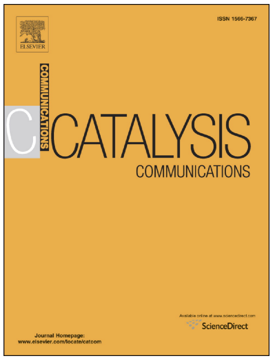

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Visible-Light Photoredox Catalyzed Cyclization of Aryl Alkynoates for the Synthesis of Trifluoromethylated Coumarins

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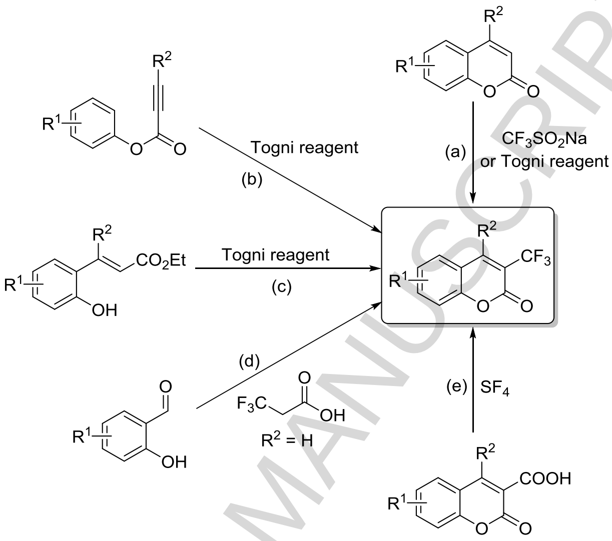
ABSTRACT

A strategy for the synthesis of coumarin derivatives *via* visible-light photoredox catalysis has been developed using *fac*-Ir(ppy)$_3$ as the photocatalyst under mild conditions. Trifluoromethanesulfonyl chloride is utilized as the trifluoromethylation reagent, which is cheap and readily available. Aryl alkynoates are trifluoromethylated, then undergo a radical cyclization and a cascade ester migration to generate target products.

Keywords:
Photoredox catalysis
Trifluoromethanesulfonyl chloride
Coumarin
Cyclization
Trifluoromethylation

1. Introduction

Coumarin derivatives are significant structures in natural products and pharmaceuticals due to their unique properties like anticancer, anti-HIV, anticoagulant, anti-inflammatory, enzyme inhibition, antimicrobial and antioxidant activities [1,2]. They could also be applied in material science as fluorescent dyes [3]. The introduction of trifluoromethyl group into the coumarin scaffold may improve the pharmacological or chemical evaluation of its derivatives, thus, great efforts have be spent exploring their synthesis. Since the synthesis of 4-trifluoromethylated coumarins has been well established [4,5], more and more attentions are paid on the preparation of 3-trifluoromethylated coumarins. Direct trifluoromethylation of coumarins serves as an efficient approach to this structure (Scheme 1a). The first example was reported as early as 1991 by refluxing coumarin with bis(trifluoroacetyl) peroxide [6]. Bi's group [7] tamed Togni reagent in the C−H 3-trifluoromethylation of hymecromone. Sodium trifluoromethanesulfinate (Langlois reagent) has also been harnessed for the direct trifluoromethylation, in which $Mn(OAc)_3$ [8], CuCl/TBHP [9], or a hypervalent iodine(III) reagent [10] was employed for the generation of trifluoromethyl radical. Construction of coumarin skeleton from aryl alkynoates *via* radical process which has been discussed in several recent reports [11-20], provides an alternative to 3-trifluoromethylated coumarins (Scheme 1b). Based on this strategy, a copper-catalyzed trifluoromethylation with Togni reagent was disclosed by Lu and Ding [11]. Other reported methods include trifluoromethylation of *ortho*-hydroxycinnamic esters [21], Perkin condensation with 3,3,3-trifluoropropionic acid [22], and treatment of coumarin-3-carboxylic acids with sulfur tetrafluoride [23]. Nonetheless, the existed methods suffer from their respective drawbacks like high temperature, excess oxidants or inaccessible starting materials, in addition, toxic or expensive trifluoromethylation reagents are required in some cases.



Scheme 1. Methods for the synthesis of 3-trifluoromethylated coumarins: (a) direct trifluoromethylation of coumarins; (b) trifluoromethylation of aryl alkynoates; (c) trifluoromethylation of ortho-hydroxycinnamic esters; (d) Perkin condensation; (e) fluorination of coumarin-3-carboxylic acids.

Visible-light photoredox catalysis has gained extensive attention over the past decade as an access for new transformations [24,25]. A great amount of methods have been developed for the photoredox catalyzed trifluoromethylation [26-28], by using reagents like CF_3SO_2Cl [29,30], CF_3SO_2Na [31], CF_3I [32,33], Togni reagent [34], Umemoto reagent [35], *etc*. Among these reagents, CF_3SO_2Cl is cheap, commercially available, and easy to operate with. The single-electron reduction of CF_3SO_2Cl by the excited state of a commonly-used photocatalyst (*e.g.*, *fac*-Ir(ppy)$_3$, $Ru(bpy)_3Cl_2$, or Eosin Y) could produce CF_3 radical, which is highly reactive for trifluoromethylation. We hypothesized that the CF_3 radical obtained in this manner would reacted with aryl alkynoates under room temperature to form 3-trifluoromethylated coumarins.

2. Experimental

2.1. General

Unless otherwise noted, all commercially available reagents were used without further purification. Photoreactions were carried out under an atmosphere of argon in an oven-dried Schlenk tube and irradiated with a 5 W blue LED lamp. The LED lamp (QB-4038) is produced by Weelte lighting factory of Longgang, Shenzhen, and was purchased from Fantesen Household Light at taobao.com. The products were purified by column chromatography over silica gel. Analytical thin-layer chromatography was performed on glass plates precoated with silica gel, and compounds were detected by visualization under an ultraviolet lamp (254 nm). ^1H, ^{13}C and ^{19}F NMR spectra were recorded on an AVANCE III 500 Bruker spectrometer operating at 500 MHz, 125 MHz and 470 MHz, respectively. Chemical shifts were reported in ppm. Coupling constants (*J* values) are reported in Hz. GC analyses were recorded on an Agilent 7890A instrument. Low-resolution mass spectra (EI) were obtained at 70 eV on a 5975C Mass Selective Detector.

2.2. Typical procedure for the synthesis of aryl alkynoate ester

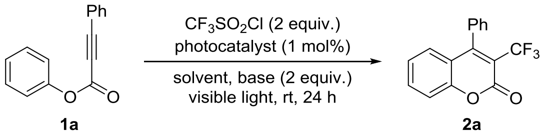
To a solution of the relative phenol (3.0 mmol, 1.0 equiv) in DCM (30 mL) was added arylpropiolic acid (3.3 mmol, 1.1 equiv) at 0 ^oC, then a mixture of DCC (929 mg, 4.5 mmol, 1.5 equiv) and DMAP (37 mg, 0.3 mmol, 0.1 equiv) in CH_2Cl_2 (15 mL) was added dropwise. The mixture was stirred at room temperature for 12 h. Then, the crude mixture was filtered and washed with DCM and concentrated. Purification was achieved by column chromatography on silica gel using hexane and ethyl acetate as eluents.

2.3. Typical procedure for the cyclization of aryl alkynoates with trifluoromethanesulfonyl chloride

A 10-mL Schlenk tube with a magnetic stirring bar was equipped with aryl alkynoate ester (0.2 mmol), K_2CO_3 (56 mg, 0.4 mmol, 2 equiv.), and Ir(ppy)$_3$ (2 mg, 1 mol%). The tube was evacuated and backfilled with dry argon (this operation was repeated three times). Dry acetonitrile (1 mL) was added by syringe, followed by the addition of CF_3SO_2Cl (43 μL, 0.4 mmol, 2 equiv.). The resulting mixture was irradiated with a 5 W blue LED lamp and stirred at room temperature for 24 h. After completion of the reaction, the solvent was removed under reduced pressure. Purification was achieved by column chromatography on silica gel using hexane and ethyl acetate as eluents.

Table 1

Optimization of the reaction conditions.[a]



Entry	Photocatalyst	Solvent	Base	Yield (%)[b]
1	Ru(bpy)$_3$Cl$_2$	CH_3CN	K_2HPO_4	48
2	Ir(ppy)$_3$	CH_3CN	K_2HPO_4	72
3[c]	Eosin Y	CH_3CN	K_2HPO_4	trace
4	-	CH_3CN	K_2HPO_4	NR
5	Ir(ppy)$_3$	DMF	K_2HPO_4	18
6	Ir(ppy)$_3$	DMSO	K_2HPO_4	trace
7	Ir(ppy)$_3$	DCM	K_2HPO_4	55
8	Ir(ppy)$_3$	DCE	K_2HPO_4	44
9	Ir(ppy)$_3$	HOAc	K_2HPO_4	48
10	Ir(ppy)$_3$	CH_3CN	K_3PO_4	56
11	**Ir(ppy)$_3$**	**CH_3CN**	**K_2CO_3**	**79**
12	Ir(ppy)$_3$	CH_3CN	Cs_2CO_3	49
13	Ir(ppy)$_3$	CH_3CN	NaOAc	54
14	Ir(ppy)$_3$	CH_3CN	KOAc	52
15	**Ir(ppy)$_3$**	**CH_3CN**	**DIPEA**	77
16	Ir(ppy)$_3$	CH_3CN	2,6-lutidine	75
17	Ir(ppy)$_3$	CH_3CN	-	trace
18[d]	Ir(ppy)$_3$	CH_3CN	K_2CO_3	NR
19[e]	Ir(ppy)$_3$	CH_3CN	K_2CO_3	79
20[f]	Ir(ppy)$_3$	CH_3CN	K_2CO_3	17

[a] Unless otherwise noted, the reaction conditions are as follows: **1a** (0.2 mmol), CF_3SO_2Cl (0.4 mmol), photocatalyst (1 mol%), base (0.4 mmol), solvent (1 mL), irradiation with a 5 W blue LED lamp under argon at rt for 24 h.

[b] Isolated yield of pure product based on **1a**.

[c] 5 mol% eosin Y was used, and the reaction was irradiated with a 5 W green LED lamp.

[d] The experiment was performed in the dark.

[e] The experiment was irradiated with a 23 W household white CFL.

[f] The experiment was irradiated with ambient light.

3. Results and discussion

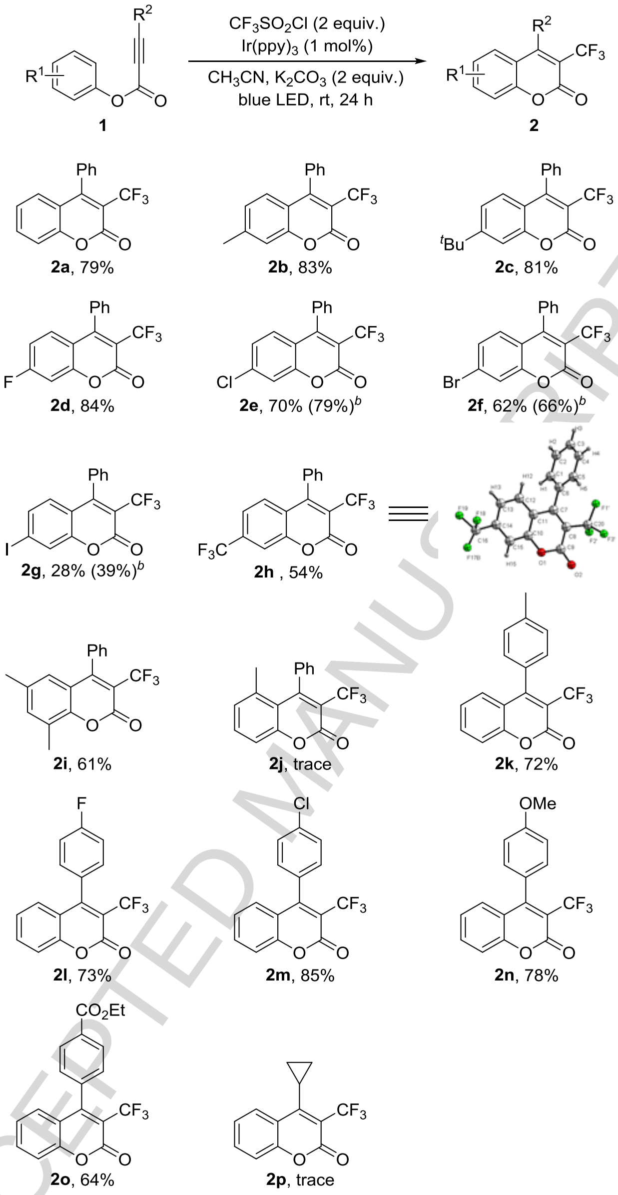
Evaluation of the proposed strategy was first examined with the reaction between phenyl 3-phenylpropiolate (**1a**) and trifluoromathanesulfonyl chloride, using K_2HPO_4 as the base and Ru(bpy)$_3$Cl$_2$ as the photocatalyst. To our delight, the desired product **2a** was obtained in moderate yield after a reaction time of 24 h (Table 1, entry 1). The yield went up to 72% when Ir(ppy)$_3$ was employed as the photocatalyst (*cf.* entry 2). Altering the photocatalyst to Eosin Y, an organic dye which was reported to be efficient for the generation of trifluoromethyl radical [30], gave only trace product in this case (entry 3). No reaction was detected when no photocatalyst was added (entry 4). The influence of solvent selection was examined (entries 5-9), and acetonitrile remained to be the optimal medium for the tandem radical trifluoromethylation/cyclization. Several inorganic and organic bases were then screened (entries 10-16). The best result was obtained by potassium carbonate, and Hünig's base also gave a similar yield. Control experiments indicated that base and light are both essential to this photocatalytic protocol (entries 17, 18). A 23 W household white CFL was compared with the 5 W blue LED, and the same yield was provided (entry 19). The 5 W LED lamp should be better from the viewpoint of energy-saving. Only 17% yield was obtained irradiated with ambient light (entry 20).

With optimized conditions available, the substrate scope and limitations were then explored regarding the substitution pattern on aryl alkynoate (**1**). It is interest to find that the reactions didn't proceed through 6-*endo* cyclization [11], instead, 5-*exo* cyclization and 1,2-migration of the ester group [15-20] might occur. As shown in Table 2, moderate to good yields of trifluoromethylated coumarin derivatives (**2**) were gained by the photocatalytic cyclization of aryl alkynoates with a few exceptions. It is obvious that the substituent

R^1 has a great effect on this visible-light-mediated reaction. Substrates bearing electron-neutral alkyl group at *para*-position of the phenyl works well, with the corresponding 7-substituted-3-trifluoromethylated

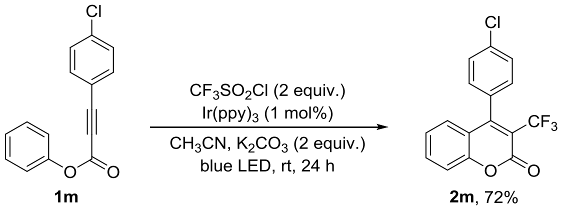
Table 2

Substrate scope of the cyclization of aryl alkynoates with CF_3SO_2Cl.[a]

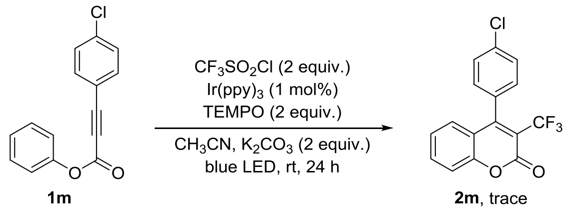


[a] Unless otherwise noted, the reaction conditions are as follows: **1a** (0.2 mmol), CF_3SO_2Cl (0.4 mmol), Ir(ppy)$_3$ (1 mol%), K_2CO_3 (0.4 mmol), CH_3CN (1 mL), irradiation with a blue LED lamp (5 W) under argon at rt for 24 h. Isolated yield.

[b] K_2CO_3 was replaced by Hünig's base (0.4 mmol).



Scheme 2. Scale-up experiment. Reaction conditions: **1m** (1 g, 3.9 mmol), CF_3SO_2Cl (7.8 mmol), Ir(ppy)$_3$ (1 mol%), K_2CO_3 (3.9 mmol), CH_3CN (19.5 mL), irradiation with three 5 W blue LED lamps under argon at rt for 36 h.



Scheme 3. Radical capturing experiment with TEMPO.

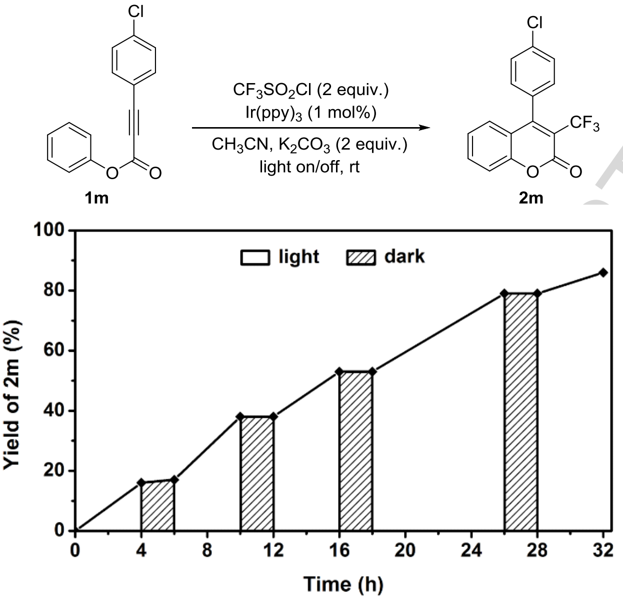
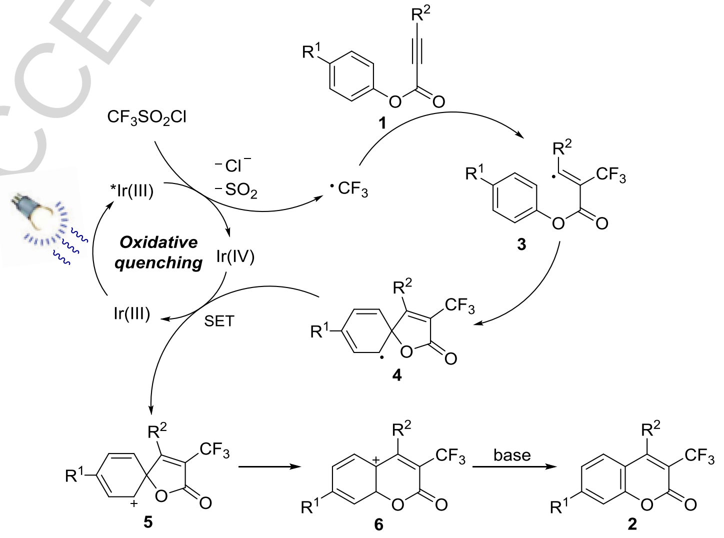


Fig. 1. Time profile of the trifluoromethylation/cyclization with and without light.

coumarins obtained in good yields (**2b**, **c**). Halogen moieties are conserved through the reaction, leaving easy handles for further functionalization *via* transition-metal catalysis (**2d-g**). Reactions of aryl alkynoates **2e-g** obtained better yields when trimethylamine was used as the base. Substrate **1h** (R^1 = *p*-CF_3) could also serve as a substrate for this transformation, and the exact structure of the product **2h** was confirmed by X-ray single crystal diffraction (Table 2). However, the reactions resulted in complex mixtures when R^1 is methoxy or cyano at *para*-position, because unexpected radicals or radical anions might be formed and strong electron-withdrawing group at *para*-position are not favorable in this kind of reactions [16,19]. When the *meta*-positions were replaced by two methyl groups, a yield of 61% was provided (**2i**). Only trace product was detected when only one *ortho* hydrogen atom was available, owing to the effect of steric hindrance (**2j**). Substrates with different substituent groups R^2 were then subjected to the optimal reaction conditions. In this



Scheme 4. Proposed mechanism for photocatalytic trifluoromethylation/cyclization.

case, aryl groups with electron-donating, -neutral, or -withdrawing substituents at *para*-position were all tolerated (**2k-o**). However, the present method seems to be incompatible when an alkyl group was employed as R^2. The cyclization of phenyl 3-cyclopropylpropiolate only led to trace product (**2p**).

The photoreaction of the substrate **1m** was conducted on a gram scale, and it proceeded smoothly with the formation of the desired product **2m** in 72% yield after a reaction time of 36 h, thus demonstrating the preparative utility of this chemistry (Scheme 2).

4. Mechanistic study

Experiments were carried out in order to gain insight into the mechanism of the photocatalytic cyclization (see supporting information for details). When the reaction of **1m** was performed in presence of 2 equivalents of TEMPO, the reaction became sluggish and the substrate was recovered almost quantitatively, suggesting a mechanism of radical pathway (Scheme 3). The reaction was monitored by ^{19}F NMR, and there is no obvious peak for TEMPO-CF_3. This is because Ir(IV) could not be reduced to Ir(III). The catalytic cycle ceased, therefore no more CF_3 radical would be formed. A light on/off experiment was then conducted under the standard reaction conditions (Fig. 1). The trifluoromethylation of **1m** ceased in the dark, which indicates the necessity of continuous irradiation and that a chain propagation is not the main mechanistic process for this visible-light-induced transformation.

Based on the above experiments and previous reports [15-20,29,30], a plausible catalytic cycle for the photocatalytic cyclization with CF_3SO_2Cl was suggested in Scheme 4. The photocatalyst $Ir(ppy)_3$ is activated by visible light to the excited state, and is oxidatively quenched by CF_3SO_2Cl. Trifluoromethyl radical is formed upon the release of Cl^- and SO_2. The addition of CF_3 radical to aryl alkynoate **1** gives the alkenyl radical **3**, which undergoes an intramolecular radical spirocyclization to form the cyclic intermediate **4**. A single-electron oxidation of the radical **4** by Ir(IV) leads to cation **5**. Ir(IV) was reduced to Ir(III), and that thereby completes the photocatalytic cycle. Intermediate **6** was produced by 1,2-migration of the ester group, and deprotonation of **6** finally provides the coumarin derivative **2**.

5. Conclusions

In this work, a mild methodology for the visible-light-mediated trifluoromethylation-cyclization-migration of aryl alkynoates has been developed. Various 3-trifluoromethylated coumarin derivatives could be afforded by this transformation under room temperature. In this chemistry, visible light is utilized as a clean source of energy, while trifluoromethanesulfonyl chloride serves as a cheap and readily available trifluoromethylation reagent.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version.

References

[1] R.O. Kennedy, R.D. Thornes, Coumarins: Biology, Applications and Mode of Action, Wiley, New York, 1997.
[2] F. Borges, F. Roleira, N. Milhazes, L. Santana, E. Uriarte, Curr. Med. Chem. 12 (2005) 887-916.
[3] A.M. Breul, M.D. Hager, U.S. Schubert, Chem. Soc. Rev. 42 (2013) 5366-5407.
[4] T. Nishiwaki, H. Kikukawa, J. Heterocycl. Chem. 31 (1994) 889-892.
[5] J. DeGrote, S. Tyndall, K.F. Wong, M. VanAlstine-Parris, Tetrahedron Lett. 55 (2014) 6715-6717.
[6] M. Matsui, K. Shibata, H. Muramatsu, H. Sawada, M. Nakayama, Synlett 1991 (1991) 113-114.
[7] Z. Fang, Y. Ning, P. Mi, P. Liao, X. Bi, Org. Lett. 16 (2014) 1522-1525.
[8] X.-H. Cao, X. Pan, P.-J. Zhou, J.-P. Zou, O.T. Asekun, Chem. Commun. 50 (2014) 3359-3362.
[9] X. Zhang, P. Huang, Y. Li, C. Duan, Org. Biomol. Chem. 13 (2015) 10917-10922.
[10] R. Sakamoto, H. Kashiwagi, S. Selvakumar, S.A. Moteki, K. Maruoka, Org. Biomol. Chem. 14 (2016) 6417-6421.
[11] Y. Li, Y. Lu, G. Qiu, Q. Ding, Org. Lett. 16 (2014) 4240-4243.
[12] X. Mi, C. Wang, M. Huang, J. Zhang, Y. Wu, Y. Wu, Org. Lett. 16 (2014) 3356-3359.
[13] W. Yang, S. Yang, P. Li, L. Wang, Chem. Commun. 51 (2015) 7520-7523.
[14] W.-C. Gao, T. Liu, B. Zhang, X. Li, W.-L. Wei, Q. Liu, J. Tian, H.-H. Chang, J. Org. Chem. 81 (2016) 11297-11304.
[15] T. Liu, Q. Ding, Q. Zong, G. Qiu, Org. Chem. Front. 2 (2015) 670-673.
[16] D. Zheng, J. Yu, J. Wu, Angew. Chem. Int. Ed. 55 (2016) 11925-11929
[17] S. Ni, J. Cao, H. Mei, J. Han, S. Li, Y. Pan, Green Chem. 18 (2016) 3935-3939.
[18] G. Qiu, T. Liu, Q. Ding, Org. Chem. Front. 3 (2016) 510-515.
[19] Y. Yu, S. Zhuang, P. Liu, P. Sun, J. Org. Chem. 81 (2016) 11489-11495.
[20] M. Zhu, W. Fu, Z. Wang, C. Xu, B. Ji, Org. Biomol. Chem. 15 (2017) 9057-9060.
[21] S. Chaabouni, F. Simonet, A. François, S. Abid, C. Galaup, S. Chassaing, Eur. J. Org. Chem. 2017 (2017) 271-277.
[22] J.K. Augustine, A. Bombrun, B. Ramappa, C. Boodappa, Tetrahedron Lett. 53 (2012) 4422-4425.
[23] W. Dmowski, K. Piasecka-Maciejewska, Org. Prep. Proced. Int. 34 (2002) 514-517.
[24] N.A. Romero, D.A. Nicewicz, Chem. Rev. 116 (2016) 10075-10166.
[25] K.L. Skubi, T.R. Blum, T.P. Yoon, Chem. Rev. 116 (2016) 10035-10074.
[26] T. Koike, M. Akita, Top. Catal. 57 (2014) 967-974.
[27] S. Barata-Vallejo, S.M. Bonesi, A. Postigo, Org. Biomol. Chem. 13 (2015) 11153-11183.
[28] T. Koike, M. Akita, Acc. Chem. Res. 49 (2016) 1937-1945.
[29] D.A. Nagib, D.W.C. MacMillan, Nature 480 (2011) 224-228.
[30] S.P. Midya, J. Rana, T. Abraham, B. Aswin, E. Balaraman, Chem. Commun. 53 (2017) 6760-6763.
[31] D.J. Wilger, N.J. Gesmundo, D.A. Nicewicz, Chem. Sci. 4 (2013) 3160-3165.
[32] D.A. Nagib, M.E. Scott, D.W.C. MacMillan, J. Am. Chem. Soc. 131 (2009) 10875-10877.
[33] W.J. Choi, S. Choi, K. Ohkubo, S. Fukuzumi, E.J. Cho, Y. You, Chem. Sci. 6 (2015) 1454-1464.
[34] Y. Yasu, T. Koike, M. Akita, Chem. Commun. 49 (2013) 2037-2039.
[35] Q. Wei, J.-R. Chen, X.-Q. Hu, X.-C. Yang, B. Lu, W.-J. Xiao, Org. Lett. 17 (2015) 4464-4467.

Highlights

- A photoredox catalyzed synthesis of 3-trifluoromethylated coumarins is reported.
- An efficient and commercially available trifluoromethylation reagent is employed.
- Visible light serves as a green source of energy for this transformation.
- The reaction undergoes a tandem trifluoromethylation-cyclization-migration process.