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# Vicinal halo-trifluoromethylation of alkenes

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Both trifluoromethyl and halide groups are widely found in medicinally and pharmaceutically important compounds and, moreover, organohalides are commonly used as versatile intermediates in synthetic organic chemistry. Due to their prevalence and easy accessibility, alkene halo-trifluoromethylation provides a convenient way to install these valuable functionalities in complex targets. In this review, we summarize recent advances and achievements in this fast-growing research field. For clarity, the reactions were classified according to the type of halogen atom.

## 1. Introduction

As a result of the unique physical, chemical, and physiological properties of the fluorine atom, fluoroorganic compounds have attracted considerable attention in diverse fields, ranging from

pharmaceuticals and agrochemicals to refrigerants and advanced materials.<sup>1–3</sup> Interestingly, over one-fourth of FDA-approved drugs and circa half of contemporary agrochemicals<sup>4</sup> contain one or more fluorine atoms in their chemical structures. Among various fluorine containing substituents, the trifluoromethyl group (CF<sub>3</sub>) is highly valuable for applications in drug discovery, as the incorporation of this substituent often significantly improves the lipophilicity, bioavailability and protein-binding affinity of a molecule and suppresses metabolic detoxification processes to increase the *in vivo* lifetime of a drug.<sup>5</sup> Therefore, the development of efficient and versatile strategies for introducing the CF<sub>3</sub> moiety into various organic molecules has become one of the hottest topics in advanced organic synthesis in recent years.<sup>6</sup> Among the many methods

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developed, particularly noteworthy is the vicinal halotrifluoromethylation of alkenes due to its high pot- and step-economy for the introduction of two versatile functional groups (*i.e.*, trifluoromethyl and a halogen) into ubiquitous feedstock materials (Fig. 1). Noteworthy, two trifluoromethylated alkyl halides, halothane and isoflurane, are on the WHO's list of essential medicines (Scheme 1).<sup>7</sup> Needless to say that halogen atoms in the titled compounds could serve as highly valuable synthons for the preparation of various types of compounds *via* the well-known nucleophilic substitution and cross-coupling reactions.

The recent growth on the trifluoromethylation reactions has led to a surprisingly large number of excellent reviews on this domain.<sup>6,8</sup> However, the literature review reveals that no comprehensive review article is available covering vicinal halo-trifluoromethylation of alkenes. In connection with our recent

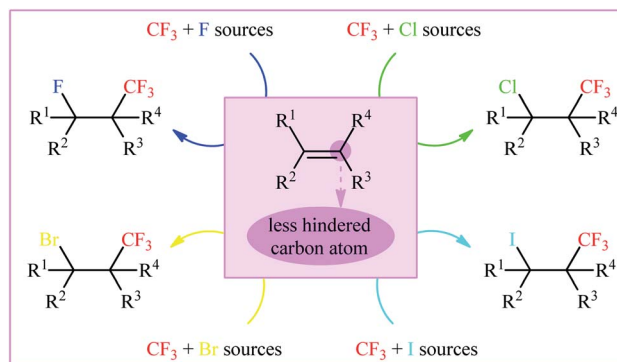


Fig. 1 Vicinal halotrifluoromethylation of alkenes.

works on organofluorine chemistry<sup>9–13</sup> and modern organic synthesis,<sup>14</sup> herein, we will summarize recent discoveries and developments in the arena of halotrifluoromethylation of alkenes, although we occasionally mention earlier work when relevant. For clarity, the reactions were organized according to the type of halogen atoms.

## 2. Fluorotrifluoromethylation

In 2015, Qing and co-workers disclosed for the first time the possibility of synthesizing  $\beta$ -CF<sub>3</sub>-substituted fluoroalkanes through the direct vicinal fluorotrifluoromethylation of the corresponding alkenes.<sup>15</sup> To determine the optimum conditions, they screened the activities of different initiators (*e.g.*, AgF, CsF, KF, NaOAc), oxidants (PhIO, PhI(OAc)<sub>2</sub>, PhI(OCOCF<sub>3</sub>)<sub>3</sub>, K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, O<sub>2</sub>, NCS, <sup>t</sup>BuOO<sup>t</sup>Bu), and additives (*e.g.*, AgNO<sub>3</sub>, AgOAc, AgOTf) in the fluorotrifluoromethylation of 5-hexen-1-yl benzoate using TMSCF<sub>3</sub> and Selectfluor as the CF<sub>3</sub> and F sources, respectively, as a model reaction. The optimal system was identified using CsF in combination with PhI(OAc)<sub>2</sub> and AgOTf in DMF at –20 °C. A variety of terminal and internal unactivated aliphatic alkenes **1** were reacted well under the



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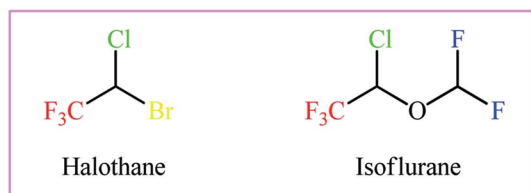
*cooperation with many research project teams around world such as in China, Malaysia, and Thailand. His interests are environmental biotechnology, biochemistry, and gene pathways in the phytoremediation processes.*



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Scheme 1 The structures of halothane and isoflurane.

standard reaction conditions to afford the corresponding fluorotrifluoromethylated products **2** in modest to good yields, ranging from 31% to 73% (Scheme 2). However, no aromatic alkene was examined in this synthetic strategy. Notably, the reaction showed complete regioselectivity for unsymmetrical alkenes, in which CF<sub>3</sub> group predominantly added to the less hindered carbon atom of the double bond. The radical trapping experiments with TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) revealed that the radical processes might be involved in this Ag-mediated oxidative fluorotrifluoromethylation reaction.

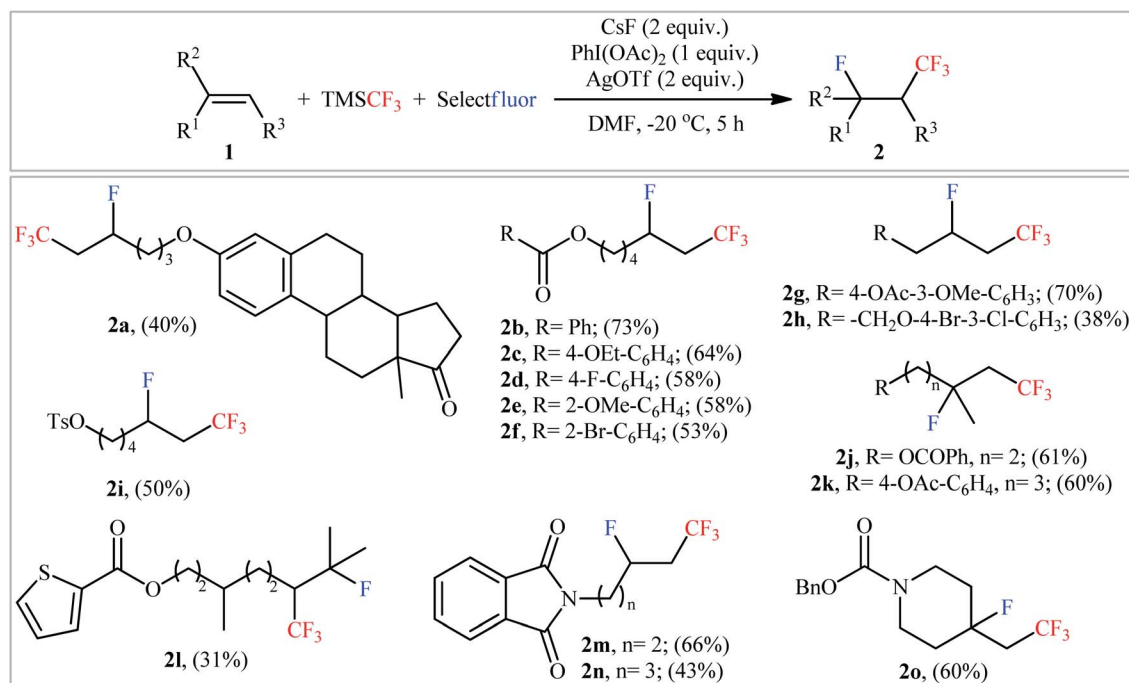
Following this work, Yu and Li along with their co-workers reported that Cu(OTf)<sub>2</sub> enabled fluorotrifluoromethylation of 1,1-disubstituted aliphatic alkenes **3** with CsF (F source) and Umemoto's reagent **4** (CF<sub>3</sub> source) in the presence of 40 mol% of 4,4'-bis(methoxycarbonyl)-2,2'-bipyridin (L3) and 20 mol% of bathocuproine (BC) as the ligands at 80 °C under an inert atmosphere.<sup>16</sup> The reactions proceeded smoothly in MeCN under visible light irradiation (11 W), tolerated various functional groups (ketone, ether, ester, amide, sulfonamide, chloro, cyano), and generally provided moderate to high yields of fluorotrifluoromethylated products **5** with only *cis*-stereochemistry

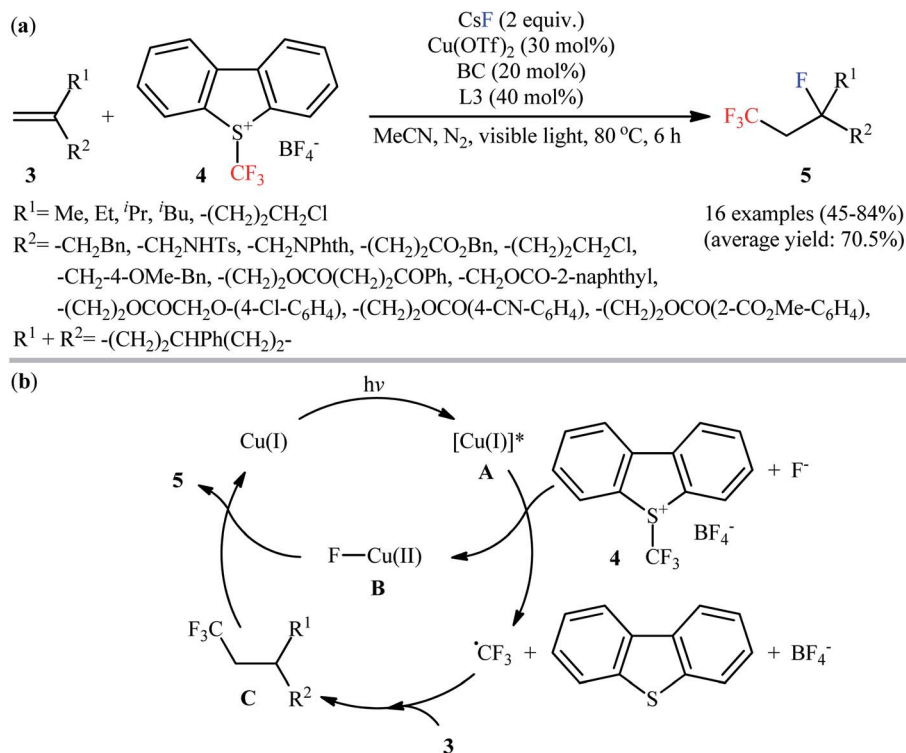
(Scheme 3a). 5-Hexen-1-yl benzoate gave the target product in only 18% yield and therefore no other monosubstituted alkenes were examined in the protocol. Internal alkenes could also undergo the fluorotrifluoromethylation but resulted in a mixture of *cis-trans* isomers. The proposed reaction mechanism involved the formation of trifluoromethyl radical (<sup>•</sup>CF<sub>3</sub>) and a Cu(II)-F complex **B** via visible-light-promoted single-electron transfer between Umemoto's reagent and the excited Cu(I) complex **A**. The addition of electrophilic <sup>•</sup>CF<sub>3</sub> to the alkene **3** produces the nucleophilic alkyl radical **C**, which abstracts a fluorine atom from the complex **B** to provide the desired product **5** and regenerate the Cu(I) complex (Scheme 3b).

Very recently, Ponomarenko-Soloshonok's research team developed an efficient conversion of monosubstituted alkenes **6** to the corresponding 1-CF<sub>3</sub>-2-F-alkanes **7**, using perfluoro-3-ethyl-2,4-dimethyl-3-pentyl radical (PPFR) as both trifluoromethylating and fluorinating agent under mediator- and additive-free conditions (Scheme 4).<sup>17</sup> The reaction was experimentally simple, performed by simple heating of the substrates at 90 °C in DCE, and was applicable to various aliphatic monosubstituted alkenes with relatively wide functional group compatibility. However, the proposed system was unfruitful with aromatic monosubstituted alkenes (styrene derivatives), and lower yields were obtained with olefins bearing aromatic groups due to the side aromatic-trifluoromethylation.

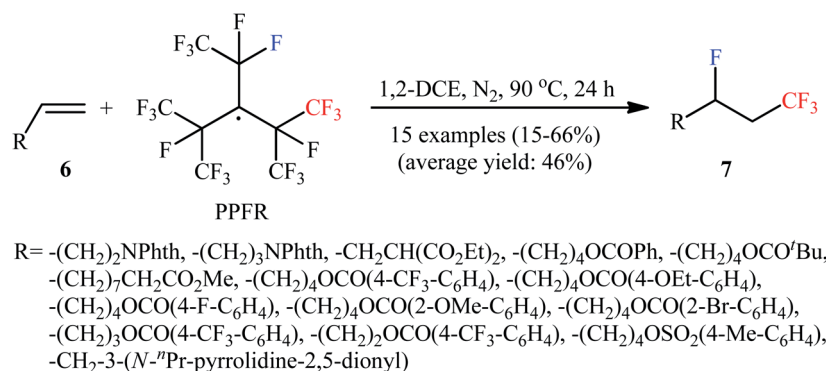
### 3. Chloro-trifluoromethylation

Synthesis of vicinal chlorotrifluoromethylated alkanes though the direct chloro-trifluoromethylation of olefinic C=C bonds is the area that has experienced the most growth in the field of

Scheme 2 Ag-mediated oxidative fluorotrifluoromethylation of alkenes **1** using TMSCF<sub>3</sub> and Selectfluor, developed by Qing.



**Scheme 3** (a) Visible light-induced Cu-catalyzed fluorotrifluoromethylation of 1,1-disubstituted alkenes **3** with CsF and Umemoto's reagent **4**; (b) proposed mechanism for the formation of **5**.



**Scheme 4** Mediator and additive-free fluorotrifluoromethylation of terminal olefins **6** developed by Ponomarenko and Soloshonok.

halotrifluoromethylation of unactivated alkenes over the past few years. In this section, we will summarize the available literature on this novel and appealing research arena with emphasize on the mechanistic proposals of the reactions. The section is organized by type of reagent used in two different subsections. The first describes chloro-trifluoromethylations using bifunctional reagents, while the second will cover examples that employ monofunctional reagents.

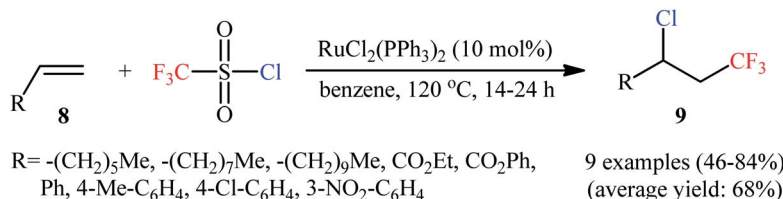
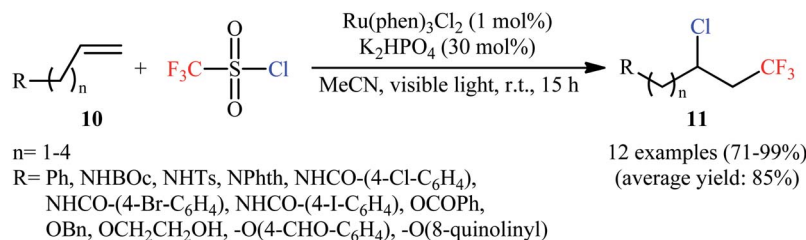
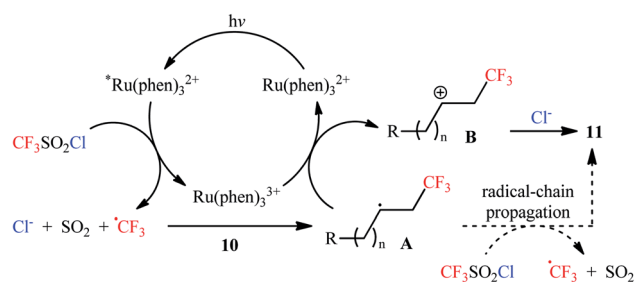
### 3.1. Bifunctional reagents

**3.1.1.  $\text{CF}_3\text{SO}_2\text{Cl}$ .** The first mention of the vicinal chlorotrifluoromethylation of unactivated alkenes using a bifunctional reagent can be found in a 1989 paper by Kamigata *et al.*,<sup>18</sup> who

showed that the treatment of monosubstituted alkenes **8** with commercially available inexpensive trifluoromethanesulfonyl chloride ( $\text{CF}_3\text{SO}_2\text{Cl}$ ) in the presence of catalytic amounts of  $\text{RuCl}_2(\text{PPh}_3)_2$  in refluxing benzene in a sealed tube afforded the corresponding  $\beta\text{-CF}_3$  alkyl chlorides **9** in moderate to high yields along with a sulfur dioxide extrusion (Scheme 5). The reaction is interesting in that both aromatic and aliphatic alkenes were well-tolerated and electronic character of the peripheral substituents on the phenyl ring had no impact on the facility of reaction. This methodology was next efficiently extended to the chloroperfluoroalkylation of alkenes possessing an electron-withdrawing group using perfluoroalkanesulphonyl



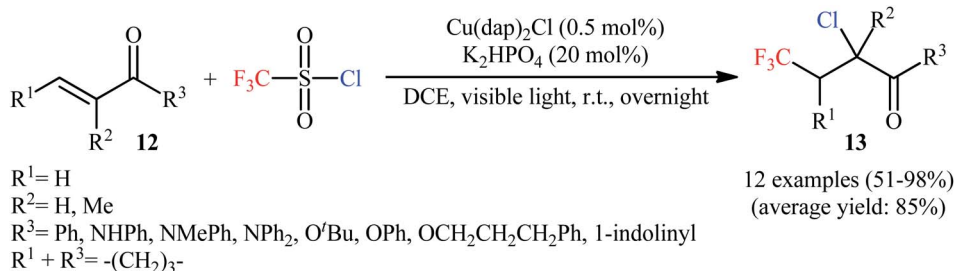


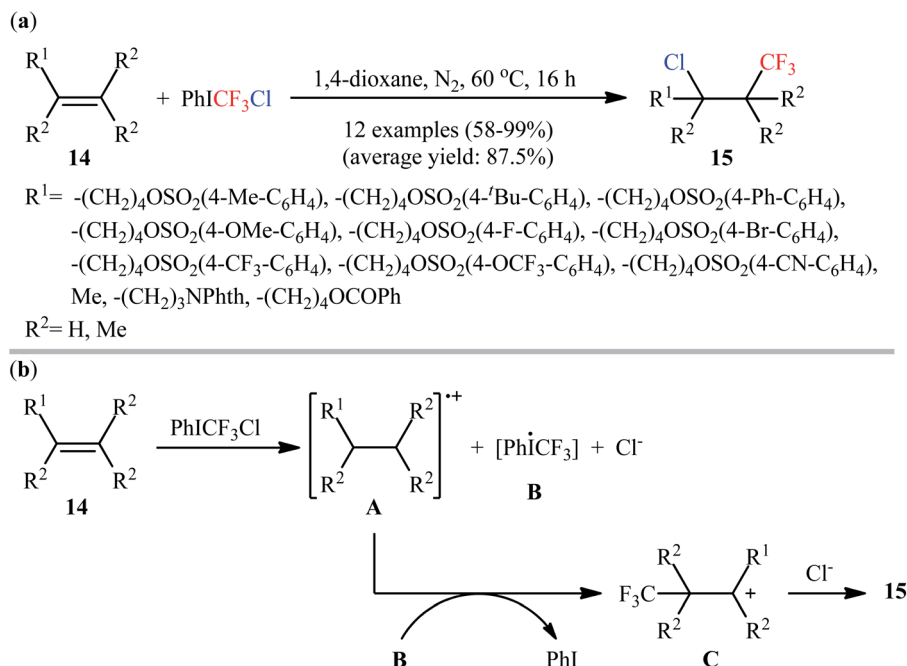
Scheme 5 Ru-catalyzed chlorotrifluoromethylation of monosubstituted alkenes **8** with  $\text{CF}_3\text{SO}_2\text{Cl}$ .Scheme 6 Photoredox-catalyzed vicinal chlorotrifluoromethylation of alkenes **10** with  $\text{CF}_3\text{SO}_2\text{Cl}$ .Scheme 7 The plausible reaction mechanism for the formation of chlorotrifluoromethylated products **11**.

chlorides as the perfluoroalkyl radical and chloride ion sources.<sup>19</sup>

Along this line, Han *et al.* disclosed that, in the presence of visible light,  $\text{Ru(Phen)}_3\text{Cl}_2$ , and  $\text{K}_2\text{HPO}_4$ , monosubstituted aliphatic alkenes **10** reacted with  $\text{CF}_3\text{SO}_2\text{Cl}$  to deliver vicinal chlorotrifluoromethylated products **11** in good to almost quantitative yields and outstanding regioselectivity (Scheme 6).<sup>19</sup> However, poor diastereoselectivities were observed in most cases. It is worthy of note that the process can be scaled up to provide multigram quantities of the desired chlorotrifluoromethylated products without sacrificing the yield or

outcome of the methodology. Of note,  $\text{Ru(bpy)}_3\text{Cl}_2 \cdot 6\text{H}_2\text{O}$  was also found to promote this double functionalization reaction, albeit in lower yields. When the reaction was performed in the absence of either visible light, or photoredox catalyst, or additive, no product was obtained. This observation indicated the a photocatalyst, buffering agent and visible light irradiation are essential for the transformation. It should also be emphasized that this catalytic system was also effective for the chlorotrifluoromethylation of 1,1-disubstituted and internal alkenes. Furthermore, this procedure was successfully applied for difunctionalization of biologically active compounds such as rotenone and (+)-nootkatone. Mechanistic investigations indicated that this interesting transformation proceeds through the following key steps (Scheme 7): (i) photoexcitation of the ground state  $\text{Ru(Phen)}_3^{2+}$  by visible light to generate the excited state  ${}^*\text{Ru(Phen)}_3^{2+}$ ; (ii) electron transfer from  ${}^*\text{Ru(Phen)}_3^{2+}$  to  $\text{CF}_3\text{SO}_2\text{Cl}$  to produce  $\text{Ru(Phen)}_3^{3+}$  and  $\text{CF}_3\text{SO}_2\text{Cl}^{\cdot-}$ , which immediately converts into  $\cdot\text{CF}_3$ ,  $\text{SO}_2$ , and  $\text{Cl}^-$  though intramolecular collapse; (iii) electrophilic addition of the  $\cdot\text{CF}_3$  to alkene **10** to form the radical intermediate **A**; (iv) oxidation of intermediate **A** with  $\text{Ru(Phen)}_3^{3+}$  to produce the carbocation intermediate **B** and regenerate  $\text{Ru(Phen)}_3^{2+}$ ; and (v) nucleophilic addition of  $\text{Cl}^-$  to cation **B** furnishes the final product **11**.

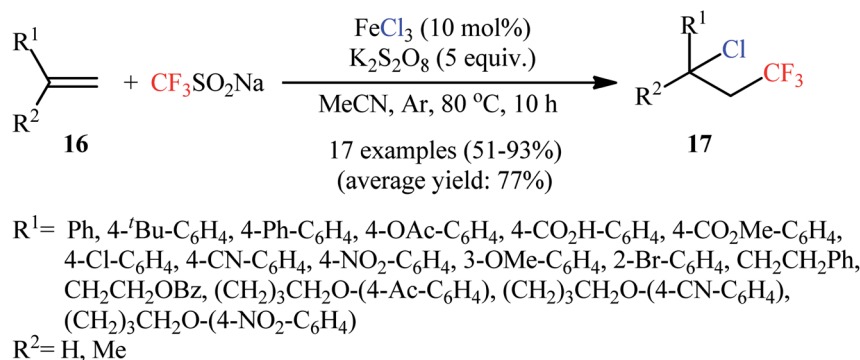
Scheme 8 Cu-catalyzed trifluoromethylchlorination of unsaturated carbonyl compounds **12** with  $\text{CF}_3\text{SO}_2\text{Cl}$ .



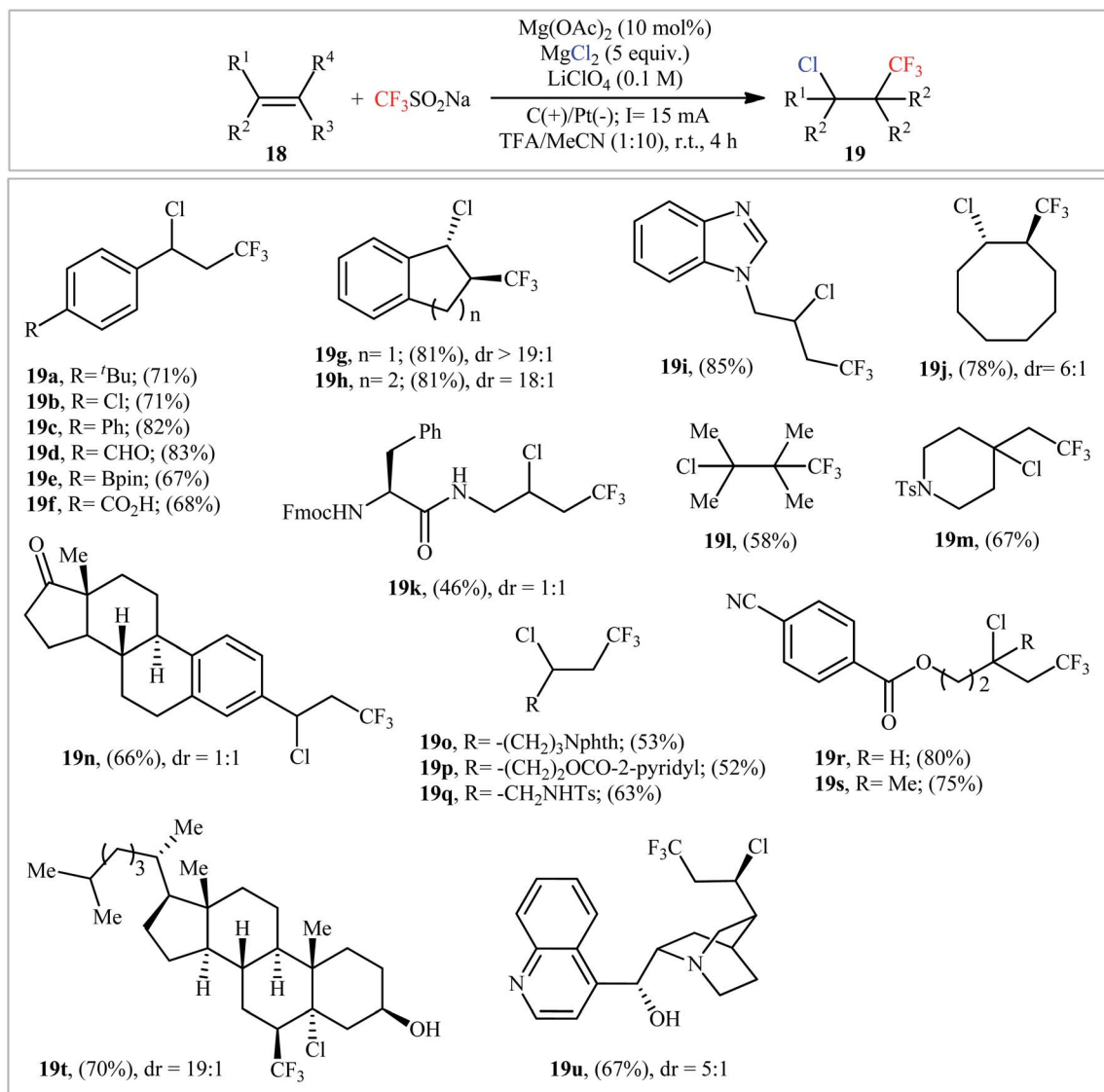
Scheme 9 (a) Catalyst-free chlorotrifluoromethylation of alkenes **14** with  $\text{PhIClCF}_3$ ; (b) mechanistic proposal for the reaction in Scheme 8a.

Subsequently, copper-catalyzed version of the titled difunctionalization reaction was developed by Tang and Dolbier.<sup>21</sup> Thus, the reaction between electron-deficient unsaturated carbonyl compounds **12** and  $\text{CF}_3\text{SO}_2\text{Cl}$  in the presence of  $\text{Cu}(\text{dap})_2\text{Cl}/\text{K}_2\text{HPO}_4$  combination as a catalytic system in DCE under visible light irradiation (r.t., overnight) afforded the corresponding  $\alpha$ -chloro- $\beta$ -trifluoromethylcarbonyl products **13** in moderate to excellent yields (Scheme 8). The reaction could also be conducted successfully on a gram scale (95% yield on a 1-gram scale). It should be mentioned that internal alkenes gave rise to mixtures of regio- and diastereoisomers unless symmetrical substrates. Besides  $\text{CF}_3\text{SO}_2\text{Cl}$ , other fluoroalkylsulfonyl chlorides (e.g.,  $\text{H}_2\text{CFSO}_2\text{Cl} \cdot \text{HCF}_2\text{SO}_2\text{Cl}$ ,  $\text{CF}_3\text{-CH}_2\text{SO}_2\text{Cl}$ , and  $\text{C}_4\text{F}_9\text{SO}_2\text{Cl}$ ) have also been successfully used as chlorofluoroalkylating reagents in this transformation. In a related study, the group of Hu also reported an efficient Cu-based photoredox catalyst for the trifluoromethylchlorination

of alkenes with  $\text{CF}_3\text{SO}_2\text{Cl}$ .<sup>22</sup> The protocol is based on the use of only 0.5 mol% of  $[\text{Cu}(\text{NN}')(\text{Xantphos})][\text{PF}_6]$ ; ( $\text{NN}' = 6\text{-methyl-4-(2,4,5-trimethylphenyl)-2,2'-bipyridine}$ ) in the presence of over-stoichiometric amounts of  $\text{K}_2\text{CO}_3$ , in DCE under blue LEDs irradiation at 40 °C. Aryl and heteroaryl substituted terminal alkenes and terminal alkenes with adjacent electron-withdrawing groups (e.g., ester, amide) were compatible with the reaction conditions. However, the reactions of alkyl substituted terminal alkenes led to chlorosulfonation at the 2-position and trifluoromethylation at the 1-position. Very recently, Xiao and co-workers improved the efficiency of this transformation in the terms of yield and reaction time by performing the process in the presence of  $\text{CuCl}_2$  (10 mol%) and pyridine (10 mol%) in 1,4-dioxane; however, elevated reaction temperature (100 °C) were necessary.<sup>23</sup> Later, Matsubara's research group identified a novel system based on  $\text{CoClTPP}$  (TPP: 5,10,15,20-tetraphenylporphyrinato) and  $\text{CF}_3\text{SO}_2\text{Cl}$  as catalyst



Scheme 10 Iron-mediated chlorotrifluoromethylation of alkenes **16** with Langlois reagent.



Scheme 11 Electrocatalytic chlorotrifluoromethylation of alkenes **18** with  $\text{CF}_3\text{SO}_2\text{Na}$  and  $\text{MgCl}_2$  developed by Lin.

in MeCN.<sup>24</sup> Although the process was efficient and provided high yields (51–100%) of products, the scope remains narrow as only a few terminal alkenes (8 examples) were evaluated.

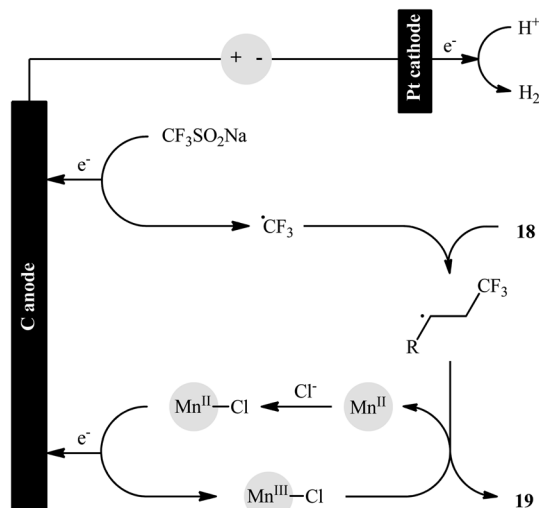
**3.1.2. PhICF<sub>3</sub>Cl.** Recently, the group of Wang prepared a super electrophilic trifluoromethylating reagent, chloro(phenyl)trifluoromethyl iodane (PhICF<sub>3</sub>Cl), by simple ligand-exchange reaction between  $\text{PhI}(\text{OCOCF}_3)_2$ ,  $\text{Me}_3\text{SiCF}_3$ , and NaCl.<sup>25</sup> Comparison studies indicated that this  $\text{CF}_3$ -containing  $\lambda^3$ -iodane reagent is much more reactive than internally coordinated and neutral Togni's reagents in a wide range of electrophilic trifluoromethylation reactions.<sup>26</sup> Interestingly, in the absence of any catalyst or additive in 1,4-dioxane under an inert atmosphere ( $\text{N}_2$ ), reaction of nonconjugated alkenes **14** with this reagent furnished the respective chlorotrifluoromethylated products **15** in good to excellent yields (Scheme 9a).<sup>27</sup> The procedure was also applied to the high yielding chlorotrifluoromethylation of a series of pharmaceutically active

substrates (e.g., oxaprozin, estrone, umbelliferone, ibuprofen, and indomethacin derivatives). However, except a few slightly electron-rich styrene derivatives, conjugated alkenes failed to participate in this reaction. A plausible mechanism is depicted in Scheme 9b. The transformation starts by a single electron transfer reaction between alkene **14** and  $\text{PhICF}_3\text{Cl}$ , leading to the formation of radical cation **A** and hypervalent iodine radical **B** along with formation of  $\text{Cl}^-$ . Subsequently, coupling of radical cation **A** with  $\text{CF}_3$  radical, generated from intermediate **B** with the concomitant release of  $\text{PhI}$ , produces carbocation **C**. Finally, nucleophilic attack of  $\text{Cl}^-$  to carbocation **C** affords the observed chlorotrifluoromethylated products **15**.

### 3.2. Monofunctional reagents

In 2016, Qing and colleagues developed an interesting protocol for chlorotrifluoromethylation of olefinic double bonds through an appropriate combination of a trifluoromethylating agent and





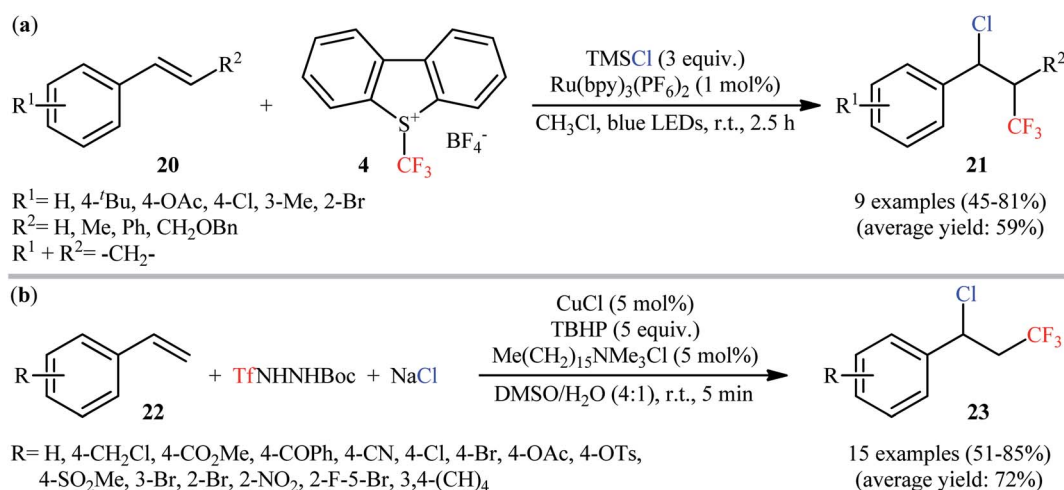
Scheme 12 Proposed mechanistic pathway for the formation of vicinal chlorotrifluoromethylated alkanes **19**.

a metal chloride.<sup>28</sup> They showed that treatment of various aromatic and aliphatic alkenes **16** with Langlois reagent ( $\text{CF}_3\text{SO}_2\text{Na}$ ) and  $\text{FeCl}_3$  in the presence of  $\text{K}_2\text{S}_2\text{O}_8$  as an oxidant gave the corresponding chlorotrifluoromethylated products **17** in good to excellent yields within 10 h (Scheme 10). In this transformation,  $\text{FeCl}_3$  playing a dual role; the chlorine source and the mediator. Noteworthy, a diverse set of versatile functional groups including cyano, nitro, chloro, bromo, ester, ether, acid, and ketone functionalities were compatible by the reaction conditions employed and optically pure substrates preserved their optical purity. An improved access to vicinal chlorotrifluoromethylated alkanes under milder and transition-metal-free conditions has subsequently been described by Liu and co-workers, using *N*-chlorophthalimide as chlorine source and

a catalytic amount of *N*-methyl-9-mesityl acridinium at room temperature.<sup>29</sup>

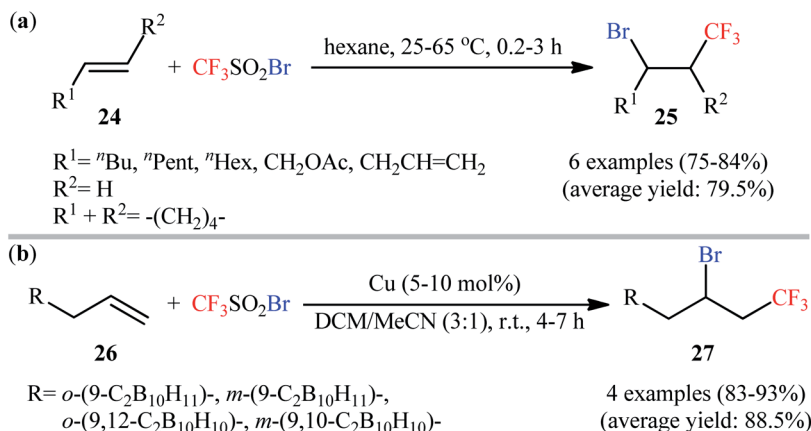
In an innovative study, the Lin laboratory demonstrated regioselective chlorotrifluoromethylation of alkenes **18** with  $\text{CF}_3\text{SO}_2\text{Na}$  and  $\text{MgCl}_2$  in an undivided carbon/Pt-cell under constant current conditions (15 mA).<sup>30</sup> The optimal conditions consisted in using  $\text{Mn}(\text{OAc})_2$  as the catalyst and  $\text{LiClO}_4$  as the electrolyte in the binary solvent  $\text{CF}_3\text{CO}_2\text{H}/\text{MeCN}$  with ratio 1 : 10 at room temperature. The established electrochemical strategy efficiently provided the target chlorotrifluoromethylated products **19** in moderate to good yields within 4 h (Scheme 11). The mechanism suggested by the authors for this electrocatalytic chlorotrifluoromethylation is shown in Scheme 12.

In this context, Masson and co-workers have described a three-component (1-chloro-3,3,3-trifluoropropyl)benzenes **21** synthesis by reaction between styrene derivatives **20**, Umemoto's reagent **4**, and  $\text{TMSCl}$  in the presence  $\text{Ru}(\text{bpy})_3(\text{PF}_6)_2$  as the photocatalyst under visible light irradiation.<sup>31</sup> This procedure efficiently provided the desired vicinal chlorotrifluoromethylated products in moderate to good yields at room temperature and without consuming any oxidant or additive (Scheme 13a). However, dibenzo[*b,d*]thiophene by-product generated from Umemoto's reagent was difficult to separate from the end products, especially when nonpolar styrenes were used as starting materials. The authors elegantly solved this problem by adding *m*-CPBA to the reaction mixture at the end of the reaction. In a closely related investigation, the group of Tian reported the use of  $\text{TfNHNHBoc}$  as the source of  $\text{CF}_3$  and  $\text{NaCl}$  as the source of  $\text{Cl}$  in this process.<sup>32</sup> Thus, by employing  $\text{CuCl}$  as a redox catalyst,  $\text{Me}(\text{CH}_2)_{15}\text{NMe}_3\text{Cl}$  as a phase-transfer catalyst, and TBHP as an oxidant in a 4 : 1 mixture of DMSO and  $\text{H}_2\text{O}$ , the electron-poor styrenes **22** quickly afforded the respective (1-chloro-3,3,3-trifluoropropyl)benzene derivatives **23** in high yields (Scheme 13b). However, arylalkenes having strong electron-donating groups, alkylalkenes, electron-deficient



Scheme 13 (a) Photoredox-mediated synthesis of (1-chloro-3,3,3-trifluoropropyl)benzenes **21** by reaction between styrene derivatives **20**, Umemoto's reagent **4**, and  $\text{TMSCl}$ ; (b) Cu-catalyzed synthesis of  $\beta$ - $\text{CF}_3$  benzyl chlorides **23** via a three-component reaction between styrenes **22**,  $\text{TfNHNHBoc}$ , and  $\text{NaCl}$ .





Scheme 14 (a) Huang's synthesis of  $\beta$ -CF<sub>3</sub> alkyl bromides **25**; (b) Cu-catalyzed bromotrifluoromethylation of allylcarboranes **27** with CF<sub>3</sub>SO<sub>2</sub>Br.

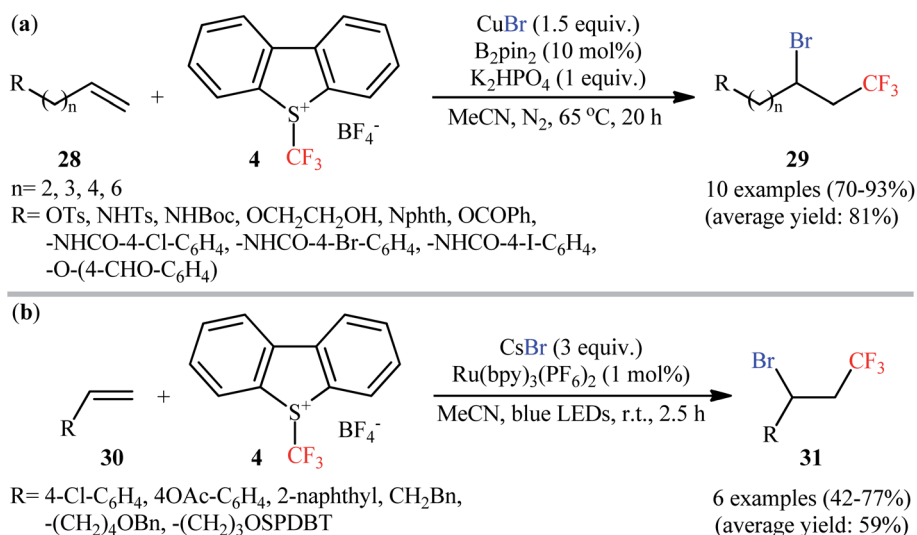
terminal alkenes, and 1,2-disubstituted alkenes failed to enter into this reaction. Interestingly, by simply replacing NaCl and CuCl with NaBr and CuBr, respectively, the optimized reaction conditions were successfully applied to the vicinal bromotrifluoromethylation of an arylalkene. However, similar modification of the reaction conditions failed to execute the corresponding vicinal iodotrifluoromethylation of arylalkenes.

## 4. Bromotrifluoromethylation

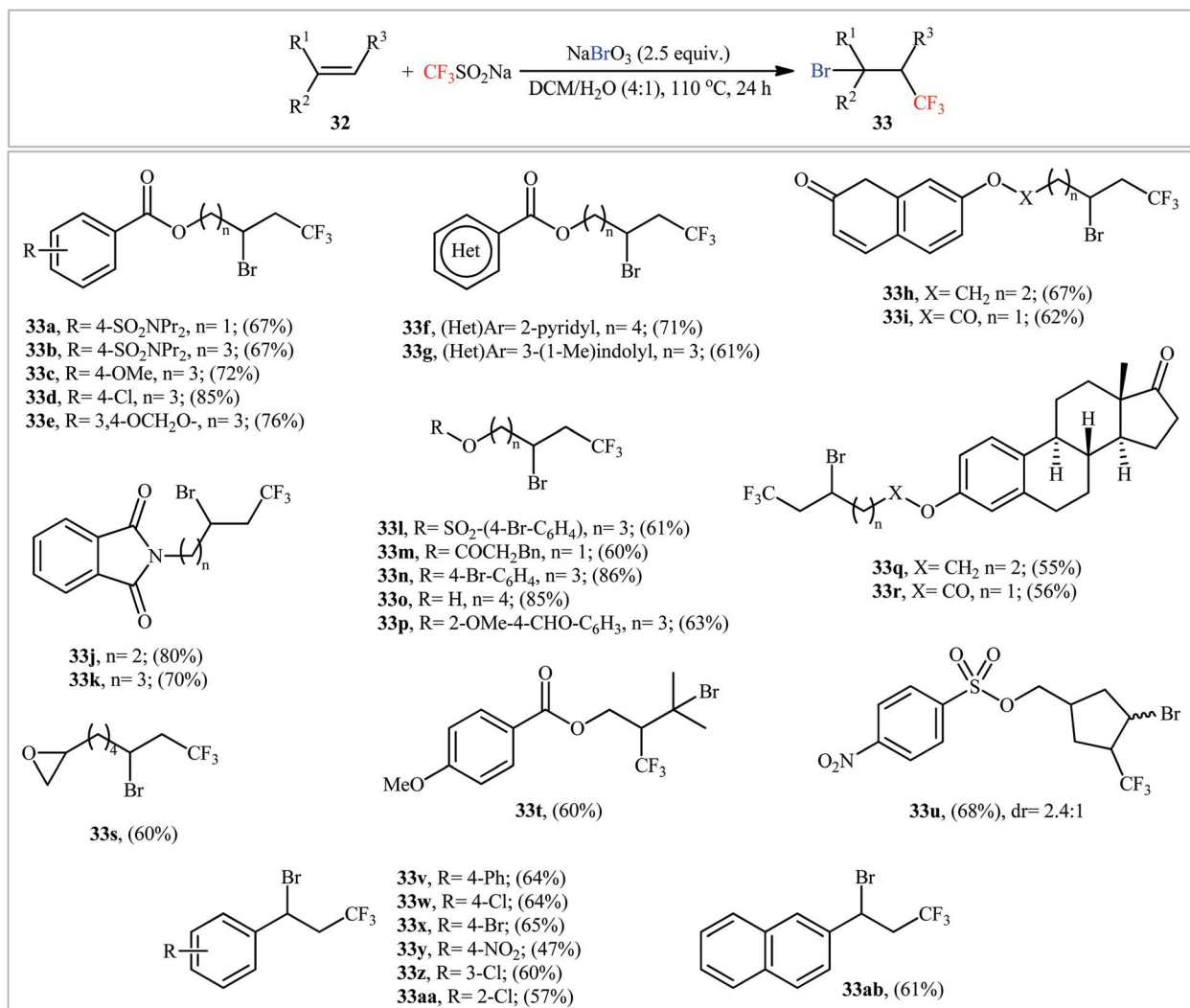
One of the earliest studies of the direct bromotrifluoromethylation of unactivated alkenes has been reported by Huang and Lü in 1992, when aliphatic alkenes underwent regioselective bromotrifluoromethylation with commercially available trifluoromethanesulfonyl bromide (CF<sub>3</sub>SO<sub>2</sub>Br) by simple heating in hexane.<sup>33</sup> The reaction was conducted in the absence of any catalyst or additive, which tolerated both terminal and internal alkenes **24**, affording the 1,2-

difunctionalized products **25** in good to high yields (Scheme 14a). Furthermore, styrene also worked well in this reaction, albeit required a higher reaction temperature and a peroxide initiator. Beside alkenes, alkynes were also compatible with this halotrifluoromethylation reaction. Twenty-seven years later, this strategy associated with copper(0) catalysis applied by Ol'shevskaya and co-workers in the functionalization of allylcarboranes **26** and achieved the respective bromotrifluoromethylated carboranes **27** in high to excellent yields (Scheme 14b).<sup>34</sup>

In 2015, Jung and Han demonstrated an efficient copper-mediated bromotrifluoromethylation of monosubstituted alkenes **28** using Umemoto's reagent **4** and CuBr, where CuBr acts as the source for both copper and bromine.<sup>35</sup> This reaction employed bis(pinacolato)diboron (B<sub>2</sub>pin<sub>2</sub>) and K<sub>2</sub>HPO<sub>4</sub> as additives and MeCN as the solvent, leading to the production of various 1-CF<sub>3</sub>-2-Br-alkanes **29** in good to excellent yields (Scheme 15a). 1,1-Disubstituted and internal alkenes were also



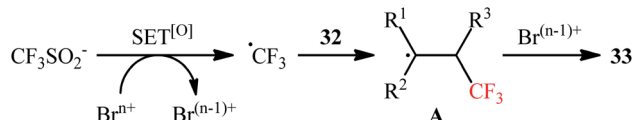
Scheme 15 (a) Cu-mediated bromotrifluoromethylation of terminal alkenes **28** developed by Jung and Han; (b) photoredox-mediated bromotrifluoromethylation of unactivated alkenes **30** with Umemoto's reagent and CsBr.

Scheme 16 Catalyst-free bromotrifluoromethylation of alkenes **32** by using  $\text{NaSO}_2\text{CF}_3$  and  $\text{NaBrO}_3$ .

effective in this reaction. However, the diastereoselectivities were poor in all cases tested. Noteworthy, by changing of CuBr with CuCl and CuI, the optimized reaction conditions were successfully applied to the chloro- and iodo-trifluoromethylation of the same set of alkenes. Concurrently, Masson found that CsBr could also be used as the source of bromine in the above-mentioned transformation.<sup>31</sup> Thus, mediated by a catalytic amount of  $\text{Ru}(\text{bpy})_3(\text{PF}_6)_2$  under constant irradiation by a blue LED, the reaction of a small series of terminal alkenes **30** with Umemoto's reagent **4** and CsBr took place readily, leading to the formation of corresponding bromotrifluoromethylated products **31** in moderate to good yields

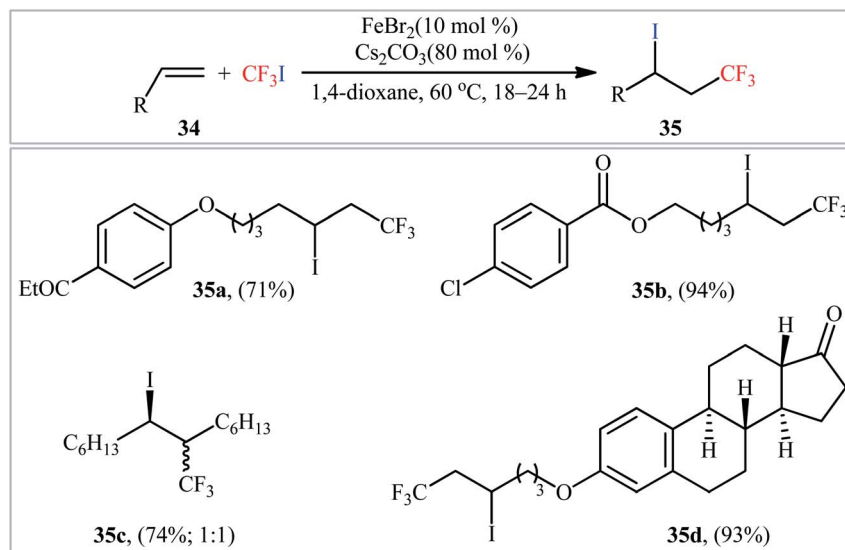
(Scheme 15b). The authors proposed mechanism for this reaction is analogous to the one depicted for Ru-catalyzed chlorotrifluoromethylation of alkenes with  $\text{CF}_3\text{SO}_2\text{Cl}$  (Scheme 7).

In 2017, Liu's research team developed an elegant metal-free method for the bromotrifluoromethylation of alkenes **32** on the use of  $\text{NaSO}_2\text{CF}_3$  in the presence of more than stoichiometric amounts of sodium bromate ( $\text{NaBrO}_3$ ).<sup>36</sup> The reactions were performed in  $\text{DCM}/\text{H}_2\text{O}$  (4 : 1) at  $110^\circ\text{C}$  in a sealed tube, tolerated various sensitive functional groups like OH, CHO, Cl, Br,  $\text{NO}_2$ ,  $\text{SONR}_2$ ,  $\text{OSO}_2\text{R}$ , ester, ether, and ketone, and afforded the corresponding  $\beta$ - $\text{CF}_3$  alkyl bromates **33** in fair to good yields (Scheme 16). Some important information of this synthetic procedure are listed below: (i) both terminal and nonterminal alkenes are compatible with this approach; (ii) optically pure substrates could be used without detected racemization; (iii)  $\text{NaBrO}_3$  acts not only as a bromine source, but also as an oxidant; and (iv) the process can be scaled up to provide multi-gram quantities of the target bromotrifluoromethylated products without sacrificing the yield and difficulty. The reaction mechanism involved single-electron oxidation of  $\text{NaSO}_2\text{CF}_3$  by



Scheme 17 Plausible mechanism for the reaction in Scheme 16.





Scheme 18 Hu's synthesis of  $\beta$ -CF<sub>3</sub> alkyl iodides **35**.

NaBrO<sub>3</sub> to generate the  $\cdot$ CF<sub>3</sub> radical, which was then attacked to the double bond to furnish radical intermediate **A**. Finally, this intermediate underwent bromination to yield the observed product (Scheme 17). The exact bromination step remains not yet completely clear. One possible pathway is bromine atom abstraction by radical intermediate **A** from Br<sub>2</sub>, which is observed in the system. However, another process involving one-electron oxidation of this radical to give a carbocation followed by Br anion addition.

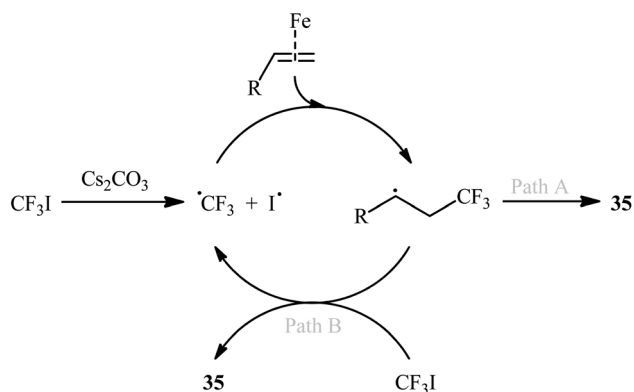
## 5. Iodotrifluoromethylation

This section is divided into two parts according to iodotrifluoromethylating reagents. The first includes the iodotrifluoromethylation of alkenes using bifunctional reagents, while the second contains the three-component reactions.

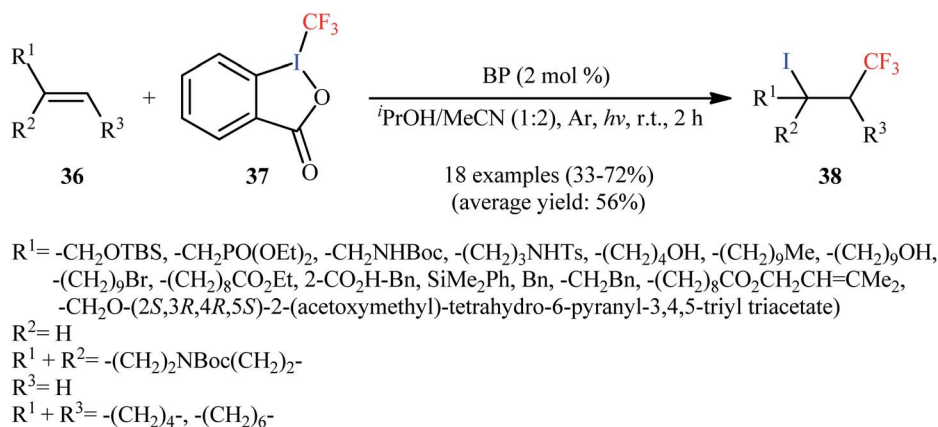
### 5.1. Bifunctional reagents

In 2004, Ogawa's research team reported a mild and fast photoinduced vicinal iodotrifluoromethylation of

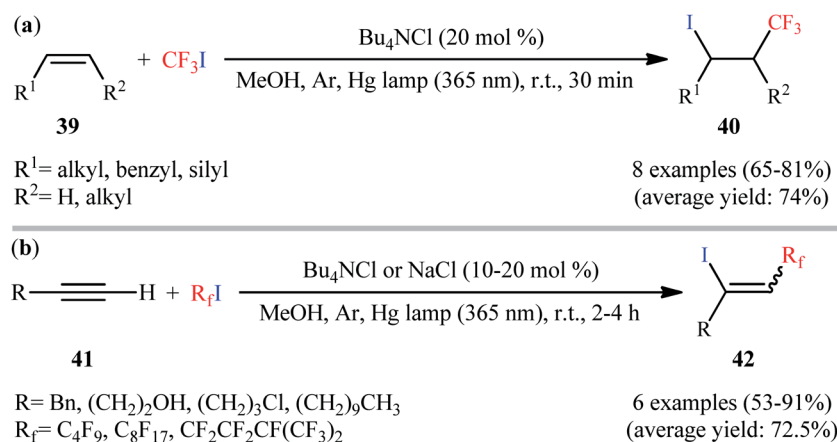
cyclohexylallene with trifluoroiodomethane (CF<sub>3</sub>I) upon irradiation with a xenon lamp under catalyst- and solvent-free conditions.<sup>37</sup> Although only one poor yield example was provided, this paper represents the first example of the direct iodotrifluoromethylation of alkene C=C double bonds. Three years later, Ignatowska and Dmowski provided two further examples of  $\beta$ -CF<sub>3</sub> alkyl iodide preparation promoted by Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub>/Na<sub>3</sub>PO<sub>4</sub> in binary solvent MeCN/H<sub>2</sub>O with ratio 1 : 1.<sup>38</sup> Concurrently, Yajima and Nagano described an interesting regioselective iodoperfluoroalkylation of acrylic acid derivatives bearing a chiral auxiliary with corresponding perfluoroalkyl iodides in the presence of an aqueous solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> under photoirradiation with a Hg lamp in a Pyrex tube.<sup>39</sup> However, in this preliminary work, only one example of the iodotrifluoromethylation with CF<sub>3</sub>I was provided, without any substrate scope exploration. In 2014, with the objective of designing a more general protocol to  $\beta$ -CF<sub>3</sub> alkyl iodides through iodotrifluoromethylation of the respective alkenes with CF<sub>3</sub>I, Hu and co-workers were able to show that a small library of 1-CF<sub>3</sub>-2-I-alkanes **35** could be obtained in good to excellent yields from the reaction of terminal alkenes **34** with CF<sub>3</sub>I in 1,4-dioxane employing FeBr<sub>2</sub>/Cs<sub>2</sub>CO<sub>3</sub> combination as the catalytic system (Scheme 18).<sup>40</sup> Other perfluoroalkyl iodides, such as IC<sub>4</sub>F<sub>9</sub>, IC<sub>6</sub>F<sub>13</sub>, IC<sub>10</sub>H<sub>21</sub>, ICF<sub>2</sub>CO<sub>2</sub>Et, and IC<sub>6</sub>F<sub>12</sub>Cl were also compatible with these conditions, and furnished the corresponding iodoperfluoroalkylated products in high yields. Furthermore, this process also allowed the synthesis of diverse iodoperfluoroalkylated alkenes through the 1,2-addition of perfluoroalkyl iodides to the carbon–carbon triple bond of the corresponding alkynes. The putative mechanism for this alkene difunctionalization reaction is depicted in Scheme 19. Along this line, Reiser and co-workers have published the direct iodotrifluoromethylation of styrene with CF<sub>3</sub>I leading to (3,3,3-trifluoro-1-iodopropyl)benzene in yield of 45% *via* the combination of [Cu(dap)<sub>2</sub>]Cl catalyst and green LED irradiation.<sup>41</sup>



Scheme 19 Proposed reaction pathway for the formation of  $\beta$ -CF<sub>3</sub> alkyl iodides **35**.



Scheme 20 Light-mediated iodotrifluoromethylation of alkenes **36** employing Togni's reagent **37** as source of  $CF_3$  and iodine.

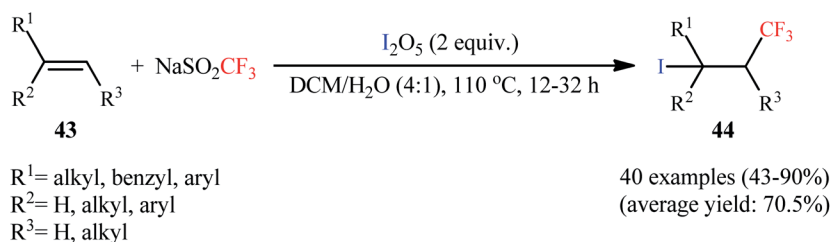


Scheme 21 (a) Light-mediated iodotrifluoromethylation of alkenes **39** with  $CF_3I$  catalyzed by  $Bu_4NCl$ ; (b) light-mediated chloride ions-catalyzed iodoperfluoroalkylations of alkynes **41**.

An improved version of this reaction was disclosed in 2017 by Vincent and colleagues, who developed a BP-sensitized (BP = benzophenone) light-promoted synthesis of  $\beta$ - $CF_3$  alkyl iodides under mild conditions.<sup>42</sup> A number of terminal and internal aliphatic alkenes **36** were rapidly converted to the corresponding iodotrifluoromethylated products **38** using 2 mol% of BP, employing Togni's reagent **37** as an effective iodotrifluoromethylating agent in a 1 : 2 mixture of  $i$ PrOH and MeCN (Scheme 20). Mechanistic studies suggested that this reaction proceeds *via* generation of isopropyl alcohol radical [ $MeC\cdot(OH)$

Me] from the reaction of BP triplet state with  $i$ PrOH. Next, this radical reduces Togni's reagent to generate 2-iodobenzoic acid, acetone, and  $\cdot CF_3$  radical. Subsequently, electrophilic addition of the latter to alkene forms the corresponding  $\alpha$ - $CF_3$  alkyl radical, which after abstraction a  $I\cdot$  radical from 2-iodobenzoic acid affords the final product.

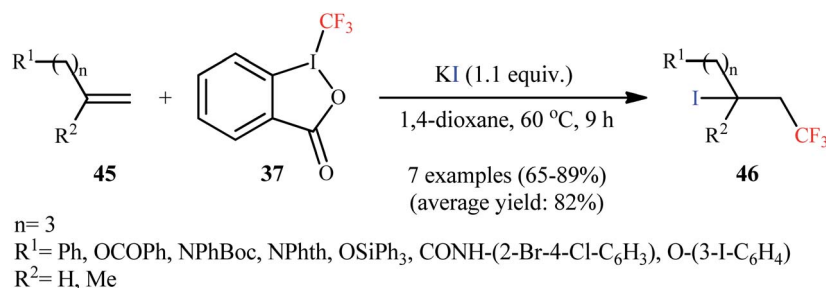
Very recently, the same group reported the direct iodotrifluoromethylation of alkenes using  $CF_3I$  with the aid of 20 mol% of  $Bu_4NCl$  under low intensity UVA irradiation (6 W) at room temperature (Scheme 21a).<sup>43</sup> Various terminal and



Scheme 22 Iodotrifluoromethylation of alkenes **43** with  $NaSO_2CF_3$  and  $I_2O_5$  developed by Liu.







Scheme 23 Iodotrifluoromethylation of alkenes **45** using Togni's reagent and KI.

internal alkenes **39** were used to establish the general applicability of the procedure. Other than  $\text{CF}_3\text{I}$ ,  $\text{IC}_4\text{F}_9$ ,  $\text{IC}_5\text{F}_{11}$ , and  $\text{IC}_8\text{F}_{17}$  have also been used in this methodology. This procedure was also applicable to aliphatic terminal alkynes **41**, giving the desired 1-perfluoroalkyl-2-iodoalkenes **42** in good yields and low to moderate stereoselectivity for the (*E*)-isomers (Scheme 21b). Noteworthy, NaCl was also found to effectively promote this iodoperfluoroalkylation reaction.

## 5.2. Monofunctional reagents

In 2014, Liu and co-workers disclosed that the iodotrifluoromethylation of various aromatic and aliphatic alkenes **43**

was feasible with the employment of two simple solids,  $\text{NaSO}_2\text{CF}_3/\text{I}_2\text{O}_5$ , in aqueous medium.<sup>44</sup> The reactions were performed in the absence of any catalyst or additive at 110 °C, tolerated a number of important functional groups (*e.g.*, fluoro, chloro, bromo, nitro, hydroxyl, sulfonate, sulfamide, ketone, ester, ether), and provided the corresponding  $\beta\text{-CF}_3$  alkyl iodides **44** in moderate to excellent yields, ranging from 43% to 90% (Scheme 22). This facile synthetic procedure was also easily scaled up to the gram-level without harming the yield or outcome of the reaction. However, just like previous works, in the cases of internal alkenes, diastereoselectivity was modest at best. Mechanistic studies by electron spin resonance (ESR)

Table 1 Comparison of results of direct halo-trifluoromethylation of alkenes

| Entry | Halo-trifluoromethylating agent(s)                         | Conditions   | Number of examples | Yield (%) |         | Ref. |
|-------|--|--|--------------------|-----------|---------|------|
|       |  |  |                    | Range     | Average |      |
| 1     | $\text{TMSCF}_3$ , Selectfluor                             | $\text{CsF}$ , $\text{PhI(OAc)}_2$ , $\text{AgTf}$ , DMF                                       | 15                 | 31–73     | 55      | 15   |
| 2     | Umemoto's reagent, $\text{CsF}$                            | $\text{Cu(OTf)}_2$ , BC, $\text{L}_3$ , MeCN   | 16                 | 45–84     | 70.5    | 16   |
| 3     | PPFR   | Catalyst-free, 1,2-DCE   | 15                 | 15–66     | 46      | 17   |
| 4     | $\text{CF}_3\text{SO}_2\text{Cl}$                          | $\text{RuCl}_2(\text{PPh}_3)_2$ , benzene  | 9                  | 46–84     | 68      | 18   |
| 5     | $\text{CF}_3\text{SO}_2\text{Cl}$                          | $\text{Ru(Phen)}_3\text{Cl}_2$ , $\text{K}_2\text{HPO}_4$ , MeCN                               | 12                 | 71–99     | 85      | 20   |
| 6     | $\text{CF}_3\text{SO}_2\text{Cl}$                          | $\text{Cu(dap)}_2\text{Cl}$ , $\text{K}_2\text{HPO}_4$ , DCE                                   | 12                 | 51–98     | 85      | 21   |
| 7     | $\text{CF}_3\text{SO}_2\text{Cl}$                          | $[\text{Cu(NN')}(Xantphos)][\text{PF}_6]$ , $\text{K}_2\text{CO}_3$ , DCM                      | 34                 | 34–98     | 73.5    | 22   |
| 8     | $\text{CF}_3\text{SO}_2\text{Cl}$                          | $\text{CuCl}_2$ , pyridine, 1,4-dioxane  | 26                 | 33–93     | 68      | 23   |
| 9     | $\text{CF}_3\text{SO}_2\text{Cl}$                          | CoCITPP  | 8                  | 51–100    | 68      | 24   |
| 10    | $\text{PhICF}_3\text{Cl}$                                  | Catalyst-free, 1,4-dioxane   | 12                 | 58–99     | 87.5    | 27   |
| 11    | $\text{CF}_3\text{SO}_2\text{Na}$ , $\text{FeCl}_3$        | $\text{K}_2\text{S}_2\text{O}_8$ , MeCN  | 17                 | 51–93     | 77      | 28   |
| 12    | $\text{CF}_3\text{SO}_2\text{Na}$ , NCP                    | Mes-Acr <sup>+</sup> , TFA, DCE  | 19                 | 41–88     | 67      | 29   |
| 13    | $\text{CF}_3\text{SO}_2\text{Na}$ , $\text{MgCl}_2$        | $\text{Mg(OAc)}_2$ , $\text{LiClO}_4$ , $\text{C(+)}/\text{Pr(-)}$ , THF, MeCN                 | 22                 | 46–85     | 66      | 30   |
| 14    | Umemoto's reagent, $\text{TMSCl}$                          | $\text{Ru(bpy)}_3(\text{PF}_6)_2$ , $\text{CH}_3\text{Cl}$                                     | 9                  | 45–81     | 59      | 31   |
| 15    | $\text{TFNHNBoc}$ , NaCl                                   | $\text{CuCl}$ , TBHP, $\text{Me(CH}_2)_{15}\text{NMe}_3\text{Cl}$ , DMSO, $\text{H}_2\text{O}$ | 15                 | 51–85     | 72      | 32   |
| 16    | $\text{CF}_3\text{SO}_2\text{Br}$                          | Catalyst-free, hexane  | 6                  | 75–84     | 79.5    | 33   |
| 17    | $\text{CF}_3\text{SO}_2\text{Br}$                          | $\text{Cu}$ , DCM, MeCN  | 4                  | 83–93     | 88.5    | 34   |
| 18    | Umemoto's reagent, $\text{CuBr}$                           | $\text{B}_2\text{pin}_2$ , $\text{K}_2\text{HPO}_4$ , MeCN                                     | 10                 | 70–93     | 81      | 35   |
| 19    | Umemoto's reagent, $\text{CsBr}$                           | $\text{Ru(bpy)}_3(\text{PF}_6)_2$ , MeCN   | 6                  | 42–77     | 59      | 31   |
| 20    | $\text{CF}_3\text{SO}_2\text{Na}$ , $\text{NaBrO}_3$       | Catalyst-free, DCM, $\text{H}_2\text{O}$   | 28                 | 47–86     | 67.5    | 36   |
| 21    | $\text{CF}_3\text{I}$                                      | Catalyst-free, BTF   | 1                  | 81        | 81      | 37   |
| 22    | $\text{CF}_3\text{I}$                                      | $\text{Na}_2\text{S}_2\text{O}_4$ , $\text{Na}_3\text{PO}_4$ , MeCN, $\text{H}_2\text{O}$      | 2                  | 57–78     | 67.5    | 38   |
| 23    | $\text{CF}_3\text{I}$                                      | $\text{Na}_2\text{S}_2\text{O}_8$ , $\text{H}_2\text{O}$                                       | 1                  | 63        | 63      | 39   |
| 24    | $\text{CF}_3\text{I}$                                      | $\text{FeBr}_2$ , $\text{Cs}_2\text{CO}_3$ , 1,4-dioxane                                       | 4                  | 71–94     | 83      | 40   |
| 25    | $\text{CF}_3\text{I}$                                      | $[\text{Cu(dap)}_2]\text{Cl}$ , MeCN   | 1                  | 45        | 45      | 41   |
| 26    | Togni's reagent  | BP, $^i\text{PrOH}$ , MeCN   | 18                 | 33–72     | 56      | 42   |
| 27    | $\text{CF}_3\text{I}$                                      | $\text{Bu}_4\text{NCl}$ , MeOH   | 8                  | 65–81     | 74      | 43   |
| 28    | $\text{CF}_3\text{SO}_2\text{Na}$ , $\text{I}_2\text{O}_5$ | Catalyst-free, DCM, $\text{H}_2\text{O}$   | 40                 | 43–90     | 70.5    | 44   |
| 29    | Togni's reagent, KI  | Catalyst-free, 1,4-dioxane   | 7                  | 65–89     | 82      | 45   |



spectroscopy suggested that the free-radical process might be involved in this reaction.

Subsequently, the Sodeoka group reported an efficient iodotrifluoromethylation of various of 1,1-disubstituted and monosubstituted alkenes **45** to afford the desired  $\beta$ -CF<sub>3</sub> alkyl iodides **46** in good to high yields (65–89%), employing Togni reagent as CF<sub>3</sub> source and KI as iodine source (Scheme 23).<sup>45</sup> NaI and CsI were also found to be effective iodine source, and I<sub>2</sub> and TBAI proved to be completely ineffective.

Finally, it should be noted that transition metal complexes play important role in halo-trifluoromethylation of alkenes and other compounds.<sup>46–65</sup>

## 6. Conclusion

Difunctionalizing trifluoromethylation of alkenes represents an extremely attractive, step- and atom-economical route to vicinal introduction of CF<sub>3</sub> and another functional group across a carbon–carbon double bond *via* a single operation and in a selective fashion. Among these trifluoromethylation-involved 1,2-difunctionalization reactions, halotrifluoromethylation of unactivated alkenes, has attracted much attention because of versatility of the resulting alkyl halides as intermediates in more complex target syntheses. As illustrated, over the past few years, several interesting halotrifluoromethylation reactions of alkenes were designed that allow the high yielding construction of various  $\beta$ -CF<sub>3</sub> alkyl fluorides, chlorides, bromides, and iodides (Table 1). Interestingly, most of these reactions were performed under catalyst-free conditions without consuming any additional chemical. Despite the extraordinary accomplishments during the last few years in this exciting research topic, several challenges still remain to be overcome: (i) the substrate scope, especially in fluoro-trifluoromethylations, is narrow and thus, expanding of the scope of these reactions are necessary; (ii) although regioselectivity of these reactions was generally high, the diastereoselectivities were poor and usually mixtures of isomers were achieved. Therefore, there is a further need for development of novel catalytic systems, which can allow for effective stereocontrolled halotrifluoromethylations for internal alkenes; and (iii) synthetic applicability of these reactions in the synthesis of natural products and biologically important compounds should be investigated.

## Conflicts of interest

There are no conflicts to declare.

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