Organic LETTERS

Letter

pubs.acs.org/OrgLett

Vicinal Difunctionalization of Alkenes: Chlorotrifluoromethylation with CF_3SO_2Cl by Photoredox Catalysis

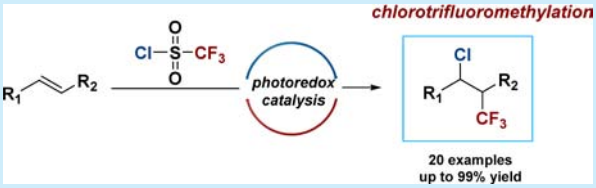
Se Hwan Oh,[†,§] Yashwardhan R. Malpani,[†,‡,§] Neul Ha,[†,‡] Young-Sik Jung,*[,†,‡] and Soo Bong Han*[,†,‡]

[†]Division of Drug Discovery Research, Korea Research Institute of Chemical Technology, P.O. Box 107, Yuseong, Daejeon 305-600, Republic of Korea

[‡]Department of Medicinal and Pharmaceutical Chemistry, University of Science and Technology, 217 Gajeongro, Yuseong, Daejeon 305-355, Republic of Korea

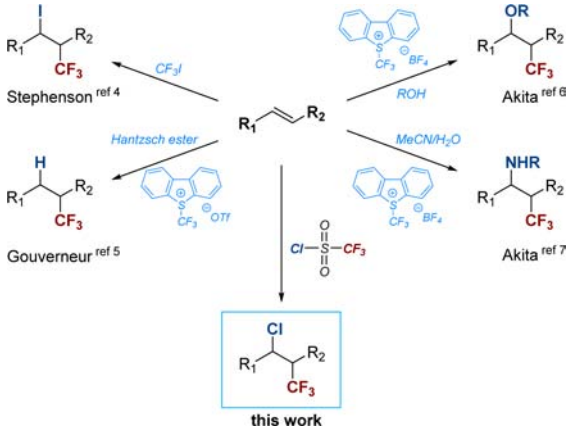
Supporting Information

ABSTRACT: Photoredox-catalyzed vicinal chlorotrifluoromethylation of alkene is described. In the presence of $Ru(Phen)_3Cl_2$, CF_3SO_2Cl was used as a source for the CF_3 radical and chloride ion under visible light irradiation. Various terminal and internal alkenes were transformed to their vicinal chlorotrifluoromethylated derivatives. Biologically active compounds were applied under the condition to obtain desired products, suggesting that the method could be feasible for late-stage modification in drug discovery.



Photoredox catalysis for organic transformations has become one of the fast growing fields in organic chemistry.[1] In particular, the difunctionalization of alkenes[2] involving the formation of a $C-CF_3$ bond by photoredox catalysis has become an important area due to its applicability to pharmaceuticals and agrochemicals.[3] Recently, halotrifluoromethylation,[4] hydrotrifluoromethylation,[5] oxytrifluoromethylation,[6] and aminotrifluoromethylation[7] have been developed with CF_3I or Umemoto's reagent[8] as a CF_3 radical source (Scheme 1). However, these reagents generally show one or more limitations such as the handling of CF_3I (gas) and generation of stoichiometric byproduct (dibenzothiophene from Umemoto's reagent). Therefore, a convenient and mild CF_3 radical source is needed. In this context, we have developed a new photoredox-catalyzed vicinal difunctionalization of alkenes with CF_3SO_2Cl,[9] incorporating not only the CF_3 group but also Cl in one pot, releasing SO_2 as a single byproduct. This transformation provides a mild and facile method for introduction of the CF_3 and Cl group together, which is a useful moiety in the field of drug discovery.[10]

Scheme 1. Difunctionalization of Alkenes with $C-CF_3$ Bond Formation



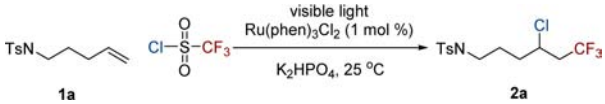
We initially examined the difunctionalization of **1a** with 1.5 equiv of CF_3SO_2Cl under visible light irradiation (Table 1). The reaction proceeded smoothly to give the chlorotrifluoromethylated product **2a** in 99% yield after 15 h when 1 mol % of $Ru(Phen)_3Cl_2$ was used as a photocatalyst with 0.3 equiv of K_2HPO_4 (Table 1, entry 3). The K_2HPO_4 was possibly buffering the reaction system. Other photocatalysts, such as $Ru(bpy)_3Cl_2{\cdot}6H_2O$ and $Ir(ppy)_3$, also gave the desired products in 74% and 99% yields, respectively (entries 4 and 5). MeCN and DCM were found to be optimal solvents based on solvent screening (entries 3, 6, and 7). When the reaction was performed without the photoredox catalyst, no product was obtained (entry 8). Also, in the absence of irradiation no desired product was generated (entry 9). These controlled experiments clearly showed that a photocatalyst and visible light irradiation are essential for the transformation.

Having the optimized conditions in hand, we examined the scope of the method (Table 2). In general, terminal alkenes showed high reactivity under the condition. Alkenes containing *N*-tosyl- and Boc-protected amines were smoothly chlorotrifluoromethylated in 99% and 91% yields, respectively (entries 1 and 2). Also, a phthalimide group was not detrimental to the desired product formation (88% yield, entry 3). A simple phenyl-containing alkene such as 4-phenyl-1-butene **1d** was efficiently transformed into the desired product in 81% yield (entry 4). Notably, unprotected hydroxyl and formyl groups

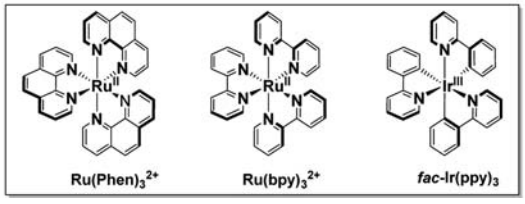
Received: December 23, 2013
Published: February 26, 2014

dx.doi.org/10.1021/ol403716t | *Org. Lett.* 2014, 16, 1310−1313

Table 1. Optimization of Chlorotrifluoromethylation of Alkenes[a]



entry	catalyst	solvent	additive (equiv)	yield (%)[b]
1	$Ru(Phen)_3Cl_2$	MeCN	none	0
2	$Ru(Phen)_3Cl_2$	MeCN	K_2HPO_4 (0.1)	38
3	$Ru(Phen)_3Cl_2$	MeCN	K_2HPO_4 (0.3)	99
4	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	MeCN	K_2HPO_4 (0.3)	74
5	*fac*-Ir(ppy)$_3$	MeCN	K_2HPO_4 (0.3)	99
6	$Ru(Phen)_3Cl_2$	DMF	K_2HPO_4 (0.3)	2
7	$Ru(Phen)_3Cl_2$	DCM	K_2HPO_4 (0.3)	99
8	none	MeCN	K_2HPO_4 (0.3)	0
9[c]	$Ru(Phen)_3Cl_2$	MeCN	K_2HPO_4 (0.3)	0

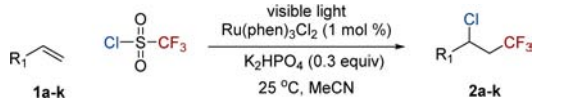


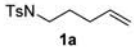
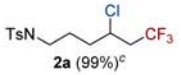
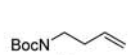
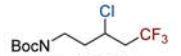
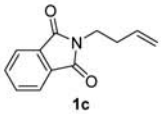
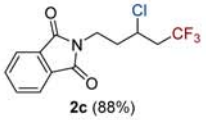
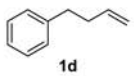
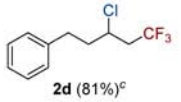
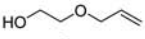
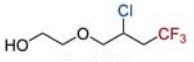
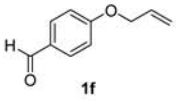
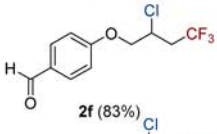
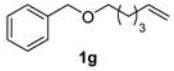
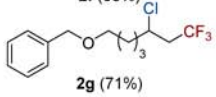
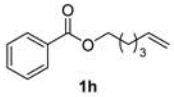
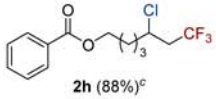
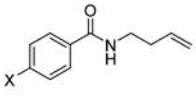
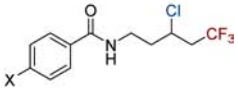
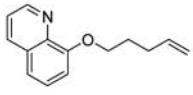
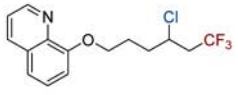
[a]The reactions were carried out under N_2 atmosphere at 25 °C for 15 h using **1a** (0.25 mmol) and CF_3SO_2Cl (0.375 mmol). [b]Yields were determined by ^1H NMR. [c]In the dark.

were very tolerant under the reaction conditions giving 75% and 83% yields, respectively (entries 5 and 6). Furthermore, alkenes with ether, ester, and amide functional groups produced the desired products in high yield (entries 7−11). Also, compounds with halogen groups on the aromatic ring showed high stability under the reaction conditions (98%, 80%, and 92% yields, entries 9−11). Surprisingly, a quinoline containing alkene **1l** was converted to its CF_3, Cl derivative **2l** in high yield (76%) without any CF_3 substitution on the aromatic ring system (entry 12).[9a] In addition, we scaled up the reaction with **1i** (2.5 mmol scale) and obtained the desired product **2i** quantitatively (entry 9). It demonstrates that this transformation can be conducted beyond the discovery scale.

To expand the scope of the method, 1,1-disubstituted alkenes were tested under the same reaction conditions (Table 3, entries 1−3). Interestingly, a chloride-containing quaternary carbon center was generated with the substrates. For example, unprotected hydroxyl-containing alkene **3a** regioselectively produced the desired product **4a** in good yield (78%, entry 1). Carvone that had an enone functional group produced the desired product **4b** in moderate yield (54%, 1:1 dr, entry 2). In addition, (*S*)-(−)-perillaldehyde **3c** was smoothly converted to the product **4c** in excellent yield (80%, 1:1 dr, entry 3). Furthermore, internal alkenes were subjected to the reaction conditions. Symmetric alkenes **3d** and **3e** generated the desired product **4d** and **4e** in good yield (71% and 61%, entries 4 and 5). In the case of asymmetric alkene **3f**, only one regioisomer **4f** was produced in moderate yield (62%, entry 6). The regioselectivity can be explained by the attack of CF_3 radical to the less hindered carbon and the generation of the more stable tertiary radical.

Table 2. Scope of Chlorotrifluoromethylation of Terminal Alkenes[a]



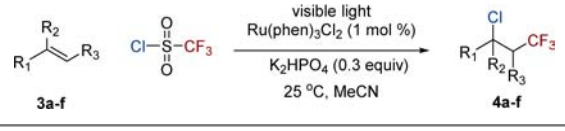
entry	substrate	product[b]
1	 **1a**	 **2a** (99%)[c]
2	 **1b**	 **2b** (91%)[d]
3	 **1c**	 **2c** (88%)
4	 **1d**	 **2d** (81%)[c]
5	 **1e**	 **2e** (75%)
6	 **1f**	 **2f** (83%)
7	 **1g**	 **2g** (71%)
8	 **1h**	 **2h** (88%)[c]
		
9	**1i** (X=Cl)	**2i** (98%, 99%[e])
10	**1j** (X=Br)	**2j** (80%)
11	**1k** (X=I)	**2k** (92%)
12	 **1l**	 **2l** (76%)

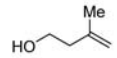
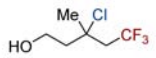
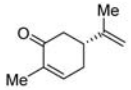
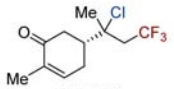
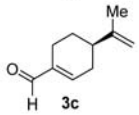
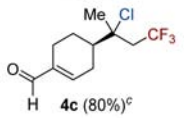
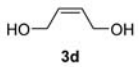
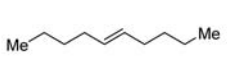
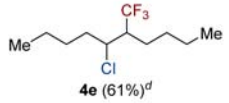
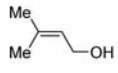
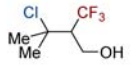
[a]The reactions were carried out under N_2 atmosphere at room temperature for 15 h using alkene (0.25 mmol) and CF_3SO_2Cl (0.75 mmol). [b]Isolated yield after purification by chromatography on SiO_2. [c]CF_3SO_2Cl (0.375 mmol) was used. [d]Reaction time is 24 h. [e]2.5 mmol scale.

This protocol offers the possibility of late-stage difunctionalization of biologically active compounds that contain alkene functional groups (Scheme 2). For example, rotenone, which has been used as an effective pesticide, was smoothly converted to its Cl- and CF_3-substituted derivative (92% yields). Also, active insecticide (+)-nootkatone was changed to the desired product (69% yield). These examples show the high functional group tolerance and the feasibility of the method toward complicated biologically active compounds.

dx.doi.org/10.1021/ol403716t | *Org. Lett.* 2014, 16, 1310−1313

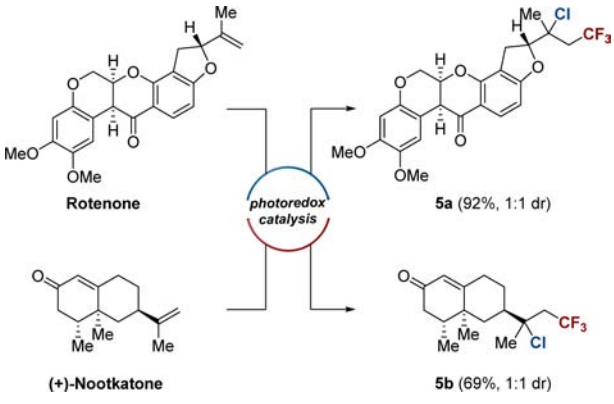
Table 3. Scope of Trifluoromethyl Chlorination of 1,1-Disubstituted and Internal Alkenes[a]



entry	substrate	product[b]
1	 3a	 4a (78%)
2	 3b	 4b (54%)[c]
3	 3c	 4c (80%)[c]
4	 3d	 4d (71%)[c,e]
5	 3e	 4e (61%)[d]
6	 3f	 4f (62%)[f]

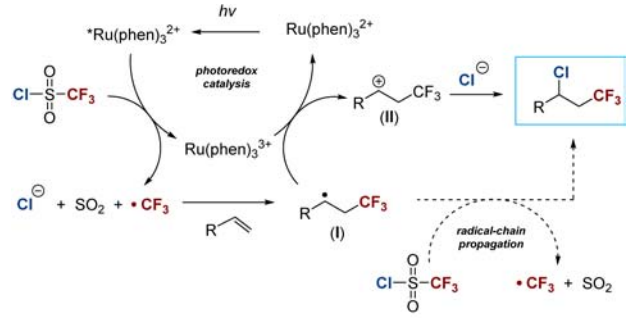
[a]The reactions were carried out under N_2 atmosphere at room temperature for 15 h using alkene (0.25 mmol) and CF_3SO_2Cl (0.375 mmol). [b]Isolated yield after purification by chromatography on SiO_2. [c]1:1 dr. [d]1.9:1 dr. [e]Yields were determined by ^1H NMR. [f]With CF_3SO_2Cl (0.75 mmol).

Scheme 2. Application to Biologically Active Compounds Containing an Alkene Functional Group

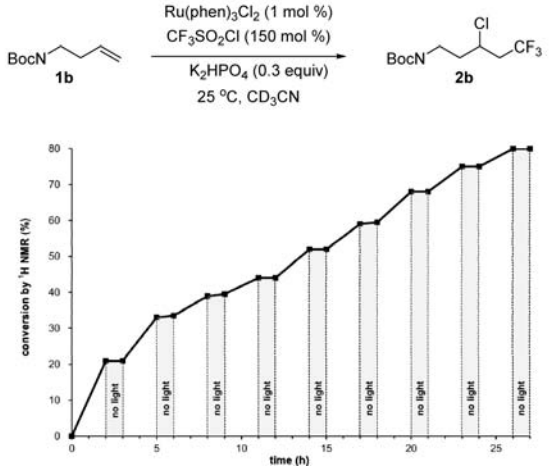


A plausible mechanism of the reaction is described in Scheme 3. Irradiation of $Ru(Phen)_3^{2+}$ with visible light generated its excited state $*Ru(Phen)_3^{2+}$. Then $*Ru(Phen)_3^{2+}$ (−0.94 V vs SCE)[11] reduced the triflyl chloride (−0.18 V vs SCE)[9a,12] and was oxidized to $Ru(Phen)_3^{3+}$. The CF_3SO_2Cl radical anion was immediately collapsed to $^{\bullet}CF_3$, SO_2, and Cl^-.[13] The stabilized electron-deficient $^{\bullet}CF_3$ was added to electron-rich alkene, and the radical intermediate **I** was formed. $Ru(Phen)_3^{3+}$ (+1.31 V versus SCE) acted as a oxidant to produce the carbocation intermediate **II**, and $Ru(Phen)_3^{2+}$ was regenerated. The resulting carbocation was trapped by Cl^- to generate the product. Even though the oxidative quenching mechanism is plausible, the radical-chain propagation mechanism can not be ruled out.[14] To investigate the significance of the chain propagation mechanism, an on/off visible light irradiation experiment was performed. The graph clearly shows that the transformation required continuous irradiation with visible light (Scheme 3). Although the possibility of the chain propagation mechanism is not completely excluded, this result indicates that radical-chain propagation is not a significant pathway for product formation. Furthermore, the determined quantum yield for the formation of **2b** is 0.34, which is supporting evidence for the proposed mechanism.[15]

Scheme 3. Proposed Mechanism of Chlorotrifluoromethylation of Alkenes



• visible light irradiation on/off experiment



In conclusion, we have developed a new photoredox-catalyzed vicinal chlorotrifluoromethylation of alkenes using CF_3SO_2Cl as CF_3 and Cl sources. This mild and efficient process enables various alkenes to be transformed to CF_3 and Cl derivatives regioselectively. In addition, "late-stage transformation" of biologically active compounds was performed to show the feasibility of the method. Considering the significance of CF_3 and Cl functional groups in medicinal chemistry, our method could be applicable for drug discovery.

dx.doi.org/10.1021/ol403716t | Org. Lett. 2014, 16, 1310−1313

■ ASSOCIATED CONTENT

Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: ysjung@krict.re.kr.
*E-mail: sbhan@krict.re.kr.

Author Contributions

§These authors contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Korea Research Institute of Chemical Technology (KK-1307-B3).

■ REFERENCES

(1) For recent reviews on photoredox catalysis, see: (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (b) Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617. (c) Maity, S.; Zheng, N. *Synlett* **2012**, 1851. (d) Xuan, J.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 6828. (e) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (f) Teplý, F. *Collect. Czech. Chem. Commun.* **2011**, *76*, 859. (g) Yoon, T. P.; Ischay, M. A.; Du, J. *Nat. Chem.* **2010**, *2*, 527.

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

(3) (a) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 308. (c) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.

(4) (a) Wallentin, C.-J.; Nguyen, J. D.; Finkbeiner, P.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2012**, *134*, 8875. (b) Nguyen, J. D.; Tucker, J. W.; Konieczynska, M. D.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2011**, *133*, 4160.

(5) 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.

(6) Yasu, Y.; Koike, T.; Akita, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9567.

(7) Yasu, Y.; Koike, T.; Akita, M. *Org. Lett.* **2013**, *15*, 2136.

(8) Umemoto, T. *Chem. Rev.* **1996**, *96*, 1757 and references cited therein.

(9) For use of CF_3SO_2Cl as a CF_3 radical source, see: (a) Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224. (b) Jiang, H.; Huang, C.; Guo, J.; Zeng, C.; Zhang, Y.; Yu, S. *Chem.—Eur. J.* **2012**, *18*, 15158.

(10) Dorwald, F. Z. *Lead Optimization for Medicinal Chemists*; Strauss GmbH: Morlenbach, 2012; pp 49−57.

(11) Skarda, V.; Cook, M. J.; Lewis, A. P.; McAuliffe, G. S. G.; Thomson, A. J. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1309.

(12) Heaton, C. A.; Miller, A. K.; Powell, R. L. *J. Fluorine Chem.* **2001**, *107*, 1.

(13) Dolbier, W. R. *Top. Curr. Chem.* **1997**, *192*, 97−163.

(14) (a) Barton, D. H. R.; Lacher, B.; Zard, S. Z. *Tetrahedron* **1986**, *42*, 2325. (b) Muller, N. *J. Org. Chem.* **1986**, *51*, 263. (c) Nicolas, R. PCT WO 01/58833 A1, Aug 16, 2001.

(15) (a) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2012**, *134*, 3338. (b) Miyake, Y.; Ashida, Y.; Nakajima, K.; Nishibayashi, Y. *Chem. Commun.* **2012**, *48*, 6966.