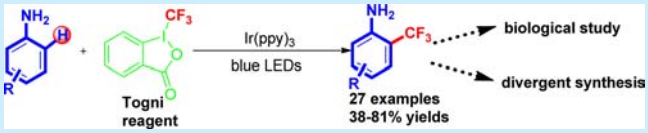
Supporting Information

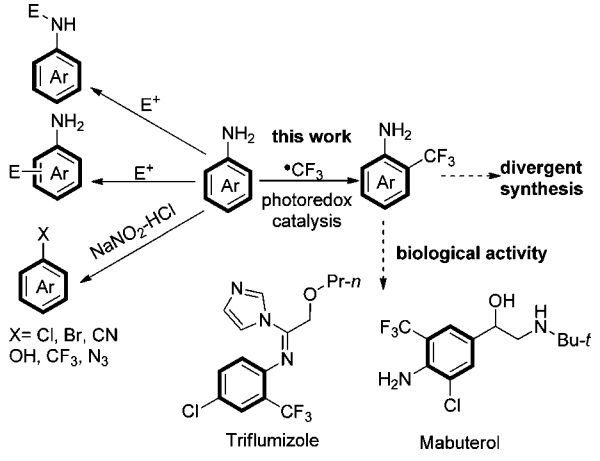
ABSTRACT: The trifluoromethyl-substituted anilines are biologically active compounds and useful building blocks. In this communication, we have developed the first visible-light-induced radical trifluoromethylation of free anilines with the commercially available and easily handled Togni reagent at room temperature. The resulting products were successfully transformed into a variety of valuable fluorine-containing molecules and heterocyclic compounds. This protocol provides an economical and powerful route to trifluoromethylated free anilines.



The trifluoromethyl-substituted arenes are very important structural motifs in pharmaceuticals, agrochemicals, and organic materials.[1] In recent years, the Cu- and Pd-catalyzed coupling protocols of haloarenes[2] and arylboronic acids[3] with nucleophilic (CF_3^-) or electrophilic (CF_3^+) CF_3 reagents were esteemed as the most efficient methods for the construction of trifluoromethylated arenes. However, prefunctionalization is always required. Therefore, the direct C−H trifluoromethylation of arenes represents a promising approach since it can obviate the prefunctionalization of substrates.[4a,b]

Free anilines are important intermediates and useful building blocks for the fine chemical, pharmaceutical, and agrochemical industries. Despite wide utilization in organic synthesis, the C−H bond trifluoromethylation of free anilines remains a great challenge.[4] The reason is due to the fact that the nitrogen atom is of high nucleophilicity and free anilines can easily undergo electrophilic substitution, oxidation, or even decomposition under harsh conditions. Owing to the remarkable biological activity of trifluoromethylated anilines[5] and lack of an efficient and direct method (Scheme 1), the *N*-protected anilines were usually employed to install a CF_3 group and also to avoid the formation of byproducts.[6,7] However, the introduction and subsequent removal of protecting groups not only require additional operations, such as removal of the protecting group (Ts, Ac, Boc, etc.) under strong acidic or basic reaction conditions, but also significantly decrease the functional group compatibility because many important functional groups are acid and base sensitive. Undoubtedly, the most attractive and ideal route to trifluoromethylated free anilines could be the direct trifluoromethylation of C−H bonds of free anilines owing to the step economy. Due to our continual efforts in C−H bond functionalization by photoredox catalysis,[8] we focused our attention on developing visible-light-induced radical trifluoromethylation of free anilines.[9] Although two examples

Scheme 1. Importance of Developing a New Method for Trifluoromethylated Free Anilines



have been reported of the visible-light-induced radical trifluoromethylation of arenes and heteroarenes, these methods suffered from the utilization of CF_3 reagents that were not easy to handle and were also corrosive (CF_3SO_2Cl,[6] a low-boiling liquid) or toxic (CF_3I,[10] a gas). To the best of our knowledge, the visible-light-induced radical C(sp^2)−H bond trifluoromethylation of free anilines with commercially available CF_3 reagent that is easily weighed and handled has never been investigated thus far.[11] Moreover, the trifluoromethylated anilines have remarkable biological activity in a large number of drug reagents, and their potential for PET imaging is highly promising. Herein, we report a visible-light-promoted direct

Received: February 13, 2014
Published: March 6, 2014

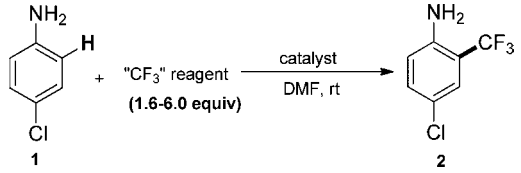
dx.doi.org/10.1021/ol500469a | *Org. Lett.* 2014, 16, 1768−1771

ortho C−H trifluoromethylation of free anilines with Togni's reagent at room temperature.

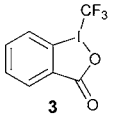
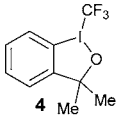
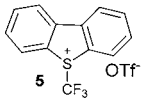
In our initial study, the C−H trifluoromethylation of 4-chloroaniline **1** was chosen as the model reaction (Table 1; also see Supporting Information for details). First, it was found that when Togni reagent **3** was used, the corresponding trifluoromethyl-substituted aniline **2** could be obtained in 60% yield (volatile compound, 83% NMR yield) by irradiation with blue LEDs at room temperature (entry 1). Then, other CF_3 reagents were screened (entries 2−7). The Togni reagent **4** and Umemoto reagent **5**[12] led to lower yields (entries 2 and 3). Much to our surprise, the reaction proceeded sluggishly when CF_3SO_2Cl,[7] CF_3I,[10,13] and CF_3SO_2Na[14] were employed under photoredox catalysis and copper catalysis, respectively (entries 4−6). Interestingly, no desired product was formed due to the decomposition of substrate by using a Ag-mediated trifluoromethylation method with $TMSCF_3$ and $PhI(OAc)_2$[15] (entry 7). By examining the Cu-catalyzed trifluoromethylation of 4-chloroaniline with Togni reagent **3**,[16] a lower yield was obtained (entry 8). Remarkably, no background reaction was observed without photocatalyst or light (entries 11 and 12). Consequently, it was found that the best results could be achieved when Togni reagent **3** was used with photoredox catalysis at room temperature (entry 1).

With the optimized reaction conditions in hand, we surveyed the reaction scope of free anilines (Scheme 2, Figure 1). The visible-light-mediated radical trifluoromethylation protocol has a very broad and impressive substrate scope.[11] Generally, the aromatic amines bearing electron-donating and -withdrawing groups can undergo the visible-light-mediated trifluoromethylation reaction smoothly to furnish products in moderate to good yields. The aniline derivatives with a halogen substituent can

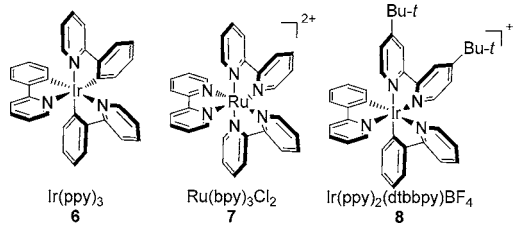
Table 1. Optimization of C−H Trifluoromethylation of Free Anilines[a]



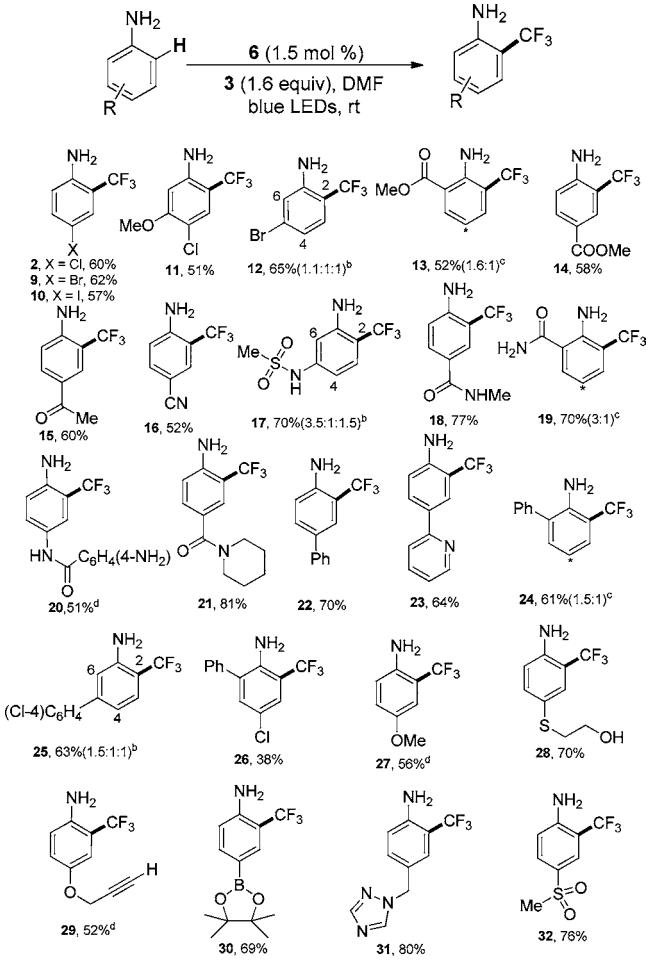
1 2

entry	CF_3 reagent	catalyst (mol %)	yield[b] (%)
1	 3	**6** (1.5)	60 (83)[c]
2	 4	**6** (1.5)	19
3	 5	**6** (1.5)	32
4[d]	CF_3SO_2Cl	**6** (1.5)	trace
5[e]	CF_3I	**6** (1.5)	trace
6[f,g]	CF_3SO_2Na	CuI (10)	(15)[c]
7[h,g]	$TMSCF_3$	$AgNO_3$ (10)	0
8[g]	**3**	CuCl (10)	48 (71)[c]
9	**3**	**7** (1.5)	27
10	**3**	**8** (1.5)	34
11	**3**	-	0
12[g]	**3**	**6** (1.5)	0

[a]Reaction conditions: **1** (0.2 mmol), CF_3 source (1.6 equiv), catalyst (1.5−10 mol %), solvent (1.0 mL), nitrogen atmosphere, blue LEDs (7 W), rt, 20 h. [b]Isolated yield. [c]The yield was determined by ^{19}F NMR analysis. [d]3.0 equiv of CF_3SO_2Cl and 3.0 equiv of K_2HPO_4 were added. [e]6.0 equiv of CF_3I and 6.0 equiv of K_2HPO_4 were added. [f]5.0 equiv of CF_3SO_2Na and 3.0 equiv of TBHP were added. [g]The reaction was performed without visible-light irradiation. [h]1.5 equiv of $PhI(OAc)_2$ and 3.0 equiv of $TMSCF_3$ were added.



Scheme 2. Reaction Scope[a]



[a]Reaction conditions: free aromatic amines (0.2 mmol), **3** (0.32 mmol), $Ir(ppy)_3$ (1.5 mol %), DMF (1.0 mL), blue LEDs (7 W), rt, 15−36 h, isolated yields. [b] The isomer ratio of C2:C4:C6. [c] The minor regioisomeric position is labeled with the respective carbon atom number. [d] 1.3 equiv of Togni reagent **3** were used.

dx.doi.org/10.1021/ol500469a | Org. Lett. 2014, 16, 1768−1771

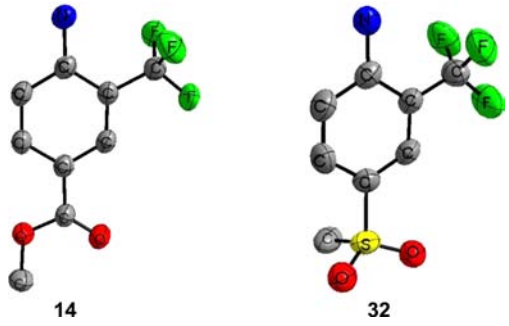
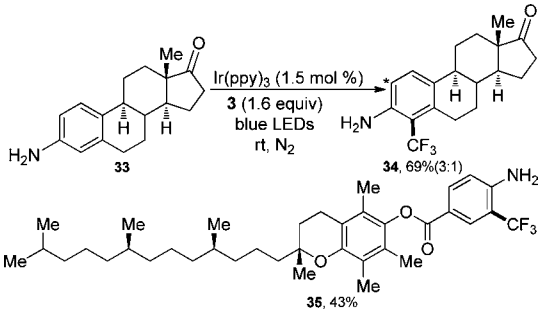


Figure 1. The crystal structure of compounds **14** and **32** (H-atoms have been omitted for clarity).[17]

give satisfying results (**2**, **9**−**12**). Notably, various primary, secondary, and tertiary amides were also compatible (**17**−**21**). There was good regioselectivity when the substrates have two different aromatic rings. For *o*-, *m*-, and *p*-aryl substituted free anilines, only the phenyl ring of anilines was trifluoromethylated, affording the desired products **22**−**26** in 38−70% yields. It was found that the oxidative sensitive groups, such as hydroxyl (**28**), alkynyl (**29**), and Bpin (**30**) groups, could well tolerate the visible-light-promoted reaction conditions. Importantly, the introduction of an electron-deficient trifluoromethyl group results in products that experience difficulty in undergoing the second trifluoromethylation process. Given the broad generality of this protocol, we sought to demonstrate its applicability in more complex free anilines. When 3-aminoestrone **33** and tocopherol 4-aminobenzoate were subjected to the standard reaction conditions, the very valuable products **34** and **35** were obtained in 69% and 43% yields with good regioselectivity (Scheme 3).

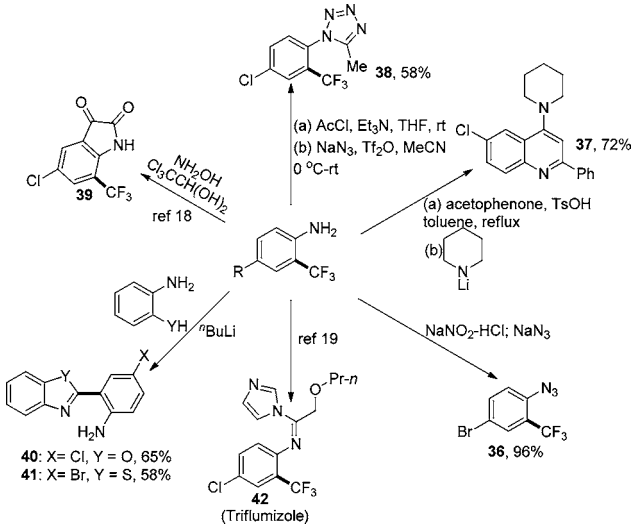
Scheme 3. Application in Complex Free Anilines[a]



[a]The minor regioisomeric position is labeled with the respective carbon atom number.

The trifluoromethylated free anilines are not only bioactive compounds but also versatile organic intermediates and building blocks. We can apply the coupling products in many important organic transformations (Scheme 4). For the classical Sandmeyer reaction, the amino group can be converted into other substituents. The 1-azido-4-bromo-2-(trifluoromethyl)-benzene **36** could also be obtained in 96% yield by a Sandmeyer reaction. Notably, one of the remarkable advantages for trifluoromethylated free anilines is that both the amino group and trifluoromethyl group are useful functional groups. Very important heterocyclic compounds, such as quinoline **37**, tetrazole **38**, isatin **39**,[18] benzoxazole **40**, and benzothiazole **41**, can be constructed in satisfying yields. Moreover, this protocol

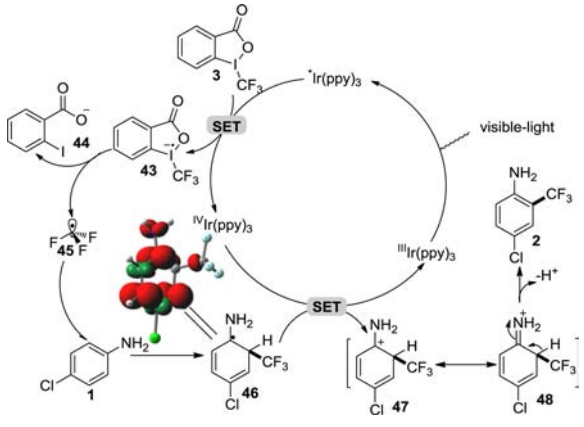
Scheme 4. Versatile Transformations of Trifluoromethylated Free Anilines



affords a new route to biologically important triflumizole **42** from cheap 4-chloroaniline.[19]

In order to gain more insights into the reaction mechanism, the kinetic isotope effect measurement, radical trapping experiments, and theoretical calculations were performed (see Supporting Information for details). Based on these results, a possible mechanism is shown in Scheme 5. First, single electron

Scheme 5. Possible Mechanism



transfer (SET) from excited-state $^*Ir(ppy)_3$ to Togni reagent **3** generates a strong oxidant $^{IV}Ir(ppy)_3$ and **43**, which would then rapidly collapse to the CF_3 radical. Second, the electron-deficient trifluoromethyl radical **45** then is added to the most electron-rich position of 4-chloroaniline to form the cyclohexadienyl radical **46**. Subsequently, the cyclohexadienyl cation species **47** is formed by SET with strong oxidant $^{IV}Ir(ppy)_3$. Finally, deprotonation of **48** could afford the desired product **2**.

In summary, we have developed the first visible-light-induced direct C−H trifluoromethylation of free anilines. It is operationally simple, and useful functional groups are well-tolerated under the mild reaction conditions. This protocol provides an economical and efficient approach to trifluoromethylated free anilines, which are of high synthetic and biological value. Further studies to achieve a clearer under-

dx.doi.org/10.1021/ol500469a | Org. Lett. 2014, 16, 1768−1771

standing of the reaction mechanism are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, crystallographic data for CCDC 958619 (**14**) and 953716 (**32**) (CIF), NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the National Natural Science Foundation of China (21372114, 21172106, 21074054, 21290192, 21273102), the National Basic Research Program of China (2010CB923303, 2011CB808600) and the Research Fund for the Doctoral Program of Higher Education of China (20120091110010) for their financial support.

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(5) It was found that more than 1500 trifluoromethylated aniline derivatives are bioactive compounds and many could be used as drug reagents.

(6) MacMillan's group reported one example of visible-light-induced trifluoromethylation of *N*-Boc aniline with CF_3SO_2Cl, and it was in agreement with our recent observation that the free anilines could form the byproduct sulphonamide (Table 1, entry 4). See: Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224.

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