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Intermolecular Aminotrifluoromethylation of Alkenes by Visible-Light-Driven Photoredox Catalysis

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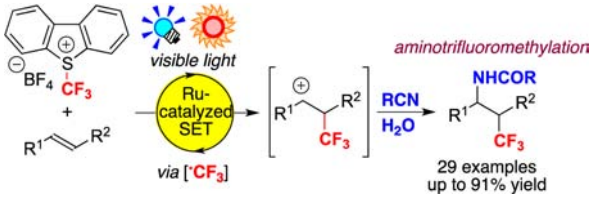
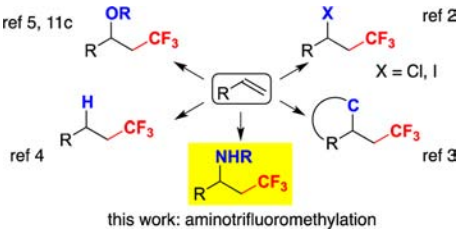
ABSTRACT



Intermolecular aminotrifluoromethylation of alkenes catalyzed by $[Ru(bpy)_3]^{2+}$ under visible light irradiation has been explored. The present photocatalytic protocol achieves highly efficient and regioselective difunctionalization of C=C bonds, leading to a variety of β-trifluoromethylamines. The reaction is applied to "late-stage aminotrifluoromethylation" of steroid and amino acid scaffolds.

Alkene difunctionalization, particularly introduction of two different functional groups across a double bond, is an attractive method for construction of diverse structures by a single transformation. Therefore, there have been a large number of studies on transition-metal-catalyzed 1,2-difunctionalization of alkenes.[1] However, transformations involving construction of C−CF_3 bonds are still limited to halotrifluoromethylation,[2] carbotrifluoromethylation,[3] hydrotrifluoromethylation,[4] and oxytrifluoromethylation[5,11c] (Scheme 1). A wide variety of trifluoromethylated derivatives have been prepared as pharmaceutical and agrochemical products because a trifluoromethyl (CF_3) group can influence chemical and metabolic stability, lipophilicity, and binding selectivity.[6,7] Thus, there has been considerable interest in development of new methodologies for highly efficient and selective incorporation of a CF_3 group and a different functional group into alkenes.

Scheme 1. Vicinal Difunctionalization of Alkenes Involving Formation of C−CF_3 Bond



Photoredox catalysis with well-defined ruthenium(II) polypyridine complexes (e.g., $[Ru(bpy)_3]^{2+}$) and the relevant cyclometalated iridium(III) derivatives has become a useful redox method in synthetic chemistry because these

(1) For recent reviews on alkene difunctionalization, see: (a) Muñiz, K. *Chem. Soc. Rev.* **2004**, *33*, 166. (b) Wolfe, J. P. *Synlett* **2008**, 2913. (c) Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem.* **2008**, *6*, 4083. (d) Cardona, F.; Goti, A. *Nat. Chem.* **2009**, *1*, 269. (e) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981. (f) Wolfe, J. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 10224.

(2) (a) Kamigata, N.; Fukushima, T.; Yoshida, M. *J. Chem. Soc., Chem. Commun.* **1989**, 1559. (b) Kamigata, N.; Fukushima, T.; Terakawa, Y.; Yoshida, M.; Sawada, H. *J. Chem. Soc. Perkin Trans. I* **1991**, 627. (c) Ignatowska, J.; Dmowski, W. *J. Fluorine Chem.* **2007**, *128*, 997. (d) Nguyen, J. D.; Tucker, J. W.; Konieczynska, M. D.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2011**, *133*, 4160. (e) Wallentin, C.-J.; Nguyen, J. D.; Finkbeiner, P.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2012**, *134*, 8875.

(3) Mu, X.; Wu, T.; Wang, H.-Y.; Guo, Y.-L.; Liu, G. *J. Am. Chem. Soc.* **2012**, *134*, 878.

(4) (a) Wu, X.; Chu, L.; Qing, F.-L. *Angew. Chem., Int. Ed.* **2013**, *52*, 2198. (b) Mizuta, S.; Verhoog, S.; Engle, K. M.; Khotavivattana, T.; O'Duill, M.; Wheelhouse, K.; Rassias, G.; Médebielle, M.; Gouverneur, V. *J. Am. Chem. Soc.* **2013**, *135*, 2505.

(5) (a) Janson, P. G.; Ghoneim, I.; IIchenko, N. O.; Szabó, K. J. *Org. Lett.* **2012**, *14*, 2882. (b) Zhu, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**, *134*, 12462. (c) Li, Y.; Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8221. (d) Egami, H.; Shimizu, R.; Sodeoka, M. *Tetrahedron Lett.* **2012**, *53*, 5503. (e) Feng, C.; Loh, T.-P. *Chem. Sci.* **2012**, *3*, 3458.

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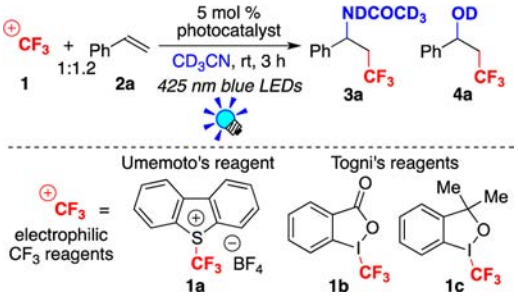
compounds can undergo visible-light-induced single-electron transfer (SET).[8−11] Recently, several examples for radical trifluoromethylation by photoredox catalysis have been reported, where CF_3SO_2Cl and gaseous CF_3I are used as the trifluoromethyl radical ($^{\bullet}CF_3$) sources.[2d,e,10] On the other hand, we found electrophilic trifluoromethylating ($^{+}CF_3$) reagents such as Umemoto's reagent **1a** (*S*-(trifluoromethyl)dibenzothiophenium tetrafluoroborate),[12a] Togni's reagents **1b** (1-trifluoromethyl-1,2-benziodoxol-3-(1*H*)-one), and **1c** (1-trifluoromethyl-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole)[12b,c] can also serve as the $^{\bullet}CF_3$ precursor in the presence of photoredox catalysts under visible light irradiation. We have previously reported the photoredox-catalyzed intermolecular oxytrifluoromethylation of alkenes with $^{+}CF_3$ reagents and *O*-nucleophiles via β-trifluoromethylated carbocation intermediates.[11c] This interesting result encouraged us to develop a new difunctionalization of C=C bonds, i.e., aminotrifluoromethylation of alkenes, which has not been reported to date. Herein we first report highly efficient and regioselective intermolecular aminotrifluoromethylation of alkenes by photoredox catalysis under visible light irradiation at room temperature. This photocatalytic protocol enables practical one-step access to a variety of 1,1,1-trifluoro-3-acetylaminopropane derivatives, which are important structural motifs in CF_3-containing biologically active compounds.[7,17,19]

We commenced to use acetonitrile (MeCN) as a *N*-nucleophile, which is known as an aminative carbocation trap agent (Ritter-type reaction).[13] We initially examined the photocatalytic reaction of 1.2 equiv of styrene **2a** with 1.0 equiv of Umemoto's reagent **1a** using 5 mol % of photoredox catalyst, [*fac*-Ir(ppy)$_3$],[14] in CD_3CN containing D_2O (1 equiv) under visible light irradiation (blue LEDs: λ_{max} = 425 nm) for 3 h (Table 1). Remarkably, aminotrifluoromethylated product **3a** was obtained in 95% yield as the sole regioisomer, accompanied by formation of a small amount of hydroxytrifluoromethylated byproduct **4a** (entry 1). The choice of the $^{+}CF_3$ reagent turned out to be crucial for the present reaction. Togni's reagents **1b** and **1c** gave no aminotrifluoromethylated product **3a** (entries 2 and 3). The amount of water significantly affected the yields of **3a**. A larger amount of D_2O resulted in formation of a substantial amount of hydroxytrifluoromethylated product **4a** (entry 4). Another photocatalyst, [Ru(bpy)$_3$](PF$_6$)$_2$,[15] also promoted the present reaction, providing the product **3a** in 95% NMR yield (entry 5). The Ru catalyst is less expensive than the Ir catalyst; thus, we chose the Ru photocatalyst for preparative experiments and reduced loadings of the catalyst to 0.5 mol %. Under these preparative conditions, product **3a** was obtained in 88% isolated yield (entry 5). Notably, product **3a** was not formed either in the dark or in the

Table 1. Photoredox-Catalyzed Aminotrifluoromethylation of Styrene **2a**[a]



entry	CF_3 source	photocatalyst	D_2O[b]	% yield of **3a** (**4a**)[c]
1	**1a**	[*fac*-Ir(ppy)$_3$]	1 equiv	95 (3)
2	**1b**	[*fac*-Ir(ppy)$_3$]	1 equiv	0 (0)
3	**1c**	[*fac*-Ir(ppy)$_3$]	1 equiv	0 (0)
4	**1a**	[*fac*-Ir(ppy)$_3$]	50 μL	18 (67)
5	**1a**	[Ru(bpy)$_3$](PF$_6$)$_2$	1 equiv	95, 88[d]
6[e]	**1a**	[Ru(bpy)$_3$](PF$_6$)$_2$	1 equiv	0 (0)
7	**1a**	none	1 equiv	0 (0)

[a] The reaction was carried out under N_2 atmosphere and irradiation of 425 nm blue LEDs at room temperature using photocatalyst (2.5 μmol), **1** (50 μmol), **2a** (60 μmol), and CD_3CN (0.5 mL) in an NMR tube. [b] The amount of added D_2O is based on the amount of **1**. [c] Yields were determined by ^1H NMR spectroscopy. [d] Yield of isolated product from the preparative-scale reaction; see the Supporting Information. [e] In the dark.

(6) Hiyama, T. *Organofluorine Compounds: Chemistry and Applications*; Springer: Berlin, 2000.

(7) (a) Ojima, I. *Fluorine in Medical Chemistry and Chemical Biology*; Wiley-Blackwell: Chichester, U.K., 2009. (b) Jeschke, P. *ChemBioChem* **2004**, *5*, 570. (c) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.

(8) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77.

(9) For recent reviews on photoredox catalysis, see: (a) Yoon, T. P.; Ischay, M. A.; Du, J. *Nat. Chem.* **2010**, *2*, 527. (b) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (c) Teplý, F. *Collect. Czech. Chem. Commun.* **2011**, *76*, 859. (d) Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617. (e) Xuan, J.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 6828. (f) Maity, S.; Zheng, N. *Synlett* **2012**, *23*, 1851.

(10) (a) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 10875. (b) Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224. (c) Iqbal, N.; Choi, S.; Ko, E.; Cho, E. J. *Tetrahedron Lett.* **2012**, *53*, 2005. (d) Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 9034. (e) Iqbal, N.; Choi, S.; Kim, E.; Cho, E. J. *J. Org. Chem.* **2012**, *77*, 11383.

(11) (a) Koike, T.; Akita, M. *Chem. Lett.* **2009**, *38*, 166. (b) Yasu, Y.; Koike, T.; Akita, M. *Chem. Commun.* **2012**, *48*, 5355. (c) Yasu, Y.; Koike, T.; Akita, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9567. (d) Koike, T.; Yasu, Y.; Akita, M. *Chem. Lett.* **2012**, *49*, 999. (e) Yasu, Y.; Koike, T.; Akita, M. *Adv. Synth. Catal.* **2012**, *354*, 3414. (f) Yasu, Y.; Koike, T.; Akita, M. *Chem. Commun.* **2013**, *49*, 2037–2039.

(12) (a) Umemoto, T. *Chem. Rev.* **1996**, *96*, 1757 and references cited therein. (b) Eisenberger, P.; Gischig, S.; Togni, A. *Chem.—Eur. J.* **2006**, *12*, 2579. (c) Kieltsch, I.; Eisenberger, P.; Togni, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 754.

(13) (a) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045. (b) Ritter, J. J.; Kalish, J. *J. Am. Chem. Soc.* **1948**, *70*, 4048.

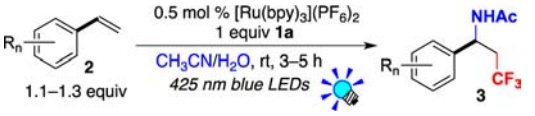
(14) Flamigni, L.; Barbieri, A.; Sabatini, C.; Ventura, B.; Barigelletti, F. *Top. Curr. Chem.* **2007**, *281*, 143.

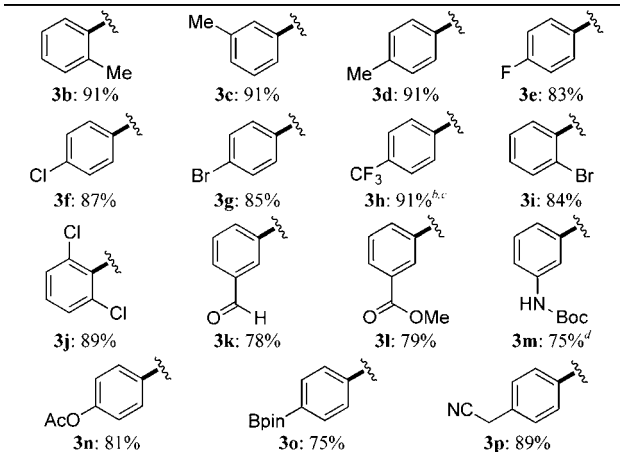
(15) Kalyanasundaram, K. *Coord. Chem. Rev.* **1982**, *46*, 159.

(16) **3n**, **3t**, and **3ae**: Molecular structures are shown in the Supporting Information. CCDC 915838, CCDC 916965, and CCDC 921846 contain the supplementary crystallographic data. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(17) For recent reviews on the synthesis of trifluoromethylated amino acids, see: (a) J. Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* **2011**, *111*, 455. (b) Qiu, X.-L.; Qing, F.-L. *Eur. J. Org. Chem.* **2011**, 3261.

Table 2. Scope of the Present Photocatalytic Aminotrifluoromethylation of Terminal Alkenes[a]



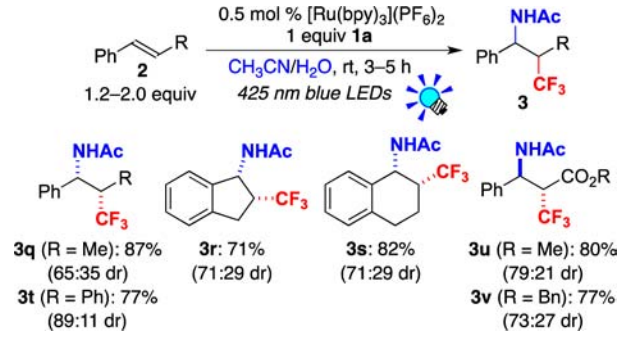


[a] The reaction was carried out under N_2 atmosphere and irradiation of 425 nm blue LEDs at room temperature using $[Ru(bpy)_3](PF_6)_2$ (1.25 μmol), **1a** (0.25 mmol), vinylarene (1.1−6.0 equiv), MeCN (5.0 mL), and H_2O (1.0 equiv) in a 20 mL Schlenk tube. [b] 6.0 equiv of alkene was used. [c] Irradiation time = 14 h. [d] 2,6-Lutidine (1.5 equiv) was used as additive.

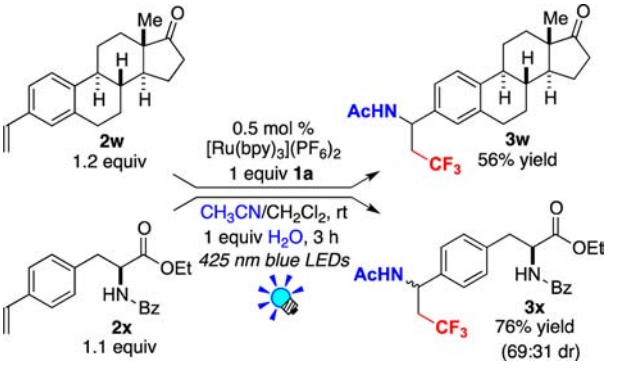
absence of photocatalysts (entries 6 and 7), strongly supporting that the photoexcited species of the photoredox catalysts play key roles in the reaction.

The scope of the present photocatalytic aminotrifluoromethylation is summarized in Table 2. Styrenes with a methyl substituent at the *ortho* (**2b**), *meta* (**2c**), or *para* (**2d**) position smoothly produced the corresponding coupling products **3b**−**d** in excellent yields (91% yields) upon irradiation for 3 h. In addition, this reaction could be applied to styrenes bearing halogen atoms, F (**2e**), Cl (**2f**, **j**), and Br (**2g**, **i**), and the aminotrifluoromethylated products (**3e**−**g**, **i** and **j**) were obtained in high yields (83−89% yields). Electron-withdrawing groups such as a trifluoromethyl group, CF_3 (**2h**), an aldehyde group, CHO (**2k**), and an ester group, CO_2Me (**2l**), did not hinder the reaction (78−91% yields). It should be noted that the transformation is tolerated with a Boc-protected amino group, NHBoc (**2m**), an acetoxy group, AcO (**2n**), and a boronic acid ester, Bpin (**2o**), and the corresponding CF_3-substituted amides (**3m**−**o**)[16] were obtained in good yields (75−81% yields). Finally, this difunctionalization protocol was also compatible with nitrile functionality and the corresponding product **3p** was obtained in 89% yield. These results indicate that the present photocatalytic aminotrifluoromethylation leads to the efficient and regioselective reactions for styrenes bearing a variety of functional groups.

Scheme 2. Scope of Internal Alkenes



Scheme 3. Application to Late-Stage Aminotrifluoromethylation of Steroid and Amino Acid Scaffolds



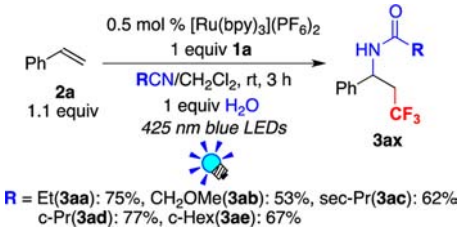
Next, to expand the scope, internal alkenes were examined (Scheme 2). The reactions of *trans*-β-methylstyrene **2q**, indene **2r**, and 1,2-dihydronaphthalene **2s** regioselectively provided the CF_3-substituted amide products **3q**−**s** in good yields (71−87%) but with a moderate level of diastereoselectivitiy. The reaction of *trans*-stilbene **2t** showed a high diastereoselectivity ((1*R**, 2*R**):(1*R**, 2*S**) = 89:11). One of the diastereomers, (1*R**,2*R**)-**3t**, was determined by X-ray crystallographic analysis (Figure S3, Supporting Information).[16] Remarkably, the cinnamic acid esters **2u** and **2v** could be also used for this photocatalytic transformation. The reactions proceeded smoothly to give the α-trifluoromethyl-β-amino acid derivatives **3u** and **3v**, which are potentially bioactive substances,[17] in good yields and high regioselectivity. It should be noted that the present photocatalytic reaction gave the aminotrifluoromethylated products in a highly regioselective manner regardless of the position of the double bond, i.e., terminal or internal.[18]

(18) It was found that scope of the present transformation is limited to vinylarenes and β-substituted styrenes (see the Supporting Information).

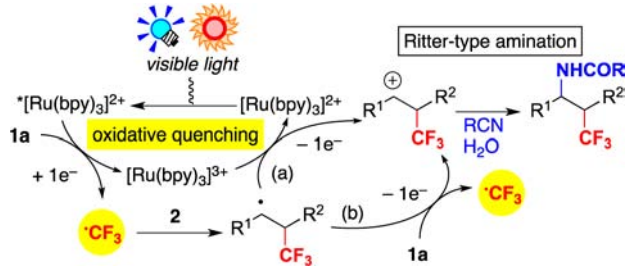
(19) For selected examples, see: (a) Kuhl, A.; Kolkhof, P.; Erguden, J.-K.; Pernerstofer, J.; Telan, L.; Peters, J.-G.; Castro-Palomino, J.; Torrejon-Nieto, J.; Lustig, K.; Kast, R.; Munter, K.; Stasch, J.-P.; Tinel, H.; Coulter, T. S.; Montalbetti, C. A. G. N.; Yarnold, C. J. PCT International Patent Application GB 2404658, February 9, 2005. (b) Brueggemeier, U.; Fuerstner, C.; Geiss, V.; Keldenich, J.; Kern, A.; Delbeck, M.; Kolkhof, P.; Kretschmer, A.; Pook, E.; Schmeck, C.; Truebel, H. PCT International Patent Application WO 2010/105770, September 23, 2010.

This facile method for simultaneous introduction of two functional groups onto diverse C=C bonds might serve as a new synthetic strategy to easily improve biological activities of natural products or drugs. The reactions of vinylestrone **2w** and vinyl-*N*-benzoyl-L-tyrosine ethyl ester **2x** smoothly proceeded to afford the corresponding CF_3-substituted amide products **3w** and **3x** in 56% and 76% isolated yields, respectively (Scheme 3). These results show that this photocatalytic system can be applicable to "late-stage aminotrifluoromethylation" of complex small molecules such as steroids and amino acids.

Scheme 4. Scope of Organic Nitriles



Scheme 5. Plausible Reaction Mechanism



As shown in Scheme 3, when CH_2Cl_2 was added to the reactions of **2w** and **2x** to dissolve them, aminotrifluoromethylation proceeded readily in the same way. These results indicate that the present reaction does not need to use organic nitrile as the solvent. Thus, we examined other organic nitriles as *N*-nucleophiles in the mixed solvent system. The reactions in mixtures of organic nitriles and CH_2Cl_2 (1:9) afforded the corresponding amides, propionamide **3aa**, 2-(methoxy)ethylamide **3ab**, isobutyramide **3ac**, cyclopropanecarboxamide **3ad**, and cyclohexylcarboxamide **3ae**[16] in moderate to good yields (53−77%) (Scheme 4).

As a demonstration of scalability of the present photocatalytic reaction, the aminotrifluoromethylation of **2a** was carried out on a gram scale using 0.3 mol % of photocatalyst. As a result, the product **3a** was isolated in 84% yield (1.14 g). Subsequent deprotection of the acetyl group furnished the ammonium salt, which is an important intermediate for a treatment agent of cardiovascular disease,[19a,b] in 70% yield (see the Supporting Information). This result suggests that we can easily access the corresponding β-CF_3-amines by the consecutive aminotrifluoromethylation and deprotection of the resultant acetylamide.

Furthermore, it was found that the present photocatalytic aminotrifluoromethylation can harness the ambient sunlight as the light source. Sunlight induced the reaction in a similar efficiency and selectivity to irradiation with blue LEDs, even though the experiment was conducted during the winter season in Japan (Supporting Information).

A plausible reaction mechanism via SET processes (oxidative quenching) is shown in Scheme 5. First, irradiation of visible light excites $[Ru(bpy)_3]^{2+}$ into $*[Ru(bpy)_3]^{2+}$. Umemoto's reagent **1a** is reduced by $*[Ru(bpy)_3]^{2+}$ to generate $^{\bullet}CF_3$. Addition of $^{\bullet}CF_3$ to alkene **2** gives the radical intermediate, which is oxidized by $[Ru(bpy)_3]^{3+}$ (path a) formed through the SET process. There is another possible pathway, i.e., radical propagation (path b). Finally, the β-trifluoromethylated carbocation intermediate is attacked by RCN, and the following hydrolysis (Ritter-type amination) affords the aminotrifluoromethylated product **3**.

In conclusion, we have developed the first intermolecular aminotrifluoromethylation of alkenes using visible-light-driven photoredox catalyst $[Ru(bpy)_3](PF_6)_2$. This highly efficient and regioselective difunctionalization protocol enables practical one-step access to a variety of β-trifluoromethylamides bearing many functional groups under mild conditions. Furthermore, this photocatalytic reaction proves "late-stage aminotrifluoromethylation" of steroid and amino acid scaffolds. Further development directed to synthesis of CF_3-containing biologically active compounds is a continuing effort in our laboratory.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.