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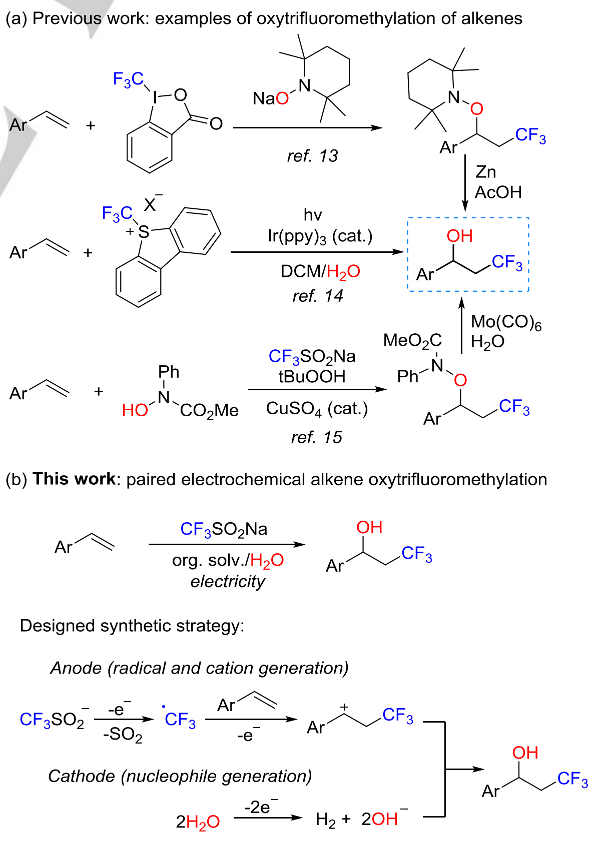
Catalyst Free Oxytrifluoromethylation of Alkenes via Paired Electrolysis in Organic-Aqueous Media

Wolfgang Jud,[a,b] C. Oliver Kappe,*[a,b] and David Cantillo*[a,b]

Abstract: A mild, catalyst free electrochemical oxytrifluoromethylation of alkenes has been developed. The procedure is based on the paired electrolysis of sodium triflinate and water in an undivided cell. Anodic oxidation of the triflinate anion generates trifluoromethyl radicals that react with the alkene. Water plays a dual role as oxidant for the cathode and nucleophile. The method has been utilized to prepare a diverse set of 1-hydroxy-2-trifluoromethyl compounds in moderate to excellent yields (27-94%). Alcohols have also been tested as nucleophiles for this versatile method with moderate yields. Facile recycling of the electrolyte has been demonstrated, and application of electricity avoids the use of stoichiometric amounts of oxidizers in a safe and environmentally benign reaction.

Organofluorine compounds have become increasingly important over the past two decades.[1] Introduction of fluorine atoms into organic molecules typically provides significant benefits on their biological properties such as improved lipophilicity, bioavailability and metabolic stability.[2] Significant research efforts have therefore been devoted to the development of synthetic tools for the fluorination and perfluoroalkylation of organic scaffolds. A particularly interesting moiety is the trifluoromethyl group (CF_3). A plethora of methods for the trifluoromethylation of many functional groups have been described during this decade.[3] Trifluoromethyl sources can be classified according to the electrophilic or nucleophilic character of the CF_3 group, and include relatively complex reagents such as the Umemoto´s or Togni´s reagents, or simple and inexpensive chemicals like trifluoroiodimethane, triflyl chloride, trifluoroacetic acid salts or sodium triflinate.[3]

Trifluoromethylations of unactivated alkenes are especially challenging transformations.[4] Electrophilic CF_3 reagents typically fail unless the olefin bond is activated by electron-donor groups in the vicinity or metal catalysts (e.g. copper catalysts) are used as additive.[5] In the latter case, radical mechanisms are usually invoked.[5,6] Thus, methods based on the generation of CF_3 radicals via photoredox catalysis are suitable and often preferred alternatives.[7] Oxytrifluoromethylation of alkenes is an attractive 1,2-difunctionalization[8] in which the CF_3 and a hydroxyl group are added to the double bond. The resulting 1-hydroxy-2-trifluoromethyl compounds provide easy access to trifluoromethylated 1,3-dioxolanes,[9] lactones,[10] imidazoles[11] and other 1,2-difunctionalized trifluoromethylated building blocks.[12] Several methods for the oxytrifluoromethylation of alkenes have been described in the literature (Scheme 1). Li and Studer utilized the Togni reagent as CF_3 source in combination with stoichiometric amounts of the sodium salt of TEMPO to generate a TEMPO-intermediate, that released the desired product upon treatment with Zn.[13] A one-pot procedure using the Umemoto reagent and $Ir(ppy)_3$ as photoredox catalyst was described by Koike and Akita.[14] Jiang and Qing combined sodium triflinate and 6 equiv tBuOOH (to generate CF_3 radicals) with hydroxamic acid to form another oxyamine intermediate.[15] The corresponding alcohol was then obtained after reducing the N-O bond with $Mo(CO)_6$.[15] Notably, these methods utilize expensive CF_3 sources,[13,14] stoichiometric amounts of oxidizing or reducing agents[13,15] or expensive metal catalysts,[14] which limits their applicability in large scale synthesis.



Scheme 1. a) Background of methods for the oxytrifluoromethylation of styrenes and (b) catalyst-free electrochemical procedure developed in this work.

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In the past few years, electrochemistry is seeing a substantial resurgence as a greener alternative to many synthetic routes involving redox processes.[16,17]. As electrons are essentially the reagent utilized for the redox process, the use of large amounts of often hazardous oxidizing or reducing reagents can be avoided. Thus, electrochemical reactions are considered safe and “inherently green”.[18] In this context, electrochemical difunctionalization of alkenes is a powerful and versatile synthetic tool very recently established.[19] The group of Li has developed an elegant methodology for the radical diazidation,[20] dichlorination[21] and chlorotrifluoromethylation[22] of alkenes based on electrocatalysis mediated by Mn(II) salts, using TFA as sacrificial oxidant. More recently Mei, Du and Han have reported the oxysulfuration of alkenes using an undivided cell and Pt electrodes,[23] while Lei has described oxy- and aminosulfuration of alkenes under similar conditions.[24]

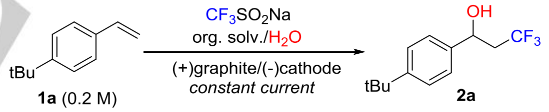
Given the important drawbacks of the oxytrifluoromethylation of alkenes using traditional synthetic methods or even photoredox catalysis, we envisaged a novel strategy to accomplish this transformation based on the paired electrolysis of cheap and readily available sodium triflinate as CF_3 source and water. Thus, anodic oxidation of the CF_3SO_2 anion releases the CF_3 radical.[25] Upon addition to the double bond, a second anodic oxidation would generate the corresponding benzyl cation (Scheme 1b). Water is concurrently reduced in the cathode, generating hydrogen gas and the hydroxide anion that acts as nucleophile.

To evaluate this hypothesis, we began our investigation with a series of reactions using 4-*tert*-butyl styrene as model substrate and several electrolytes, electrodes, and solvent combinations (Table 1). In a typical experiment the substrate (0.2 M), the electrolyte (0.1 M) and CF_3SO_2Na were dissolved in a 10:1 organic solvent/water mixture and electrolyzed under argon atmosphere at constant current. Optimization reactions were carried out on 0.5 mmol scale. Apart from serving as oxidant and nucleophile, water helped to solubilize the sodium triflinate salt. Initial attempts (Table 1, entries 1-3) demonstrated the viability of this synthetic approach. Good conversions and moderate selectivities were obtained in MeCN/water using graphite, platinum and stainless steel (SS) cathodes after applying 2.2 F/mol (10% excess over the theoretical required current) and 60 mA. Variable amounts of the products derived from the trifluoromethylation and trifluoromethanesulfonylation of the styrene aromatic ring were obtained as the main side-products of the reaction. These side reactions support a radical mechanism with both CF_3 and CF_3SO_2 radicals as intermediates (vide infra). Graphite was utilized as anode in all cases. Stainless steel showed a slightly better performance as a cathode and was therefore chosen for subsequent experiments as an inexpensive and practical material.

The organic solvent utilized had a significant influence on the reaction performance (Table 1, entries 3-7). Best results were achieved in dioxane, THF and acetone (entries 5-7). Despite the presence of the electrolyte, the maximum current that could be applied to the cell (keeping the potential within the desired ca. 3-4 V range) depended on the solvent utilized. As expected, the values correlated well with the dielectric constant of the solvent, which ultimately determines the conductivity.[26] While 60 mA could be applied to the reaction mixtures in MeCN/water and acetone/water (ε = 35.7 and 20.5 for MeCN and acetone, respectively), electrolyses in THF and MeTHF (ε = 7.5 and 7.0) were carried out at 20 mA. For dioxane (ε = 2.2) only 10 mA could be applied. The electrolyte used as additive had a minor influence on the reaction outcome (entries 8-10), and its concentration negligible influence (see Figure S2 in the Supporting Information). Conversion increased with the substrate concentration (Figure S2c). However, at concentrations higher than 0.2 M the triflinate was not fully soluble in the solvent mixture.

^{19}F-NMR monitoring of the reaction mixture revealed consumption of more than 1 equiv CF_3SO_2Na even at conversions below 90%. We hypothesized that part of the CF_3 radicals are trapped by e.g. H_2O, forming side-products that could not be detected (e.g. gaseous CF_3OH). This effect was more pronounced at higher conversions. Applying 2.2 F/mol of electricity (10% excess) 85% conversion was achieved with the optimal solvent combination. 3.2 F/mol were required to increase the conversion to 97% (see Figure S4 in the Supporting Information). Ultimately, excellent conversion and selectivity for the desired product **2a** was achieved by increasing the amount of charge applied to 3.2 F/mol and 1.6 equiv of CF_3SO_2Na, both in acetone and THF as solvent (Table 1, entries 11 and 12) (a GC-FID chromatogram of the crude reaction mixture is shown in Figure S5). Unsurprisingly, minor amounts (<10%) of the acetone aldol condensation product were observed when acetone was used as co-solvent. This compound is likely formed as a result of the basic conditions due to OH- formation during the reaction.[27] Gratifyingly, this volatile impurity could be removed from the product by simple evaporation.

Table 1. Optimization of the electrochemical oxytrifluoromethylation of alkenes using t-butyl styrene **1a** as model sobstrate.[a]



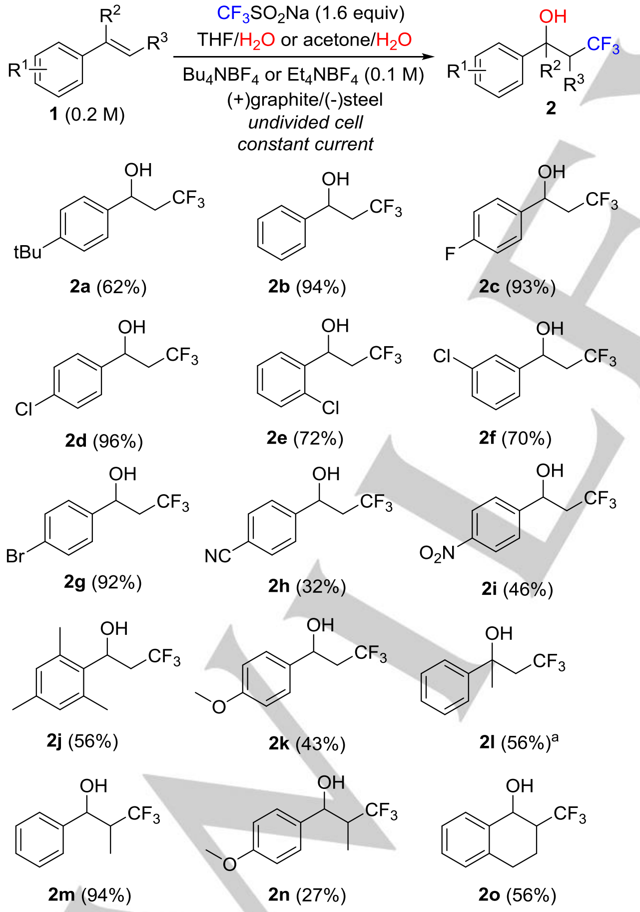
1a (0.2 M) **2a**

Entry	Solvent[b]	Cathode	Electrolyte	Q [F/mol]	CF_3 [equiv][c]	Conv. [%][d]	Selec. [%][d]
1	MeCN	Graphite	Bu_4NBF_4	2.2	1.5	85	67
2	MeCN	Pt	Bu_4NBF_4	2.2	1.5	85	67
3	MeCN	SS	Bu_4NBF_4	2.2	1.5	89	73
4	MeTHF	SS	Bu_4NBF_4	2.2	1.5	73	77
5	Dioxane	SS	Bu_4NBF_4	2.2	1.5	93	87
6	THF	SS	Bu_4NBF_4	2.2	1.5	86	82
7	Acetone	SS	Bu_4NBF_4	2.2	1.5	80	88
8	THF	SS	Bu_4NBF_4	3.0	1.5	95	86
9	THF	SS	$LiClO_4$	3.0	1.5	95	87
10	THF	SS	Et_4NBF_4	3.0	1.5	92	82
11	THF	SS	Et_4NBF_4	3.2	1.6	98	87
12	Acetone	SS	Et_4NBF_4	3.2	1.6	93	89

[a] Conditions: 0.5 mmol scale, constant current electrolysis under Ar atmosphere and 400 rpm stirring in a IKA Electrasyn 2.0 reactor. [b] A 10:1 mixture of the solvent and water was used. [c] Equiv of CF_3SO_2Na. [d] Determined by GC-FID.

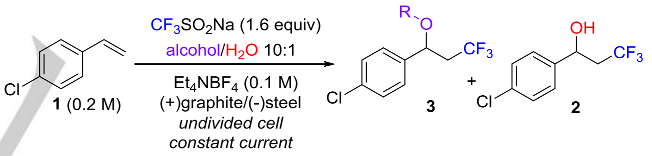
Recovery and reuse of the electrolyte was possible and was tested for Et_4NBF_4, further increasing the value of this synthetic protocol. Thus, a reaction mixture performed under optimal conditions in either THF or acetone (Table 1, entries 11 and 12) was evaporated under reduced pressure. Sequential addition of MeCN and diethyl ether enabled the separation of NaOH and then the electrolyte (soluble in MeCN but insoluble in Et_2O). This simple procedure resulted in an electrolyte recovery of ca. 93%, which could be used for subsequent reactions without any loss of efficiency.

With the optimal conditions in hand, a diverse set of alkenes was subjected to the electrochemical oxytrifluoromethylation procedure (Scheme 2). Substrates were typically subjected to electrolysis both in THF/H_2O and acetone/H_2O for comparison (see Table S3). Electrolyses for preparative purposes were then performed in the best solvent on a 2 mmol scale. In the cases where the conversion and selectivity were very high (> 95%), isolation of the pure products could be accomplished by simply filtering the reaction mixture through a plug of silica and evaporating the solvent (excess of triflinate, hydroxide, and electrolyte remained in the silica). Products obtained with lower purity were isolated by column chromatography. Substrates bearing halogens as electron withdrawing groups typically performed best (**2c-g**). As expected, the amount of side-products derived from the CF_3 or CF_3SO_2 radical addition to the aromatic ring was higher for electron-rich substrates (**2j**, **2k**, **2n**). In such cases purification by column chromatography was required, thus decreasing the isolated yield. Previously reported oxytrifluoromethylation procedures[13-15] were also based on the generation of CF_3 radicals, mediated by light or oxidizing agents. Selectivity issues related to the radical reactivity would therefore be analogous to the present electrochemical method. Oxidation of the alkene was not observed in any case (as expected from CV analysis of both electron rich and poor styrenes – see Figure S7). Non-terminal alkenes were also successfully oxytrifluoromethylated (**2m-o**). Notably, during the electrochemical functionalization of α-methyl styrene (product **2l**) acetophenone was observed as side product. This side reaction most likely occurred via a olefin cleavage pathway similar to that described by Fry and coworkers.[28]



Scheme 2. Reaction scope for the electrochemical oxytrifluoromethylation of alkenes. See Supporting Information for experimental details. [a] Essay corrected; the isolated product (70%) contained acetophenone as impurity.

Reactions in alcohols as nucleophilic solvents were also tested to evaluate the extent of alkoxytrifluoromethylation produced in a 10:1 mixture with water (Scheme 3). As expected, the proportion of alkoxy vs hydroxyl derivative augmented with the nucleophilic character of the solvent (MeOH > EtOH > iPrOH). Isolation of the alkoxytrifluoromethylated compounds **3a-c** was problematic due to their low boiling point. As they partially evaporated with the solvent relatively low yields were obtained. The reaction in MeOH did not require the use of water as additive. Using pure MeOH as solvent and following the general reaction conditions excellent yield and selectivity for the corresponding methoxytrifluoromethylated compound was obtained (see Figure S6).



R =	Me	Et	iPr
Ratio **3**/**2**	10:1	7:1	3:1
Isolated Yield **3**	**3a** (59%)[a]	**3b** (23%)	**3c** (17%)

Scheme 3. Reactions in alcohols as nucleophilic solvents. Alkoxytrifluoromethylation products are typically favored. Electrolysis in MeOH could also be performed without water as additive.

To gain some insights into the reaction mechanism a series of cyclic voltammetry and radical trapping experiments were carried out (Figure 1). Cyclic voltammetry only revealed that anodic oxidation of the triflinate, followed by an irreversible reaction, occurs at a potential of ca. 1.3 V (vs Ag/AgCl), well below the potential required for the oxidation of the styrene substrate **1a** (2.2 V) (Figure 1a) and even electron rich compounds such as 4-methoxystyrene (2.1 V) (Figure S7), explaining the good selectivity observed in most cases. The voltammogram of a mixture of triflinate, substrate and water did not reveal any other features, apart from the two expected consecutive oxidation peaks. Although formation of trifluoromethylated and trifluomethanesulfonylated aromatics as side products during many reactions suggested the formation of the corresponding radicals (*vide supra*), we performed a radical trapping control experiment using butylated hydroxytoluene (2,6-di-tert-butyl-4-methylphenol) (BHT) as additive. BHT was selected as radical trapping agent because its oxidation occurs at higher potential than for the triflinate, as determined by CV (see Figure S7). Thus, electrochemical oxytrifluoromethylation of **1a** was carried out in THF adding 1 equiv BHT. GC analysis of the resulting solution revealed a complex mixture of products, including a large amount of unreacted alkene (a detailed description of this experiment is included in the Supporting Information). Gratifyingly, evidence of the intermediacy of the elusive benzyl radical species **4** (Figure 1c) could be provided by the GC-MS detection of compound **6** (Figure 1b).

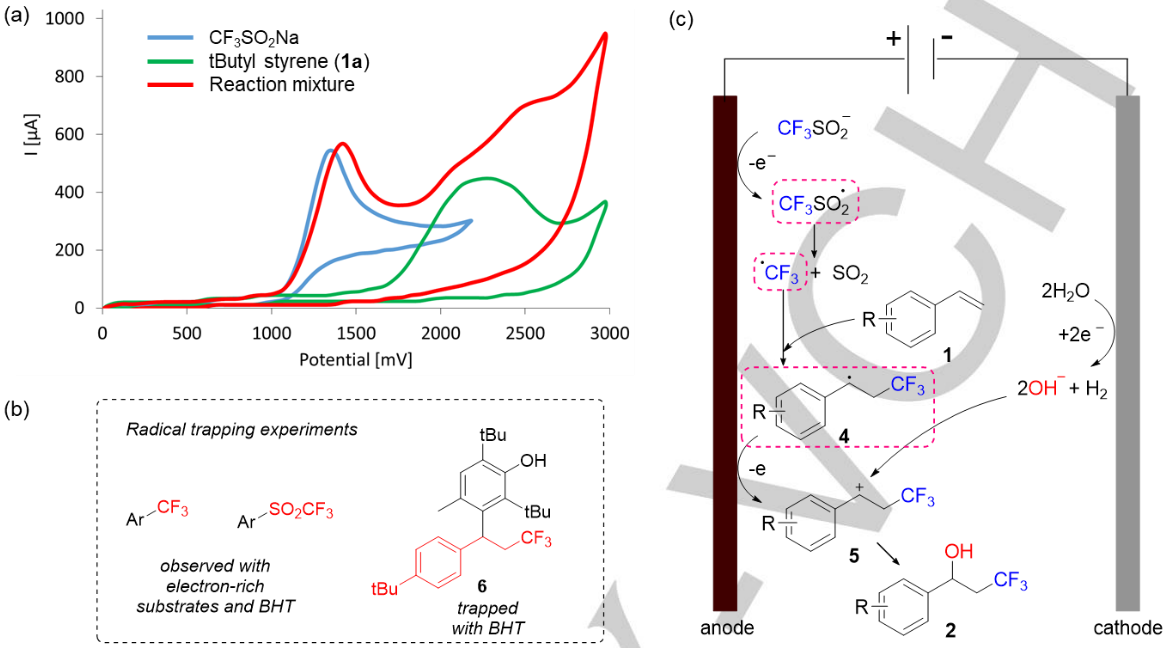


Figure 1. (a) Cyclic voltammograms of CF_3SO_2Na, t-butyl styrene (**1a**) and a typical reaction mixture (see Supporting Information for details), (b) compounds observed by GC-MS chromatography that point to the presence of the radical species highlighted red, and (c) proposed pathway for the electrochemical oxytrifluoromethylation. Radicals for which experimental evidence has been provided are highlighted.

Thus, in the proposed mechanism (Figure 1c) anodic oxidation of the triflinate anion produces the corresponding radical that decomposes to a CF_3 radical releasing SO_2. Addition of the CF_3 radical to the alkene, in the vicinity of the anode, results in intermediate **4**, which is further oxidized to the benzyl cation **5**. Two molecules of water are concurrently reduced on the cathode, releasing hydrogen and two hydroxide anions. Reaction of **5** with OH^- (or with water present in the solution) produces the desired oxytrifluoromethylated product **2**.

In summary, we have developed a mild, electrochemical procedure for the oxytrifluoromethylation of alkenes. This catalyst-free protocol is based in the paired electrolysis of sodium trifluoromethanesulfinate and water in an undivided cell. Anodic oxidation of the CF_3SO_2 anion is the source of CF_3 radicals, while water plays a dual role as oxidant at the cathode and nucleophile to provide the hydroxyl groups for the reaction. Evidence of the proposed mechanism, in which a benzyl radical (**4**) is oxidized at the anode in a second reaction step has been provided by radical trapping experiments with BHT. The electrochemical method has been tested for a diverse set of substituted terminal and non-terminal alkenes, providing moderate to excellent yields for the desired 1-hydroxy-2-trifluoromethyl compounds.

Acknowledgements

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Keywords: trifluoromethylation • alkenes • electrochemistry • radical reactions • sustainable chemistry

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Layout 2:

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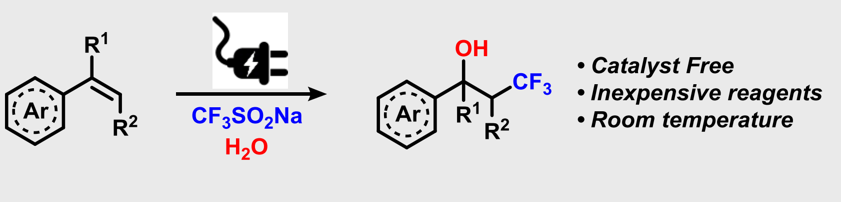

Electricity and water are key ingredients in this alkene difunctionalization method. Paired electrolysis of sodium trifluoromethanesulfinate and water in an undivided cell enables a mild, catalyst-free oxytrifluoromethylation of styrenes. Trapping experiments provide evidence of a mechanism involving three radical intermediates.

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