DOI: 10.1002/anie.201202624

Trifluoromethylation

# A “Renaissance” in Radical Trifluoromethylation

*Armido Studer**

aromatic substitution · radical reactions · synthetic methods · trifluoromethylation

*This Minireview highlights recent developments in radical trifluoromethylation reactions. The trifluoromethyl group belongs to the privileged moieties in medicinal chemistry. Many drugs and drug candidates contain a trifluoromethyl substituent. Also in agrochemicals, the $CF_3$ moiety often appears. The present article addresses the radical trifluoromethylation of alkenes and arenes mainly focussing on recent achievements. However, important earlier work in this field is also covered.*

## 1. Introduction

In the year 2011, 3 of the 10 best-selling drugs and 7 of the 35 newly approved drugs contained fluorine atoms. In these biologically highly relevant structures, F atoms are mostly present as substituents on arene subunits or integrated in $CF_3$ groups.[1,2] The introduction of F atoms leads to a change in the physical properties of a compound. Fluorinated compounds display better membrane permeability and increased bioavailability than their non-fluorinated analogues because of a change in their solubility and lipophilicity. In general, fluorinated compounds are more difficult to oxidize which leads to an increased metabolic stability. Importantly, fluorine is also found in many agrochemicals.[3] It is therefore apparent that the development of new methods for selective fluorination (C−F bond formation) and trifluoromethylation (C−$CF_3$ bond formation) is important.

Transition-metal (TM)-mediated or -catalyzed trifluoromethylation has received great attention recently.[4] In the present article only those TM-mediated reactions in which C−$CF_3$ bond formation likely occurs by a radical process will be covered.

## 2. Structure and Reactivity

The structure, reactivity, and properties of fluoroalkyl radicals were comprehensively reviewed by Dolbier in 1996.[5] Because of its high electronegativity, the F atom exerts a strong σ-inductive effect on the carbon radical. At the same time the F atom behaves as a weak π-donor, because the lone pairs of the F substituents show good overlap with the singly occupied molecular orbital (SOMO) at carbon. These two opposing effects act in concert. In contrast to the planar $CH_3$ radical, the $CF_3$ radical is pyramidal (nearly tetrahedral, $\Theta = 17.8°$) and shows a large barrier for inversion (Figure 1).[6] The radical stabilization energy of the $CF_3$ radical is 2.4 kcal mol$^{-1}$ which means that it is less stable than the $CH_3$ radical.[7] The stability of the $CF_3$ radical is strongly influenced by stereoelectronic effects. There is a donor–acceptor interaction between the lone pairs at the F atoms and the adjacent σ*(C−F) orbitals.[7] However, the same interaction, even more pronounced, is also observed for the parent $CF_3H$. Therefore, the radical destabilization of the $CF_3$ radical is likely a result of reduced stabilization caused by stereoelectronic effects on going from $CF_3H$ to the $CF_3$ radical. Because of the lack of heteroatoms, such stereoelectronic effects are absent in the $CH_3$ radical.

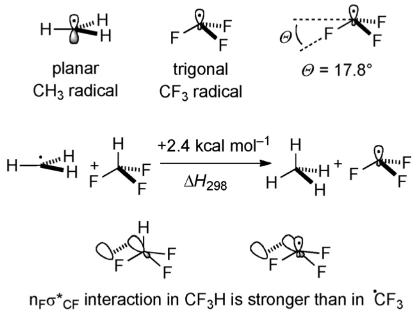


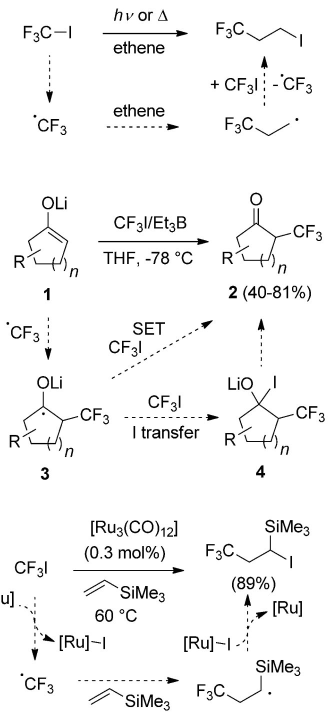
**Figure 1.** Structure of the $CF_3$ radical and stereoelectronic effects.

The proper understanding of kinetics is fundamental for planning radical reactions. The $CF_3$ radical is a typical electrophilic radical with a low-lying SOMO.[5] Consequently, reactions should be faster with electron-rich alkenes with high-lying highest occupied molecular orbitals (HOMOs). In 1,1,2-trichloro-1,2,2-trifluoroethane (Freon 113) at 298 K the

---

[*] Prof. Dr. A. Studer
Organisch-Chemisches Institut
Westfälische Wilhelms-Universität
Corrensstrasse 40, 48149 Münster (Germany)
E-mail: studer@uni-muenster.de

$CF_3$ radical adds to styrene with a rate constant $k$ of $5.3\times10^7\,\text{M}^{-1}\text{s}^{-1}$, whereas addition to $C_6F_5CH{=}CH_2$ occurs with a rate constant of $2.6\times10^7\,\text{M}^{-1}\text{s}^{-1}$. For this particular example, the polar effect is measurable but not that pronounced. Unfortunately, only few experimentally determined absolute rate constants for addition reactions of $CF_3$ radicals reactions to alkenes have been published and rate constants for additions to arenes are completely lacking. Clearly, additional absolute rate constants for the additions of $CF_3$ radicals to various π-acceptors would be highly valuable and helpful for chemists working in this area. The $CF_3$ radical is significantly more reactive than the $CH_3$ radical towards alkenes.[8] For example, styrene reacts 440 times faster with the $CF_3$ radical than with the methyl radical.[5b] Factors governing the high reactivity are the pyramidalization of the $CF_3$ radical and polar effects in reactions with electron-rich alkenes.[9]



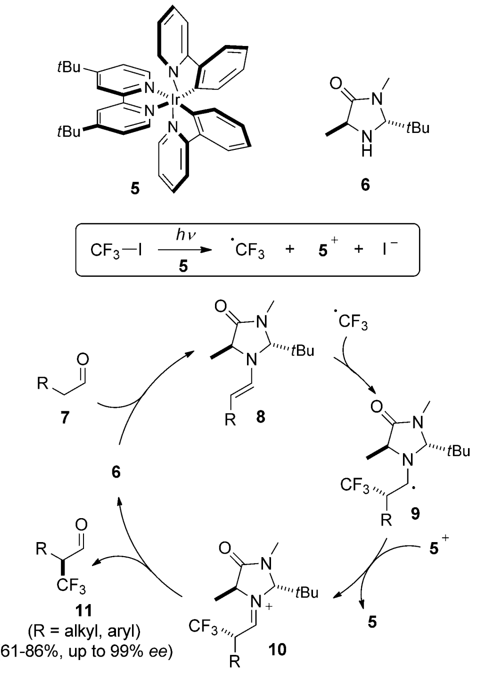
***Scheme 1.*** Radical trifluoromethylation of alkenes with $CF_3I$ ($n=1$–3).

## 3. Radical Trifluoromethylation of Alkenes

Haszeldine reported already in the late 1940s that $CF_3$ radicals are generated from $CF_3I$ through C−I bond homolysis upon irradiation or heating.[10] In the presence of ethene he observed the formation of 3-iodo-1,1,1-trifluoropropane as the major product resulting from a radical addition/iodine transfer reaction (Scheme 1). The $CF_3$ radical adds to ethene generating the corresponding adduct radical, which abstracts an iodine atom from the starting $CF_3I$ to give 3-iodo-1,1,1-trifluoropropane and the $CF_3$ radical which propagates the chain. Since that initial report, this type of intermolecular I-atom transfer/radical addition (ATRA) using $CF_3I$ as the C-radical precursor has been performed successfully with various alkenes. In addition to irradiation,[11] $Me_3Al$,[12] $Et_3B/O_2$,[13] $Na_2S_2O_4$,[14] $Et_2Zn$,[15] and $FeSO_4/H_2O_2$/DMSO[16] have been used to initiate radical trifluoromethylation. Thanks to the electrophilic nature of the $CF_3$ radical, such reactions work particularly well with electron-rich alkenes such as enamines[11] and silyl enol ethers.[13a,15] Mikami and Itoh showed that Li enolates **1** derived from cyclic ketones undergo α-trifluoromethylation with $CF_3I$ at −78 °C under radical conditions to give ketones **2**.[13c] In these transformations, the $CF_3$ radical adds to **1** to give the adduct radical **3**, which can further react by single-electron transfer (SET) to $CF_3I$ leading to **2** and the chain-propagating $CF_3$ radical along with LiI. Alternatively, **3** can abstract an iodine atom from $CF_3I$ (likely endothermic) to give **4** which eventually provides **2** by LiI elimination. Endothermic I-transfer reactions are feasible if the atom-transfer products can undergo fast ionic follow-up reactions.[17] Transition-metal catalysts have been successfully used for the ATRA of $CF_3I$ to alkenes. $[Ru_3(CO)_{12}]$ showed high activity in such reactions (see Scheme 1).[18a] The mechanism was not discussed in the original paper. We believe that the metal can either act as an initiator for an atom-transfer addition reaction or can actively participate in the chain reaction. If one considers the low catalyst loading used (0.3 mol%), the latter scenario seems to be more likely in this particular case. Hence, an active [Ru] complex first abstracts the iodine atom from $CF_3I$ to give the $CF_3$ radical and the corresponding ruthenium complex in a higher oxidation state ([Ru]-I, see Scheme 1). Radical addition to the alkene and trapping of the adduct radical with [Ru]-I eventually affords the I-transfer product and the starting [Ru] complex. Although not directly shown for $CF_3I$ but for longer-chain perfluoroalkyl iodides, similar addition reactions can be conducted using $[Fe_3(CO)_{12}]$,[18a] $[Co_2(CO)_8]$,[18a] $[Pd(PPh_3)_4]$,[19] $[Ni(CO)_2(PPh_3)_2]$,[20] $[W(CO)_5P\{(OEt)_3\}]$,[20] $[Mo(CO)_5PPh_3]$,[20] $Mo(CO)_5PPh_3$,[20] $Ag/Al_2O_3$,[20] Pt/active carbon,[20] and Ru/active carbon[20] as precatalysts/catalysts or initiators. Zakarian and co-workers reported the Ru-catalyzed, highly diastereoselective radical trifluoromethylation of chiral N-acyloxazolidinones with $CF_3I$. $[(PPh_3)_3RuCl_2]$ (5 mol%) served as the catalyst, and Zr enolates generated in situ with $ZrCl_4$ and $Et_3N$ act as radical acceptors in these transformations.[18b]

Recently, MacMillan et al. elegantly used photoredox organocatalysis for the mild enantioselective α-trifluorome-

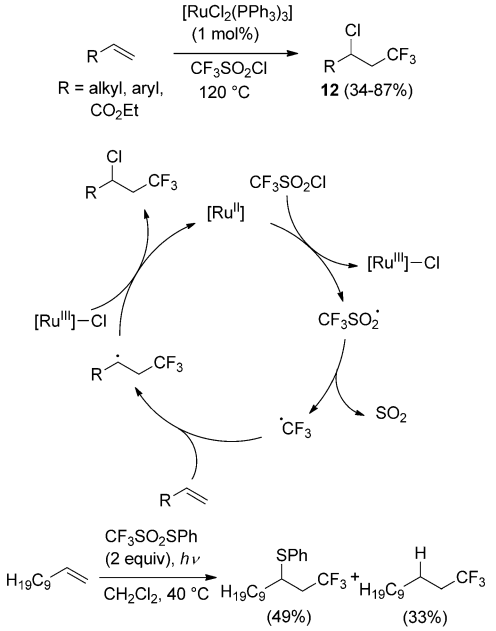
*Armido Studer received his Diploma in 1991 and his PhD in 1995 from ETH Zürich (Switzerland) under the direction of Prof. Dieter Seebach. He completed post-doctoral studies at the University of Pittsburgh with Prof. Dennis P. Curran. In 1996 he started his independent career at the ETH Zürich. In 2000, he was appointed as Associate Professor of Organic Chemistry at the Philipps-University in Marburg (Germany)and in 2004 as Full Professor of Organic Chemistry at the Westfälische Wilhelms-University in Münster (Germany). In 2006 he received the Novartis Young Investigator Award in Chemistry and in 2007 he was recipient of the Solvias Ligand Contest Award.*



**Scheme 2.** Enantioselective radical α-trifluoromethylation of aldehydes using photoredox organocatalysis.

thylation of various aldehydes (Scheme 2).[21] It was shown that irradiation of catalyst **5** with a 26 W fluorescent light bulb leads to the corresponding excited Ir complex, which undergoes SET to $CF_3I$ to give the $CF_3$ radical along with the oxidized catalyst $\mathbf{5}^+$ ($\mathbf{5}^+/PF_6$ was used as catalyst in the experiment in 0.5 mol% loading). In a second catalytic cycle, organocatalyst **6**, added as a $CF_3CO_2H$ salt (20 mol%), reacts with the starting aldehyde **7** to give chiral enamine **8**. Diastereoselective addition of the $CF_3$ radical onto the electron-rich enamine generates the adduct radical **9**, which in turn is oxidized by $\mathbf{5}^+$ to iminium ion **10**. This redox step results in the regeneration of catalyst **5**. Hydrolysis of **10** eventually affords the fluorinated aldehyde **11**, thereby regenerating the organocatalyst **6**.

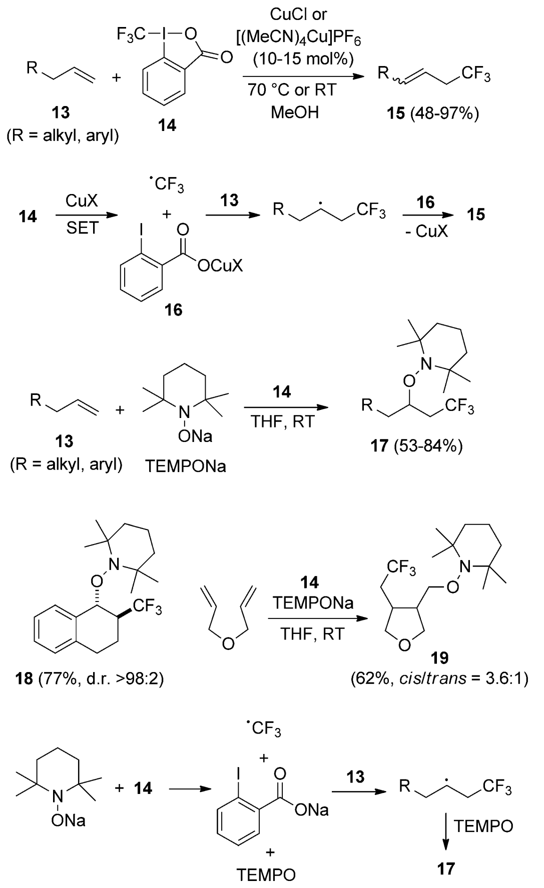
From a practical point of view, experimentation with gaseous $CF_3I$ is not convenient. It is not easy to control the concentration, in particular when the reactions are conducted at higher temperature. Therefore, scientists have been looking for more convenient alternatives and have found that the electrochemical oxidation of trifluoroacetic acid cleanly generates $CF_3$ radicals.[22] The Barton thiohydroxamic trifluoromethyl ester was also suggested as an easily prepared precursor of $CF_3$ radicals.[23] In addition, trifluoromethylsulfonyl chloride turned out to be a valuable source for $CF_3$ radicals. Various unactivated alkenes and styrene derivatives were successfully transformed to the corresponding ATRA products **12** by reaction with $CF_3SO_2Cl$ in the presence of $[RuCl_2(PPh_3)_3]$ as the catalyst (Scheme 3).[24] In these reactions, the $Ru^{II}$ complex first abstracts a chlorine atom from $CF_3SO_2Cl$ to give a $Ru^{III}Cl$ complex along with the $CF_3SO_2$ radical, which undergoes $SO_2$ elimination to give the $CF_3$ radical. Radical addition to the alkene provides the adduct radical, which in turn abstracts a chlorine atom from the $Ru^{III}Cl$ complex to finally give product **12** and the starting $Ru^{II}$ complex. It is important to note that this reaction is not restricted to electron-rich alkenes. Good results were also achieved with acrylates as radical acceptors, thus documenting the broad scope of this process.



**Scheme 3.** ATRA of various alkenes with $CF_3SO_2Cl$ or $CF_3SO_2SPh$ as the $CF_3$ radical precursors.

Phenyl trifluoromethanethiosulfonate ($CF_3SO_2SPh$) was tested in light-initiated phenylthiyl group transfer addition reactions.[25] Initiation likely occurs by homolytic cleavage of the S–S bond to provide the trifluoromethylsulfonyl radical along with the phenylthiyl radical. The sulfonyl radical then eliminates $SO_2$ and the $CF_3$ radical thus formed adds to the alkene to give the corresponding adduct radical. This secondary alkyl radical can react with $CF_3SO_2SPh$ in a group-transfer process[26] to provide the final thioether and the chain-propagating trifluoromethylsulfonyl radical. As an example, the reaction of $CF_3SO_2SPh$ with undec-1-ene is depicted in Scheme 3. In a side reaction, 1,1,1-trifluorododecane was formed in large amounts (33%). This side product results from H-abstraction of the secondary alkyl radical, which is generated from the starting alkene by addition of the $CF_3$ radical. Hence, the phenylthiyl group-transfer step is too slow to fully suppress the undesired H-transfer reaction.

Buchwald et al.[27] and Wang et al.[28] reported independently that the commercially available Togni reagent **14**[29] can be used as a source of the $CF_3$ radical (Scheme 4). Various unactivated alkenes **13** underwent allylic trifluoromethylation to give **15** upon reaction with **14** in the presence of a $Cu^I$ salt as a catalyst (10–15 mol%). The trifluoromethylated alkenes **15** were isolated in moderate to excellent yields (48–97%) with high *E*/*Z* diastereoselectivtiy. CuCl[27,28] and $[(MeCN)_4Cu]PF_6$[27] delivered the best yields and the latter Cu salt provided slightly higher diastereoselectivities. The radical nature of the trifluoromethylation was unambiguously experimentally proven. A likely mechanism for this interest-

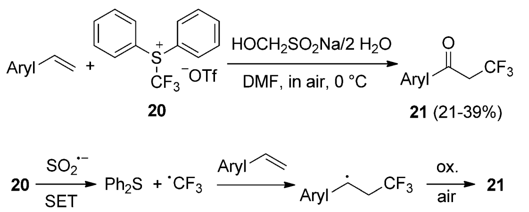


**Scheme 4.** Radical trifluoromethylation using the Togni reagent **14**.

ing and highly useful transformation is presented in the Scheme 4. The Cu$^I$ salt first likely undergoes SET to the Togni reagent **14** providing the Cu$^{II}$ salt **16** along with the CF$_3$ radical. Radical addition to the alkene generates the secondary alkyl radical, which reacts with **16** to eventually provide **15** and *ortho*-iodobenzoic acid, thereby regenerating the Cu$^I$ salt.

Very recently, we showed that TEMPONa, which is readily generated in situ upon treatment of the commercially available 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO)[30] with Na in THF, reacts quantitatively at room temperature with Togni reagent **14**[29] to give TEMPOCF$_3$.[31] In the presence of an alkene, the CF$_3$ radical adds to the radical acceptor to give the corresponding secondary alkyl radical, which in turn is trapped by TEMPO to eventually provide the trifluoromethylaminoxylation product **17** in moderate to good yields. The selective cross-coupling reaction of TEMPO with the C-centered radical (trapping) is steered by the persistent radical effect (PRE).[32] In contrast to the above-discussed reactions, this process occurs without any transition metal. It is important to note that the organic reducing reagent TEMPONa turns into an oxidizing reagent (TEMPO) during the reaction. Internal alkenes can also be trifluoromethylated using this mild and convenient method and excellent diastereoselectivities are obtained as shown by the successful preparation of **18**. Radical CF$_3$ addition can initiate a radical cyclization process that is terminated by the TEMPO-trapping reaction. This was documented by the successful transformation of diallyl ether to the tetrahydrofuran derivative **19**.

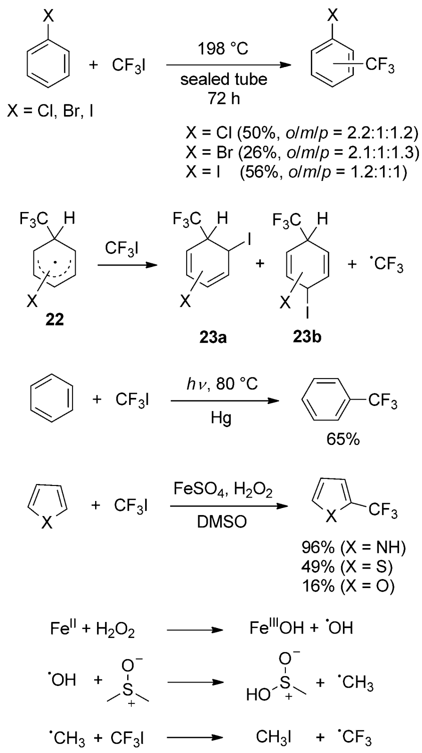
The Shreeve–Umemoto reagent **20**[33] generally applied as an electrophilic trifluoromethylation reagent can also be used as CF$_3$ radical precursor (Scheme 5).[34] For example, the reaction of styrene or its derivatives with **20** in the presence of HOCH$_2$SO$_2$Na/2H$_2$O under air provided the trifluoromethylated aryl ketones **21** in moderate yields. HOCH$_2$SO$_2$Na was suggested to act as a source for the SO$_2$ radical anion which reacts with **20** by SET to give Ph$_2$S and the CF$_3$ radical. The radical addition is followed by air oxidation of the benzylic secondary radical to eventually provide a ketone of type **21**.



**Scheme 5.** Radical trifluoromethylation with *S*-(trifluoromethyl)diphenylsulfonium triflate **20**.

## 4. Radical Arene Trifluoromethylation

Homolytic aromatic substitution has become a frequently applied process for arene alkylation and biaryl synthesis.[35] More than 50 years ago, Tiers reported the successful perfluoroalkylation of benzene by homolytic aromatic substitution upon heating perfluoroheptyliodide (2 equiv) in benzene at 250 °C.[36] Perfluoroheptylbenzene was isolated in 62 % yield. The same procedure was later applied to trifluoromethylate chloro-, bromo-, and iodobenzene (Scheme 6).[37] With chloro- and iodobenzene the yield was good and all three isomers were obtained in moderate selectivity. The low regioselectivity is a general problem in the homolytic aromatic substitution of substituted arenes.[35] Along these lines, heteroarenes provide better selectivities in radical trifluoromethylations. Thermal homolysis of CF$_3$I generates the CF$_3$ radical (initiation) which reacts with the arene to provide the cyclohexadienyl radical **22**. We believe that radical **22** abstracts an iodine atom from CF$_3$I to give the cyclohexadienes **23a** and **23b** along with the chain-propagating CF$_3$ radical. The endothermic I-transfer step is followed by the fast rearomatization of **23** through HI elimination. Small amounts of trifluoromethane observed indicate that the cyclohexadienyl radical **22** can react with the CF$_3$ radical in a H-transfer reaction. However, since the concentrations of the CF$_3$ radical and **22** are low during reaction, this route must be a minor pathway. Other pathways for the formation of trifluoromethane, such as the reaction of the CF$_3$ radical with HI, are also feasible. It cannot be ruled out that the cyclohexadienyl radical **22** is oxidized by CF$_3$I to give the corresponding cyclohexadienyl cation **22**$^+$ along with the CF$_3$

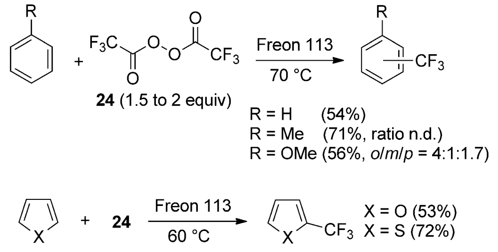


***Scheme 6.*** Arene trifluoromethylation with $CF_3I$.

radical and the iodide anion, which eventually deprotonates the cation $22^+$ to give the product arene. The yield for the radical trifluoromethylation of bromobenzene was later improved to 61 % under slightly modified conditions.[38] It was also shown that the reaction temperature could be lowered to 80 °C when the trifluoromethylation was conducted with irradiation in the presence of elemental mercury.[39] $CF_3I$ was also successfully used for the radical trifluoromethylation of arenes and heteroarenes in the presence of $FeSO_4$, $H_2O_2$, and DMSO.[40] Yields range between 20 and 96 % depending on the reactivity of the aromatic substrate. Representative results for the trifluoromethylation of pyrrole, furan, and thiophene are presented in Scheme 6. In these reactions, $FeSO_4$ and $H_2O_2$ react by electron transfer resulting in the hydroxide anion along with the reactive hydroxyl radical.[16] This O-centered radical reacts with DMSO to give the methyl radical and HOSOMe. The $CH_3$ radical then abstracts the I atom from $CF_3I$ to give iodomethane and the $CF_3$ radical, which in turn adds to an arene to give an adduct of type **22**. The cyclohexadienyl radical **22** is likely oxidized by the $Fe^{III}$ complex, which is formed as an intermediate in the initial electron-transfer step. The cyclohexadienyl cation is eventually deprotonated to give the trifluoromethylated arene.

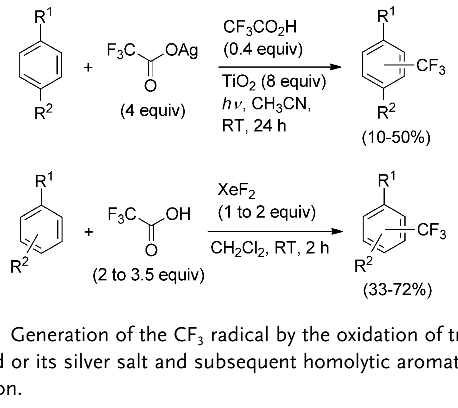
$CF_3Br$ is significantly cheaper than $CF_3I$. However, the C–Br bond is stronger than the C–I bond, and both thermal and photochemical C–Br homolysis (initiation) is less efficient.[41a] It was found that trifluoromethylation of electron-rich arenes with $CF_3Br$ can be achieved in moderate to good yields in the presence of sodium dithionite.[41b] Efficient photochemical or thermal trifluoromethylation was also possible by using $(CF_3)_2Te$ as the $CF_3$ radical precursor.[42]

In addition, arene trifluoromethylation was also achieved with bis(trifluoroacetyl) peroxide **24** as the $CF_3$ radical precursor.[43] When an arene and **24** were heated in Freon 113 at 70 °C, the corresponding trifluoromethylated compounds were obtained in 54–71 % yield (Scheme 7). In these transformations, the $CF_3$ radical is generated by homolysis of the peroxide and subsequent elimination of $CO_2$ from the trifluoromethylcarboxyl radical intermediate. As expected, substituted benzene derivatives delivered the homolytic aromatic substitution products as mixture of regioisomers. However, trifluoromethylation of furan and thiophene occurred with complete regiocontrol and the α-isomers were obtained in good yields.



***Scheme 7.*** Bis(trifluoroacetyl) peroxide **24** as the $CF_3$ radical precursor in aromatic substitutions.

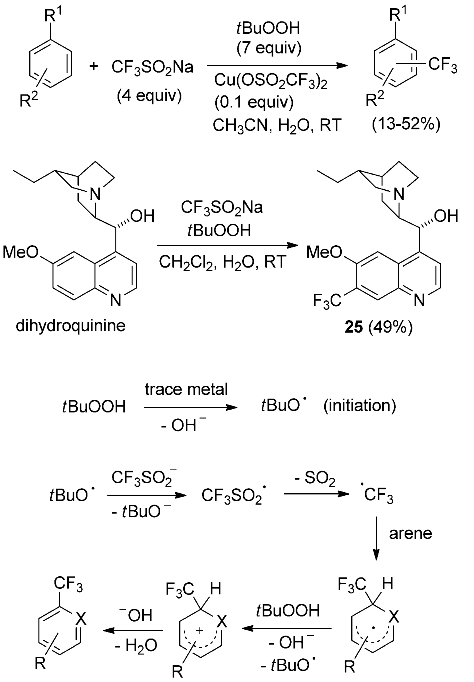
Trifluoroacetate was successfully used as a source of the $CF_3$ radical in photochemical homolytic aromatic substitutions. Reaction of an arene or heteroarene with silver trifluoroacetate in the presence of powdered $TiO_2$ as the photocatalyst upon irradiation (500 W Hg lamp equipped with a 340 nm broadband filter) afforded the corresponding trifluoromethylated products in moderate to good yields (Scheme 8).[44] The trifluoroacetate is likely oxidized by the excited $TiO_2$ to the corresponding carboxyl radical, which upon $CO_2$ elimination gives the $CF_3$ radical. Radical addition to the arene then provides the trifluoromethylated cyclohexadienyl radical (see **22**), which is oxidized either by $Ag^+$ or by the excited $TiO_2$ to give the cyclohexadienyl cation, which readily deprotonates to give the product arene. The $TiO_2$ radical anion formed in the initial electron-transfer step



***Scheme 8.*** Generation of the $CF_3$ radical by the oxidation of trifluoroacetic acid or its silver salt and subsequent homolytic aromatic substitution.

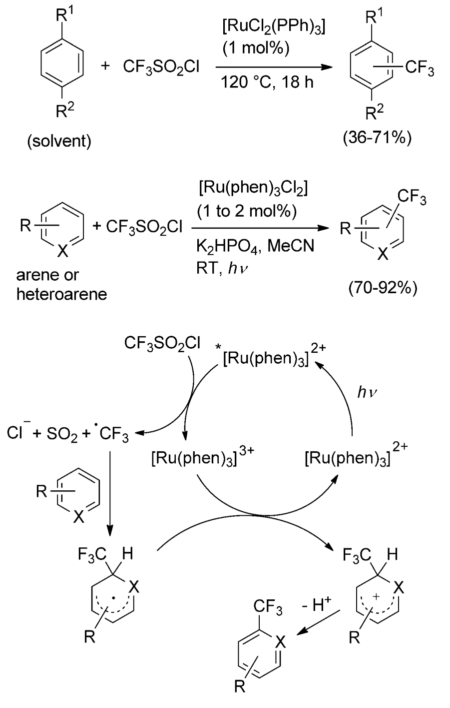
reduces $Ag^+$ to regenerate the photocatalyst $TiO_2$, thereby forming elemental silver as a byproduct. Xenon difluoride was also successfully used as an oxidant for the generation of $CF_3$ radicals from trifluoroacetic acid.[45] Various mono-, di-, and trisubstituted arenes were trifluoromethylated in moderate to good yields using this method. The reactions were proposed to occur via xenon(II) trifluoroacetate as an intermediate, which acts as source of the trifluoromethyl radical.

Langlois et al. showed that sodium trifluoromethanesulfinate can be used to generate the $CF_3$ radical upon oxidation with catalytic amounts of $Cu(OSO_2CF_3)_2$ in the presence of an excess of *t*BuOOH as a terminal stoichiometric oxidant (Scheme 9).[46] Various mono-, di-, and trisubstituted electron-rich benzene derivatives were successfully transformed to the corresponding trifluoromethylated arenes, which were isolated in 13–52% yield as mixtures of regioisomers. For the oxidation of 1,3-dimethoxybenzene, the yield was improved to 86% by switching to $Fe(NO_3)_3/9\,H_2O$ as the catalyst. This electron-rich system reacted even in the absence of any catalyst, although in slightly lower yield (67%). Very recently, Baran et al. showed in an elegant study that radical trifluoromethylation of arenes with sodium trifluoromethanesulfinate can be efficiently performed in absence of any transition metal.[47] Various hetereoarenes such as pyridines, pyrroles, indoles, pyrimidines, pyrazines, phthalazines, quinoxalines, deazapurines, thiadiazoles, uracils, xanthines, and pyrazolinopyrimidines were successfully trifluoromethylated using this procedure in moderate to good yields (33–96%). As an impressive example, the regioselective homolytic aromatic substitution of dihydroquinine to give **25** is presented in Scheme 9. The following mechanism was suggested for these radical arene alkylations: The reaction is likely initiated by transition-metal impurities which can be found in sodium trifluoromethanesulfinate (Langlois reagent). Reaction of a transition metal (or metal salt) with *t*BuOOH provides the hydroxide anion along with the *tert*-butoxyl radical, which is reduced with Langlois reagent to give *t*BuONa and the $CF_3SO_2$ radical (initiation). The sulfinyl radical further reacts by elimination of $SO_2$ to give the $CF_3$ radical, which in turn adds to the arene. The thus-formed cyclohexadienyl radical is then oxidized by *t*BuOOH to give the cyclohexadienyl cation along with the chain-propagating *tert*-butoxyl radical. The cyclohexadienyl cation is eventually deprotonated to afford the trifluoromethylated arene.



***Scheme 9.*** Generation of the $CF_3$ radical by the oxidation of sodium trifluoromethanesulfinate.

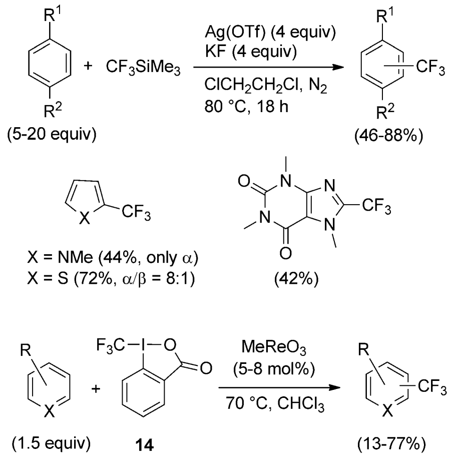
The trifluoromethylation of arenes was also achieved with trifluoromethylsulfonyl chloride as the $CF_3$ radical precursor. $[RuCl_2(PPh_3)_3]$ (1 mol%) was applied as the catalyst and the arene was used as the solvent in these reactions (Scheme 10).[48a] The yields ranged from 36 to 71%, and as expected for a homolytic aromatic substitution, the reactions of toluene and anisole provided the corresponding products as mixtures of regioisomers. The $[RuCl_2(PPh_3)_3]$-catalyzed reactions likely proceed by initial abstraction of Cl from $CF_3SO_2Cl$ by the Ru catalyst to give $\{RuCl_3\}$, $SO_2$, $Cl^-$, and the $CF_3$ radical (see also Scheme 3). The cyclohexadienyl radical generated by the addition of the $CF_3$ radical to the arene is then oxidized by $\{RuCl_3\}$ to give a cyclohexadienyl cation and chloride anion, thereby regenerating the $\{RuCl_2\}$ complex. Deprotonation eventually provides the product arene. It cannot be ruled out that the cyclohexadienyl radical abstracts a chloride atom from $\{RuCl_3\}$ in a likely endothermic process which is followed by fast rearomatization through HCl elimination.



***Scheme 10.*** Ru-catalyzed trifluoromethylation of arenes using $CF_3SO_2Cl$.

This method was later also successfully used for the radical trifluoromethylation of heteroarenes.[48b] MacMillan and Nagib recently showed that photoredox catalysis can be applied to the trifluoromethylation of arenes using $CF_3SO_2Cl$ as the $CF_3$ radical source under mild conditions.[49] Commercially available $[Ru(phen)_3Cl_2]$ served as the photocatalyst (phen = phenanthroline). In contrast to the $[RuCl_2(PPh_3)_3]$-catalyzed processes, the reaction could be conducted at room temperature and significantly higher yields were achieved. The substrate scope of the photoredoxcatalysis is broad and various heteroarenes were also successfully trifluoromethylated with high regioselectivity. Irradiation of $[Ru(phen)_3]^{2+}$ generates the excited $*[Ru(phen)_3]^{2+}$ complex, which reacts with $CF_3SO_2Cl$ by single-electron transfer to give $[Ru(phen)_3]^{3+}$ along with $SO_2$, $Cl^-$, and the $CF_3$ radical. Radical addition to the arene generates the corresponding cyclohexadienyl radical, which is oxidized by $[Ru(phen)_3]^{3+}$ to give a cyclohexadienyl cation and regenerated $Ru(phen)_3]^{2+}$. Deprotonation of the cyclohexadienyl cation by $Cl^-$ eventually provides the trifluoromethylated arene. As already discussed in the previous section, the trifluoromethyl radical can be generated from $CF_3I$ by photoredox catalysis.[21] This approach was recently also used for the mild trifluoromethylation of indole, furan, pyrrole, and thiophene.[50]

Sanford et al. presented silver-mediated trifluoromethylation of arenes using $Me_3SiCF_3$ (Scheme 11).[51,52] These reactions were conducted by using an excess of the arene (5 to 20 equiv) with superstoichiometric amounts of AgOTf and KF (4 equiv each) at elevated temperature. Monosubstituted benzene derivatives delivered trifluoromethylbenzenes in moderate regioselectivity. The ratio of regioisomers recorded for these reactions provides evidence that these trifluoromethylations likely occur by a radical process. Moreover, the yield drastically decreased when the reaction was conducted in the presence of TEMPO. The high selectivities obtained for the trifluoromethylation of *N*-methylpyrrole, thiophene, and caffeine also support the radical nature of these transformations. It was suggested that $Me_3SiCF_3$ first reacts with AgOTf to give $AgCF_3$. This organosilver(I) compound decomposes upon heating to give elemental silver ($Ag^0$) along with the $CF_3$ radical, which adds to the arene to provide a cyclohexadienyl radical; this intermediate is subsequently oxidized by AgX to give the corresponding cyclohexadienyl cation, which readily rearomatizes by deprotonation. Very recently, Togni and Mejía described the rhenium-catalyzed trifluoromethylation of arenes and heteroarenes using reagent **14**.[53] Methyltrioxorhenium ($ReO_3Me$, 5–8 mol %) was used as the catalyst in chloroform at 70 °C. The reactions were efficient since only a slight excess of the radical acceptor (1.5 equiv) was used. The trifluoromethylation of substituted arenes occurred with moderate regioselectivity which is a typical indication of the radical nature of this process. Moreover, EPR monitoring revealed that radical species appear during the reaction. Yields ranging from 13 % (electron-poor arenes such as nitrobenzene) to 77 % (1,3,5-trimethoxybenzene) were obtained.



***Scheme 11.*** Ag-mediated and Re-catalyzed trifluoromethylations of arenes.

## 5. Conclusions

The great importance of the trifluoromethyl group in medicinal chemistry has fostered research on the development of new and improved methods for C–$CF_3$ bond formation in recent years. Along with transition-metal-catalyzed or -mediated processes, radical trifluoromethylation has attracted renewed interest and has undoubtedly made an impact on this rapidly growing field. As shown in this Minireview, methods for radical trifluoromethylation have been known for decades and valuable $CF_3$ radical precursors have also been around for some time. New exciting research in this area has focused on the further improvement of existing methods and on the identification of novel $CF_3$ radical sources. Whereas generally harsh reaction conditions were used in the "older" protocols, the new procedures facilitate convenient radical trifluoromethylation under mild conditions. In the pioneering studies, the authors mainly focused on rather simple substrates; however, recent contributions convincingly document that radical trifluoromethylations can be conducted on complex substrates with high regioselectivity. We expect that these novel methods will find application in industry and are confident that the development of new methods for radical trifluoromethylation will continue. In particular, the stereoselective (enantioselective) trifluoromethylation of unactivated alkenes is a challenging problem that remaines to be addressed.

*The University of Münster is acknowledged for continuous support.*

Received: April 4, 2012

---

[1] K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881 – 1886.
[2] a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320 – 330; b) T. Yamazaki, T. Taguchi, I. Ojima in *Fluorine in Medicinal Chemistry and Chemical Biology* (Ed.: I. Ojima), Wiley-Blackwell, Chichester, **2009**.
[3] P. Jeschke, *ChemBioChem* **2004**, *5*, 570 – 589.

[4] a) S. Roy, B. T. Gregg, G. W. Gribble, V.-D. Le, S. Roy, *Tetrahedron* **2011**, *67*, 2161 – 2195; b) O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475 – 4521; c) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470 – 477; d) T. Besset, C. Schneider, D. Cahard, *Angew. Chem.* **2012**, *124*, 5134 – 5136; *Angew. Chem. Int. Ed.* **2012**, *51*, 5048 – 5050.

[5] a) W. R. Dolbier, Jr., *Chem. Rev.* **1996**, *96*, 1557 – 1584; See also: b) W. R. Dolbier Jr., in *Topics in Current Chemistry*, *Vol. 192* (Ed.: R. D. Chambers), Springer, Heidelberg, **1997**, pp. 97 – 163; c) S. Barata-Vallejo, A. Postigo, *Eur. J. Org. Chem.* **2012**, 1889 – 1899.

[6] P. J. Krusic, R. C. Bingham, *J. Am. Chem. Soc.* **1976**, *98*, 230 – 232.

[7] J. Hioe, H. Zipse in *Encyclopedia of Radicals in Chemistry, Biology and Materials*, *Vol. 1* (Eds.: C. Chatgilialoglu, A. Studer), Wiley, Chichester, **2012**, pp. 449 – 475.

[8] a) D. V. Avila, K. U. Ingold, J. Lusztyk, W. R. Dolbier, Jr., H.-Q. Pan, *J. Org. Chem.* **1996**, *61*, 2027 – 2030; b) D. V. Avila, K. U. Ingold, J. Lusztyk, W. R. Dolbier, Jr., H.-Q. Pan, *Tetrahedron* **1996**, *52*, 12351 – 12356.

[9] H. Fischer, L. Radom, *Angew. Chem.* **2001**, *113*, 1380 – 1414; *Angew. Chem. Int. Ed.* **2001**, *40*, 1340 – 1371.

[10] R. N. Haszeldine, *J. Chem. Soc.* **1949**, 2856 – 2861.

[11] a) D. Cantacuzène, R. Dorme, *Tetrahedron Lett.* **1975**, *16*, 2031 – 2034; b) K. Tsuchii, M. Imura, N. Kamada, T. Hirao, A. Ogawa, *J. Org. Chem.* **2004**, *69*, 6658 – 6665.

[12] K. Maruoka, H. Sano, Y. Fukutani, H. Yamamoto, *Chem. Lett.* **1985**, 1689 – 1692.

[13] a) K. Miura, M. Taniguchi, K. Nozaki, K. Oshima, K. Utimoto, *Tetrahedron Lett.* **1990**, *31*, 6391 – 6394; b) T. Yajima, H. Nagano, C. Saito, *Tetrahedron Lett.* **2003**, *44*, 7027 – 7029; c) Y. Itoh, K. Mikami, *Org. Lett.* **2005**, *7*, 4883 – 4885; d) Y. Itoh, K. Mikami, *Tetrahedron* **2006**, *62*, 7199 – 7203.

[14] Reviews: a) W.-Y. Huang, *J. Fluorine Chem.* **1992**, *58*, 1 – 8; b) C.-P. Zhang, Q.-Y. Chen, Y. Guo, J.-C. Xiao, Y.-C. Gu, *Chem. Soc. Rev.* **2012**, *41*, 4536 – 4559; See also: c) Z. Wang, X. Lu, *Tetrahedron* **1995**, *51*, 2639 – 2658; d) G. Foulard, T. Brigaud, C. Portella, *J. Fluorine Chem.* **1998**, *91*, 179 – 183; e) V. Petrik, D. Cahard, *Tetrahedron Lett.* **2007**, *48*, 3327 – 3330; f) J. Ignatowska, W. Dmowski, *J. Fluorine Chem.* **2007**, *128*, 997 – 1006.

[15] a) K. Mikami, Y. Tomita, Y. Ichikawa, K. Amikura, Y. Itoh, *Org. Lett.* **2006**, *8*, 4671 – 4673; b) Y. Tomita, Y. Itoh, K. Mikami, *Chem. Lett.* **2008**, *37*, 1080 – 1081.

[16] Y. Ohtsuka, D. Uraguchi, K. Yamamoto, K, Tokuhisa, T. Yamakawa, *Tetrahedron* **2012**, *68*, 2636 – 2649.

[17] a) D. P. Curran, S.-B. Ko, *Tetrahedron Lett.* **1998**, *39*, 6629 – 6632; b) I. Ryu, *Chem. Soc. Rev.* **2001**, *30*, 16 – 25.

[18] a) T. Fuchikami, I. Ojima, *Tetrahedron Lett.* **1984**, *25*, 303 – 306; b) A. T. Herrmann, L. L. Smith, A. Zakarian, *J. Am. Chem. Soc.* **2012**, *134*, 6976 – 6979.

[19] T. Ishihara, M. Kuroboshi, Y. Okada, *Chem. Lett.* **1986**, 1895 – 1896; See also: Q.-Y. Chen, Z.-Y. Yang, C.-X. Zhao, Z.-M. Qiu, *J. Chem. Soc. Perkin Trans. 1* **1988**, 563 – 567.

[20] K. von Werner, *J. Fluorine Chem.* **1985**, *28*, 229 – 233.

[21] D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875 – 10877.

[22] a) N. Muller, *J. Org. Chem.* **1983**, *48*, 1370 – 1370; b) N. Muller, *J. Org. Chem.* **1986**, *51*, 263 – 265; c) K. Uneyama, H. Nanbu, *J. Org. Chem.* **1988**, *53*, 4598 – 4599.

[23] D. H. R. Barton, B. Lacher, S. Z. Zard, *Tetrahedron* **1986**, *42*, 2325 – 2328.

[24] N. Kamigata, T. Fukushima, Y. Terakawa, M. Yoshida, H. Sawada, *J. Chem. Soc. Perkin Trans. 1* **1991**, 627 – 633.

[25] T. Billard, N. Roques, B. R. Langlois, *Tetrahedron Lett.* **2000**, *41*, 3069 – 3072.

[26] D. P. Curran, A. A. Martin-Esker, S.-B. Ko, M. Newcomb, *J. Org. Chem.* **1993**, *58*, 4691 – 4695; Review on radical halogen- and chalcogen-transfer chemistry: C. Li in *Encyclopedia of Radicals in Chemistry, Biology and Materials*, *Vol. 2* (Eds.: C. Chatgilialoglu, A. Studer), Wiley, Chichester, **2012**, pp. 943 – 963.

[27] a) A. T. Parsons, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 9286 – 9289; *Angew. Chem. Int. Ed.* **2011**, *50*, 9120 – 9123; b) See also: A. T. Parsons, T. D. Senecal, S. L. Buchwald, *Angew. Chem.* **2012**, *124*, 3001 – 3004; *Angew. Chem. Int. Ed.* **2012**, *51*, 2947 – 2950; c) R. Shimizu, H. Egami, Y. Hamashima, M. Sodeoka, *Angew. Chem.* **2012**, *124*, 4655 – 4658; *Angew. Chem. Int. Ed.* **2012**, *51*, 4577 – 4580; d) P. G. Janson, I. Ghoneim, N. O. Ilchenko, K. J. Szabó, *Org. Lett.* **2012**, *14*, 2882 – 2885.

[28] X. Wang, Y. Ye, S. Zhang, J. Feng, Y. Xu, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2011**, *133*, 16410 – 16413.

[29] a) P. Eisenberger, S. Gischig, A. Togni, *Chem. Eur. J.* **2006**, *12*, 2579 – 2586; b) V. Matoušek, A. Togni, V. Bizet, D. Cahard, *Org. Lett.* **2011**, *13*, 5762 – 5765, and references therein.

[30] a) T. Vogler, A. Studer, *Synthesis* **2008**, 1979 – 1993; b) L. Tebben, A. Studer, *Angew. Chem.* **2011**, *123*, 5138 – 5174; *Angew. Chem. Int. Ed.* **2011**, *50*, 5034 – 5068.

[31] Y. Li, A. Studer, *Angew. Chem.* **2012**, DOI: 10.1002/ange.20120262; *Angew. Chem. Int. Ed.* **2012**, DOI: 10.1002/anie.201202623.

[32] a) H. Fischer, *Chem. Rev.* **2001**, *101*, 3581 – 3610; b) A. Studer, *Chem. Eur. J.* **2001**, *7*, 1159 – 1164; c) A. Studer, *Chem. Soc. Rev.* **2004**, *33*, 267 – 273; d) A. Studer, T. Schulte, *Chem. Rec.* **2005**, *5*, 27 – 35.

[33] T. Umemoto, S. Ishihara, *J. Am. Chem. Soc.* **1993**, *115*, 2156 – 2164; Recent review on electrophilic trifluoromethylation, see: Y. Macé, E. Magnier, *Eur. J. Org. Chem.* **2012**, 2479 – 2494.

[34] a) C.-P. Zhang, Z.-L. Wang, Q.-Y. Chen, C.-T. Zhang, Y.-C. Gu, J.-C. Xiao, *Chem. Commun.* **2011**, *47*, 6632 – 6634; For a recent paper on Cu-catalyzed allylic trifluoromethylation of unactivated alkenes using the Umemoto reagent as the $CF_3$ donor, see: b) J. Xu, Y. Fu, D.-F. Luo, Y.-Y. Jiang, B. Xiao, Z.-J. Liu, T.-J. Gong, L. Liu, *J. Am. Chem. Soc.* **2011**, *133*, 15300 – 15303. However, there is some experimental evidence that in this case a radical mechanism is not operating.

[35] a) A. Studer, M. Bossart, *Tetrahedron* **2001**, *57*, 9649 – 9667; b) W. R. Bowman, J. M. D. Storey, *Chem. Soc. Rev.* **2007**, *36*, 1803 – 1822; c) M. A. J. Duncton, *Med. Chem. Commun.* **2011**, *2*, 1135 – 1161; d) S. E. Vaillard, A. Studer in *Encyclopedia of Radicals in Chemistry, Biology and Materials*, *Vol. 2* (Eds.: C. Chatgilialoglu, A. Studer), Wiley, Chichester, **2012**, pp. 1059 – 1093; e) For more recent developments on the radical biaryl synthesis, see: A. Studer, D. P. Curran, *Angew. Chem.* **2011**, *123*, 5122 – 5127; *Angew. Chem. Int. Ed.* **2011**, *50*, 5018 – 5022.

[36] G. V. D. Tiers, *J. Am. Chem. Soc.* **1960**, *82*, 5513 – 5513.

[37] E. S. Huyser, E. Bedard, *J. Org. Chem.* **1964**, *29*, 1588 – 1590.

[38] A. B. Cowell, C. Tamborski, *J. Fluorine Chem.* **1981**, *17*, 345 – 356.

[39] J. M. Birchall, G. P. Irvin, R. A. Boyson, *J. Chem. Soc. Perkin Trans. 2* **1975**, 435 – 439.

[40] T. Kino, Y. Nagase, Y. Ohtsuka, K. Yamamoto, D. Uraguchi, K. Tokuhisa, T. Yamakawa, *J. Fluorine Chem.* **2010**, *131*, 98 – 105.

[41] a) T. Akiyama, K. Kato, M. Kajitani, Y. Sakaguchi, J. Nakamura, H. Hayashi, A. Sugimori, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3531 – 3537; b) M. Tordeux, B. Langlois, C. Wakselman, *J. Chem. Soc. Perkin Trans. 1* **1990**, 2293 – 2299.

[42] a) D. Naumann, B. Wilkes, J. Kischkewitz, *J. Fluorine Chem.* **1985**, *30*, 73 – 87; b) D. Naumann, J. Kischkewitz, *J. Fluorine Chem.* **1990**, *47*, 283 – 299; c) D. Naumann, J. Kischkewitz, *J. Fluorine Chem.* **1990**, *46*, 265 – 281.

[43] H. Sawada, M. Nakayama, M. Yoshida, T. Yoshida, N. Kamigata, *J. Fluorine Chem.* **1990**, *46*, 423 – 431; See also: M. Yoshida, T. Yoshida, M. Kobayashi, N. Kamigata, *J. Chem. Soc. Perkin Trans. 1* **1989**, 909 – 914.

[44] C. Lai, T. E. Mallouk, *J. Chem. Soc. Chem. Commun.* **1993**, 1359–1361.

[45] Y. Tanabe, N. Matsuo, N. Ohno, *J. Org. Chem.* **1988**, *53*, 4582–4585; For electrochemical oxidation, see: C. Depecker, H. Marzouk, S. Trevin, J. Devynck, *New J. Chem.* **1999**, *23*, 739–742.

[46] B. R. Langlois, E. Laurent, N. Roidot, *Tetrahedron Lett.* **1991**, *32*, 7525–7528; For electrochemical oxidation, see: J.-B. Tommasino, A. Brondex, M. Médebielle, M. Thomalla, B. R. Langlois, T. Billard, *Synlett* **2002**, 1697–1699.

[47] Y. Ji, T. Brueckl, R. D. Baxter, Y. Fujiwara, I. B. Seiple, S. Su, D. G. Blackmond, P. S. Baran, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 14411–14415; See also: Y. Fujiwara, J. A. Dixon, R. A. Rodriguez, R. D. Baxter, D. D. Dixon, M. R. Collins, D. G. Blackmond, P. S. Baran, *J. Am. Chem. Soc.* **2012**, *134*, 1494–1497.

[48] a) N. Kamigata, T. Fukushima, M. Yoshida, *Chem. Lett.* **1990**, 649–650; b) N. Kamigata, T. Ohtsuka, T. Fukushima, M. Yoshida, T. Shimizu, *J. Chem. Soc. Perkin Trans. 1* **1994**, 1339–1346.

[49] D. A. Nagib, D. W. C. MacMillan, *Nature* **2011**, *480*, 224–228.

[50] N. Iqbal, S. Choi, E. Ko, E. J. Cho, *Tetrahedron Lett.* **2012**, *53*, 2005–2008.

[51] Y. Ye, S. H. Lee, M. S. Sanford, *Org. Lett.* **2011**, *13*, 5464–5467.

[52] Review on the use of $Me_3SiCF_3$, see: G. K. S. Prakash, A. K. Yudin, *Chem. Rev.* **1997**, *97*, 757–786.

[53] E. Mejía, A. Togni, *ACS Nano* **2012**, *2*, 521–527.